ISSN 2219-2808 (online)

World Journal of *Clinical Pediatrics*

World J Clin Pediatr 2023 December 9; 12(5): 244-364

Published by Baishideng Publishing Group Inc

WJCP

World Journal of Clinical Pediatrics

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Quarterly Volume 12 Number 5 December 9, 2023

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The primary aim of the *World Journal of Clinical Pediatrics* (*WJCP*, *World J Clin Pediatr*) is to provide scholars and readers from various fields of pediatrics with a platform to publish high-quality clinical research articles and communicate their research findings online.

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INDEXING/ABSTRACTING

The *WJCP* is now abstracted and indexed in PubMed, PubMed Central, Scopus, Reference Citation Analysis, China Science and Technology Journal Database, and Superstar Journals Database. The *WJCP*'s CiteScore for 2022 is 1.7 and Scopus CiteScore rank 2022: Pediatrics, perinatology and child health is 176/306.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: *Xiang-Di Zhang*; **Production Department Director:** *Xiang Li*; **Editorial Office Director:** *Xu Guo*.

NAME OF JOURNAL
World Journal of Clinical Pediatrics

ISSN
ISSN 2219-2808 (online)

LAUNCH DATE
June 8, 2012

FREQUENCY
Quarterly

EDITORS-IN-CHIEF
Toru Watanabe, Consolato M Sergi, Elena Daniela Serban, Surjit Singh

EDITORIAL BOARD MEMBERS
https://www.wjgnet.com/2219-2808/editorialboard.htm

PUBLICATION DATE
December 9, 2023

INSTRUCTIONS TO AUTHORS
https://www.wjgnet.com/bpg/gerinfo/204

GUIDELINES FOR ETHICS DOCUMENTS
https://www.wjgnet.com/bpg/GerInfo/287

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ONLINE SUBMISSION
https://www.f6publishing.com

E-mail: bpgoffice@wjgnet.com https://www.wjgnet.com

World Journal of Clinical Pediatrics

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World J Clin Pediatr 2023 December 9; 12(5): 244-262

DOI: 10.5409/wjcp.v12.i5.244

ISSN 2219-2808 (online)

FRONTIER

Comments by opponents on the British Medical Association's guidance on non-therapeutic male circumcision of children seem one-sided and may undermine public health

Stephen Moreton, Guy Cox, Mark Sheldon, Stefan A Bailis, Jeffrey D Klausner, Brian J Morris

Specialty type: Pediatrics

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): A
Grade B (Very good): 0
Grade C (Good): C
Grade D (Fair): D
Grade E (Poor): 0

P-Reviewer: Anaya-Prado R, Mexico; Cassell III AK, Liberia; Shalaby MN, Egypt

Received: June 30, 2023
Peer-review started: June 30, 2023
First decision: August 24, 2023
Revised: September 7, 2023
Accepted: September 25, 2023
Article in press: September 25, 2023
Published online: December 9, 2023

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Abstract

The British Medical Association (BMA) guidance on non-therapeutic circumcision (NTMC) of male children is limited to ethical, legal and religious issues. Here we evaluate criticisms of the BMA's guidance by Lempert *et al*. While their arguments promoting autonomy and consent might be superficially appealing, their claim of high procedural risks and negligible benefits seem one-sided and contrast with high quality evidence of low risk and lifelong benefits. Extensive literature reviews by the American Academy of Pediatrics and the United States Centers for Disease Control and Prevention in developing evidence-based policies, as well as risk-benefit analyses, have found that the medical benefits of infant NTMC greatly exceed the risks, and there is no reduction in sexual function and pleasure. The BMA's failure to consider the medical benefits of early childhood NTMC may partly explain why this prophylactic intervention is discouraged in the United Kingdom. The consequence is higher prevalence of preventable infections, adverse medical conditions, suffering and net costs to the UK's National Health Service for treatment of these. Many of the issues and contradictions in the BMA

guidance identified by Lempert *et al* stem from the BMA's guidance not being sufficiently evidence-based. Indeed, that document called for a review by others of the medical issues surrounding NTMC. While societal factors apply, ultimately, NTMC can only be justified rationally on scientific, evidence-based grounds. Parents are entitled to an accurate presentation of the medical evidence so that they can make an informed decision. Their decision either for or against NTMC should then be respected.

Key Words: Circumcision, Male; Child; Infections; Risk; Policy; Public health

Core Tip: This article assesses arguments by circumcision opponents Lempert *et al* criticizing the British Medical Association (BMA)'s guidance on non-therapeutic male circumcision (NTMC) for failing to consider all of the issues. We find that the BMA's focus on non-medical issues expose it to such claims by NTMC opponents. Indeed, the medical evidence, as used for evidence-based NTMC policies in the United States, does not support their claims. The lifetime benefits of early infant NTMC greatly exceed the risks, and the procedure has no adverse effect on sexual function or pleasure. The neonatal period is the optimal time for parent approved NTMC.

Citation: Moreton S, Cox G, Sheldon M, Bailis SA, Klausner JD, Morris BJ. Comments by opponents on the British Medical Association's guidance on non-therapeutic male circumcision of children seem one-sided and may undermine public health. *World J Clin Pediatr* 2023; 12(5): 244-262
URL: https://www.wjgnet.com/2219-2808/full/v12/i5/244.htm
DOI: https://dx.doi.org/10.5409/wjcp.v12.i5.244

INTRODUCTION

In 2019 the BMA released practical guidance for doctors on non-therapeutic male circumcision (NTMC) of boys[1]. This stated that it "abhors the harassment of individual doctors through intimidating and threatening behaviour on the basis of their involvement in the provision of NTMC". As with vaccination, NTMC attracts criticism from activists. Opponents argue that NTMC of a nonconsenting child violates their human rights to genital integrity and that circumcision should be delayed until they are old enough to make the decision for themselves. There are, however, sound scientific reasons why early NTMC is beneficial to the child's health. These include protection against infections in infancy and infections, including sexually transmitted ones, disease and other adverse medical conditions over the lifespan. Reduced risk of penile[2-4] and possibly prostate[5,6] cancer is greatest the earlier the NTMC is performed, being particularly strong (40% lower) in Black men[6]. Risk was lower in men circumcised after age 36 years in the Canadian study[6]. In the current "post-truth era", in which individuals and lobby groups dispute scientific evidence by way of on-line rhetoric, threats and intimidation using social media and protests to promote their views, the challenge for scientists and society is considerable[7-15]. As with other decisions by parents made in what they consider to be the best interest of the child, such as vaccination, lobbying by opponents can involve inappropriate pressuring of parents to reconsider their decision to have their sons circumcised.

The most recent reviews by the American Academy of Pediatrics (AAP)[16] and the United States (US) Centers for Disease Control and Prevention (CDC)[17] concluded that the health benefits of NTMC exceeded the risks and recommended the procedure for parents who choose it (Table 1).

NTMC opponents responded by denouncing the new policies. The claims were evaluated by the AAP, CDC, and academic authorities and found not to be consistent with the consensus of scientific evidence (Table 2).

Selective citation, obfuscation and denial of scientific evidence are features of anti-NTMC arguments. Most of these and the evaluation of each publication by medical authorities can be found in a systematic review[18].

The BMA guidance attracted the attention of NTMC opponents Antony Lempert, Chair of the Secular Medical Forum which advises the United Kingdom's National Secular Society, in an article with ethicist Brian Earp as author for correspondence, and two others[19]. The aim of the present article is to evaluate their arguments.

ANTI-NTMC SENTIMENTS BY OTHER MEDICAL BODIES

Lempert *et al*[19] support particular statements in the BMA's guidance[1] disfavoring NTMC. They refer to negative NTMC policies by Dutch (Kindermishandeling en huselijk geweld [KNMG]: Royal Dutch Medical Association), Danish and Finish medical bodies. Then refer to the Finnish Medical Association as being "more forward in their approach, offering a clear medical-ethical stance for consideration". They argue that "mainstream, non-partisan, national-level professional societies that have formally studied the issue", with the exception of those in the United States, "have concluded that NPC [NTMC] of children cannot be justified on medical grounds in the sense of conferring a net health

Table 1 Conclusions and recommendations by the American Academy of Pediatrics in its non-therapeutic male circumcision policy statement

The AAP Systematic evaluation of English-language peer-reviewed literature from 1995 through 2010 indicates that preventive health benefits of elective circumcision of male newborns outweigh the risks of the procedure
Benefits include significant reductions in the risk of urinary tract infection in the first year of life and, subsequently, in the risk of heterosexual acquisition of HIV and the transmission of other sexually transmitted infections
The procedure is well tolerated when performed by trained professionals under sterile conditions with appropriate pain management. Complications are infrequent; most are minor, and severe complications are rare. Male circumcision performed during the newborn period has considerably lower complication rates than when performed later in life
Although health benefits are not great enough to recommend routine circumcision for all male newborns, the benefits of circumcision are sufficient to justify access to this procedure for families choosing it and to warrant third-party payment for circumcision of male newborns. It is important that clinicians routinely inform parents of the health benefits and risks of male newborn circumcision in an unbiased and accurate manner
Parents ultimately should decide whether circumcision is in the best interests of their male child. They will need to weigh medical information in the context of their own religious, ethical, and cultural beliefs and practices. The medical benefits alone may not outweigh these other considerations for individual families. Findings from the systematic evaluation are available in the accompanying technical report. The American College of Obstetricians and Gynecologists has endorsed this statement

HIV: Human immunodeficiency virus.

Table 2 Nontherapeutic male circumcision policy statements showing arguments by opponents (left column) and responses to each (right column)

2012 AAP policy on NTMC[16,67]	
Frisch *et al*[95], 2013	AAP Task Force[15], 2013
Svoboda & Van Howe[96], 2013	Morris *et al*[99], 2014
Jenkins[97], 2014	Morris *et al*[100], 2014
Darby[98], 2014	Morris[170], 2014
Darby[171], 2015	Morris *et al*[101], 2016
Svoboda *et al*[172], 2016	Brady[102], 2016; Morris *et al*[103], 2017
2014 CDC MC draft policy[17,88]	
Earp[150], 2015	Morris[151], 2015
Adler[173], 2016	Rivin *et al*[174], 2016
Frisch *et al*[175], 2018	Morris *et al*[177], 2017; CDC[153], 2018
Van Howe[177], 2015	CDC[178], 2018
2015 CPS policy on NTMC[27]	
Sorokan *et al*[27], 2015	Morris *et al*[70], 2016
Robinson *et al*[180], 2017	Morris *et al*[180], 2017
RACP policy on NTMC[183], 2010	
RACP[181], 2010	Morris *et al*[182], 2012
Forbes[183], 2012	Morris *et al*[184], 2012
Jansen[185], 2016	Wodak *et al*[186], 2017

AAP: American Academy of Pediatrics; CDC: Centers for Disease Control and Prevention; CPS: Canadian Paediatric Society; NTMC: Non-therapeutic male circumcision; RACP: Royal Australasian College of Physicians.

benefit". Infant NTMC was endorsed in high human immunodeficiency virus (HIV) settings by various bodies combatting the HIV epidemic. According to a recent editorial[20], however, the World Health Organization (WHO) no longer endorses NTMC of infants in its voluntary medical male circumcision (VMMC) program. Reasons likely include immediate cost-effectiveness of NTMC for men in combatting the HIV epidemic, as opposed to the long lag that would occur between infant NTMC and its potential benefit for HIV risk reduction. Another factor may be reports of adverse events by inadequately skilled and over-stretched providers.

In a 2017 report, the CDC recommended routine infant NTMC for HIV prevention in 12 high priority countries[21]. Various local bodies fighting the epidemic have also endorsed the procedure[21-26]. But presumably Lempert *et al*[19] had in mind socio-economically advantaged countries such as the UK and North America that have a relatively low HIV prevalence. The negative Canadian Paediatric Society policy nevertheless concluded that in Canada "there may be a benefit [from NTMC] for some boys in high-risk populations and circumstances"[27].

Lempert *et al*[19] quote the KNMG as saying "it is reasonable to put off circumcision until the age at which [the] boy himself can decide about the intervention or can opt for any available alternatives". But this disregards the fact that, in early infancy, risk is minimized, and lifetime health benefits are maximized by NTMC. By postponing the procedure until the "boy himself can decide", the boy is deprived of the early benefits, such as a 10-fold reduction in risk of urinary tract infection (UTI)[28], as well as reduced risk of inflammatory and physical problems during childhood. Since procedural risk is lowest for NTMC performed in early infancy[29], delay also means an increased risk of harm to the boy from an adverse event. Thus, the longer the delay the lower will be the benefit to risk ratio.

The benefits of neonatal NTMC (and % affected based on population prevalence of uncircumcised males and of the medical condition) are: (1) A 90% decreased risk of UTI at age 0–1 years (with 1.3% affected), 85% lower risk at 1–16 years (2.7% affected), 70% reduced risk at > 16 years (28% affected), as found in a meta-analysis of males of all ages)[28]; (2) almost complete elimination of risk of phimosis, with an observational study finding 12% of uncircumcised British males still have phimosis by the age of 18 years[30]; (3) a 68% decreased risk of balanitis (10% being affected), as found in a meta-analysis of 8 studies[31]; (4) 60% decreased risk of candidiasis (thrush; with 10% affected)[31]; (5) a 70% decreased risk of HIV infection during heterosexual sex or insertive anal intercourse (with 0.1% affected), as found in a meta-analysis[32]; (6) a 53%–65% decreased risk of high-risk human papillomavirus (HPV) infection (4%–10% affected) according to meta-analyses[33-35]; (7) a 30% decreased risk of herpes simplex virus type 2 infection (with 4% being affected) based on randomized controlled trial (RCT) findings[36-39]; (8) a 50% decreased risk of genital ulcer disease (with approximately 1% affected), based on observational studies[40-42] and a meta-analysis[43]; (9) a 40%–55% decreased risk of syphilis infection (with 1% affected) based on the findings of a meta-analysis[43] and observational studies[44,45]; (10) a 50% decreased risk of *Trichomonas vaginalis* infection (with 1% affected), according to a RCT[46]; (11) a 40% decreased risk of *Mycoplasma genitalium* infection (with 0.5% affected) as revealed by RCT findings[47]; (12) a 50% decreased risk of chancroid (with < 1% affected), according to a meta-analysis[43]; (13) a 67%–99% decreased lifetime risk of penile cancer (with 0.11%–0.15% affected), as found in the most recent meta-analysis[4] and observational studies[48-50]; and (14) 10% decreased risk of prostate cancer (with 1% being affected), as determined by meta-analyses[51-53].

A common cause of inflammatory foreskin conditions such as balanitis can be poor hygiene, medications (such as antibiotics), allergens (including latex condoms, propylene glycol in lubricants), some spermicides, and corticosteroids. Ammonia released from urine by bacterial hydrolysis of urea can cause inflammation of the glans and foreskin. Frequent washing with soaps containing topical allergens or irritants is another common cause of contact dermatitis. Microorganisms are often responsible.

No adverse effect on sexual function or pleasure was found in multiple systematic reviews and meta-analyses[54-58]. The most recent found pain during intercourse and erectile dysfunction were significantly lower in circumcised men[57].

A drawback of NTMC includes risk of a minor adverse event, which affects 0.4% in infancy, 8% at age 1–10 years, and 4% at ages ≥ 10 years[29]. Risk of a major complication is extremely low. Another is cost, which can be substantial if the procedure is not covered by third party insurance. In the UK the National Health Service (NHS) covers medical MC, but not NTMC. If either is performed later, the time taken for the procedure and for the immediate recovery period will mean disruption of daily activities, including employment and school attendance. If the mature male is sexually active, then abstinence from sexual activities will be required during the healing period, which is generally 6 weeks.

PROCEDURAL RISKS MISUNDERSTOOD

The suggestion by Lempert *et al*[19] that procedural risks are similar "between infants and adults" is not the case. A US study of 1.4 million NTMCs by CDC researchers found risk of adverse events is 10–20 times higher after the neonatal period[29].

At "age 2–18" circumcision is often for treatment of medical problems, usually phimosis, excessive foreskin and lichen sclerosus, which would have been prevented by NTMC in early infancy. Lempert *et al*[19] ignore many key issues, such as those associated with UTIs that are 10-fold higher in uncircumcised infants. These include the excruciating pain of UTI, the need for blood collection, lumbar puncture, hospitalization for intravenous antibiotic administration, and risk of sepsis, death, and treatment challenges from burgeoning antibiotic resistance[59-62]. Early NTMC also means immediate and lifetime abatement of risk of numerous other adverse medical conditions that have varying degrees of morbidity, and, for some, a risk of mortality. Various clinical experts have likened NTMC to a "surgical vaccine"[63,64]. In contrast, the overwhelming majority of procedural complications from NTMC in early infancy are minor, and easily and fully resolvable[29].

MEDICAL NEED VERSUS PREVENTION

Lempert *et al*[19] state that "circumcision is rarely required for medical reasons", citing studies that reported the need for surgery in 1.7%–2.5% of boys < 18 years[65,66]. These figures do not, however, include the much greater number who will develop a foreskin-related problem (mostly phimosis) that infant NTMC would have prevented. Nor do they include

infections and diseases that will occur over the lifetime of uncircumcised males with a healthy foreskin. As well, some will require therapeutic circumcision to treat a medical condition at ages > 18 years. The benefits of circumcision when indicated for treatment include treatment of the devastating foreskin inflammatory condition lichen sclerosus, for paraphimosis when emergency intervention must be performed to prevent ischemia and gangrene, as a cure for intractable phimosis that has failed to respond to other interventions such as steroid treatment, and for treatment of cancerous tissue which frequently involves the foreskin of penile cancer patients.

The potential benefits of foreskin retention are its potential use as a skin graft during surgical repair of hypospadias, or to treat burns or other injuries in some specific areas of the body. There may be cultural reasons for retaining the foreskin, in which having the same general genital appearance as other males in non-circumcising cultures may help the boy or man fit in. This was recognized by the AAP in its recommendation that parents "will need to weigh the medical information in the context of their own religious, ethical, and cultural reasons and practices"[16,67]. Another is the requirement of a foreskin in the uncommon sexual practice of "docking"[68].

Health authorities have provided advice on care of an uncircumcised penis[69]: Gently, not forcefully, pull the foreskin away from the tip of the penis. Rinse the tip of the penis and the inside part of the foreskin with soap and water. Return the foreskin back over the tip of the penis.

As calculated in risk-benefit analyses for Anglophone countries[70-72], including the United Kingdom[73], approximately half of British males will likely experience a medical condition during their lifetime that NTMC might have protected against. Men can be reluctant to see a medical practitioner when they have a medical problem, especially when it involves their genitalia or sexual dysfunction.

COMPARISON WITH LABIAPLASTY

Lempert *et al*[19] argue that if "the 'better in infancy' view applied with equal force to 'infant labiaplasty'", and that "even if the data were unambiguous … the presumable consensus of Western medical ethicists and legal experts would be that such data are irrelevant"[19], citing Reis *et al*[74]. But data *are* relevant, and it is far from clear that the consensus would be otherwise. Evidence-based medicine is held in high regard by professionals for good reason – it works. The ethics (and legality) of a medical procedure must be guided by the best available scientific data, or else incorrect decisions, adverse outcomes and bad laws can result. In the case of labiaplasty the science is clear – it has no significant benefits, so there is no rational justification for performing it on a minor in the absence of a clear medical indication. NTMC, in contrast, does have clear benefits established by a very large body of scientific research data, and the optimal time is early infancy, as supported by the data. NTMC is thus unequivocally evidence based. The reference[74] used by Lempert *et al*[19] to support their argument is to an opinion piece about surgery on intersex infants. This is a poor analogy as intersex is a complex set of conditions. These may be associated with hormonal imbalances in the womb, or chromosomal abnormalities, and patients have a high risk of later identifying with a gender other than the one decided for them in infancy by a surgeon.

ETHICS

Because NTMC involves surgery on the healthy tissue of a child who is too young to give his consent (consent instead being given by his parents or guardians), and the health benefits during infancy and early childhood are modest (although high over the lifetime), individuals such as Lempert *et al*[19] argue that childhood NTMC is unethical. Public health ethics attempts to be practical by seeking decisions that will likely produce the greatest net benefit. Well-informed public health authorities might logically be persuaded by the strong evidence favoring NTMC. The extensive reviews by the AAP and CDC led these major authorities to conclude that since the benefits of infant NTMC exceed the risks, parents have a right to choose NTMC for a child. It has been argued that NTMC is justifiable as a public health necessity[75].

The Brussels Collaboration on Genital Integrity (BCGI)[76] decided that an intervention to alter a bodily state should be regarded as a medical necessity when the bodily state poses a threat to the person's well-being. While absence of NTMC may not pose a "threat" at the time at which NTMC is usually performed, the scientific evidence shows that if not circumcised early in life, approximately half of uncircumcised males will suffer an adverse medical condition over their lifetime because of their uncircumcised state[70-73]. Given the degree and breadth of benefits conferred by NTMC, performing infant and childhood NTMC appears consistent with the BCGI's statement.

Given the wide-ranging protection afforded by NTMC against diverse medical conditions and infections in infancy and childhood, including sexually transmitted infections (STIs) in sexually active adolescent males, it has been argued that it would be unethical not to circumcise boys early in childhood[77,78]. Article 24 of the United Nations Convention on the Rights of the Child[79] contains the statement:

"States Parties recognize the right of the child to the enjoyment of the highest attainable standard of health ... States Parties shall strive to ensure that no child is deprived of his or her right of access to such health care services".

Article 24 states that the definition of health includes preventative health. Thus, not advising parents of benefits and risk of NTMC may violate the rights of the child. Logically, Article 24 might be seen as mandating NTMC, since not circumcising boys poses a threat to their health[78].

Article 5 is also noteworthy. The text reads: "States Parties shall respect the responsibilities, rights and duties of parents or, where applicable, the members of the extended family or community as provided for by local custom, legal guardians or other persons legally responsible for the child, to provide, in a manner consistent with the evolving capacities of the

child, appropriate direction and guidance in the exercise by the child of the rights recognized in the present Convention" [79].

Should NTMC be delayed until later, the BMA guidance advises in "card 2, Ten good practice points" that "3. Children who are able to express views about NTMC should be involved in the decision-making process. 4. Where a child (with or without competence) refuses NTMC, the BMA cannot envisage a situation in which it will be in a child's best interests to perform circumcision, irrespective of the parents' wishes." Curiously, item 5 states: "It is the parents' responsibility to explain and justify requests for circumcision, in terms of the individual factors in relation to a particular child's best interests." In contrast, the AAP guidance states: "It is important that clinicians routinely inform parents of the health benefits and risks of male newborn circumcision in an unbiased and accurate manner".

THE "*DELAY UNTIL THE MALE CAN DECIDE FOR HIMSELF*" ARGUMENT

The policy of deferring early NTMC until an age of consent is reached involves an appeal to "autonomy". Whilst superficially and emotionally appealing, it is not consistent with evidence and thus appears to be misplaced as we will now explain. The argument fails to consider a more valid concern about beneficence or the best interests of the infant, and a fairer allocation of resources in society. In high-HIV settings, where striving for as high an uptake of NTMC as possible is vital to curb the HIV epidemic, a policy of deferring the procedure would mean fewer circumcisions and hence more infections, increased pressure on health systems, as well as higher health care costs (because later NTMC is more expensive), suffering, social costs and deaths. Even without the risk of HIV infection, deferring infant NTMC would still mean higher incidence of medical conditions that NTMC protects against, and thus higher morbidity, mortality, and costs. We therefore question if that is ethical?

Lempert *et al*[19] assert that "only a small minority of non-circumcised men report 'ever' wishing that they 'had been' circumcised—even in the United States, where infant circumcision remains a dominant cultural practice". As support they cite two articles by their article's co-author Earp. The first[80] cites a YouGov poll that found 10% of circumcised US men wished they had not been circumcised. But Lempert *et al*[19] ignore the same poll's finding that 29% of uncircumcised US men wished they were circumcised. Twenty-nine percent is not a "small" minority, as claimed. Their second citation[81] is to a survey of Amazon Mechanical Turk cohort participants. These were described in their first citation[80]. In the latter article, 15.9% of uncircumcised men wished they were circumcised, whereas 13.6% of circumcised men wished they were not[81]. Thus, slightly more uncircumcised than circumcised men were unsatisfied (1 in 6 *vs* 1 in 7). Since both surveys showed higher dissatisfaction amongst uncircumcised men, and the percentages are not small, the references cited by Lempert *et al*[19] do not support their claim.

Lempert *et al*[19] reference an article by Earp & Darby that states that "nontherapeutic circumcisions are rarely sought by adults with intact genitals, even in cultures in which circumcision is common and normative"[80]. A footnote on page 43 of that article cites a US study of men-who-have-sex-with-men (MSM) that found most were unwilling to have NTMC to prevent HIV. But a single study asking just MSM a hypothetical question is not representative of the majority view. In contrast, a systematic review of over 40 studies across multiple countries and cultures found that when all men are properly informed about NTMC they usually respond positively, and are more positive the better informed they are[82]. The VMMC program to combat the African HIV epidemic resulted in circumcision of almost 30 million men by 2020[20], and men continue to queue in some African countries to obtain the procedure. This does not support the critics' "rarely sought" statement. That many uncircumcised men outside of high-HIV settings (or circumcising cultures) do not wish or seek circumcision may reflect their lack of motive (low HIV risk), lack of free availability, or lack of education about the procedure's benefits.

Lempert *et al*[19] go on to argue that men who wish to be circumcised at least have the option of undergoing the procedure, unlike those circumcised as infants, who cannot reverse the decision. Whilst true, this overlooks the barriers to adults seeking the procedure. Lempert *et al*[19] acknowledge that there will be "certain costs and inconveniences". But their argument downplays the broad spectrum of barriers (Table 3).

CDC researchers conducted a study of adverse procedural events involving 1.4 million medical NTMCs in the US across all ages[29]. Amongst the 1.3 million infant NTMCs, adverse event frequency was 0.4%. The CDC referred to these findings in its 2018 policy statement[17]. Of the 1400920 reimbursement claims, 95.3% were for males aged ≤ 1 year, 2.0% were for ages 1–9 years, and 2.7% were for ages ≥ 10 years and above. Compared with infancy, adverse events were 20-times higher in boys aged 1–9 years, and 10-times higher in those aged ≥ 10 years[29]. The most common risks were minor bleeding, post-operative clearing of adhesions and removal of excess foreskin[29]. Such adverse events are easily and quickly resolved with no lasting effect. An exception is very rare fatal hemorrhage as a result of undiagnosed hemophilia and botched circumcision by poorly trained or negligent operators. In a large California study, frequency of complications was 0.5% in neonates, but in non-neonates was 18.5 times greater[17]. A United Kingdom study found complications were 1% amongst boys aged 3–16 years receiving therapeutic MC[83]. All were minor and there were no major complications.

A risk-benefit analysis for the United Kingdom[104] found benefits exceeded risks by > 100:1 and estimated that if not circumcised early a large proportion of males would be at risk of an adverse medical condition during their lifetime from a condition attributable to foreskin retention.

In settings where the procedure is freely and readily available, many men who would like to have a circumcision are nevertheless deterred by barriers such as fear of pain, need for sexual abstinence during the healing process, loss of earnings, inconvenience, embarrassment, and various psychosocial factors, as demonstrated by a voluminous literature (see review[84]). In developed countries, a man wanting to be circumcised, but who does not have a medical indication

Table 3 The advantages of non-therapeutic male circumcision in neonates compared with older boys and men

Neonatal non-therapeutic male circumcision	Non-therapeutic male circumcision of older boys and men
Is a simple surgical procedure for a well-trained competent medical practitioner	More complex
No psychological considerations	Possibility of adverse peer pressure, especially in societies such as the UK where MC is uncommon
Quick: Takes several minutes	Takes 30 min or more
Cost is lower	Much more expensive and often unaffordable
Low risk of adverse events (0.4%), and almost all are minor	Higher risk of adverse events (4%–8%)
Any bleeding is minimal and easily stopped	Bleeding is more common, requiring cautery or other interventions
Sutures not needed	Sutures or tissue glue are needed
Convenient since the baby sleeps most of the day	Inconvenient owing to need for time off school or work
Local anesthesia used if the infant is less than 2 mo of age	General anesthesia for age 2 mo to age 9 yr. For men local anesthesia may be used, although general anesthesia is sometimes preferred by the surgeon
Healing is fast (less than 2 weeks)	Healing takes 6 weeks or more
Cosmetic outcome usually good	If stitches are used, stitch marks may be visible permanently
No long-term memory of the procedure, or anxiety in anticipation	May be a source of fear in the boy or man of undergoing an operation
Does not disrupt breast-feeding or other activities	Abstinence from sexual intercourse required for the healing period of 6 or more weeks

MC: Male circumcision; UK: United Kingdom.

for circumcision, would have to attend a private clinic. In the UK, the cost of an elective adult NTMC is approximately £2259[85], which would be unaffordable to many. In contrast, the cost of an infant NTMC by a private provider is about 10-times lower[86,87]. One might wonder whether the "delay until the male is old enough to decide for himself" argument is used by NTMC opponents such as Lempert *et al*[19] to reduce the likelihood of NTMC ever happening. The multiple advantages of infant NTMC over adult NTMC have been highlighted in multiple reviews[16,17,71-73,88-90] (Table 3).

A systematic review of arguments opposing NTMC found that these were supported mostly by low-quality evidence and opinion and were contradicted by strong scientific evidence[18,91]. Many of those arguments have been stated above. Others included in the first systematic review[18] were that opponents appear to favor waiting until an adverse medical condition arises and then treating it by methods other than circumcision. However, such methods tend to be only partially effective, require prolonged intervention, and may have side effects. Steroids to treat phimosis is an example. In the meantime, the male will continue to suffer. Circumcision can not only be the definitive choice up front – but will provide at least partial protection against the elevated risk of the array of other adverse medical conditions over the lifetime of the uncircumcised male. Although penile cancer affects only about 0.1% of males over their lifetime[4,90,92], the consequences are devastating. Since childhood NTMC may provide almost complete protection against this cancer, that patient may regret his parents' failure to have him circumcised. Sexual function and pleasure are often referred to by opponents, likely because problems with these may not be discussed by men affected. A later section is devoted to this issue.

AN ALTERNATIVE TO NTMC FOR JEWISH FAMILIES

Just as is true of the BMA guidance document, Lempert *et al*[19] see NTMC as mostly a religious practice. They point out the existence of Jewish groups that reject NTMC. Those groups instead practice "Brit Shalom" (Covenant of Peace), a "gender-inclusive welcoming ceremony for children of Jewish parents" who prefer not to have their male children circumcised[93]. Brit Shalom arose in recent decades. It provides ritual options for families not affiliated with a synagogue and who may question NTMC. Instead of NTMC, the ceremony may involve cutting a pomegranate instead of a foreskin, and mainly focuses on naming the baby and welcoming him (or her) into the Jewish faith[93]. The reasons for replacing Brit Milah with Brit Shalom by some families appear to be respect for gender equality, response to local culture, acceptance of the arguments of NTMC opponents, perception of stigma being associated with circumcision, and Jewish feminism[93]. But Lempert *et al*[19] fail to acknowledge that the practice of Brit Shalom is by a very small minority within Judaism[93]. Orthodox Jews reject such alternatives to Brit Milah. The fastest growing section of the Jewish community, at least in Israel, is the Ultra-Orthodox[94] who would never relinquish NTMC on the eighth day of life. In addition, the Reform and Conservative movements, which essentially represent mainstream Judaism, continue their support and

practice of Brit Milah. The following is a statement provided to author Mark Sheldon by Rabbi Mark Cooper, Director of the National Organization of American Mohalim (NOAM) and Brit Milah Program of Report Judaism, a program under the auspices of the Hebrew Union College (HUC), Jewish Institute of Religion (JIR):

"Brit Milah, or Jewish ritual or ceremonial circumcision, is widely endorsed in the American Jewish community for Jewish families of various configurations. The Reform Movement of Judaism, under the academic supervision of HUC-JIR in Los Angeles, has sponsored the Brit Milah Program since 1984, with the aim of recruiting, training, and supporting physicians who wish to serve their communities as mohalim. Graduates of the program, currently numbering over 100 physicians and nurse midwives, belong to NOAM. The Conservative Movement of Judaism, under the organizational supervision of the Rabbinical Assembly, likewise sponsors its Brit Kodesh program, with a similar aim. Both movements are committed to perpetuating Brit Milah as Judaism's oldest continuously practiced ritual and enduring symbol of an unyielding commitment to the continuity of the Jewish way of life".

Lempert *et al*'s statement that "Children do not always grow up to share the religious or metaphysical beliefs, nor the associated cultural values, of their parents" is a valid point, and is one reason why infant NTMC can only be rationally justified on scientific, evidence-based grounds[19].

EVIDENCE-BASED *VS* NON-EVIDENCE BASED

Unlike the BMA's guidance and European position statements on NTMC of boys, those of the AAP[16,67] and CDC[17,88] are evidence-based and were supported by comprehensive reviews of the best data available at the time. Contrary to these are ones, such as Dutch and Scandinavian, cited by Lempert *et al*[19], that ignore most of the literature concerning the established benefits of the procedure, and focus instead on issues of ethics, human rights, consent, and legalities, making them essentially ideological positions rather than scientific evidence-based ones.

Lempert *et al*[19] disparage the AAP's infant NTMC policy statement, saying it "was met with unprecedented criticism from international experts for falling short of its usual scientific standards and exhibiting strong evidence of cultural bias" [95-98]. However, they fail to acknowledge the detailed rebuttals that those claims attracted[15,99-103] (Table 2). The "cultural bias" argument by Frisch and his mostly northern European (in particular Scandinavian) co-authors[95] was rebutted by the AAP Task Force on circumcision as applying more logically to northern Europe, where NTMC is rare, than to the US where the proportion of circumcised and uncircumcised males is more equal[15]. In response to the AAP, Earp & Darby argued that in Western medicine the bias is "against medically unnecessary surgeries performed on nonconsenting minors"[80]. But, unlike the anti-NTMC position, Western medicine might be seen as having a "bias" that is in favor of evidence-based medicine. Two of the most highly rated clinical practice guidelines for NTMC[104]were found by Canadian authors, who could be regarded as non-partisans in the debate, to be the evidence-based policy recommendations by the AAP and CDC.

Lempert *et al*[19] point out that all AAP policy statements automatically "expire" after 5 years, thus implying that the AAP's infant NTMC policy is no longer valid. It nevertheless remains the most up-to-date, evidence-based statement by a pediatric body to date. The AAP is, moreover, the world's largest pediatric body.

QUESTIONABLE ASSERTIONS ABOUT PROTECTION AGAINST HIV

Lempert *et al*[19] claim that there is no evidence anywhere in the world that NTMC of infants or children reduces the risk of HIV transmission, whether to males or to females. That is not true. Some of the observational studies in Africa that identified the connection between lack of NTMC and risk of HIV were in countries where NTMC of infants and children is the norm[105,106]. And studies in Asia and the developed world where NTMC is usually performed in infancy or childhood have found the same[107,108]. The evidence favoring childhood NTMC for HIV risk reduction has been reviewed recently[134].

Lempert *et al*[19] refer to "recent evidence from United Kingdom-comparable epidemiological environments within the Global North, including Canada and Denmark" that show NTMC does not protect against HIV. In support, they cite a Canadian study by Nayan *et al*[109] that found a non-significant 2% lower HIV prevalence amongst circumcised men. But a detailed analysis of those data by one of the present authors showed that the apparent lack of a significant effect stemmed from the disproportionately high prevalence of HIV infections amongst MSM, the majority of whom adopt the receptive role during anal intercourse, a sexual practice in which being circumcised affords no protection against HIV infection[110,111]. Circumcised men in the study who engaged in heterosexual intercourse or who were MSM practicing insertive anal intercourse were at 70% lower risk of HIV infection ($P = 7.2 \times 10^{-10}$)[110,111], just as found in the most recent meta-analysis of all studies globally[112]. Nayan *et al*[113] agreed with those calculations[110].

The same problem of failing to consider MSM in the analyses affected findings in the Danish study cited by Lempert *et al*[19] of HIV and other STIs amongst men who had undergone NTMC in childhood[114]. This was pointed out in a brief critique[115], and in much more detail in a comprehensive critique that also identified multiple other problems with the Danish study[111].

Lempert *et al*[19] also assert that "there is no evidence of a benefit to female partners of circumcised men, whether in Africa or elsewhere". This is untrue. Systematic reviews have found that NTMC protects the female partners of circumcised men indirectly by reducing the likelihood that a sexual partner will become infected[116,117]. Furthermore, the studies cited by Lempert *et al*[19] do not support their claim. Two[118,119] were general discussions that predate by up to a decade the data-based studies we cite above. The other[120] was to a trial in which some HIV-infected men

ignored advice and resumed sex before their circumcision wounds were fully healed, leading to infection of some female partners, a situation that may not have arisen had they been circumcised in infancy.

SEXUAL FUNCTION AND PLEASURE

Lempert *et al*[19] criticize the BMA's guidance for failing to address this topic. In common with assertions by other NTMC opponents, Lempert *et al*[19] claim that "the foreskin is the most sensitive part of the penis to light-touch sensation both to light touch stimulation and sensations of warmth" and "is a potential source of pleasure in its own right"[19]. In support, they cite a weak study[121] critiqued previously[122]. That study[121] appeared as a chapter in a 2006 book by NTMC opponents. They also cite a 2007 San Francisco study funded by NOCIRC (an anti-circumcision organization) of sensitivity to light touch[123], but not the critique pointing out flaws in the study's statistical analyses, methodology and recruitment[124]. In contrast, a Canadian study by Bossio *et al*[125] tested touch, pain, warmth and heat pain, finding that the foreskin is not the most sensitive part of the adult penis across all sensation types examined. Lempert *et al*[19] ignored the latter study and its findings that tactile sensation of the foreskin was similar to a control point on the forearm, and that there were no differences in sensitivity of other penile sites between circumcised and uncircumcised men.

The "light-touch sensation" Lempert *et al*[19] focus on involves Meissner's corpuscles. The histological data confirms the physiological data by showing that the foreskin has no role in sexual sensation or pleasure. Histologically, the neuroreceptors responsible for sexual sensation and thus pleasure have been described as genital corpuscles which are concentrated in the highly innervated coronal ridge of the glans and the underside of the distal shaft of the penis, thus ruling out the foreskin as a histological source of sexual pleasure[126]. Meissner's corpuscles, which are mechanoreceptors, are the most abundant sensory corpuscles in the glabrous skin of the prepuce, and are identical in structure to Meissner's corpuscles in fingers[127]. Whatever the neurological origins of erogenous sensation may be, it is not Meissner's corpuscles. Thus, the fixation on the light-touch sensation type in publications opposing NTMC is irrelevant. The BMA was right to disregard it in its guidance.

There is abundant high-quality evidence from randomized controlled trials, cohort and case-control studies, and large, well-designed cross-sectional surveys, that medical NTMC has no adverse effect on sexual function, pleasure or satisfaction in men, as summarized in all systematic reviews[54,56,57,128] and meta-analyses[55,57]. Significantly, three of these were not by individuals often involved in the NTMC debate and were from non-circumcising countries (Denmark and China, although one author of the Danish study was of Jewish heritage).

Systematic reviews found women, including those from non-circumcising cultures, overwhelmingly prefer a circumcised penis for sexual activity[154,155]. Across countries, cultures and sexual preference, a majority of men too regard being circumcised as esthetically pleasing and more sexually desirable to women[129-135]. While esthetics is clear-cut, sexual pleasure may be purely physical, or could be influenced by psychological factors. Women may have a valid perception of better hygiene and lower risk of STIs if their male partner is circumcised.

Lempert *et al*[19] quote from a recent review by Tye *et al*[136] that speculated about the inability of circumcised men to experience the phenomena of "gliding", "rocking", "rolling" or "moving" of the foreskin, and their supposed need for lubrication during sexual intercourse. But they failed to acknowledge that Tye & Sardi's review stressed that there are no data supporting such phenomena. A recent article examined the claims made by Tye & Sardi and found no evidence that any were of importance[122]. When asked which were the most erogenous parts of the penis, men put the glans first, and the foreskin last[137].

INAPPROPRIATE ANALOGIES

Lempert *et al*[19] wondered why NTMC should be legal whereas "female genital mutilation" (FGM) "is illegal in the United States and most other developed countries". But this is a false analogy. Most forms of FGM are anatomically dissimilar to MC. FGM confers no medical benefits, only risks. In contrast, NTMC confers a wide range of benefits that greatly exceed risks, especially when performed early in infancy. The two are therefore not comparable, and thus represent separate issues. A FGM case in the United Kingdom, in which the presiding magistrate was Sir James Munby, was misconstrued by NTMC opponents[138]. The latter failed to reveal that items 72 and 73 of the judgement recognized substantial health benefits of childhood NTMC that differentiated it from FGM[139]. A critical evaluation of the judgement can be found in McAlister[140].

The female equivalent of MC is "hoodectomy" – the removal or reduction of the clitoral hood (female prepuce). It may be done for medical reasons – such as inflammation – the female equivalent of balanitis[141] but can be chosen by women for perceived improvement in sexual function. A number of clinics in the UK offer the procedure. This is not remotely equivalent to the mutilations practised in some North African countries, so to bundle these all together as FGM is unhelpful.

The Lempert *et al*[19] critique referred to tattooing as being "analogous" to NTMC of minors. But they failed to state whether tattooing confers medical, sexual, or hygienic benefits. For an analogy to be valid, the two must be comparable. Tattooing is not a prophylactic procedure, and we are unaware of it having any proven health benefits. NTMC would appear unique as far as benefits are concerned. Childhood vaccination has some parallels but does not involve removing body parts. Tooth extraction – for example when teeth cause overcrowding of the mouth – comes to mind, but then an overcrowded mouth is a pre-existing problem that can be serious in that it may lead to impacted molars. Various procedures commonly performed on minors and that attract little criticism include cosmetic surgery, such as the removal

of birthmarks, or straightening of crooked teeth. But it is curious to us that removal of the foreskin, a well-known haven for bacteria and other microorganisms that play varying degrees of responsibility in the etiology of UTI, HIV, oncogenic HPV genotypes and some other STIs, inflammatory dermatological conditions, physical problems, penile cancer, and prostate cancer in uncircumcised men, and an increased risk of cervical cancer and several STIs in female partners, is a topic of derision by particular minority groups who oppose NTMC of children.

UNTRAINED PRACTITIONERS

Lempert *et al*[19] raise concerns about NTMC being carried out by untrained practitioners. We share these concerns insofar as the procedure should only be carried out by those who are well-trained and who abide by accepted clinical practice guidelines. This should not preclude a well-trained Jewish mohel, for example, from carrying out the procedure. Research both in developing and developed world settings has shown that, if properly trained and provided with adequate resources, nurses, midwives and physician assistants can perform the procedure to just as high a standard as doctors and surgeons[142-146]. Consistent with the studies cited, the BMA guidance states "Male infant circumcision does not require a medical professional"[1]. This contradicts Lempert *et al*[19], who claim the BMA guidance states: "Male infant circumcision does not require medical expertise". Their misquote is somewhat out of context. The only place in the BMA guidance where the word "expertise" is used is in the preamble, entitled "About this toolkit" on the second page, which states, "We note that there is no requirement in law for these practitioners to have proven expertise, although there are standards that some practitioners ascribe to set by external collectives, associations and societies." The BMA's guidance goes on to acknowledge that there have been rare cases of serious injury or death caused by "non-doctor practitioners" and "urge parents who are considering having their child circumcised, to ensure that the practitioner who carries out the circumcision has undergone relevant training and has proven experience and competence in the practice", a caution the guidance repeats two pages later.

Clearly the BMA was aware of the problem of inadequately trained practitioners causing harm and urge parents to seek trained and experienced providers. We share Lempert *et al*'s concern that there is no legal requirement in the United Kingdom for a provider to have appropriate training in NTMC, or to abide by particular standards. It is right and proper to draw attention to this issue[19].

LEGAL CONCERNS BY THE CRITICS

In part (1) of their 2nd table, Lempert *et al*[19] state that NTMC "has been ruled to amount to 'significant harm' within the meaning of the Children Act 1989 by the High Court (Family Division) in the context of care", and in part (2) that it "has been held, again by the High Court, to amount to greater harm than at least some of WHO Types 1, 2, and/or 4 FGM which are agreed to be unethical and unlawful procedures"[19]. Each is followed by a footnote ("p"), which discusses the ruling by Lord Justice Munby in 2015[139] in which Lempert *et al*[19] point out that Munby decided that NTMC constituted "significant harm" on the grounds that it was more invasive than some forms of FGM which were already considered "significant harm" in law. We disagree. Munby set out to decide whether a case of FGM amounted to "significant harm" and agreed that it did. In item 69 Munby states "In my judgment, if FGM Type IV amounts to significant harm, as in my judgment it does, then the same must be so of male circumcision." Then in item 73, Munby states "there is a very clear distinction between FGM and male circumcision. FGM in any form will suffice to establish 'threshold' in accordance with section 31 of the Children Act 1989; male circumcision without more will not." Lempert *et al*[19] therefore appear to have misrepresented Munby's judgement.

Sir William Patrick Dean, a High Court Judge (and former Governor General of Australia), stated in a 1992 case that NTMC, "for perceived hygienic – or even religious – reasons…plainly lies within the authority of parents of an incapable child to authorize surgery on the basis of medical advice"[147]. It should be noted that at that time the medical evidence favoring NTMC was not as strong as it is today.

Thus, our evaluation of much of the legal evidence referred to by Lempert *et al*[19] shows that they have ignored key statements by judges and authoritative organizations that contradict their stance that is opposed to NTMC of boys[19].

As an aside, in relation to FGM, it seems to us difficult to comprehend how the mildest forms of FGM, which may be no more than a prick or scratch, can be construed as "significant harm." An accidental scratch, cut, or bruise that heals fully within a week or two should not be considered "significant harm", even though it may damage more skin, cause more pain, and shed more blood than type IV FGM. The definition of "significant harm" is too broad here. There is unarguably a temporary harm in NTMC as the wound heals, but once healed (a process which is much faster in the neonate than the 6–8 weeks required for post-circumcision healing in an adult) there is no harm, as indicated by the multiple studies referred to above showing that sexual function, pleasure, and satisfaction are unimpaired, even improved following the procedure. The "significant harm" assertion was also heavily criticised by a British Law postgraduate[140]. Lempert *et al*[19] ignored this. They also ignored items 72 and 73 of Munby's judgement which recognized health benefits of boyhood circumcision that distinguish it from FGM.

Lempert *et al*'s 2nd table, part (e)[19], states that "Under English criminal law, the imposition of [NTMC] on a non-consenting adult certainly amounts to the criminal offence of Actual Bodily Harm, and very likely amounts to the offence of Grievous Bodily Harm"[148]. But does it? This comment refers the reader to their footnote "s" which states: "See Crown Prosecution Service, Code for Crown Prosecutors, 'Offences against the Person, incorporating the Charging Standard' [available at cps.gov.uk/Legal-guidance/offences-against-person-incorporating-charging-standard]." Since the

word "circumcision" does not appear in that document, the reference fails to support Lempert *et al*'s argument[19].

The authors go on to suggest that "Either 'minor' forms of FGM will have to be allowed, as prominent defenders of child [NTMC] are increasingly proposing …. or [NTMC] of minors will have to be brought into closer alignment with existing standards applied to other practices". We would, however, question whether the authors of the 9 references they cite are "prominent defenders" of NTMC. If having just a few publications on the topic of NTMC makes one a "prominent" defender of NTMC, one wonders what Lempert *et al*[19] would make of authors with a prolific publication record, whose findings agree with the medical evidence supporting NTMC. We are, moreover, unaware of any prominent defender of NTMC who also defends any version of FGM. The "prominent defenders" that Lempert *et al*[19] refer to do not defend FGM on "medical grounds" but recognize the existence of cultural issues.

At the end of their article, Lempert *et al*[19] provide Notes to their Table 3, where their item marked "l" states: "A subsequent report by the U.S. Centers for Disease Control, apparently produced in coordination with the AAP, was met with similar international criticism[149]. For further discussion of the specific problems with these American analyses by one of us see Ref.[151]" Lempert *et al*[19] ignore the responses to those criticisms[151]. They cite a criticism by Kupferschmid *et al*[149], which was just one of many submissions to the CDC that followed release of the CDC's draft policy in 2014[17,151]. The Kupferschmid web reference is now unobtainable. The CDC reviewed and provided answers addressing virtually all of the various objections in a separate document in 2018[153]. Their "by one of us" article cited in Lempert *et al*'s quote above was by Earp[150] (the author for correspondence on the Lempert *et al* article[19]). They do not, however, cite the co-published rebuttal[151] of Earp's article.

SUMMARY OF THE CRITICISMS BY LEMPERT *ET AL.*

The basic tenets of Lempert *et al*'s criticisms of the BMA's guidance are encapsulated in their statement: "More generally, we find that selective quotes and evidence, where discussed, operate throughout the guidance in the direction of minimizing problems with [NTMC] and downplaying reasons to object to it, while alluding to unproven or intangible (*e.g.* prophylactic or psychosocial) benefits of the practice." Lempert *et al*[19] can be accused of doing the same, but in the opposite direction. Thus, their article appears to be projection.

Many of the issues and contradictions in the BMA guidance identified by Lempert *et al*[19] stem from the BMA's statement not being sufficiently evidence-based. Ultimately, NTMC can only be justified rationally on scientific, evidence-based grounds. Religious circumcision may, however, have had a sound practical basis. The reason for Jewish circumcision is lost in the mists of time, although, if we believe Genesis, Abraham was unable to father a child by his wife Sara until he was circumcised. Islamic circumcision is not a command from on high but part of a whole suite of recommendations for practical health and hygiene, which make sense in the scientific era of today. Modern bathing facilities may have improved on some Islamic cleanliness recommendations, but the health and hygiene benefits of circumcision are unchanged. Many children and adults who drift away from their birth religion understand this and continue to favor circumcision. Although, as Lempert *et al*[19] correctly point out, there is no guarantee that the infant will continue to follow religious traditions when they grow up. Moreover, performing the procedure for religious and cultural reasons may not be accepted by some individuals outside of those traditions and may even be vehemently rejected.

CLAIMS BY OTHER NTMC OPPONENTS IN THE UK

London urologists Matthew Deacon and Gordon Muir recently published a review[155] examining pros and cons of infant NTMC. Although not addressing the BMA's statement directly, being UK-based, their review is relevant to the BMA's guidance, so it would be remiss not to mention it here. Several of the present authors examined it and found it was selective with the literature, misleading and contradictory[155].

Deacon *et al*'s reply[156] was also problematic. Their complaint about self-citing by their critics was *ad hominem*. Self-citing shows that an author has published copiously on a topic, it says nothing about the quality of their work. Besides, some on the negative side of the NTMC debate also extensively cite their own and each other's publications[81]. Deacon & Muir ignored a systematic review and meta-analysis of all 27 studies of meatal stenosis[157], instead "cherry picking" an outlier study by an anti-NTMC activist, ignoring the strong criticism it attracted[158]. They complain that risk-benefit analyses by the present last author and colleagues have not been replicated …. but no one has tried. They dismissed criticism of their claim that NTMC may increase the need for antibiotics as getting "lost in a statistical debate", but their claim was based on a gross over-estimate of post-procedural infections, and a false assumption that all such infections require antibiotics. They also misunderstood evidence that circumcision protects against HIV during vaginal intercourse by heterosexual men[108,110,111,159,160] and insertive anal intercourse by MSM[110,111,161,162] in developed countries. Deacon & Muir exaggerate perceived pain from NTMC by including "Minimal pain" and "Acceptable pain" responses in a study on parent's perception of procedural pain from NTMC, arriving at 70.7%, instead of the more realistic 3.7% for "More than acceptable", or "Much more pain" in their infant child. Finally, they persist in misunderstanding that it is erogenous sensation, not light touch or heat, that matters during sexual intercourse, and that erogenous sensation is concentrated around the glans and distal shaft, not the foreskin[126,136,137]. In short, Deacon *et al*'s reply failed to properly address the original criticisms[155].

An article by Sutton *et al*[163] argued that general practitioners (GPs) in the United Kingdom were guilty of referring too many uncircumcised males with foreskin problems to their regional pediatric surgery clinic. A critique pointed out that "circumcision as soon as a problem becomes apparent is by far the most cost-effective solution"[164]. In a reply to the

criticisms, the article's co-authors Corbett *et al*[165] cited dated guidelines in 2006 by the British Association of Pediatric Urologists that has a disclaimer that "this statement is not evidence based"[166]. Instead, they refuse to circumcise – even 16-year-old boys who are unable to consummate sexual relations – if they regard their phimosis as "physiological", that is foreskin constriction without evidence of pathology. The tendency to conserve the foreskin ignores the fact that 50% of cases of lichen sclerosus are only discovered after circumcision, when clinical assessment is conducted[167]. Those authors then complained that health care providers lack education about foreskin health in children and that many "would welcome further educational resources." We hope the present article will address this need. Their claim that on average a GP working in the NHS has an annual caseload of "1700 thousand" patients, is a figure three orders of magnitude higher than the likely actual caseload. Corbett *et al al*[165] ended by promoting their own website[168], which makes the curious claim that "Your penis produces smegma to help keep it lubricated and prevent dryness".

TAKING AN EVIDENCE-BASED POSITION

As scientists and professionals, we take a strictly evidence-based approach. If infant NTMC is favored by both risk-benefit and cost-benefit analyses, which the present article affirms, then a logical, evidence-based case can be made independently of religious and cultural considerations. As should be apparent from the evidence presented, such a case can be made, and indeed has been made, by several professional bodies, such as the AAP[16,66], the CDC[17,87], and the Circumcision Academy of Australia[71]. Opponents of the procedure are welcome to debate these assessments. That is how science proceeds, but to date the contributions to such debates by opponents have been marred by poor science.

Based on high quality scientific evidence, NTMC has minimal or no adverse effect on sexual function, pleasure, or satisfaction[53-57] – if anything, as shown by the most recent meta-analysis, it reduces sexual dysfunction (less pain, less erectile dysfunction, and more favorable intravaginal ejaculatory latency time)[56]. This does not by itself justify the procedure, but it does refute one of the main objections by NTMC opponents, namely that NTMC reduces sexual function and pleasure. NTMC also confers a range of medical, health, sexual and practical benefits, and those benefits are maximal and the risks minimal if the procedure is carried out during the neonatal period. If, as the cumulative evidence strongly suggests is the case, neonatal NTMC is favored based on risk-benefit analyses and is cost saving with minimal harm to the recipient, then it is in the male child's best interests to be provided with the procedure. As a corollary, it would be unethical to deny infant NTMC to parents who want their sons to be circumcised. It also follows that religious or cultural NTMC, provided it is performed to a high clinical standard, is simply doing a medically beneficial procedure for non-medical reasons, so neutralizing the ethical objections Lempert *et al*[19] raise against it.

NTMC is a one-off procedure that is most conveniently performed in early infancy using local anesthesia. In early infancy it is simpler, safer, quicker, cheaper, more convenient, cosmesis is optimum, and healing is faster than later circumcision which presents multiple other challenges, as listed in Table 3. The BMA guidance recognizes the need for the procedure to "be in the child's best interests". This should prioritize the child's immediate and long-term health, and its medical benefits to the United Kingdom population as a whole, rather than merely appeasing the religious and cultural requirements of minorities. Medical practitioners, nurses and other health professionals in the United Kingdom have an ethical duty to present clear and unbiased information to parents of boys and to men regarding the diversity of benefits afforded by NTMC, the net level of lifetime protection against these, the low prevalence of procedural risks, that are especially low for neonatal NTMC, and that, unless otherwise indicated, circumcision will be performed using local anesthesia at that age. If the medical practitioner is unable or unwilling to perform the procedure, she or he should direct parents to a medical practitioner who is competent, experienced, and willing.

Given the evidence, infant NTMC might be considered in a similar manner to childhood vaccination. Vaccination is also an early intervention providing considerable benefits, with low risks. Denial of vaccination by medical professionals is unethical. Infant NTMC confers cost-savings to health systems and individuals[169].

A recent evaluation by Canadian researchers of 13 clinical practice guidelines for NTMC in different countries[103] found the best included those by the CDC and the Canadian Urological Association, followed by the AAP. These were chosen because of the thorough reviews of the medical literature each had performed in developing their NTMC policies. The BMA's guidance was not amongst the 13 chosen.

Alignment of medical thinking in the United Kingdom – that seems to have changed little over the years – with current high-quality scientific evidence and evidence-based policy statements in the US would better inform practitioners, health authorities, policy makers and governments in the United Kingdom. The outcome would likely be improvements in public health, cost coverage by the NHS, as well as long-term cost savings for the NHS and the United Kingdom taxpayer by reducing the case load of infections and diseases that NTMC protects against.

CONCLUSION

The present review finds that extensive criticism of the BMA's guidance on NTMC by a member of the United Kingdom's National Secular Society and his co-authors does not stand up to scrutiny. Their opinions are at odds with widely available high-quality scientific evidence and evidence-based policies by major medical bodies such as the CDC and AAP.

FOOTNOTES

Author contributions: Moreton S and Morris BJ conceived the study, Moreton S and Morris BJ prepared the initial draft of the manuscript, Moreton S, Cox G, Sheldon M, Bailis SA, Klausner JD and Morris BJ provided input to successive drafts. All authors have read and approve the final manuscript.

Conflict-of-interest statement: Stephen Moreton is an editor of, and contributor to http://www.circfacts.org, an online facility that provides evidence-based information on male circumcision. Brian J Morris is a member of the Circumcision Academy of Australia, a not-for-profit, government registered, medical society that provides evidence-based information on male circumcision to parents, practitioners and others, as well as contact details of doctors who perform the procedure. Research performed by Brian Morris is supported by U.S. National Institutes of Health Center of Biomedical Research Excellence grant 1P20GM125526-01A1 but was not used for the present publication. None of the authors receive income from their affiliations or work related to circumcision.

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L-Editor: A
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World Journal of Clinical Pediatrics

Submit a Manuscript: https://www.f6publishing.com

World J Clin Pediatr 2023 December 9; 12(5): 263-272

DOI: 10.5409/wjcp.v12.i5.263

ISSN 2219-2808 (online)

OPINION REVIEW

Prediabetes in children and adolescents: An updated review

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Specialty type: Pediatrics

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): A
Grade B (Very good): 0
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Gaman MA, Romania; Pop TL, Romania

Received: July 25, 2023
Peer-review started: July 25, 2023
First decision: August 31, 2023
Revised: October 5, 2023
Accepted: October 16, 2023
Article in press: October 16, 2023
Published online: December 9, 2023

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Abstract

Prediabetes, the precursor of type 2 diabetes mellitus, is an intermediate stage between normal glucose homeostasis and overt diabetes. This asymptomatic metabolic state is increasingly prevalent in pediatric population and is very difficult to detect without appropriate screening. Studies have shown that a certain proportion of children with prediabetes will develop diabetes in a few years. Even more alarming is the evidence that youth-onset diabetes has a more aggressive clinical course with progressive beta-cell decline and accelerated end-organ damage. Despite its importance, several aspects involving prediabetes in childhood are disputed or unknown. This review presents the latest insights into this challenging entity and outlines a simplified screening approach to aid clinical practice. In summary, childhood prediabetes is an important clinical condition indicating the need for proper screening and timely intervention.

Key Words: Prediabetes; Screening; Diagnosis; Management; Obesity; Type 2 diabetes mellitus; Children

Core Tip: Prediabetes, an intermediate stage before type 2 diabetes mellitus, has increased in parallel with the growing burden of pediatric obesity worldwide. However, child health practitioners are struggling with the definition, significance, diagnostic approach, trajectories, implications, outcomes, and management of prediabetes. This review aims to provide pediatricians and primary care providers with an updated overview of this important, yet controversial, condition.

Citation: Ng HY, Chan LTW. Prediabetes in children and adolescents: An updated review. *World J Clin Pediatr* 2023; 12(5): 263-272
URL: https://www.wjgnet.com/2219-2808/full/v12/i5/263.htm
DOI: https://dx.doi.org/10.5409/wjcp.v12.i5.263

INTRODUCTION

Childhood obesity has long been a public health challenge worldwide and has emerged as one of the most significant concerns. It poses an enormous health burden. The prevalence of childhood obesity has increased exponentially in recent years. This is further exacerbated by the novel coronavirus disease 2019 (COVID-19) pandemic, which negatively impacted the lifestyle and nutritional habits of children[1-3].

Prediabetes is a prominent clinical condition characterized by asymptomatic prodromal phase before the onset of diabetes mellitus. In adult population, prediabetes is considered a precursor to type 2 diabetes mellitus (T2DM)[4]. It is therefore tempting to infer a dramatic rise in prediabetes among pediatric population, given the increase in the prevalence of both obesity and T2DM in childhood[5]. A recent systematic review and meta-analysis showed a rapid increase in the prevalence of prediabetes in children globally. The pooled prevalence of 48 community-based studies was up to 8.84%[6]. Notably, prediabetes in children is associated with youth-onset T2DM, which is regarded as a more aggressive entity with increased cardiovascular and metabolic risk[7,8]. Significant damage to beta-cells may also occur prior to the development of dysglycemia[9]. The various adverse health effects in adulthood can be traced to prediabetes in childhood[10]. Fortunately, the occurrence and progression of dysglycemia in T2DM is more insidious compared with type 1 diabetes mellitus (T1DM) allowing more time for prevention and intervention.

Early diagnosis and management *via* screening represents a unique opportunity to intervene and is both logical and appealing. However, our current understanding of childhood prediabetes is mainly based on studies involving adult population and is poorly characterized[10]. The diagnosis and management of this important clinical condition is still imperfect, and is often disputed and debated. Thus, the need for a literature review to identify the latest evidence, insight and knowledge gaps cannot be overstated.

With this background, a comprehensive literature search was conducted in an effort to provide an overview of current understanding regarding prediabetes. It covers the latest epidemiology, diagnostic means, related controversies, and the need for future research. The span of our review is limited to articles published within the last 10 years in an effort to provide pediatricians and primary care providers with recent updates of this complex yet important condition.

LITERATURE SEARCH

For this narrative review, a literature search was conducted using MEDLINE, EMBASE, RCA, and Google Scholar databases. Search terms included "prediabetes", "hyperglycemia", "dysglycemia", "abnormal glucose homeostasis", "children", and "adolescents". Articles published between January 2013 to March 2023 were considered with the exception of landmark studies or articles. Additional publications were also retrieved by snowballing.

Specifically, articles reporting prediabetic children younger than 18 years old were reviewed, with full-text available in English. Exclusion criteria included T1DM (autoimmune β-cell destruction), gestational diabetes mellitus (GDM), and other specific types of diabetes, such as monogenic diabetes syndromes, pancreatogenic diabetes, and drug-induced diabetes[11].

CHILDHOOD OBESITY

Childhood obesity has evolved into a major public health crisis both in developed and developing countries[12-14]. Globally, studies showed a high level of obesity and a rising trend particularly in low-and middle-income countries[15]. The United Nations Children's Fund estimated that 380 million children below 19 years of age were overweight, with the rate increasing to 18% in 2018 from 10% in 2000 among 5- to 19-year-old individuals[16].

The situation is further complicated by the unprecedented public health challenge due to coronavirus disease 2019 (COVID-19) pandemic. Response to global COVID-19 pandemic by decision-makers had a further impact on the obesity landscape as more than 80% of children worldwide experienced school closures, movement restrictions, physical inactivity, and drastic changes to their way of life[13,17,18]. These changes in lifestyle, daily routines, and nutritional habits contributed to weight gain[3]. Consequently, a significant rise in childhood obesity is imminent and inevitable[19, 20].

Recently, two systemic reviews and meta-analyses demonstrated a significant increase in weight gain, body mass index (BMI), and prevalence of obesity in children during the COVID-19 pandemic[21,22]. In another study evaluating the net impact of the COVID-19 Lockdown, Dietz[23] reported that the changes in obesity prevalence among children aged below 12 years were 28- to 37-fold higher than the annual expected changes observed in the National Health and Nutrition Examination Survey of United States. Particularly, the highest weight gain observed among youth with severe obesity was a cause for serious concern[24]. As the obesity rates and levels continue to rise in childhood, the prevalence of prediabetes and diabetes in children also increases rapidly with alarming trends worldwide[6].

TYPE 2 DIABETES MELLITUS

In brief, the pathophysiology of T2DM involves insulin resistance (IR) accompanied by insufficient insulin release[8,9,25]. Clinical signs suggesting insulin resistance, such as acanthosis nigricans, are risk factors indicated in various guidelines. Acanthosis nigricans is closely associated with insulin resistance and provides a prominent visual cue that can aid in early intervention[25-28]. Although the underlying risk for IR is not completely understood, genetic and environmental factors are largely implicated[8,25].

Youth-onset T2DM is a more aggressive disease with rapid deterioration of beta-cell function and poor response to treatment. Eventually, it progresses to complications more rapidly and earlier than in adult-onset T2DM, impacting the most productive years of life[29-33]. A substantial number of patients with youth-onset T2DM exhibit micro-vascular and macro-vascular complications in the early stages of the disease, suggesting prior ongoing vascular damage[34]. In an observational study of 500 cases of youth-onset T2DM conducted over 10 years, the cumulative incidence of hypertension, dyslipidemia, retinal disease, and diabetic kidney disease recorded exceeded 50%. Among these participants who were diagnosed with diabetes for 13.3 years (mean), 28.4% carried more than two diabetes complications at a mean age of 26.4 years[35]. At the time of first diagnosis, youth-onset T2DM often presents with comorbidities, including but not limited to hypertension, dyslipidemia, and hepatosteatosis[36]. Given this grim threat, early identification of youth who are at-risk is imperative.

PREDIABETES

Prediabetes is a condition that is characterized by dysregulated glucose homeostasis[25]. Advocating prediabetes as a distinct pathological condition is controversial despite its recent inclusion in the ICD-10 coding[37,38]. While some authors caution against medicalization of prediabetes[39,40], others believe that it is essential and helpful to encourage positive lifestyle changes[41,42]. Emerging evidence suggests that individuals with prediabetes have pathophysiological changes in organs that are traditionally affected by diabetes, further validating it as a distinct disease entity[37].

Prevalence

For decades, the global prevalence of prediabetes in children was largely unknown. A recent systematic review and meta-analysis of 6630296 participants from 48 community-based pediatric studies found that the pooled prevalence of childhood prediabetes was 8.84% [95%CI (6.74, 10.95)] using a random-effects model. However, these data should be interpreted with caution given the heterogeneity of included studies, potential publication bias, and limited comparability based on different definitions and study designs[6]. Generally, the prevalence of prediabetes is substantially higher in the cohort targeting children with obesity. In an Italian study, the prevalence was 21.1%[43]. Our group demonstrated a prevalence of 15.4% in 879 Chinese pediatric patients from Hong Kong[44]. Another study conducted in German-speaking countries reported a prevalence of 11.9%[45]. Prevalence rate increases with age or deteriorating weight status [43,44].

Natural history

Despite the large number of studies involving T2DM in children, little is known about the natural history of prediabetes, which is an intermediate stage along the continuum of normal glucose regulation to overt diabetes[10,46-48]. Using data from a cohort of White Canadian children with a parental history of obesity, Harnois-Leblanc *et al*[49] reported that 73% of children with prediabetes at baseline (8-10 years of age) reverted to normoglycemia by the end of adolescence. In contrast, only 53% of children with prediabetes detected at 10-12 years of age reverted to normoglycemia at 15-17 years of age. However, it should be noted that their complete cohort (with complete 7-year data covering the three evaluations) consisted of 350 children, including those with normal weight. Hence, the prevalence of dysglycemia was only 10% at baseline and first evaluation. Indeed, what is more alarming is that one in five children (21%) in their cohort, recruited based on parental history of obesity, developed prediabetes or diabetes over 7 years.

In another multiethnic, prospective observational study carried out in the United States, 526 adolescents with obesity completed two evaluations with a median follow-up of 2.9 years. Galderisi, Giannini[50] reported that 65% adolescents with dysglycemia at baseline (n = 162) reverted to normal glycemia. Notably, the remaining 27% showed persistent dysglycemia and 8% progressed to T2DM. One of the strengths of their study was confirmation of T2DM with a second oral glucose tolerance test to eliminate any reproducibility issue. Although it was an observational study, the standard of care during follow-up included dietary assessment and advice every 6 mo, suggestion to limit sugary drinks and screen time, and promotion of physically active lifestyle.

A recent search of PubMed/ MEDLINE and the Cochrane Library for articles published through May 3, 2021 by the United States Preventive Services Task Force (USPSTF) revealed few studies suggesting that 22% to 52% children and adolescents with prediabetes returned to normal glycemia without intervention over 6 mo to 2 years[51].

Understanding the natural history of disease is critical to recognizing and responding to preventive efforts. It offers a framework to conceptualize the illness and preventive strategies. In a strict sense, the natural history of a disease refers to the natural progression over time without any treatment or intervention. In modern medicine, this is constructed from multiple sources to form a composite clinical picture of underlying disease dynamics[41].

Outlining the real natural progression of prediabetes in children is of great interest to clinicians. However, children with prediabetes are mostly asymptomatic and cannot usually be identified. If they are screened due to obesity, health care providers are obligated to provide appropriate advice regarding dietary and lifestyle intervention. Even in a research

setting, children and family are not blinded to their blood test results because it is not ethical to do so. Under such circumstances, they may exert substantial efforts to prevent further progression[34]. Simply informing participants of their abnormal results, even without intervention, can improve their dysglycemia[52]. This argument is supported by a retrospective cohort study in United States. Using data from the Children's Hospital of Philadelphia Primary Care Network, Vajravelu *et al*[53] found a stable BMI Z-score trajectory in all adolescents screened for prediabetes comparing with unscreened individuals. The improvement was even more striking among youth testing positive for prediabetes, suggesting that screening may have an important role in motivating the youth to take appropriate measures to diminish the risk. Indeed, screening and education about prediabetes can improve follow-up rates[54]. Therefore, caution is necessary when interpretating and extrapolating clinical research findings. Also, participants included in the analysis of the "natural course" of disease are those attended follow-up, and with complete data available. It is well known that a large number of children and adolescents are lost to follow-up, even after they are diagnosed with T2DM[36,55,56]. It is inaccurate or misleading to assume that more than half of these dysglycemic children will revert to normal glycemia eventually.

Screening of prediabetes, strategies and limitations

Early detection and timely intervention of dysglycemia can delay or prevent microvascular complications in adults[48]. While screening for prediabetes and T2DM in adults is considered cost-effective, it is highly complicated in children[57-60]. The latest USPSTF concluded that evidence to recommend screening for prediabetes in asymptomatic children and adolescents is unavailable[61]. Explicitly, their position is neither for nor against screening prediabetes. Pediatricians and health care providers should continue to use their clinical judgement in deciding whether or not screening is warranted [61,62].

Going back to year 2000, a consensus group of expert representatives from American Academy of Pediatrics (AAP) and the American Diabetes Association (ADA) first recommended screening of asymptomatic youth carrying at least two risk factors[63,64]. In view of persistent surge in prevalence and incidence of prediabetes, the ADA expanded its recommendation to include youth with only one risk factor in 2018[65]. In the latest publication, ADA continuously recommends screening of high-risk children and adolescents. Screening should be carefully considered in children and youth with overweight or obesity who have at least one of the following risk factors: maternal diabetes or GDM; family history of T2DM; vulnerable race or ethnicity; and signs or conditions associated with insulin resistance. Screening should be started when they turn 10 years of age, or after the onset of puberty, whichever occurs first. Testing should be repeated in cases of deteriorating BMI or risk factor profiles, or at a minimum of 3-year intervals[11]. Currently, the International Society for Pediatric and Adolescent Diabetes (ISPAD) recommends risk-based screening, which is largely similar to the one recommended by ADA[48,66]. By adopting such strategy, it is hoped that early diagnosis can enable early interventions to slow down or prevent disease progression[57,67,68]. In a recent study, the prevalence of dysglycaemia was found to be 23% with individuals carrying only one risk factor referred for assessment in an academic center, suggesting that a single risk factor is sufficient to warrant screening[69].

Despite most authorities proposing risk-based screening, the optimal or the best strategy remains a matter of debate[43,62]. According to the latest ADA and ISPAD recommendations, fasting plasma glucose (FPG), 2-h plasma glucose level measured during oral glucose tolerance test (OGTT), and hemoglobin A1c (HbA1c) can be used to diagnose prediabetes and diabetes in childhood and adolescence[48,70]. Notably, studies reveal an overlap among the subgroups using different diagnostic tests and criteria. The three different tests cannot identify consistently the same group of individuals [43,71]. Indeed, it is now believed that each individual test may analyze different components of glucose metabolism[7,72]. This may complicate the understanding and comparison of this condition in different clinical studies[73]. The prevalence of prediabetes will differ largely if disparate test combinations are used[6,62], and the discussion is further complicated by the different impaired fasting glucose cutoffs adopted by international organizations[73-76]. Additionally, the cutoff thresholds used are derived and adopted from adult studies instead of longitudinal prospective studies involving children and adolescents. The suitability of these criteria will remain a matter of debate for years to come[48,62].

In accordance with ADA, prediabetes should be viewed as risk factor for developing diabetes and cardiovascular disease. The risk starts below the lower end of the reference range and increases largely toward the higher end of the range, and is continuous[75]. Despite its reversibility in some children, prediabetes suggests that the beta-cell function is at its maximal capacity, predisposing to future failure[77].

HbA1c: According to ADA, an HbA1c value of 5.7%-6.4% has been used to define prediabetes in children[75]. It is an indicator of the average blood glucose concentration over the past three months. This test should be performed using a method that is certified by the National Glycohemoglobin Standardization Program to minimize bias[78]. It has the advantages of being stable at room temperature, without the need for fasting, and is associated with minimal day-to-day variations. Nonetheless, ethnic, racial, and age differences in levels of HbA1c exist. Medical conditions, such as anemia, hemoglobinopathies, malaria, and post transfusion, which affect red cell turnovers can affect its validity. Various medications and supplements may also interfere with the assay and alter the value[72,79,80]. It is also noteworthy that the use of HbA1c in children remains controversial[79,81]. The recommendation in adult population is based on epidemiological studies[75]. Some pediatric studies using adult cutoff underestimated the prevalence of diabetes and prediabetes [79,82]. In a study involving Caribbean and African-American children with obesity, investigators found that HbA1c alone, using adult cutoff value, is not a good differentiator of dysglycemia[83]. In recent studies from different countries and jurisdictions, various HbA1c values had been suggested[81,82,84]. This is not surprising as HbA1c is known to depend on age, race, and ethnicity. Further, in a large cohort of ethnically and racially diverse youth (n = 4603) who have normal weight and are otherwise healthy, researchers found that 2.2% have HbA1c values exceeding ADA cutoff, which

prompted clinicians to apply and adopt the cutoff value cautiously[48,85]. In sum, the optimal operational HbA1c cutoff in children remains uncertain and requires further study.

FPG and OGTT: FPG has been included as a screening test for dysglycemia in a majority of guidelines regarding management of youth with obesity[86]. It requires a single blood test and is easily available in all laboratories. However, it requires fasting and the result is affected by illness, stress, and time of the day[62,87]. Besides, it is not capable of detecting impaired glucose tolerance (IGT), which is common in children with prediabetes.

OGTT has been considered the "gold standard" for many decades although it has disadvantages of fasting requirement, complicated testing logistics, and reproducibility issues[72,85,88,89]. Although not ideal, it is the only test to assess post-prandial hyperglycemia[77]. Clinically, some individuals may have hyperglycemia only if challenged with a glucose load[48]. If OGTT is not done, half of children with prediabetes were missed in a Korean study[81]. We also demonstrated that 73% of children with prediabetes or diabetes were left out in a large cohort of Chinese Hong Kong Children. IGT is related to insulin resistance in the muscle and defective insulin secretion[90]. This phenotype was found to be associated with a worse cardiometabolic profile[91-93] and a high risk of developing T2DM and cardiovascular disease[57,62,93]. Contrary to usual belief, OGTT was well tolerated in our cohort of children and adolescents with more than 99.8% success rate[44]. Accordingly, it is suggested as the preferred screening method by some experts[94].

Additional parameters, or morphological features, can be obtained during OGTT at the expense of multiple venipunctures. These include but not limited to 1-hour glucose concentration, glucose response curve, and time to glucose peak. They are being investigated as a tool for prediabetes risk stratification. Nevertheless, further research and longitudinal studies are needed before their clinical utility can be considered[62,94-96].

Alternative tests or approaches: Instead of using OGTT, various studies have attempted to use a combination of blood tests or parameters, in an attempt to detect prediabetes. Combining fasting glucose with homeostatic model assessment of insulin resistance (HOMA-IR) cutoff of 3.4, van der Aa, Fazeli Farsani[97] detected all cases of diabetes while missing 36% of IGT. Poon *et al*[98] derived a clinical pathway using family history, HbA1c, and alanine transaminase. They omitted 50% of OGTTs, but 18.3% of children with dysglycemia were overlooked. Alternative glycemic markers, such as 1,5-anhydroglucitol, glycated albumin, and fructosamine, have been studied as screening tools. However, relevant and meaningful cutoff values associated with long-term risk and complications are still under investigation in pediatric population[62,99]. With the advent of diabetes technology, continuous glucose monitoring (CGM) is more capable of capturing detailed information and parameters of glucose fluctuations. There has been a growing interest in applying CGM technology in non-diabetic individuals[100]. However, its use in predicting prediabetes is still exploratory and preliminary[101].

Screening algorithms

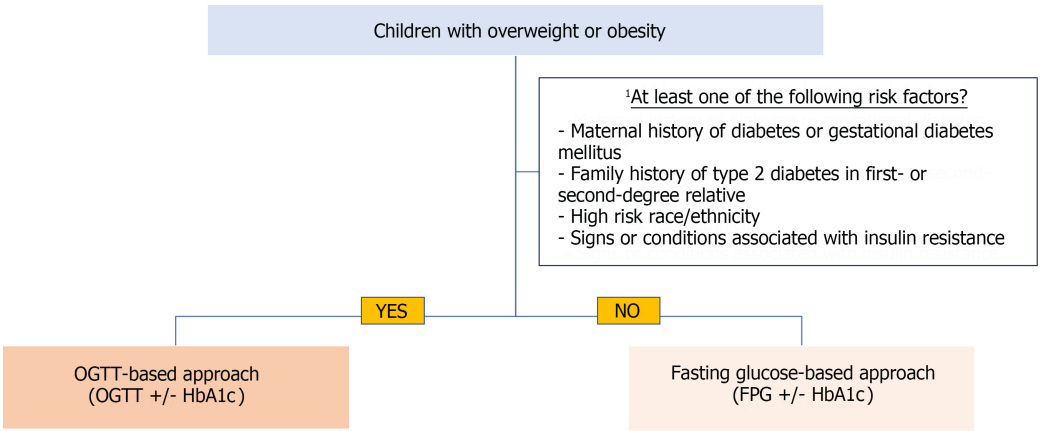
Even though some management algorithms are reported in the literature, there is no consensus on the optimal screening approach for prediabetes and diabetes in children with obesity[10]. Magge *et al*[80] proposed a management algorithm for screening of high-risk youth. However, it is based on the definition of high risk as two or more risk factors instead of the 2018 ADA recommendation of a single risk factor or more. Nonetheless, it is complicated for daily clinical use. In a recent review article, Garonzi *et al*[62] proposed a flowchart based on the strengths and weaknesses of different screening tests, suggesting screening of children and adolescents with overweight or obesity using FPG and HbA1c. In case of abnormal findings, OGTT was suggested. Likewise, OGTT was recommended for high-risk children (with one or more risk factors).

To further simplify and streamline the screening process, we suggest a fasting glucose-based approach for overweight and obese children. An OGTT-based approach is warranted in the presence of risk factors suggested by the ADA. HbA1c is considered optional in both approaches as there is no evidence-based operational cutoff value. Limited data support the use of HbA1c in children and adolescents. Figure 1 outlines the simplified framework, as a starting point, for laboratory assessment.

MANAGEMENT OF PREDIABETES

Presumably, early identification of children at risk enables practitioners to intervene and interrupt the progression toward diabetes[102]. In the absence of consensus regarding optimal management of children with prediabetes, lifestyle interventions are still the cornerstone in this population[7,28]. A balanced diet consisting of adequate fruits and vegetables, less sugar and processed foods is key. Home-cooked meals are preferred to dining out. Regular daily exercise with limitation of screen time should be reinforced. Innovative strategies for patient education should be explored so that knowledge can be translated into behavioral changes[8,103,104].

Currently, there is no United States Food and Drug Administration (FDA)-approved pharmacologic agent for prediabetes in children. Nevertheless, metformin has been used off-label in pediatric weight-management programs for children with prediabetes and insulin resistance. It is relatively well tolerated with gastrointestinal intolerability being the most common side effect[34,55]. Lactic acidosis is rare and can be monitored during treatment[34,105]. Proponents suggest metformin as a second-line management in those refractory to lifestyle interventions[34]. Liraglutide, a glucagon-like peptide-1 receptor agonist, was approved by the FDA in 2019 for use in childhood T2DM[106]. It may improve beta-cell mass and function and represents a potential treatment for prediabetes in future[56,107].



DOI: 10.5409/wjcp.v12.i5.263

Figure 1 Simplified approach for risk-based dysglycemia screening in asymptomatic children and adolescents. [1]Risk factors adopted from American Diabetes Association[75]. OGTT: Oral glucose tolerance test; FPG: Fasting plasma glucose; HbA1c: Hemoglobin A1c.

FUTURE PERSPECTIVES

The recent USPSTF attempted to search for direct evidence supporting screening of asymptomatic children for prediabetes and T2DM to improve health outcomes. However, their commissioned review found insufficient evidence to assess any benefits or harms of screening, mainly, due to a lack of studies[51,60,61]. The lack of prospective long-term longitudinal data to inform evidence-based practice for disease prevention and complication avoidance is the real challenge and major gap in pediatric prediabetes research. Clinical trials of pharmaceutical agents face the challenge of inadequate number of participants[108]. Further, the use of different screening tests and cutoff values in studies has led to discrepant results in different race and ethnicity. A "one-size-fits-all" approach may not be the best, suggesting the need for further validation[72]. Additionally, randomized controlled trials are urgently needed to evaluate the effectiveness of various preventive and management options in prediabetes[109].

CONCLUSION

Prediabetes is increasingly common in childhood and frequently goes unnoticed. It remains a challenging entity facing child health practitioners. Traditionally, it is diagnosed using adult criteria, which may not be readily applicable for children. This extrapolation of adult data is problematic and results in controversial and questionable approaches to prognosis, diagnostic criteria, investigation strategies, and management. The latest AAP guideline alerts pediatricians and healthcare providers to be aware of the pros and cons of each test based on clinical context, patient preferences, and accessibility issues[110]. Apparently, until effective prevention measures for childhood obesity can be found, managing and reversing the growing crisis of diabetes and prediabetes is still a major challenge.

FOOTNOTES

Author contributions: Ng HY reviewed the literature, wrote the manuscript, revised it and approved the final version; Chan LTW reviewed the literature, revised it and approved the final version.

Conflict-of-interest statement: All the authors report no conflicts of interest for this article.

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S-Editor: Liu JH
L-Editor: A
P-Editor: Cai YX

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World Journal of Clinical Pediatrics

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World J Clin Pediatr 2023 December 9; 12(5): 273-294

DOI: 10.5409/wjcp.v12.i5.273

ISSN 2219-2808 (online)

REVIEW

Pre-autism: What a paediatrician should know about early diagnosis of autism

Mohammed Al-Beltagi

Specialty type: Pediatrics

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Li Q, China

Received: July 10, 2023
Peer-review started: July 10, 2023
First decision: September 4, 2023
Revised: September 7, 2023
Accepted: September 25, 2023
Article in press: September 25, 2023
Published online: December 9, 2023

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Abstract

Autism, also known as an autism spectrum disorder, is a complex neurodevelopmental disorder usually diagnosed in the first three years of a child's life. A range of symptoms characterizes it and can be diagnosed at any age, including adolescence and adulthood. However, early diagnosis is crucial for effective management, prognosis, and care. Unfortunately, there are no established fetal, prenatal, or newborn screening programs for autism, making early detection difficult. This review aims to shed light on the early detection of autism prenatally, natally, and early in life, during a stage we call as "pre-autism" when typical symptoms are not yet apparent. Some fetal, neonatal, and infant biomarkers may predict an increased risk of autism in the coming baby. By developing a biomarker array, we can create an objective diagnostic tool to diagnose and rank the severity of autism for each patient. These biomarkers could be genetic, immunological, hormonal, metabolic, amino acids, acute phase reactants, neonatal brainstem function biophysical activity, behavioral profile, body measurements, or radiological markers. However, every biomarker has its accuracy and limitations. Several factors can make early detection of autism a real challenge. To improve early detection, we need to overcome various challenges, such as raising community awareness of early signs of autism, improving access to diagnostic tools, reducing the stigma attached to the diagnosis of autism, and addressing various culturally sensitive concepts related to the disorder.

Key Words: Autism; Pre-autism; Biomarkers; Autism spectrum disorder; Biophysical profile; Neurodevelopment; Antenatal; Neonatal

Core Tip: Pre-autism refers to an early stage of autism during which signs and symptoms may appear and indicate a potential risk of developing autism later in life. Early detection and intervention are crucial to improve outcomes for individuals with autism. Various physical, biochemical, hormonal, and imaging biomarkers are developed to assist prenatal and early-life diagnosis of autism. To improve the early detection of autism, we should try to overcome the various challenges that involve the diagnosis, such as enhancing community awareness, easing the diagnostic tools access, and removing and dealing with the autism-related stigma and culturally sensitive concepts.

Citation: Al-Beltagi M. Pre-autism: What a paediatrician should know about early diagnosis of autism. *World J Clin Pediatr* 2023; 12(5): 273-294
URL: https://www.wjgnet.com/2219-2808/full/v12/i5/273.htm
DOI: https://dx.doi.org/10.5409/wjcp.v12.i5.273

INTRODUCTION

Autism is a word derived from the Greek word "autos," which means self, described in 1943 for the first time by Leo Kanner from Johns Hopkins University[1]. This word reflects the different perspectives by which the child sees the world. Autism, or autism spectrum disorder (ASD), is a complex neurodevelopmental disorder affecting specific brain developmental areas, impacting communication abilities, social interaction, and child behavior. It is typically diagnosed during the first three years of life with a spectrum of symptoms ranging from mild to severe and varies from child to child[2]. There is a wide variation of autism prevalence from one country to another and from one ethnicity to another, with an average prevalence of 0.1%. However, the prevalence could reach 1/64 in the United Kingdom and 1/36 in the United States. These differences could be related to the availability of diagnostic tools[3]. In other countries, *e.g.*, the Kingdom of Bahrain, the prevalence could be much lower with underestimation (0.1%), probably due to missed diagnosis of some cases and the absence of official recording due to the fear of stigma[1]. In addition, there are significant gender differences as boys are affected 4-5 times more than girls. Ethnicity also impacts the prevalence as it is more common in non-Hispanic white populations than in Hispanic and African American/black people, with vast differences in Asian/Pacific residents [4].

The exact pathogenesis of autism is still not precisely obvious. It is multifactorial mainly due to the interaction between genetic, environmental, advanced parental age, biological, psychological, and immunological factors[5]. About 80%-90% of the autism risk is heritable, which explains why autism runs in families[6]. With the enormous advances in genetic studies, we recently recognized various genetic mutations in the affected children, which can eventually provoke brain changes and inflammation during the early developmental phases[7]. Many genetic disorders are implicated in autism pathogenesis, from simple genetic mutation to complex numeric variations with large deletions, inversions, duplications, or chromosomal translocations[8]. These genetic mutations, such as Fragile X syndrome, may be inherited, de novo mutation, or due to accumulative changes over generations. These genetic factors raise the recurrence rate to between 2% and 8% in siblings of children with autism. Children with autism may have other chromosomal or genetic co-morbidities, such as Down syndrome, Fragile X syndrome, Duchenne muscular dystrophy, tuberous sclerosis complex, and neurofibromatosis type I[9]. However, the increased risk of recurrence does not take root only from the genetic factor but also from sharing the same environmental and epigenetic factors[10]. Various ecological factors could induce epigenetic changes through deoxyribonucleic acid (DNA) methylation, histone modifications, or microRNAs; all these can affect gene expression without modifying the primary underlying DNA sequence. These environmental factors include dietary modification, exposure to stressful conditions, environmental pollution, and toxin exposure. The increased awareness of autism, in addition to the interaction between genes and environment, are important causes for the rising autism prevalence[11].

Autism is classically diagnosed according to the basic criteria summarized in the Diagnostic and Statistical Manual of Mental Disorders (DSM-5)[12]. ASD is characterized by the impairment of at least two out of three main domains that describe the fundamental features and symptoms of autism: impaired social interaction and/or communication and restricted, repetitive, or stereotyped behavior, interests, and activities with the onset of these changes occurs during early development[13]. Impaired social interaction is manifested by difficulties in making friends, playing with others, or sharing their interests. Children with autism may struggle to make eye contact and understand social rules and their perspectives. Impaired social communication includes verbal and nonverbal communication difficulties, such as using and understanding facial expressions, gestures, body language, or voice tone. In addition, they have difficulty initiating and maintaining dialogues, understanding jokes or sarcasm, and using appropriate social clues[14]. Restricted and repetitive behaviors observed in children with autism appear as repetitive or stereotyped actions, such as hand flapping and persistent routines with a strong interest or obsession with a limited spectrum of topics or activities. They may also have abnormal sensory processing mechanisms with atypical responses to sensory stimuli. The child becomes hypersensitive to specific sensory stimuli, such as lights, sounds, tastes, or textures, or hyposensitive to other stimuli, such as pain or temperature changes[15]. It is crucial to note that the symptoms of these domains vary in severity and

presentation from one child to another, with different strengths and challenges. Some individuals may also have other co-morbidities or challenges. Diagnosis of autism is complex and not an easy task. It requires a thorough evaluation by a competent healthcare professional and teamwork, such as a paediatrician, child psychiatrist, developmental and behavioral paediatrician, and clinical childhood psychologist[16].

Diagnosis of autism is usually achieved around the age of two to four years, depending on many factors, including the severity of autism, availability of healthcare access, parents' education level, and cultural and community factors[17]. Diagnosis of autism can be made at any age and could even be done for the first time during adolescence or adulthood. However, early diagnosis significantly impacts the child's management, prognosis, and welfare[18]. Early diagnosis allows early intervention, which helps children develop proper communication and social skills and enhances patient functioning and independence later in life. It also allows parents and caregivers to better understand the child's strengths and challenges. In addition, early diagnosis helps to improve the child and family's quality of life with a significant reduction in the long-term cost[19]. As the cost of autism may reach up to US$3.2 million lifetime per capita, and early intervention may improve the prognosis and decrease the cost, we need to detect autism early. Directed actions could delay the autism progression, especially for language and cognitive abilities, and may help autism regression before it becomes irreversible. No well-established early fetal or newborn biomarker screening programs exist for autism. Therefore, this review will try to shed some light on the early detection of autism prenatally and in early life.

METHODS

To establish an evidence-based view of this aim, we accomplished a systematic literature review by searching the available electronic databases, including PubMed, PubMed Central, Cochrane Library, Embase, Web of Science, Cumulative Index to Nursing and Allied Health Literature, Scopus, Library and Information Science Abstracts, and the National Library of Medicine catalog up until May 8, 2023, using the keywords: Autism, Pre-autism, Biomarkers, Autism spectrum Disorder, Biophysical Profile, Neurodevelopment, Antenatal, Neonatal. We included a total of full-text articles (175 articles), including research articles (102 articles), metanalysis (9 articles), systematic reviews (4 articles), reviews (58 articles), and consensus guidelines (2 articles). We included articles that were written in English and concerned with the effects of early diagnosis of autism. Figure 1 shows the study flow chart. Reference lists were checked, and citation searches were performed on the included studies. We also reviewed the articles that are available as abstracts only. We excluded articles with a commercial background.

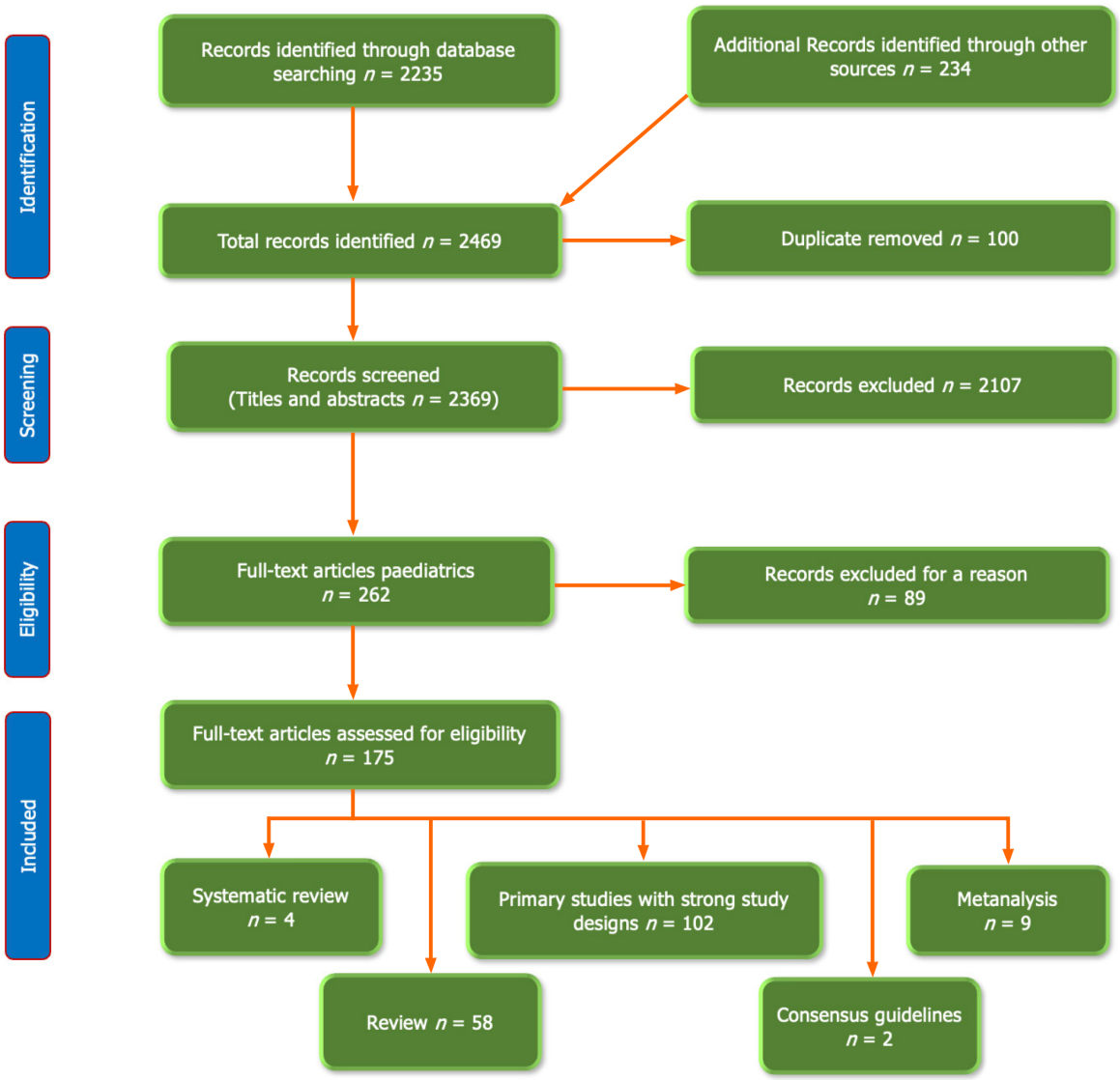
DISCUSSION

Pathophysiology of autism

Autism results from genetic and environmental developmental factors disrupting normal brain development and affecting many or all brain functions by activating pathological pathways. Despite the extensive efforts over the last few decades to elaborate the exact mechanism of autism, we are still in the first steps of a long way to be achieved, and its precise mechanism is still poorly understood. However, two critical domains are being tried to explain what could lead to the manifestations of autism. The first domain is the changes in the brain structure and pathophysiology usually observed in individuals with autism. The second domain is the neuropsychological and neurobiological links between the changes in the brain structure and the development of behavioral changes characteristic of autism[20,21]. Different theories tried to explain the occurrence of autism. One of them is related to the presence of excess neurons with significant changes in synaptic density and plasticity, which causes local overconnectivity in critical brain regions, which explains the high brain weight and volume and the large head circumference observed in children with autism, together with the enhanced expansion of the grey matter of cortical surface area in children with autism resulting in reduced maturation of the cortical white matter. However, these pathological changes' molecular and cellular mechanisms are not fully addressed, nor is it known whether the brain's overgrown causes the characteristic autism signs[22].

In addition, specific brain regions are affected in children with autism, such as the frontoparietal cortex, frontotemporal lobe, amygdala, basal ganglia, hippocampus, and anterior cingulate cortex[23]. For example, defects in social attention and social language processing are associated with abnormalities in Broca's area (inferior frontal gyrus), Wernicke's area (located in the posterior part of the upper temporal convolution of the left-brain hemisphere and concerned with speech comprehension), and superior temporal sulcus[24]. Impaired social behaviors are associated with abnormal functioning of the frontal lobe, parietal cortex, superior temporal cortex, and enlargement of the laterobasal amygdala[25]. Meanwhile, abnormalities in size, structure, and activity of the orbitofrontal cortex (which is involved in decision-making, social behavior, and emotion regulation) and caudate nucleus (which is involved in motor control, reward processing, and learning) are associated with increased risk of autism[26]. Accelerated cortical thinning was also observed in patients with autism aged 3-39 years after accelerated expansion in early childhood[27].

Neuronal migration is an essential process in fetal brain development, during which neurons migrate from their original place to their final destination. Disturbance of neuronal migration during early pregnancy alters neural connectivity and induces abnormal neural circuits, contributing to abnormal behavioral and impaired cognitive functions. Irregular neuronal migration with abnormal positioning and organization of neurons in the brain are implicated in developing a range of neurological conditions, including autism. Prenatal exposure to specific hazardous environmental hazards, such as environmental toxins, drugs (*e.g.*, thalidomide or valproic acid), and maternal infections, inflammation,



DOI: 10.5409/wjcp.v12.i5.273

Figure 1 The flow chart of the included studies.

or immune dysfunction, can induce gene mutation (*e.g.*, gene CNTNAP2 which regulates neuronal migration and axon guidance or gene RELN, which regulates neuronal migration in the cerebral cortex, Lis1, DCX, and TUBA1A genes) and altering their expression, interrupting the normal neuronal migration, and raising the risk of autism[28,29]. Imaging studies showed that patients with autism have abnormal brain white matter organization, which could be related to neuronal migration disturbances during early development[30].

In addition to the structural and ultrastructural changes observed in patients with autism, there is growing evidence of altered brain connectivity and function due to imbalances in brain excitatory and inhibitory signaling. The excitatory neurons release the neurotransmitter glutamate, which promotes neuronal firing. In contrast, inhibitory neurons release the neurotransmitter Gamma-aminobutyric acid (GABA), suppressing neuronal activity[31]. An overall rise in neuronal excitation and reduced neuronal inhibition led to the social and communication deficits commonly observed in autism. This imbalance mostly results from decreased GABAergic inhibitory neurons' number or function, *e.g.*, reduced parvalbumin-positive interneurons, that naturally assist in controlling the excitatory neurons' activity. This imbalance could result from several factors, including genetic mutations, harmful environmental factors, and disturbed neural circuit development during early childhood[32]. This imbalance was proved by genetic analysis of the expression of the functional genes responsible for the inhibitory function and post-mortem and animal studies that demonstrated the reduction of the inhibitory neurons[33]. Treating this imbalance using medications that boost GABAergic signaling, such as certain antiepileptics, benzodiazepines, and GABAB receptor agonist STX209, has been proven effective in treating some autism symptoms, with variable degrees of success[34].

We can admit from the previously described pathophysiological mechanisms that autism results from genetic and environmental interaction with some predominance of the genetic factor. However, a growing list of exposures for mother and baby may sway the odds and affect the onset time of symptoms. There are three different pathways or trajectories for the development of autism, according to the timing of the insult that triggers the changes observed with autism. The first pathway is caused by in-utero insult/injury; obstetric complications at birth activate the second

pathway, while the third pathway is caused by environmental triggers of autism affecting infants 0-3 years of age[35]. In addition, we can classify autism according to the presence or absence and the number of minor physical defects into essential and complex autism. In essential autism, there is no evidence of an early embryological abnormality with no or very few minor physical defects. Conversely, in complex autism, the affected children have six or more minor physical defects. They are more likely to have genetic disorders, brain anatomical abnormalities, seizures, and a low intelligence quotient. They may also have peculiar facial features with a broader upper face, a shorter middle face comprising cheeks and a nose, wider eyes, a bigger mouth, and a philtrum. These facial features are better recognized using a 3-D camera with the help of artificial intelligence[36,37].

Pre-autism ("Preclinical")

We are using the term "pre-autism" for the first time to describe the early prodromal period that precedes the development of the full-blown and formal clinical picture of classic autism when the symptoms and signs of autism or ASD are not yet clearly evident. During the pre-autism phase, some risk factors, with few and/or non-classic signs, appear during the early developmental stage of the child's life that could indicate the increased potential risk of autism later in life. These early signs are often subtle, not yet fully developed, or may not be easily recognizable. The pre-autism phase typically happens during the neonatal period, infancy, or early childhood. It could be challenging to distinguish these early signs from typical developmental variations. It is central to admit that not all kids who display these early signs or risk factors will develop autism, and some children who develop autism may not show all these early signs. Therefore, a comprehensive evaluation by a trained professional is necessary to determine if a child has autism.

Presently, no newborn biomarker screening programs exist to detect autism. We should think about pre-autism in the presence of a positive family history of a patient with autism and or other antenatal or post-natal risk factors. The more risk factors, the higher the risk of autism[38,39]. These risk factors are summarized in Table 1.

Preconception risk

Having a child with autism increases the risk of having another child with autism by 20-fold, especially in full-siblings compared to half-siblings and in the maternal half-siblings than paternal half-siblings. This supports the genetic and uterine environment effects in the pathogenesis of autism[40]. The risk further increases with a shorter time between the birth of a previous child with autism and the birth of the next sibling. The risk of autism recurrence reached 14.4% with an interbirth interval equal to or less than 18 mo, compared with 6.8% for an interval equal to or more than four years[41].

The birth order may also affect the risk of having autism. The first-born child might have a higher risk of having autism than later-born children. The increased risk in the firstborn child may be related to a higher exposure rate to pregnancy and delivery complications such as infections, stress, and inflammation. In contrast, the lower risk of the later-born children may be related to the social support and help provided by the first-born child to the later-born children[42]. On the other hand, Alvares *et al*[43] showed that intelligence scores and adaptive functioning decrease with increasing birth order. The later-born children are more prone to have an intellectual disability. However, they showed that first-born children without siblings have decreased cognitive functioning compared to those with siblings. This controversy may be related to other confounding factors, such as differences in the ethnicity of the studied group.

The age of the parents at the time of conception can predict the chance of having autism. Both the father and mother's age at the time of conception is independently associated with an increased risk of autism in the offspring. The risk will be higher if both parents are old[44]. Increased risk of autism with increasing paternal age may be due to increased risk of de novo mutations in their sperm or increased risk of having some features of autism phenotype that cause them to marry late[45]. Conversely, mothers over 35 have a 1.5 higher risk of having a child with autism than mothers between 25-29 years. Younger mother age gives more protection against autism. Higher maternal age is associated with a higher risk of chromosomal abnormalities and more exposure to environmental risk factors that affect DNA methylation in germ cells, with an increased risk of developmental consequences on the offspring[46]. The effect of higher maternal age is more evident in the male offspring, while higher paternal age is more evident in the female offspring[47].

Some data show that pre-conceptional maternal obesity might raise the risk of autism in the offspring. Wang *et al*[48] showed a linear dose-response relationship between pre-pregnancy maternal BMI and the risk of autism, with a relative risk of 1.16 for each 5 kg/m^2 increase in Mother BMI. Jo *et al*[49] showed that children born to mothers with severe obesity before pregnancy had a high risk for adverse developmental outcomes, including autism. Hinkle *et al*[50] also observed an increased incidence of learning and behavior disorders by kindergarten among children born to mothers with severe pre-pregnancy obesity. Pre-conceptional maternal obesity may alter the intrauterine milieu, increasing inflammation, t affecting the function of insulin and other metabolic hormones, and affecting the developing fetal brain[51].

Antenatal Markers for the risks of autism

As mentioned before, no screening test can tell us that the baby will develop autism, as autism's aetiology and pathogenesis are not fully understood. However, some fetal and infant biomarkers may expect an increased risk of autism in the coming baby. These biomarkers could allow us to develop a biomarker array that, when properly developed and analyzed, could give us an objective diagnostic tool to diagnose and rank the severity of autism for each patient. These biomarkers could be genetic, immunological, hormonal, metabolic, amino acids, acute phase reactants, body measurements, or radiological markers[52] (Table 2).

Genetic profile

As our understanding of the genetic and environmental factors that contribute to the development of autism is improving, it may be feasible to develop more accurate techniques to predict the risk of autism based on examining

Table 1 Factors that increase the risk for autism

Risk	Details
Preconception risks	Presence of another child previously affected with autism
	Increased maternal and paternal age at birth (3.8% increase)
	Birth order: 61% increase in risk in firstborn
	Maternal Obesity or being overweight before pregnancy increases the risk of autism by 36%
Antenatal risk factors for autism[36]	Maternal asthma, allergies
	Preeclampsia
	Maternal bleeding (81% elevated risk)
	Maternal depression or emotional strain. It is believed that stress hormones can cross the placenta-blood barrier and affect the development of fetal brain
	Gestational diabetes (two-fold increased risk of autism)
	Hypothyroidism
	Phthalates (plasticizers) and pesticide exposure: *e.g.*, chlorpyrifos →, sex-hormone pathways disruption → Autism.
	Folate deficiency
	Vitamin D deficiency
	Maternal Infections, *e.g.*, congenital rubella infection, increase the rate of autism to 1:13
	Hospitalization due to antenatal infection increases the risk of autism by 30%
	Abnormal fetal growth could indicate disrupted fetal brain development. Being small or large for gestational age increases the risk of autism
	Prenatal Hormone Levels: Higher levels of prenatal testosterone may be related to an increased risk of autism
Postnatal risk factors for autism	Urbanization of birthplace
	Prematurity by more than 9 wks → higher odds of autism
	Birth injuries to the cerebellum increase the risk of autism by 3.8-fold
	Neonatal seizure
Potential risk factors for autism in neonates requiring NICU	Family history of neuropsychiatric disorders
	Maternal psychological distress during pregnancy
	Duration of stay ≥ 26 d in the NICU
	Tube feeding tube for ≥ 15 d
	Retinopathy of prematurity
	The need to use three or more antibiotics
	Co-sleeping until two years of age

NICU: Neonatal Intensive Care Unit.

genetic profiling. The presence of specific genetic markers in amniotic fluids or cord blood may indicate an increased risk of developing autism. Single-gene disorders such as Fragile X syndrome (FMRI mutations), neurofibromatosis (NF1), tuberous sclerosis complex (TSC1 and TSC2 mutation), Dup15q syndrome, Rett syndrome (MeCP2 mutation), and deletions in the 16p11.2 region are present in about 3%–5% of patients with autism[53]. Other chromosomal and genetic disorders, such as Down syndrome (40% of them have autism or autism-like symptoms), Duchenne muscular dystrophy, and tuberous sclerosis complex, are associated with an increased risk of autism[9]. Large-scale genome-wide association studies have also identified numerous common genetic variants that are associated with an increased risk of autism. Among these mutations, mutations involving the SHANK3, NRXN1, CNTNAP2, and CHD8 genes increase the risk of autism[54,55]. 16p11.2 is a chromosomal region linked to autism and other neuropsychiatric conditions. The 16p11.2 genetic mutation with either deletion or duplication is associated with an increased risk of motor speech disorder, motor coordination difficulties, language disorder, and various psychiatric conditions, including autism. Detection of deletions or duplication in 16p11.2 in the cord blood might expect that the child may develop autism and other neuropsychiatric conditions[56]. However, the resulting severity varies significantly, and not all the patients with the mutation or deletion

Table 2 Antenatal markers for the risks of autism

Marker	Details
Genetic markers	Single-gene disorders: Fragile X syndrome (FMRI mutations), neurofibromatosis (NF1), tuberous sclerosis complex (TSC1 and TSC2 mutation), Dup15q syndrome, Rett syndrome (MeCP2 mutation), 16p11.2 region deletions, SHANK3, NRXN1, CNTNAP2, and CHD8 genes mutations
	Chromosomal Disorders: Down syndrome, aberrations on the long arm of Chromosome 15, and reciprocal chromosomal translocation between long arms of chromosomes 4 and 14
	Messenger RNA (mRNA) and microRNA (miRNA) expression abnormality
	Abnormal DNA methylation patterns
Cytokines biomarkers	Abnormal profile of interleukin-6, tumor necrosis factor-alpha, interleukin-1 receptor antagonist, TNF- α, Serpin E1, vascular cell adhesion molecule 1, vascular endothelial growth factor D, Epidermal growth factor, Colony Stimulating Factor 1, and 2
Autoantibodies biomarkers	The presence of circulating maternal autoantibodies, especially anti-brain autoantibodies, during pregnancy
	Maternal autoantibody response against Collapsin Response Mediator Protein 1 (CRMP1)
	Simultaneous reactivity against bands at 39 kDa and 73 kDa is associated with early-onset autism.
Oxidative stress biomarkers	Maternal urinary levels of free 8-iso-prostaglandin F2α (8-iso-PGF2α)
Hormonal biomarkers	High prenatal testosterone levels
	Polycystic ovary syndrome
	Elevated levels of steroidogenic hormones (cortisol, androstenedione, testosterone, 17α-hydroxy-progesterone, and progesterone) in amniotic fluid
	Mid-pregnancy thyroid-stimulating hormone (inverse relationship)
Maternal nutritional biomarkers	Fetal levels of manganese and zinc
	Abnormal zinc-copper cycles (altered rhythmicity, shorter cycle duration, reduced regularity, and diminished complexity)
	Vitamin D deficiency
	Poor folic acid intake
Biophysical markers	Presence of multiple fetal abnormalities (especially cardiac, urinary, cranial, and brain anomalies)
	Presence of a narrower head and a relatively broader ocular distance
	Altered prenatal brain growth
	Abnormal Kurjak's antenatal neurodevelopmental scoring test in the last trimester
Radiological profile	Isolated ventriculomegaly
	Altered cortical development
	Enlarged insula lobe
	Increased amygdala volume and fast growth rate

CHD8: Chromodomain helicase DNA binding protein 8; CNTNAP2: Contactin Associated Protein 2; Dup15q syndrome: Duplications of the portion of 15q11.2-13.1 chromosome; kDa: Kilodalton; MeCP2 mutation: Mutations of the methyl-CpG binding protein 2; NRXN1: Neurexin 1 RNA: Ribonucleic acid; SHANK3: SH3 and multiple ankyrin repeat domains 3; TNF-α: Tumor Necrosis Factor Alpha; TSC1: Tuberous sclerosis complex 1; TSC2: Tuberous sclerosis complex 2.

have the same clinical picture. Not all patients with these mutations will develop autism[57].

Another important genetic variation that could increase the risk of autism is the presence of single nucleotide polymorphisms (SNPs). The SHANK2 gene is an important gene for glutamate neurotransmission and synaptogenesis. A synergistic interaction between SNPs and the SHANK2 gene increases the risk for autism[58]. Other SNPs that affect the expression of genes that increase the risk of autism are MTHFR (Methylenetetrahydrofolate reductase has a significant role in folate metabolism.), RFC (genes encoding the reduced folate carrier), MTR (methionine synthase responsible for the regeneration of methionine from homocysteine and involved in the folate/homocysteine pathway), OXTR gene (a gene correlated with aggression, social dysfunction, and irritability), and CD38 gene (a gene linked to low CD38 expression and a lack of emotions)[59].

Not only structural gene changes can be used as a marker for risk autism, but also markers of gene expression, including messenger RNA (mRNA) and microRNA (miRNA) expression. mRNA is a single-stranded RNA molecule. It undergoes post-transcriptional modifications to carry the genetic information from nuclear DNA from the nucleus to

ribosomes in the cell cytoplasm to be used as a template for protein synthesis[60]. On the other hand, microRNA is a small, non-coding RNA molecule transcribed from DNA. It undergoes several processing steps before its incorporation into the RNA-induced silencing protein complex to guide this complex protein to its target mRNA through base pairing. Once base-paired with the targeted mRNA, it inhibits it by degradation or inhibiting its translation. A single miRNA can combine with several hundred targeted sites in the 3′ untranslated regions of mRNAs, thus controlling the expression of many genes. There are about 5104 miRNA variants have been identified till now[61]. Studies have suggested the role of miRNAs in the development of autism. Wong *et al*[62] identified variants in five brain-expressed miRNAs, which target 326 genes, and 3′ UTR miRNA target regions of 152 genes potentially involved in neurodevelopmental disorders, including autism. miRNA could post-transcriptionally regulate autism-related risk genes and affect various molecular pathways related to autism and associated disorders. In addition, Noroozi *et al*[63] identified five modules linked with neurexins and neuroligins, cell adhesion molecules, glutamatergic synapse, L1CAM interactions, MECP2 and circadian clock pathways, NOTCH, and neurotransmitter release cycle. Functional analysis of these genes helps to determine critical pathways related to neurological disorders and the pathogenesis of autism.

Methylation is a process of adding a methyl group to a DNA molecule to affect gene expression. Changes in the methylation patterns of certain genes could influence the development of autism. Patients with autism are in their DNA methylation patterns in specific genes from typically developing children. DNA methylation Epimutations can be developed throughout life. Reprogramming of the global DNA methylation is a dynamic process that occurs during the embryonic and the early postnatal period that parallels the peak time of synaptogenesis[64]. Abnormal methylation of specific genes could result in an increased risk of autism. García-Ortiz *et al*[65] detected higher Neural Cell Adhesion Molecule and Nerve Growth Factor methylation levels in children with autism. Testing abnormal methylation patterns in biological specimens obtained from the parents could help to predict the possibility that the child may be born with autism. Global DNA hypomethylation was observed in mothers of children with autism. In addition, specific methylation patterns were observed in sperms obtained from fathers of children with autism[66,67]. Despite being a promising antenatal marker of autism, methylation has a complex nature and interaction with other environmental factors such as vitamin intake and prenatal tobacco exposure[68].

Cytokines profile

Cytokines are specific proteins that have an essential function in the immune system and could affect brain development and function. Specific cytokines, such as interleukin-6 and tumor necrosis factor-alpha, could play a role in brain development as they may initiate neuroinflammation, contributing to autism development. Therefore, the irregular profile of these cytokines, especially interleukin-6 in the fetus, might be related to the increased risk of autism during childhood[69]. Another study by Abdallah *et al*[70] showed increased levels of TNF-alpha in the amniotic fluid in mothers of children with autism than in mothers of children with typical development. In addition, Che *et al*[71] showed that the maternal mid-gestational and neonatal cord blood immune markers are strongly associated with increased risk of autism in the offspring, including but not limited to interleukin-1 receptor antagonist, TNF-alpha, Serpin E1, vascular cell adhesion molecule 1, vascular endothelial growth factor D, Epidermal growth factor, Colony Stimulating Factor 1, and 2. Maternal mid-gestational findings were outstanding, with remarkably great effect sizes in girls. However, Brynge *et al*[72] found no strong evidence of the association of maternal immune markers during early pregnancy with autism. Therefore, it is critical to endorse that the relationship between abnormal intrauterine cytokine profiles and the risk of autism is not fully understood and needs more research. We should consider other genetic and environmental factors that can impact the development of autism.

In addition to the previous markers, Ji *et al*[73] found in their prospective study that cord biomarkers of fetal acetaminophen exposure, such as 3-[N-acetyl-l-cystein-S-yl]-acetaminophen, acetaminophen glucuronide, or unchanged acetaminophen were associated with a significantly high risk of developing attention deficit hyperactivity disorder and autism during childhood in a dose-response fashion. Acetaminophen can cross the placental barrier and remain in the infant's blood circulation for a long time[74]. However, no specific time window was confirmed during which the developing brain is most sensitive to acetaminophen exposure. At the same time, we could not ensure whether the effects are due to the direct acetaminophen exposure or the cause of its use, *e.g.*, maternal fever during pregnancy, which increases the risk of autism. Even the observed dose-response effects can be related to the severity of the cause of its use and not to acetaminophen itself. However, we need more animal studies to confirm acetaminophen's direct brain toxic effects.

Maternal plasma or fetal blood anti-fetal brain autoantibodies profile

Many studies correlated the presence of circulating maternal autoantibodies, especially anti-brain autoantibodies during pregnancy, to the occurrence of neonatal neuronal dysfunction. These autoantibodies can cross the placental blood barrier and access the developing fetal brain and inducing the development of autism[75-77]. Dalton *et al*[77] performed a very interesting experiment. They injected 0.5-1 mL of sera obtained from mothers of children with autism and mothers of typically developed children into pregnant mice daily. They found that the offspring of mice injected with sera from mothers of children with autism developed altered motor coordination and exploration and had cerebellar changes in magnetic resonance spectroscopy in the mouse offspring, compared with offspring of mice injected with sera from mothers of typically developed children. Fox-Edmiston *et al*[78] recognized maternal autoantibodies against seven neurodevelopmental proteins associated with developing maternal autoantibody-related (MAR) autism in the offspring. Ramirez-Celis *et al*[79] found that maternal autoantibody response against Collapsin Response Mediator Protein 1 is associated with a significant increase in the chance that the child has autism, indicating the potential use of these autoantibodies as potential biomarkers of autism risk in up to 18% of autism cases termed as MAR autism.

The mechanism and the triggers for developing these autoantibodies are not clear. These autoantibodies against the fetal brain can be identified in the mother's blood and can be used as a marker for autism risk[80]. Croen *et al*[81] showed that maternal mid-gestation autoantibody against human fetal brain protein (especially reactivity to a band at 39 kDa) is associated with the risk of developing autism. In addition, simultaneous reactivity against bands at 39 kDa and 73 kDa is associated with early-onset autism. However, identifying these anti-fetal brain autoantibodies has two critical implications: diagnostic and potential therapeutic benefits. Preventing the development of these maternal autoantibodies can prevent the irreversible damage that could happen to the developing fetal brain. More searches are needed to elucidate the trigger for these autoantibodies, prevent their generation, and develop different therapeutic modalities to remove these antibodies, such as *in vivo* autoantibody competition or *ex vivo* autoantibody removal.

Oxidative stress biomarkers

Oxidative stress may have a role in the pathogenesis of autism. Oxidative stress means excessive production of reactive oxygen species beyond the detoxification ability of cells, leading to damage of the cellular components such as lipids (peroxidation), proteins (*e.g.*, post-translational changes}, DNA, and toxic build-up by these reactive radicles, causing cellular dysfunction and damage[82]. Many studies have figured out the relationship between intrauterine oxidative stress markers and the increased risk of developing autism. For example, Rommel *et al*[83] found that maternal urinary levels of free 8-iso-prostaglandin F2α (8-iso-PGF2α) and its metabolites (markers of oxidative stress) were significantly increased in mothers of children who developed autism than in mothers of typically developing children. Maternal immune activation (MIA) during pregnancy is another example of the effects of oxidative stress and one of the common environmental risk factors for developing autism. MIA induces an unusual immune reaction in the pregnant woman, causing further inflammation and increasing oxidative stress in the placenta, crossing it to affect the fetal brain, causing activation and accumulation of microglia, dysregulating neurodevelopmental and autism-associated genes, inducing neurodevelopmental impairments in the developing fetal brain, and afterward triggering behavioral problems in the offspring[84-86].

In addition, oxidative stress is one of the possible mechanisms by which gestational diabetes and some antenatal infections increase the risk of autism. Lanté *et al*[87] experimentally prevented the harmful neurodevelopmental damage induced by bacterial endotoxin lipopolysaccharide with strong oxidant stress effects by using the antioxidant N-acetyl-cysteine, confirming the effect of oxidative stress on the pathogenesis of autism. However, Carey *et al*[88] found weak or no association between oxidative stress markers (glutathione, glutathione disulfide, 8-oxo-deoxyguanine, and nitrotyrosine) in late pregnancy and the risk of autism in the offspring. This discrepancy between their results and previous studies can be explained by the differences in the markers used and the time points they investigated the mothers (late trimester). We should also consider that association is not equal to causation. Therefore, we need more research to confirm the role of oxidative stress, choose the proper marker, and also the proper timing for the test to give more reliable results.

Hormonal profile

Antenatal exposure to steroid hormones can directly impact fetal gene transcription and expression during vulnerable stages of embryonic development. High prenatal testosterone levels can predict an elevated prevalence of behavioral and cognitive traits that are usually associated with autism in both typically developing males and females from early to late childhood, even if they did not develop frank autism with long-lasting effects on brain structures and organization and emotional reward processing in late childhood[89,90]. Therefore, female offspring (but not male) of mothers with hyperandrogenism, such as in polycystic ovary syndrome, have an increased prevalence of autism features than girls born to mothers without hyperandrogenism[91]. The effect is higher when polycystic ovary is combined with maternal obesity due to more hyperandrogenism[92]. Baron-Cohen *et al*[93] showed that. Elevated levels of steroidogenic hormones (cortisol, androstenedione, testosterone, 17α-hydroxy-progesterone, and progesterone) in amniotic fluid samples are associated with an increased risk of autism due to their effects on early fetal brain development. The difference in sex steroid hormone exposure can explain why autism affects males more than females and can be used as an early biological risk factor marker. Steroid hormones have a substantial impact on the biological sexual differentiation of autism. Perinatal testicular androgen surge is responsible for brain sexual differentiation as prenatal sex hormones affect microglial activation during early neurodevelopment and consequently affect many neurodevelopmental disorders [94]. An exciting study by Yau *et al*[95] showed an inverse association between autism and mid-pregnancy thyroid-stimulating hormone levels in maternal serum samples, indicating the critical role of thyroid hormones for in-utero normal brain development. Therefore, the in-utero hormonal environment could increase or alleviate the risk of autism, explaining the male dominance and female protection of autism[96].

Maternal nutritional profile

Metals are essential to neurodevelopment. Essential elements deficiency during specific critical developmental windows could increase autism risk and severity, indicating a state of systemic elemental dysregulation in autism. Arora found that fetal levels of manganese and zinc were reduced in infants who developed autism than their monozygotic or dizygotic twin discordant for autism[97]. In addition, Curtin *et al*[98] studied zinc-copper cycles in a Sweden nationwide study of twins using unique tooth-matrix biomarkers that directly measure fetal elemental uptake. They found an altered fetal and postnatal zinc-copper rhythmicity in autism with shorter cycle duration, reduced regularity, and diminished complexity than in those who did not develop autism. This altered pattern of zinc-copper cycles had a sensitivity between 85% and 100% and a specificity between 90% and 100% for the diagnosis of autism. Some studies showed that maternal vitamin D deficiency in the first or second trimester is associated with an increased risk of autism[99,100]. However, a more recent

study by Madley-Dowd found no significant association or causation of maternal vitamin D deficiency during pregnancy with an increased risk of autism in the offspring[101]. These contradictory results of studies may need more research to confirm or rule out the effects of vitamin D deficiency on the increased risk of autism. Folic acid is an essential nutrient for cell division and rapid tissue growth during fetal development, affecting all the tissues, including the brain[102]. In the same way as vitamin D, gestational folic acid has a complex relationship with autism development. There are some contradictory results about the effects of folic acid deficiency during pregnancy and the risk of the development of autism. It is suggested that poor folic acid intake during pregnancy may raise the risk of neurodevelopmental disorders, including autism[103]. Steenweg-de Graaff *et al*[104] found no association of maternal folic acid concentration at 13 wk of gestation with the risk of autism in the offspring. However, they found that maternal antenatal supplementation with folic acid is associated with fewer child autistic traits. On the other hand, Egorova *et al*[105] found weak evidence that high maternal serum folate during early pregnancy may increase the risk of autism in offspring. This contradiction of the result may be explained by the differences between the reduced (folinic acid or methyl-tetrahydrofolate) and the synthetic oxidized forms of folic acid. The oxidized form inhibits folate metabolism, while reduced forms do not[106]. Because of the conflicting results of different studies, we need to do more research at different gestational periods and with reduced forms of folic acid supplementation.

Biophysical profile

Fetal ultrasound is an outstanding tool for studying abnormal fetal development. It is commonly used to follow up on fetal growth and detect early fetal anomalies throughout pregnancy. Multiple fetal abnormalities (especially cardiac, urinary, cranial, and brain anomalies) are significantly more prevalent in patients with autism, especially in severe cases [107]. Fetuses with autism have a narrower head and a relatively broader ocular distance than typically developed fetuses. The more anomalies present, the more severe the autism is. The association between fetal anomalies and autism may be due to underlying genetic and/or environmental factors that cause autism and congenital disabilities, or the birth presence of abnormalities may predispose a child to develop autism[108]. The presence of these multi-anomalies may also indicate the abnormal multiorgan embryonic development in patients with autism and suggest the importance of using fetal ultrasonography as a biomarker for autism. Regev *et al*[109] observed that female patients with autism have significantly more ultrasonography-detected fetal anomalies and a higher prevalence of multiple abnormalities than male patients with autism.

During antenatal life, the brain goes through complex and coordinated differentiation and growth processes, which are critical for typical brain structure and function development. Abnormalities in these processes can cause brain structure and function changes and increase the risk of neurodevelopmental disorders[110]. Altered brain growth is often observed in individuals with autism, specifically during the first year of life. Several studies have recognized numerous abnormalities in different brain regions and structures in individuals with autism, particularly the cortex, amygdala, and cerebellum[22]. Blanken *et al*[111] also reported this abnormal brain growth, who prospectively examined the altered fetal brain growth trajectories by examining prenatal head growth in babies who further developed autism. They compared them with typically developed children and related this finding to the severity of autism symptoms. They studied 3,820 children from two population groups: The Netherlands and Australia; 60 children developed autism. They used latent growth curve models to examine the relationship between fetal head circumference measured by fetal ultrasound at three different time points (at first, second, and third trimesters) and autistic features measured in postnatal life using the Social Responsiveness Scale or the Autism-Spectrum Quotient. They found a weak association between lower initial prenatal head circumference and increasing autistic traits in the Dutch cohort but not in the Australian cohort, nor when the two cohorts were analyzed together. These mixed findings suggest that we need more research on this point. Altered prenatal brain growth seems to be a significant risk factor for autism. Although the exact mechanisms underlying this association are still not fully realized, studies suggest that neural circuit development and connectivity changes may have a role[112].

Fetal ultrasound can provide useful information about fetal motor activity, heart rate variability, and other behavioral markers. Many studies have suggested that there may be some differences in fetal neurodevelopmental behavior between children who later have typical development and those who develop autism[113]. Fetal ultrasound is also used to assess fetal neurodevelopmental behavior, which could predict the neuronal outcome of the baby. Hata *et al*[114] used antenatal four-dimensional ultrasound to assess fetal neurodevelopment using Kurjak's antenatal neurodevelopmental scoring test between 28 and 38 wk of gestation. A low score between 0 and 5 is abnormal and denotes a strong possibility of postnatal developmental disabilities, including autism. Conversely, a score between 6 and 9 is borderline, and a score between 10 and 16 is considered normal. They suggested that the KANET assessment may be a helpful diagnostic tool to predict postnatal developmental disabilities. However, many confounding factors could affect the fetus's behavior, such as maternal stress or medication use and other environmental factors that could affect the fetus and consequently affect the scoring. These factors make it challenging to determine whether fetal behavior differences accurately indicate the increased risk of autism.

Radiological profile

Antenatal magnetic resonance imaging magnetic resonance imaging (MRI) brain is a diagnostic method that can be used to assess the fetal brain during pregnancy and might be applied as a potential tool to identify the risk of autism in infants. Recently, there has been a growing interest in the relationship between fetal MRI brain and the risk of having autism in childhood[115]. However, studies brought mixed results. Kyriakopoulou *et al*. investigated the presence of autism in twenty-four children [20 males/4 females] with isolated ventriculomegaly and altered cortical development by fetal MRI brain, compared with ten controls. Children with ventriculomegaly were more liable to have difficulties in sustained attention, working memory, and sensation-seeking behaviors and were more likely to have autistic features[116]. In addition, a group of scientists from Harvard University and Boston Children's Hospital, United States, examined MRI

scans of thirty-nine fetuses with an average gestational age of 25 wk. They noted two enlarged brain areas in fetuses who developed autism in infancy and childhood. Babies who developed autism had an enlarged insula lobe (seen as early as 25 wk). Insula is linked to sensory stimuli processing, socialization, and decision-making processes. It appeared more prominent than the typically developed fetuses. They also showed increased amygdala volume. The amygdala is also responsible, among other brain areas, for emotional processing and interpretation of the facial expressions of others[117]. This observed hypertrophism was previously discovered a few years ago in school-age children with autism[118].

On the other hand, a study from the University of North Carolina, United States, showed that the amygdala was normal in babies who developed autism up to 6 mo of age, then began to enlarge between 6 and 12 mo before the appearance of the clinical manifestations of autism, and continue to grow to 12-24 mo, the age at which the first clinical manifestations of autism including interpersonal difficulties usually appear. There is a positive correlation between the Amygdala growth rate and the severity of autism. The faster the growth rate, the worse the autism manifestations of the condition[119]. We should consider the safety of fetal MRI as it may induce maternal stress, high acoustic noise, and induction of preterm labor. However, the benefits of fetal MRI mostly outweigh the risks, mainly when experienced radiographer technicians perform the procedure. Table 2 summarises the various antenatal markers of autism.

Neonatal and early infancy markers for the risks of autism

Early identification of autism allows the timely launching of targeted therapies, which can help optimize different cognitive functions impaired in autism. Different studies tried to identify autism early in newborns and early infancy, depending on different physical, behavioral, biochemical, and imaging markers (Table 3).

Neonatal physical and behavioural profile of autism

Even though clinicians are identifying autism earlier than before, some children still have a delayed diagnosis till the age of six years. Differences in screening tools and diagnostic abilities in various clinical settings can affect the timing of autism diagnosis. A neonatal physical and behavioral profile of autism refers to the physical and behavioral characteristics identified in infants who later develop autism. However, we should emphasize that there is no one standard set of features that could predict the development of autism. Some patterns have emerged and are associated with an increased risk of autism[120].

Many studies focused on studying the motor and behavioral response changes that could be observed during the first year of life and their relation to later diagnosis of autism. Physically, neonates with future diagnoses of autism may have large or abnormal head sizes at birth and throughout early childhood, which may reflect early brain overgrowth in children with autism[121]. However, in their meta-analysis, Crucitti *et al*[122] showed age and sex differences in the head circumference of neonates and infants who developed autism. They found that girls with autism aged 12-17 mo had smaller head sizes, while boys were more likely to have significant head size differences at birth and between 60 and 100 mo, being small between 6 and 11 mo and large between 12 and 17 mo. They also found that average head size was not atypical finding in autism. Moreover, girls were more likely to have significant head size differences between 36 and 59 mo and were less likely at birth.

They may also have hypertelorism (Increased intra-ocular distance), anteriorly rotated ears, long nose back, abnormal mouth shape, and facial asymmetries[123]. Gorczyca *et al*[124] found a statistically non-significant connection between the degree of dysmorphia and the presence of some physical disorders in first-degree relatives. In addition, some studies reported that infants who develop autism later in childhood tend to have longer birth body lengths than typically developed infants[125]. This finding may be related to genetic or environmental effects on fetal growth and development.

Some studies have reported that infants who later develop autism may show subtle changes in the neonatal period before the onset of more overt symptoms. Therefore, it could be challenging to be recognized. They may have abnormalities in motor development during the first year of life. For example, by the age of one month, they may have arm tone deficits and asymmetric visual tracking. They may also have hypotonia, hyperreflexia, poor movement quality, head lag, delayed or missing major motor development, and delayed milestones, such as sitting or crawling, or prefer using one hand over the other[126,127]. Children with autism have lower heart rate variability, as shown by Lory *et al*[128], who found significantly lower tonic heart rate variability in children with autism than in children with typical development. Reducing noradrenergic activity could enhance and improve different aspects of network processing and thus improve cognitive abilities, such as verbal problem-solving, in children with autism[129]. Moreover, the presence of reduced heart rate variability could predict the response to propranolol therapy in improving cognitive functions in children with autism[130]. In addition, Nyström *et al*[131] found that the presence of enhanced pupillary light reflex during infancy is associated with a greater risk of developing autism in toddlerhood, which may indicate the important role of sensory atypicality in the pathogenesis of autism. They also are more liable for sleep disturbances and gastrointestinal symptoms, such as constipation, diarrhea, or gastroesophageal reflux, in the neonatal period than typically developing infants[132, 133].

As abnormal motor behaviors are a very characteristic feature of autism, movement analysis during early infancy may be a valuable tool for the early diagnosis of autism. However, autism-associated movement disorders vary from child to child, with disturbances in some or all of the development milestones, including lying, righting, sitting, crawling, and walking[134]. Disturbances of movement could be identified obviously at the age of 4–6 mo and occasionally even at birth, using the Eshkol–Wachman Movement Analysis System using still-frame videodisc analysis. Movement disturbances represent an intrinsic part of autism that could present at birth. It can be used to diagnose the presence of autism even during the first few months of life[135].

Infants later diagnosed with autism may demonstrate early deficits in social behavior, specifically in joint attention, eye contact, orienting to names, facial expressions, social smiles, attention, and tolerance of social touch. They may exhibit atypical sensory processing, with hypersensitivity or hyposensitivity to touch, sounds, or visual stimuli, representing

Table 3 Neonatal and early infancy markers for the risks of autism

Marker	Details
Physical markers	Large or abnormal head sizes at birth and throughout early childhood
	Smaller head sizes in girls
	Long body lengths at birth
	Hypertelorism, anteriorly rotated ears, long back of the nose, abnormal shape of the mouth, and facial asymmetries
	Abnormal motor development during the first year of life *e.g.*, hypotonia, hyperreflexia, poor movement quality, head lag, delayed or missing major motor development, and delayed milestones, such as sitting or crawling, or prefer using one hand over the other
	Asymmetric visual tracking
	Reduced heart rate variability
	Enhanced pupillary light reflex during infancy
	More liable for sleep disturbances and gastrointestinal symptoms, such as constipation, diarrhea, or gastroesophageal reflux
Social & behavioural markers	Deficits in social behavior, specifically in joint attention, eye contact, orienting to names, facial expressions, social smiles, attention, and tolerance of social touch
	Atypical sensory processing, with hypersensitivity or hyposensitivity to touch, sounds, or visual stimuli
	Dislike being touched and cuddled
	Lie in the bassinet constantly and cry when being held up
	Avoid eye contact or have difficulty following a person's gaze when directing the infant's attention to something
	Reduced visual attention to social stimulation
	Impaired orienting to novel stimuli at the age of two months
	Reduced interest in social interaction or decreased responsiveness to social cues
	Lie on one of the extremes of being very low or very high needs
Immunological profile	Neonatal cord blood anti-brain antibodies, especially against both 39kDa and 73kDa proteins
	Abnormalities in the concentrations of total IgG and IgG 4
	Presence of anti-dopamine D2L receptors and anti-tubulin autoantibodies and the ratio of the anti-dopamine D2L to D1 receptor antibodies
	Folate receptor-alpha autoantibodies
	High immunoglobulin A in the stool
Inflammatory profile	High neonatal C-reactive protein levels
	Decreased levels of α-2-macroglobulin, ferritin, and serum amyloid P
	High IL-1B, IL-4, IL-6, IL-8, interferon-gamma, eotaxin, and monocyte chemotactic protein-1 levels
	Low transforming growth factor-β1 levels
Biochemical & metabolic profile	Low blood levels of Brain-derived neurotrophic factor
	Neonatal hyperbilirubinemia
Hormonal profile	Reduced neonatal CSF or plasma vasopressin concentration
	Low plasma or salivary oxytocin levels
	Reduced oxytocin receptor number
Brainstem function	Abnormal neonatal auditory brainstem responses

CSF: Cerebrospinal fluid; IgG: Immunoglobulin G; IL: Interleukin; kDa: Kilodalton.

manifestations of atypical sensory processing. They dislike being touched or cuddled, constantly lie in the bassinet, and cry when held up. Infants who later develop autism may also show differences in eye gaze compared to typically developing infants. They may avoid eye contact or have difficulty following a person's gaze when directing the infant's attention to something[136-138]. They also do not look at the face and try to avoid eye contact even during nursing, which may appear too early by the age of two weeks. They may have reduced visual attention to social stimulation and impaired orienting to novel stimuli at the age of two months[139]. They may also show differences in social respons-

iveness, such as reduced interest in social interaction or decreased responsiveness to social cues. They also lie on one of the extremes of having very low or very high needs, *e.g.*, needing to be held constantly or avoiding touching. They also may lack proper response to sounds after rolling out hearing problems[140,141]. These early signs could be hard to detect and are not always apparent in all infants who will develop autism. Still, they may be crucial and helpful for early autism identification and intervention.

Prematurity is a significant risk factor for autism. Wong *et al*[142] showed that premature babies below 30 wk of gestation had more significant social-communication problems and autistic behavior in early childhood than seen in full-term babies as assessed by the Quantitative Checklist for Autism in Toddlers (Q-CHAT). Less attention maturation observed in preterm babies can negatively impact how long they can stay actively interested in social interaction. Eye gaze is an indisputable means of communication. Preterm babies are different from full term in many behavioral aspects. They typically avert their gaze more often and for longer periods in early social interactions than full-term infants due to less optimal attention maturation in preterm children[143]. Therefore, preterm babies who demonstrated gaze aversion and endpoint nystagmus had better language scores on the Bayley–III. On the other hand, Pineda *et al*[144] found that preterm babies with absent gaze aversion and absent endpoint nystagmus during the neonatal period showed positive screening for autism using Modified Checklist for Autism in Toddlers (M–CHAT) at the age of two years.

In neonates, a fascinating Japanese study by Tokunaga *et al*[145] prospectively demonstrated the relationship between behavioral features during the neonatal period and social behavior and sensory disorders at 18 mo to early detect and intervene in children with autism. They studied apparently healthy 105 full-term neonates for the behavioral features using the Neonatal Behavioral Assessment Scale (NBAS) between 2 and 7 d after birth. Then, they were re-assessed at 18 mo of age using the Japanese version of M–CHAT (M-CHAT-JV) and the Infant/Toddler Sensory Profile (ITSP). They found that 15.2% of the infants were M-CHAT-JV-positive, with significant differences between the M-CHAT-JV-positive and M-CHAT-JV-negative groups in two of the NBAS clusters: motor and orientation. They also found a significant negative correlation between the NBAS orientation cluster and the "low registration" and "auditory processing" sections in the ITSP. In addition, they found a negative correlation between the NBAS motor cluster and the "sensation avoiding" and "tactile processing" sections in ITSP. Logistic regression analysis also showed a significant association between the NBAS orientation cluster and ITSP low registration with the M-CHAT-JV at 18 mo. Their results suggested a significant relationship between the NBAS orientation cluster in full-term neonates and the social behavior and sensory features at 18 mo[145]. These findings imply the need to develop therapeutic methods that can be applied from the first few months of life to manage autism.

Neonatal immunological profile of autism

As previously mentioned, prenatal and/or postnatal exposure to anti-brain antibodies plays an important pathoplastic role in autism as they enhance autism severity by damaging cognitive processes and adaptive functioning, boosting motor stereotypies, altering the sleep/wake cycle, and delaying or halting neurodevelopment, primarily verbal and non-verbal language. Some mothers of children with autism (about 7%) had antibodies to 39kDa and 73kDa proteins during gestation. Detection of antibodies against both 39kDa and 73kDa proteins during mid-gestation predicts early and severe autism in the offspring[81]. Anti-brain antibodies can be used as biomarkers predicting autism severity and clinical features and possibly providing new avenues for preventive and therapeutic strategies, including predicting the response to treatment. A systematic review and meta-analysis by Rossignol *et al*[146] showed abnormalities in the total IgG and IgG 4 subclass concentrations related to social impairments and aberrant behavior. They also studied the immunomodulatory effects of intravenous immunoglobulins in children with autism. Using intravenous immunoglobulins showed clinical improvements in irritability, hyperactivity, cognition, attention, communication, social interaction, eye contact, speech, response to commands, echolalia, drowsiness, and decreased activity. In some cases, the early use of intravenous immunoglobulins led to the complete resolution of autism symptoms. The presence of anti-dopamine D2L receptors and anti-tubulin autoantibodies and the ratio of the anti-dopamine D2L to D1 receptor antibodies can predict the treatment response to intravenous immunoglobulin. These antibodies can serve as a marker to predict patients who may respond better to intravenous immunoglobulin therapy[147].

Another interesting finding is the high prevalence of folate receptor-alpha autoantibodies in children with autism (71%) compared to children with typical development or children with developmental disabilities but not with their siblings[148]. These antibodies induce cerebral folate deficiency and consequently induce autism symptoms. Consequently, the presence of folate receptor-alpha autoantibodies in infancy may help to predict the risk of autism as well as the response to leucovorin (folinic acid) treatment[149]. Another crucial immunological marker of autism in infants and children is immunoglobulin A (Ig A) in the stool. Ig A is the main immunoglobulin secreted by the gastrointestinal immune cells. Zhou *et al*[150] found higher stool Ig A levels in children with autism than in typically developed children, suggesting the presence of gut immune abnormalities in patients with autism and can explain the gene-environmental interaction in the pathogenesis of autism. It also suggests the possible use of stool Ig A as a possible marker of autism.

Neonatal and infancy inflammatory profile of autism

As previously mentioned, the immune activation and signaling pathways can impact the child's neurodevelopment and may contribute to the pathogenesis of autism. However, this effect varies considerably with the genetic background and many perinatal environmental factors[151]. High neonatal C-reactive protein levels are consistently associated with an increased risk of autism compared to the controls. On the other hand, decreased levels of α-2-macroglobulin, ferritin, and serum amyloid P are associated with increased autism risk in the matched sibling comparison. The changes observed in these acute-phase reactant proteins are indications of maternal immune activation, which in turn increases the risk of autism[152]. In addition, a meta-analysis by Masi *et al*[153] showed that elevated levels of IL-1β, IL-6, IL-8, interferon-

gamma, eotaxin, and monocyte chemotactic protein-1, and lower levels of transforming growth factor-β1 in children who have autism than healthy control. Another study by Krakowiak *et al*[154] showed that high neonatal levels of IL-1β are associated with an increased risk of mild to moderate autism. Furthermore, high neonatal levels of IL-4 are independently associated with an increased risk of severe autism. However, there is no single cytokine abnormality can be used as a marker of increased risk of autism. We need more extensive prospective studies to investigate the abnormal cytokine profiles that could be strongly associated with autism at different stages of development.

Neonatal and infancy biochemical and metabolic profile of autism

Brain-derived neurotrophic factor (BDNF) is essential for neuronal survival and growth. It serves as a neurotransmitter modulator and contributes to neuronal plasticity, which is critical for learning and memory[155]. A Meta-analysis by Liu *et al*[156] found that the blood levels of BDNF were lower in neonates who later developed autism than in children with typical neurodevelopment. However, contradictory results with previous studies warrant more studies to facilitate a more robust conclusion[157]. There is substantial evidence for the possible association between neonatal hyperbilirubinemia and the later risk of developing autism. The risk increases in the presence of prematurity, severe jaundice, insufficient milk intake, phototherapy, and dark-skinned babies due to a heightened risk of missed diagnosis, delayed care access, and poorer settings[158,159].

Neonatal and infancy hormonal profile

Besides the antenatal effects of sex and steroid hormones on brain development and the risk of autism, other hormones could also play a role. Vasopressin, a social neuropeptide arginine, is found to be significantly lower in the cerebrospinal fluid (CSF) of children with autism than in healthy controls. Oztan *et al*[160] studied CSF samples from 913 febrile infants between 0-3 mo as a part of their medical care. They stored the collected samples at -70°C. Eleven children out of 913 developed manifestations of autism. They compared the vasopressin concentration in the CSF samples obtained from these eleven children with 22 children with typical neurodevelopment (Ratio 1:2). They found a significant reduction of vasopressin concentration in the neonatal CSF samples from children who developed autism compared to those with typical development, with the highest accuracy when patients who had comorbid attention-deficit/hyperactivity disorder with autism were removed from the analysis. These findings suggest the beneficial use of CSF vasopressin levels as an early marker for autism in neonates with a high risk of developing autism and in behaviourally symptomatic infants. In addition, Zhang *et al*[161] found lower plasma levels of vasopressin in mothers of children with autism than in mothers of typically developed children. They also found that children with autism with higher vasopressin levels are less likely to have repetitive behavior. They also found that children with higher plasma oxytocin levels have less verbal communication impairment[161]. Moreover, Pichugina *et al*[162] found lower salivary oxytocin levels in children with autism and intellectual disabilities than in children with Intellectual disabilities without autism. They also found a direct negative correlation between salivary oxytocin levels and the severity of autism. Another study by Gottlieb *et al*[163] showed that the severity of autism is inversely proportional to the normalized number of oxytocin receptors, indicating the significant role of the oxytocin receptor number in the severity of autism. It also suggests the potential use of vasopressin and promising therapeutic tool to improve social cognition in children with autism[164].

Neonatal brainstem function

Only the lower parts of the nervous system (the brain stem and spinal cord) are very well developed by birth. In contrast, the higher regions (the limbic system and cerebral cortex) are still relatively primitive. Therefore, the lower brain mainly controls a newborn's behavior. Therefore, kicking, grasping, rooting, crying, sleeping, and feeding are mainly functions of the brain stem and spinal cord[165]. The brainstem has a revolutionary role in developing humans' social development. Therefore, the integrity of brainstem sensory information transmission during the final weeks of gestation and the early neonatal period may support the development of social engagement[166].

Cohen *et al*[167] evaluated the contribution of initially abnormal neonatal auditory brainstem responses (ABRs) and 4-month arousal-modulated attention visual preference to later autism behaviors in neonatal intensive care unit graduates. They compared NICU graduates with normal ABRs (n = 28) to those with initially abnormal ABRs (n = 46) that later resolved. At four months post-term age, visual preference (measured after feeding) for a random check pattern flashing at 1, 3, or 8 Hz and gestational age served as additional predictors. Outcome measures were Pervasive Developmental Disorder Behavior Inventory (PDDBI) scores at 3.4 years and developmental quotients (DQ) obtained around the same age with the Griffiths Mental Development Scales (GMDS). They found that the preferences for higher stimulation rates at four months were highly correlated with PDDBI scores and the GMDS Hearing and Speech DQ, but only in those with initially abnormal ABRs. The effects were most potent for a PDDBI social competence measure most associated with a diagnosis of autism. For those with abnormal ABRs, increases in preference for higher stimulation rates as infants were linked to nonlinear increases in the severity of autism at three years and an autism diagnosis. Therefore, abnormal ABRs were associated with later reports of repetitive and ritualistic behaviors irrespective of a 4-mo preference for stimulation. The common occurrence of initially abnormal neonatal ABRs and preference for more stimulation at four months, both indices of early brainstem dysfunction, may be a marker for the development of autism in this cohort[167].

Challenges to early detection of autism

Several reasons make early detection of autism a real challenge. Lack of parental, family, caregivers, or even healthcare providers' awareness about the disorder is one of the main challenges that enface early detection of autism. Despite rising awareness of autism, many people are not familiar with the symptoms and signs of autism, resulting in delayed diagnosis and treatment. Another critical challenge is the variability in symptoms[136]. Autism is a complex and common

neurodevelopmental disorder that affects children differently, with various symptoms and severity levels. Symptoms may also vary depending on the child's age, gender, and cultural background. This observation is particularly evident in young infants and children under 24 mo of age who may not yet display many characteristic symptoms[168]. In addition, the lack of specific biological markers or diagnostic tests for a definitive diagnosis of autism is another real challenge (Table 4).

Furthermore, the diagnostic criteria for autism are changing over time, and experts continuously debate about what establishes a diagnosis of autism. Diagnosis is typically based on behavioral observations and evaluations, and the screening tools are not always accurate. These diagnostic tools are very subjective and vary between clinicians. All these together can result in false positives or negatives, leading to overdiagnosis, underdiagnosis, misdiagnosis, or delayed diagnosis[169]. Moreover, autism frequently occurs with many neurological, psychological, and physical co-morbidities and overlaps with many other conditions, such as attention deficit hyperactivity disorder, intellectual disability, and language disorders, making it hard to differentiate between them[170].

Differences in cultural and linguistic backgrounds harden the abilities of healthcare providers to recognize early signs of autism, remarkably in minority or immigrant populations with significant cultural and linguistic barriers. Healthcare providers may not be familiar with cultural customs, norms, and practices that can impact the presentation of symptoms [171]. Even with the increased awareness about autism, many families still suffer from the stigma and fear surrounding autism, making it difficult for parents and caregivers to ask for help for their children. This stigma may prevent early diagnosis and intervention, significantly impacting children's development, well-being, and long-term outcomes of children with autism[172]. In addition to all these obstacles, limited funding may prevent the early detection and treatment of children with autism. Early detection and intervention for autism require resources and funding, which may be limited in some areas or for some families[173].

In addition, screening tools, such as the Modified Checklist for Autism in Toddlers (M-CHAT), which are used to identify children who may be at risk for autism, are not always readily available, and many pediatricians and healthcare providers may not be familiar with them, particularly in rural or low-income areas. These limited financial and expert resources can make it challenging to obtain a timely diagnosis of autism, resulting in delayed treatment and poorer outcomes for children with autism[174]. Handling these challenges requires raising awareness, improving access to diagnostic tools, dealing with culturally sensitive concepts, and defining straightforward approaches to screening and diagnosis. Early recognition and management are critical for improving outcomes for children with autism. It is crucial to continue addressing these challenges to enhance the quality of life of children with autism and their families[175].

Limitations of the study

As autism is a multi-dimensional disorder, various techniques and approaches have been used to develop different biomarkers to diagnose autism. However, only some biomarkers underwent validation studies. In addition, many other potential diagnostic biomarkers underwent just preliminary investigation and still need further optimization. Moreover, many of the included studies were based on questionnaires depending on the parents or the caregiver's memories and subjective judgment, therefore carrying the risk of memory effects bias such as rosy retrospection, egocentric bias, and cross-race effect, and consequently affecting the accuracy of the results. In addition to the memory bias, many studies used typically developing non-sibling children as controls and did not include typically developed siblings or children with developmental delays without autism. These two types of controls are clinically ideal and relevant as a comparison population as they share many risk factors with the children who developed autism and consequently improve the biomarkers' sensitivity, specificity, and predictive values. One more limitation of the suggested biomarkers is the stage of measurement. Many of the suggested biomarkers were measured after the child was diagnosed with autism, therefore missing the early detection phase and may not be accurate or sensitive enough if used early.

CONCLUSION

Autism is a complex neurodevelopmental disorder, typically diagnosed during the first three years. Of life with a spectrum of symptoms ranging from mild to severe and varies from one child to another. Pre-autism refers to the early stage of autism and the signs and symptoms that appear during the developmental stages of a child that may indicate a potential risk for developing autism later in life. Early detection and intervention are crucial for improving outcomes for individuals with autism. Various physical, biochemical, hormonal, and imaging biomarkers are developed to assist in prenatal and early-life diagnosis of autism. However, every biomarker has its accuracy and limitations. To improve early detection of autism, we should try to overcome the various challenges that enface the diagnosis, such as improving the community awareness of early signs of autism, easing the access to diagnostic tools, trying to remove the stigma attached to the diagnosis of autism, and dealing with the different culturally sensitive concepts related to it. In addition, the scientific community must work hard to replicate studies with more different targeted populations, perform more randomized controlled studies with larger numbers of participants, and define straightforward and accessible gold standard screening and diagnostic approaches to detect autism early among newly developing young infants and children. We also should consider that autism is a heterogeneous spectrum with different presentations, symptomatology, and severity. Therefore, we may need to develop a group of biomarkers and diagnostic tools that could fit the various conditions we may face, aiming to provide optimized and individualized types of treatment. Therefore, we can say that we have just started our first step in screening autism. However, the journey is too long to achieve the aim.

Table 4 Challenges to early detection of autism

Challenges	Details
Cultural & educational	Lack of adequate awareness
	Cultural and linguistic barriers
	Stigma and fear
Disease-related	Continuous variability in symptoms and signs
	Diagnosis is largely subjective
	Frequent co-morbidities and overlapping with other disorders
	Lack of specific biological markers and diagnostic criteria and tests
Resources-related	Limited funding, access to screening, and healthcare facilities

ACKNOWLEDGEMENTS

We thank the anonymous referees and editors for their valuable suggestions.

FOOTNOTES

Author contributions: Al-Biltagi M collected the data, wrote, and revised the manuscript; The guidelines of the PRISMA 2009 were adopted while writing the manuscript.

Conflict-of-interest statement: Authors declare no conflict of interests for this article.

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S-Editor: Liu JH
L-Editor: A
P-Editor: Zhang XD

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World Journal of Clinical Pediatrics

Submit a Manuscript: https://www.f6publishing.com

World J Clin Pediatr 2023 December 9; 12(5): 295-309

DOI: 10.5409/wjcp.v12.i5.295

ISSN 2219-2808 (online)

REVIEW

Renal calcification in children with renal tubular acidosis: What a paediatrician should know

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Specialty type: Pediatrics

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Cabezuelo AS, Spain

Received: July 29, 2023
Peer-review started: July 29, 2023
First decision: September 14, 2023
Revised: September 15, 2023
Accepted: October 16, 2023
Article in press: October 16, 2023
Published online: December 9, 2023

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Abstract

Renal tubular acidosis (RTA) can lead to renal calcification in children, which can cause various complications and impair renal function. This review provides pediatricians with a comprehensive understanding of the relationship between RTA and renal calcification, highlighting essential aspects for clinical manage-

ment. The article analyzed relevant studies to explore the prevalence, risk factors, underlying mechanisms, and clinical implications of renal calcification in children with RTA. Results show that distal RTA (type 1) is particularly associated with nephrocalcinosis, which presents a higher risk of renal calcification. However, there are limitations to the existing literature, including a small number of studies, heterogeneity in methodologies, and potential publication bias. Longitudinal data and control groups are also lacking, which limits our understanding of long-term outcomes and optimal management strategies for children with RTA and renal calcification. Pediatricians play a crucial role in the early diagnosis and management of RTA to mitigate the risk of renal calcification and associated complications. In addition, alkaline therapy remains a cornerstone in the treatment of RTA, aimed at correcting the acid-base imbalance and reducing the formation of kidney stones. Therefore, early diagnosis and appropriate therapeutic interventions are paramount in preventing and managing renal calcification to preserve renal function and improve long-term outcomes for affected children. Further research with larger sample sizes and rigorous methodologies is needed to optimize the clinical approach to renal calcification in the context of RTA in the pediatric population.

Key Words: Renal tubular acidosis; Nephrocalcinosis; Renal calcification; Hypercalciuria; Kidney stones; Metabolic acidosis; Children

Core Tip: Children with renal tubular acidosis (RTA) may develop renal calcification, leading to complications and negatively affecting kidney function. This comprehensive review aims to provide pediatricians with a better understanding of the connection between RTA and renal calcification, emphasizing key aspects of clinical management. Relevant studies were analyzed to examine the prevalence, risk factors, underlying mechanisms, and clinical implications of renal calcification in children with RTA. Nephrocalcinosis in type 1 RTA is mainly associated with a higher risk of renal calcification. Further research with larger sample sizes and rigorous methodologies is necessary to improve our understanding of RTA-related renal calcification.

Citation: Al-Beltagi M, Saeed NK, Bediwy AS, Elbeltagi R, Hasan S, Hamza MB. Renal calcification in children with renal tubular acidosis: What a paediatrician should know. *World J Clin Pediatr* 2023; 12(5): 295-309
URL: https://www.wjgnet.com/2219-2808/full/v12/i5/295.htm
DOI: https://dx.doi.org/10.5409/wjcp.v12.i5.295

INTRODUCTION

Renal tubular acidosis (RTA) is a group of inherited or acquired disorders. It is characterized by impaired renal tubules' ability to reabsorb bicarbonate or excrete hydrogen ions. This results in an inability to maintain acid-base balance in the body[1]. Different types of RTA are based on the specific defect in renal tubular function. Distal RTA (dRTA), also known as type 1 RTA, is the most common form of RTA. It is characterized by impaired hydrogen ion secretion in the distal renal tubules, causing reduced kidney ability to acidify urine, with acid buildup in the blood inducing metabolic acidosis. It is often associated with and can lead to the formation of calcium phosphate kidney stones[2]. Proximal RTA (type 2 RTA) is characterized by defective bicarbonate reabsorption in the proximal renal tubules, resulting in increased urinary bicarbonate loss and metabolic acidosis. Unlike type 1 RTA, type 2 RTA is associated with urinary phosphate wasting, resulting in hypophosphatemia[3]. Combined proximal and distal RTA (type 3 RTA) is a rare form of RTA that involves defects in both proximal and distal tubular acidification mechanisms with combined features of type 1 and type 2 RTA. Type 4 RTA (RTA 4), also known as RTA due to hyporeninemic hypoaldosteronism, is characterized by impaired renal acidification due to hypoaldosteronism or aldosterone resistance, resulting in reduced secretion of hydrogen ions and impaired potassium excretion[4,5].

The cause of RTA varies depending on the specific type. RTA can be inherited and caused by genetic mutations affecting the transport proteins responsible for renal tubular acidification[6]. Other causes include autoimmune diseases (such as systemic lupus erythematosus), medications (such as certain diuretics), chronic kidney disease, or urinary tract obstruction[7]. Symptoms can range from mild to severe, depending on the underlying cause and extent of acid-base imbalance. Symptoms include fatigue, weakness, poor growth or weight gain (in children), increased urinary frequency, and bone abnormalities due to metabolic acidosis[8].

RTA can cause various complications in multiple organ systems, depending on the type and severity of acid-base imbalance. The primary complication of RTA is metabolic acidosis, which occurs due to the kidneys' inability to excrete hydrogen ions or reabsorb bicarbonate effectively[1]. This can cause issues such as impaired growth and development, muscle wasting, bone demineralization (osteoporosis), and an increased risk of kidney stone formation. RTA can also disrupt electrolyte balance, leading to abnormalities like hypokalemia or hyperkalemia[9]. Hypokalemia can result in muscle weakness, fatigue, and cardiac arrhythmias, while hyperkalemia can be life-threatening and cause cardiac

abnormalities. Chronic metabolic acidosis in children with RTA can impact growth and development and lead to developmental delays. Long-standing metabolic acidosis can also affect bone health, leading to osteoporosis or rickets in children due to compensatory mechanisms like increased bone resorption to buffer the acidosis[10,11].

In some cases of RTA, the increased excretion of calcium in the urine can cause calcium deposits in the kidneys and nephrocalcinosis. This can lead to kidney function impairment and the development of chronic kidney disease[12]. RTA can also increase the risk of kidney stone formation due to urinary abnormalities, such as increased calcium, phosphate, and oxalate excretion. If left untreated, RTA can cause chronic kidney disease and renal damage. Children with RTA and recurrent kidney stone formation or nephrocalcinosis are at higher risk for renal complications[13]. This review provides an overview of renal calcification in children with RTA, including its pathophysiology, clinical presentation, diagnostic evaluation, and management strategies. By enhancing our understanding of this complex condition, clinicians can improve early detection, implement appropriate interventions, and optimize long-term outcomes for children affected by renal calcification associated with RTA.

METHODS

We conducted a systematic literature review to gain an evidence-based understanding of our goal. This review involved searching various electronic databases like PubMed, PubMed Central, Cochrane Library, Embase, Web of Science, CINAHL, Scopus, LISA, and NLM catalog up until July 28, 2023. We used specific keywords like Renal Tubular acidosis, Nephrocalcinosis, Renal Calcification, Hypercalciuria, Kidney Stones, Metabolic Acidosis, and Children. Our review included 111 full-text articles comprising 70 reviews, 20 research articles, 16 case reports, four consensus guidelines, one systematic review, one editorial, and one more systematic review. We only included English-language articles discussing the effects of RTA on the risk of renal calcification. Figure 1 illustrates the study's flow chart. We also checked reference lists and conducted citation searches on the included studies. We excluded articles with commercial backgrounds and reviewed those available as abstracts only.

DISCUSSION

Role of the kidneys in acid-base homeostasis

The kidneys play a crucial role in maintaining the body's acid-base balance through various mechanisms such as acid secretion and excretion, bicarbonate reabsorption and generation, ammonia regulation, and response to pH changes. One of its primary functions is to excrete excess acid by releasing hydrogen ions (H^+) into the urine. This process is essential in preventing the buildup of acid in the blood, which can result in a condition known as acidosis[14].

Bicarbonate plays a crucial role in neutralizing excess acids in the blood. The majority (85%-90%) of filtered bicarbonate is reabsorbed in the proximal tubules of the kidneys[15]. This reabsorption occurs through the secretion of protons (H^+) *via* sodium hydrogen exchangers and proton pumps (H^+-ATPase). In the lumen, hydrogen ions combine with HCO_3^- to form carbonic acid, which quickly dissociates into water and carbon dioxide. This reaction is catalyzed by the enzyme carbonic anhydrase. The generated carbon dioxide diffuses freely into the proximal tubule cell and reacts with water to form carbonic acid, catalyzed by carbonic anhydrase (CA II). The bicarbonate ions resulting from the dissociated carbonic acid exit through the basolateral membrane *via* the sodium bicarbonate exchanger[16,17].

In the kidneys' distal tubules are specialized cells known as alpha-intercalated cells that secrete hydrogen ions into the urine. At the same time, beta-intercalated cells generate new bicarbonate ions to maintain a balance between acid and base by replenishing bicarbonate in the blood. Principal cells reabsorb sodium and water while secreting K^+ to fine-tune the acid, base excretion, and urine output[18]. The bicarbonate (HCO_3^-) generated is transported to the blood in exchange for chloride (Cl^-) through the basolateral Cl^-/HCO_3^- exchanger. Additionally, the kidneys can produce ammonia (NH_3), which can combine with hydrogen ions to form ammonium (NH_4^+). Ammonium is then excreted into the urine, further contributing to acid excretion and acid-base balance[19].

The kidneys can respond to changes in blood pH by adjusting their acid-base handling mechanisms. When blood pH is too acidic, the kidneys can increase the excretion of hydrogen ions and generate more bicarbonate to restore balance. Conversely, when blood pH is too basic (alkaline), the kidneys can reduce bicarbonate reabsorption and retain more hydrogen ions, promoting acid excretion and balancing pH[16]. This intricate control of acid-base balance is essential for proper cellular function, enzyme activity, and overall physiological processes throughout the body. Any disruption in these mechanisms can lead to acid-base imbalances, such as metabolic acidosis or alkalosis, which can have significant health implications if not appropriately managed[20].

Role of the kidneys in calcium homeostasis and prevention of urolithiasis

The kidneys play a vital role in maintaining calcium homeostasis by regulating the reabsorption and excretion of calcium in response to changes in blood calcium levels and hormonal signals[21]. This fine-tuned control of calcium levels is essential for various physiological functions and for maintaining healthy bones and tissues throughout the body. Disruptions in the kidneys' ability to regulate calcium homeostasis can lead to disorders such as hypercalcemia (elevated blood calcium levels) or hypocalcemia (low blood calcium levels), which can significantly affect various organ systems and overall health. Proper kidney function is crucial for maintaining optimal calcium balance and overall calcium homeostasis in the body. Calcium homeostasis is the process of maintaining optimal calcium levels in the bloodstream

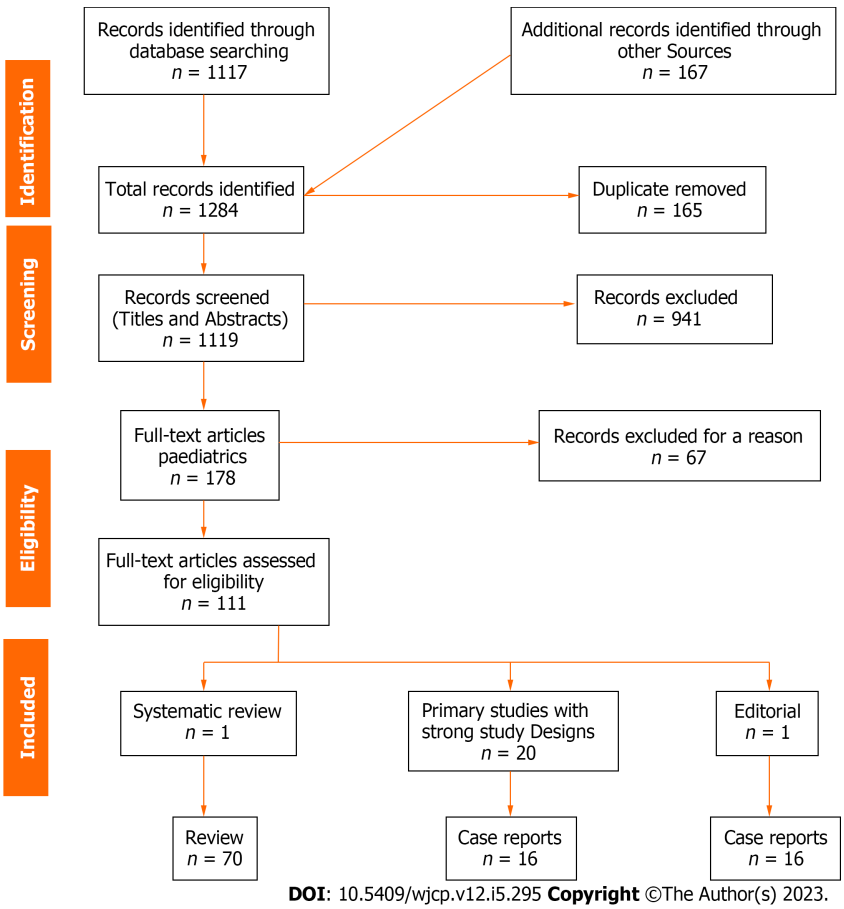

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Figure 1 Flow chart of included studies.

[22]. The kidneys play a crucial role in this process by reabsorbing filtered calcium, producing parathyroid hormone, metabolizing vitamin D, and excreting excess calcium. Disruptions in kidney function can lead to disorders like hypercalcemia or hypocalcemia, affecting overall health. Proper kidney function is essential for maintaining optimal calcium balance and overall calcium homeostasis in the body[23].

The kidneys play a vital role in maintaining acid-base homeostasis, which influences the solubility of minerals in the urine. Imbalances in acid-base levels can promote the formation of specific types of stones, such as uric acid stones. The kidneys are also involved in regulating calcium levels in the bloodstream. Proper calcium balance helps prevent the formation of calcium-containing stones, such as calcium oxalate stones[24]. The urinary stones, also known as uroliths, can block the urinary system and cause urolithiasis. The kidneys play a crucial role in preventing the formation of these stones. They filter waste products and excess substances from the bloodstream to form urine and regulate the amount of water reabsorbed in the renal tubules to maintain an appropriate urine concentration. Dilute urine reduces the risk of supersaturation of minerals in the urine, making it less likely for crystals to form and lead to stone formation[25].

The kidneys filter various substances from the blood, including crystal precursors like calcium, oxalate, and uric acid. Adequate fluid intake and maintaining proper urine pH are essential in preventing the accumulation of crystal precursors [26]. The kidneys produce and excrete substances like citrate, magnesium, and glycosaminoglycans that inhibit the formation and growth of crystals in the urine. These substances prevent the aggregation of crystal precursors and promote their dissolution, reducing the risk of stone formation[27]. Citrate inhibits the formation of calcium oxalate stones, a common type of kidney stone. Citrate chelates calcium ions in urine, interfering with the growth of crystals and enhancing the solubility of calcium oxalate, making it less likely for crystals to form and cause stones[28]. Proper citrate levels can be maintained through adequate fluid intake, diet, and necessary supplementation.

Efficient kidney function ensures the timely clearance of waste products and excess minerals from the urinary system. Proper acid-base balance prevents specific kidney stones like uric acid[29]. The kidneys regulate calcium levels in the bloodstream, which helps prevent the formation of calcium-containing stones like calcium oxalate stones. The kidneys play a vital role in maintaining acid-base homeostasis, which influences the solubility of minerals in the urine. Imbalances in acid-base levels can promote the formation of specific types of stones[30].

Etiology and pathogenesis of RTA

RTA refers to a group of kidney disorders that impair acid-base regulation. This results in the kidneys being unable to excrete acid or maintain the body's pH balance properly. There are various types of RTA, each with its own etiology and pathogenesis (Table 1).

Table 1 Comparison of different renal tubular acidosis types based on their etiology, pathogenesis, and key features.

Type of RTA		Type 1 RTA	Type 2 RTA	Type 3 RTA	Type 4 RTA
Prevalence		The most common type of RTA (1-2/100.000)	Less common than type 1 RTA (0.5/100.000)	Very rare	Slightly less common than type 1 RTA (1/100.000)
Location of defect		Distal nephron	Proximal nephron	Variable	Collecting duct
Etiology	**Primary**	Sporadic or hereditary (mutation of SLC4A1, H^+-K^+-ATPase, H^+-ATPase)	Sporadic or hereditary (mutation of CA-IV, NHE-3, NBC-1)	Mutation in CA-II	PHA-1, PHA-2 (Gordon's syndrome)
	Secondary	Autoimmune: Sjogren's, SLE, RA, PBC; Nephrotoxins: Amphotericn B, trimethoprim, lithium; Miscellaneous: Sarcoidosis, amyloidosis, obstructive uropathy	Autoimmune: Sjogren's; Nephrotoxins: Tetracycline, topiramate, valproate, acetazolamide; Metabolic: Wilson's disease, cystinosis, Lowe's syndrome, galactosemia, chronic hypocalcemia; Hereditary fructose intolerance, tyrosinemia; Miscellaneous: Multiple myeloma, amyloidosis	Type 1 RTA with secondary proximal tubule dysfunction, type 2 RTA with secondary distal tubule dysfunction	Aldosterone deficiency or aldosterone resistance: Hypoaldosteronism, ACEIs, ARBs; Hyporeninemic hypoaldosteronism: Diabetes, sickle cell disease; Tubulointerstitial disease (eGFR: 20-50 ml/min); Drugs: Potassium sparing diuretics, NSAIDs, trimethoprim, pentamidine, cyclosporine, tacrolimus
Pathogenesis		Impaired hydrogen ion secretion & reduced bicarbonate reabsorption in the distal tubules	Impaired bicarbonate reabsorption in the proximal tubules	Impaired distal acidification and reduced bicarbonate reabsorption	Impaired hydrogen ion secretion and decreased potassium excretion due to reduced aldosterone activity
Degree of acidosis		Severe	Mild to moderate	Mild	Mild to moderate
Key features		Acidemia, hypobicarbonatemia, inability to acidify urine properly, and loss of bicarbonate ions in urine. Hypokalemia is common	Metabolic acidosis, loss of bicarbonate ions in urine, hypobicarbonatemia, electrolyte imbalances (*e.g.*, hypokalemia, hypophosphatemia)	Metabolic acidosis, hypobicarbonatemia, variable features depending on the underlying systemic disease or medication	Metabolic acidosis, hyperkalemia, associated with hypoaldosteronism or resistance to aldosterone, potential electrolyte imbalances (*e.g.*, hyponatremia, mild hyperchloremic acidosis)
Risk of renal calcification		High	Lower than type 1 RTA	Very low (variable)	Unknown

AE1: Anion exchanger 1; CA: Carbonic anhydrase; NHE-3: Sodium-hydrogen exchanger 3; NBC-1: Sodium-bicarbonate cotransporter 1; PHA: Pseudohypoaldosteronism; SLE: Systemic lupus erythematosus; RA: Rheumatoid arthritis; PBC: Primary biliary cirrhosis; ACE: Angiotensin converting enzyme; ARB: Angiotensin receptor blocker; RTA: Renal tubular acidosis.

Usually, 80% of the bicarbonate ions filtered by the glomerulus are reabsorbed from the urine back into the blood in the proximal tubules of the kidneys, and the remainder are reabsorbed in the distal nephron[31]. An autosomal recessive genetic defect in the *SLC4A1* gene causes RTA type 1. This gene encodes the anion exchanger protein AE1, which transports bicarbonate ions out of the alpha-intercalated cells in the distal tubules of the kidneys[32]. The genetic defect impairs the function of the AE1 protein, which reduces the distal tubules' ability to secrete hydrogen ions into the urine and reabsorb bicarbonate ions from the urine. The defective AE1 protein reduces the transport of hydrogen ions into the urine, leading to acid buildup in the blood and acidaemia. In type 1 RTA, the defective AE1 protein also impairs the reabsorption of bicarbonate ions, resulting in a loss of bicarbonate in the urine. This leads to decreased bicarbonate concentration in the blood, which causes metabolic acidosis and various RTA symptoms[33].

Another genetic defect in the *ATP6V1B1* gene, which encodes for a subunit of the proton pump in the alpha-intercalated cells of the distal tubules, can cause type 1 RTA[34]. This type of RTA can also be associated with other systemic genetic diseases, such as Ehler-Danlos syndrome, Marfan syndrome, congenital urinary tract obstruction, or sickle cell disease[35]. It may also occur secondary to chronic kidney diseases such as chronic hypercalcemia, familial hypercalciuria, medullary sponge kidney, chronic interstitial nephritis, chronic pyelonephritis, obstructive uropathy, and renal transplant rejection. Systemic disorders can also induce type 1 RTA, such as glue sniffing and hypergammaglobulinemic states[36,37]. The inherited form of type 1 RTA is mainly diagnosed in early life or young adulthood, while the acquired secondary form can be seen at any age but commonly in adulthood. The incomplete form of type 1 RTA has an incompletely understood pathogenesis. Patients with this disorder have a constantly elevated urinary pH and hypocitraturia, as in the complete form. However, they can maintain adequate acid excretion to keep the plasma bicarbonate levels within the normal range. Meanwhile, these patients suffer from nephrolithiasis due to hypercalciuria and hypocitraturia. Therefore, an incomplete form of type 1 RTA should be considered in every calcium stone former[37].

Type 2 RTA is often caused by underlying conditions or medications affecting the function of the proximal tubules in the kidneys. However, genetic disorders like Dent disease can also lead to type 2 RTA[3]. Fanconi syndrome, which impairs reabsorption in the proximal tubules, can be inherited or acquired. It can occur due to conditions such as multiple myeloma, Wilson's disease, or certain medications (*e.g.*, ifosfamide or outdated tetracyclines)[38]. The pathogenesis of type 2 RTA involves impaired bicarbonate reabsorption in the proximal tubules, leading to a decreased net reabsorption of bicarbonate from the glomerular filtrate and contributing to metabolic acidosis. The critical pathogenic mechanism is dysfunction in the transporters or enzymes needed for bicarbonate reabsorption in the proximal tubules from the

glomerular filtrate back into the blood[39]. This dysfunction reduces bicarbonate reabsorption with bicarbonate loss in the urine instead of reabsorbing, leading to decreased blood bicarbonate levels and subsequent metabolic acidosis, which can cause various symptoms of RTA[40].

Type 3 RTA is a complex condition often caused by underlying systemic diseases or certain medications. Systemic diseases, such as autoimmune diseases (*e.g.*, systemic lupus erythematosus and Sjögren's syndrome), primary biliary cirrhosis, sickle cell disease, Marble bone disease (due to congenital carbonic anhydrase deficiency type II), and some metabolic disorders, can lead to dysfunction or renal tubular damage, impairing acid-base regulation[41,42]. Medications such as carbonic anhydrase inhibitors and some chemotherapeutic agents can cause type 3 RTA[43]. The pathogenesis of type 3 RTA is not fully understood and may vary depending on the underlying systemic disease or medication. However, the main pathogenic mechanisms include a combination of impaired distal acidification and reduced bicarbonate reabsorption. Similar to type 1 RTA, type 3 RTA may involve impaired hydrogen ion secretion in the distal tubules, resulting in reduced distal acidification of the urine. The mechanisms underlying diseases or medications that disrupt this acidification process may vary. Type 3 RTA can also involve impaired bicarbonate reabsorption, which leads to metabolic acidosis with decreased blood pH and bicarbonate levels[44,45]. The combination of impaired distal acidification and reduced bicarbonate reabsorption contributes to metabolic acidosis, with decreased blood pH and bicarbonate levels. The severity and clinical manifestations of type 3 RTA can vary depending on the underlying systemic disease or medication involved[46].

Type 4 RTA is primarily caused by conditions that affect the production or action of the hormone aldosterone. The main etiological factors include hypoaldosteronism or aldosterone resistance[47]. Aldosterone plays a crucial role in maintaining electrolyte balance and acid-base regulation. In aldosterone deficiency or dysfunction, there is impaired renal acidification, as aldosterone promotes the distal tubules of the kidneys to secrete hydrogen ions into the urine, reducing the ability to acidify the urine[48]. Hypoaldosteronism can be caused by adrenal gland disorders such as Addison's disease, congenital adrenal hyperplasia, or adrenal gland destruction, resulting in a deficiency in the production or release of aldosterone[49]. In aldosterone resistance, the kidneys fail to respond adequately to the action of aldosterone. This resistance can result from conditions like certain medications (*e.g.*, spironolactone, eplerenone), kidney diseases, or genetic disorders affecting the mineralocorticoid receptor[50]. As aldosterone also regulates potassium levels in the body by enhancing its excretion in the urine, the reduced aldosterone activity in type 4 RTA leads to impaired potassium secretion, resulting in hyperkalemia. Patients with type 4 RTA can present with muscle weakness, arrhythmia, or even cardiac arrest due to hyperkalemia[9,51].

Renal calcification in RTA

Calcification of the kidneys occurs when calcium deposits accumulate in the kidneys, leading to various issues such as kidney stones, nephrocalcinosis, and chronic kidney disease[52]. Nephrocalcinosis happens when calcium salts accumulate in the renal tubules and interstitium of the kidneys. Kidney stones, on the other hand, form due to the presence of solid masses or calculi made of hard calcium deposits in the renal pelvis, calyces, or ureters[53]. Nephrocalcinosis can occur at three levels. Molecular or chemical levels are usually observed in patients with evident hypercalcemia and can be treated by correction of hypercalcemia. Microscopic nephrocalcinosis occurs when the mineral deposits of renal tissue can be seen by light microscopy, and it is often a precursor to the macroscopic type. The macroscopic type can be identified by different imaging methods[54]. Renal calcification can be a complication of RTA, and its severity is influenced by the level of acidosis, hypercalciuria, and other risk factors such as dehydration and a high protein diet, which increase the risk of nephrocalcinosis in RTA. Nephrocalcinosis occurs more frequently in type 1 RTA, less frequently in type 4 RTA and 2 RTA, and rarely in type 3 RTA[4]. About 20% of patients with nephrocalcinosis have either inherited or acquired type 1 RTA. Therefore, when a patient presents with kidney stones and nephrocalcinosis, it is essential to consider a diagnosis of type 1 RTA, as the prevalence of either complete or incomplete type 1 RTA in nephrolithiasis is about 7% and 14%, respectively[55].

Renal calcification in RTA can arise from various factors, including low urinary citrate, high urinary calcium, and metabolic acidosis. Chronic metabolic acidosis stimulates bone resorption, releasing calcium into the bloodstream and potentially depositing it in the kidneys[56]. The severity of metabolic acidosis directly affects the prevalence of renal calcification. Type 1 RTA (classical RTA) exhibits an H^+ excretion defect in the distal nephron, leading to urinary alkalinization and calcium phosphate precipitation, eventually forming stones[57]. Additionally, patients with RTA have kidneys that cannot synthesize enough citrate, which helps prevent calcium deposition in the kidneys. Citrate is filtered into the urine but is partly reabsorbed in the proximal tubule, where its absorption depends on pH and systemic and intracellular factors[58]. Acidosis increases citrate reabsorption and its intracellular metabolism, resulting in low urinary citrate levels that increase the risk of renal calcification. Low citrate levels, combined with increased bone resorption, elevate urinary calcium levels, further increasing the risk of renal calcification. Other factors such as hyperparathyroidism, increased dietary calcium intake, and certain medications can also contribute to serum calcium levels, potentially increasing the risk of renal calcification[59].

Factors that increase the risk of renal calcification

It has been previously mentioned that the type and severity of RTA can increase the risk and magnitude of acidosis. Other conditions that a child with RTA may experience can also increase the risk of renal calcification. One of the most common risk factors for renal calcification is hypercalciuria. Hypercalciuria may be primary, such as idiopathic hypercalciuria, or secondary due to hyperparathyroidism, hypervitaminosis D, bone resorption caused by immobilization, or long-term use of medications like furosemide, corticosteroids, or adrenocorticotropic hormone[54,60,61].

Hyperoxaluria is another critical factor that can induce urinary crystallization. Most oxalates come from an endogenous source, as nutrition only provides about 10% of urinary oxalates. Primary hyperoxaluria type 1 is a rare, autosomal recessive disease of the glyoxylate metabolism due to weak or absent activity of hepatic-specific peroxisomal alanine-glyoxylate aminotransferase[62]. Primary hyperoxaluria type II is even rarer and is caused by defects in D-glycerate dehydrogenase and hydroxy pyruvate reductase[63]. Primary hyperoxaluria type III is due to a recently discovered mutation in the *HOGA1* gene on chromosome 10, which encodes for a mitochondrial 4-hydroxy-2-oxoglutarate aldolase[64]. Secondary enteric hyperoxaluria occurs due to increased intestinal oxalate absorption caused by intestinal surgery, necrotizing enterocolitis, inflammatory bowel disease, celiac disease, cystic fibrosis, abetalipoproteinemia, and ethylene glycol intoxication[65]. Hypocitraturia is another risk factor in the pathogenesis of nephrocalcinosis, commonly seen in the complete type of RTA, especially with severe metabolic acidosis. However, it can also be observed in patients with malabsorption syndromes, hypokalaemia, and persistent mild or latent metabolic acidosis. Hypocitraturia is common in certain parts of the world, such as Turkey. Preterm infants are also more likely to have hypocitraturia[66,67]. Certain medications may also increase the risk of nephrolithiasis. Poorly soluble drugs can act as a nidus for stone formation. Other medications have lithogenic effects, such as vitamin D supplementation and loop diuretics, while some drugs, such as carbonic anhydrase inhibitors, can induce hypercalciuria[68,69].

Clinical presentation and diagnosis of renal calcification in RTA

The diagnosis and clinical manifestations of renal calcification in RTA depend on the specific type of RTA. Renal calcifications can appear as kidney stones or nephrolithiasis, which is caused by the buildup of calcium and other minerals in the renal tubules. To diagnose renal calcification in RTA, doctors use a combination of clinical evaluation, laboratory tests, and imaging studies. Kidney stones can cause symptoms such as nausea, vomiting, severe flank pain, haematuria, polyuria, polydipsia, and recurrent urinary tract infections[24]. Other symptoms of RTA vary depending on the type. For instance, acidotic breathing, salt cravings, and electrolyte imbalances such as hypokalaemia can lead to weakness, muscle cramps, and cardiac arrhythmias[70]. In the long term, metabolic acidosis associated with RTA can hinder a child's growth and development, causing failure to thrive, poor mineralization of bones, resistant rickets, and bone pain in some instances. Therefore, physicians need to measure infants and young children's length/height and weight and calculate their body mass index every 3 mo and every 6 mo for older children until they reach their final height. Chronic and progressive nephrocalcinosis may lead to chronic renal failure and its typical manifestations[71]. Other systemic symptoms depend on the underlying cause of RTA. For example, autosomal recessive forms of type 1 RTA are associated with hearing loss. In addition, Fanconi syndrome, a potential cause of type 2 RTA, may cause symptoms such as hypokalaemia, bicarbonate wasting, polyuria, low-molecular-weight proteinuria, glycosuria, generalized aminoaciduria, and phosphaturia, leading to hypophosphatemia[72,73].

Various laboratory tests can help determine the electrolyte levels, kidney function, and acid-base balance of a person with RTA and nephrocalcinosis. Urine tests help measure the pH and citrate levels of urine, which can provide information about the presence of kidney stones, crystals, and other abnormalities[74]. A safe and simple acid load test is performed to confirm the diagnosis of RTA and determine its type. This test assesses the ability of the kidneys to excrete and remove a predetermined acid load. The patient is given a known amount of ammonium chloride, which acidifies the blood for 3 d. Then, the patient's urine pH is monitored over time to test the kidneys' ability to excrete acid in the urine. In persons with normal kidney function, the urine pH will decrease to less than 5.3 after administering ammonium chloride. However, in patients with RTA, the urine pH may not decrease due to the kidneys' inability to excrete acid properly[75]. The test helps differentiate between different types of RTA. For instance, in type 2 RTA, the urine pH will decrease after administering ammonium chloride, but the fractional bicarbonate excretion will be elevated. In type 1 RTA, the urine pH will not decrease, and the fractional bicarbonate excretion will be normal or reduced[76]. The results of the acid load test in different types of RTA are summarized in Table 2. In some cases, genetic testing may be done to identify underlying genetic causes of RTA. Prenatal genetic testing can also be performed in high-risk families with a known case of hereditary RTA[77]. Table 3 compares clinical and laboratory data between type 1 and type 2 RTA. Table 4 shows some of the genetic disorders that may cause different types of RTA.

In addition, laboratory investigations are necessary for serial follow-up of already diagnosed patients. For example, in patients with hereditary type 1 RTA, fasting venous blood gas analysis, blood urea, serum creatinine, potassium, sodium, chloride, phosphate, calcium, alkaline phosphatase, and albumin are needed every 3-4 mo in infants and young children and every 6 mo for older children and adults[7]. Annual urinalysis, urine creatinine, sodium, potassium, calcium, and citrate are also required. The analysis frequency may be increased in individual cases. Annual audiometry is necessary for cases with type 1 RTA due to the high risk of hearing impairment[78].

When diagnosing renal calcification in patients with RTA, imaging studies can help detect kidney stones or calcifications within the kidneys. The type of imaging used depends on availability, patient characteristics, and the suspected extent of calcification (Table 5). X-rays commonly detect kidney stones, which appear as dense, white shadows in the kidneys and urinary tract. Ultrasound is a non-invasive technique that is useful in creating images of the kidneys and surrounding structures to detect kidney stones. Ultrasound can be done annually to evaluate nephrocalcinosis, urolithiasis, and cysts in asymptomatic individuals[79]. Computed tomography (CT) scans provide detailed cross-sectional images of the kidneys, allowing for a more precise evaluation of renal calcifications and any associated complications. Non-contrast CT is to be done first; then, contrast study may sometimes be helpful to clarify complex or confusing cases. However, contrast can obscure calcific densities. Therefore, contrast scans are usually indicated during the follow-up evaluation of patients with kidney stones[80]. Magnetic resonance imaging (MRI) is used in cases where CT scans are contraindicated or not preferred, such as in patients with allergies to contrast agents used in CT scans. MRI can also provide detailed images of the kidneys, but it may not be as readily available as other imaging modalities[81]. Imaging studies, especially ultrasound and CT scans, are crucial for diagnosing and managing renal calcification in patients with

Table 2 Acid load test in different types of renal tubular acidosis

Type of RTA	Urine pH	Fractional bicarbonate excretion
Type 1 RTA	Does not decrease	Normal or decreased
Type 2 RTA	Decreases	Increased
Type 3 RTA	Variable	Variable
Type 4 RTA	Does not decrease	Decreased

RTA: Renal tubular acidosis.

Table 3 Comparison of clinical and laboratory data between type 1 and type 2 renal tubular acidosis

Feature		Type 1 RTA	Type 2 RTA
Prevalence		More common than type 2 RTA	Less common than type 1 RTA
Cause		Usually isolated, inherited, autosomal recessive forms are associated with hearing loss	Usually secondary to a systemic disease, most often metabolic disease, *e.g.*, Fanconi syndrome
Clinical features	Nephrocalcinosis	Often present	Occasionally present
	Polyuria (increased urine output)	Common	Common
	Polydipsia (increased thirst)	Common	Common
	Dehydration	Less common	Less common
	Bone abnormalities	Usually, severe	Variable
	Failure to thrive (children)	Occasional	Uncommon
	Rickets/osteomalacia (children)	Occasional	Uncommon
	Metabolic acidosis	Severe acidosis; is easily corrected with bicarbonate supplementation	Usually milder but difficult to correct; requires high doses of bicarbonate supplementation
Laboratory Finding	Serum HCO_3^- (bicarbonate)	Decreased	Decreased
	Serum potassium	Low	Normal/low
	Urine pH	> 5.5	< 5.5
	Fractional excretion of bicarbonate	< 5%	> 15%
	Urine-blood PCO_2	< 20 mmHg	> 20 mmHg
	Phosphaturia and hypophosphatemia	Absent	Present (variable)
	Tubular defects – low-molecular-weight proteinuria, aminoaciduria, glycosuria	Absent	Present (variable)
	Hypercalciuria	Often present	Occasionally present

RTA: Renal tubular acidosis.

RTA. They allow clinicians to visualize the extent and nature of the calcifications, determine appropriate treatment strategies, and monitor treatment response over time[82]. However, it is essential to remember that the choice of imaging modality should be based on the specific clinical scenario, and imaging findings should be integrated with other clinical information to arrive at a comprehensive diagnosis and treatment plan. Early diagnosis and treatment of renal calcification in RTA can help prevent serious complications[1].

Management of nephrocalcinosis

Managing nephrocalcinosis in RTA involves identifying the root cause and addressing the complications associated with the condition. The treatment method utilized depends on the type of RTA and the severity of nephrocalcinosis. The primary objectives of management are to correct the acidosis, reduce urinary calcium excretion, and prevent further calcification. For type 1 RTA, the primary management goal is to decrease urinary calcium excretion. Oral alkaline therapy, such as oral sodium bicarbonate or citrate, is utilized to correct metabolic acidosis. The average dosage is 1.9 mEq/kg/d and is adjusted based on the blood and urine pH. Young patients typically require higher doses due to their high growth rate[83]. Patients with type 1 RTA caused by vacuolar H^+-ATPase variants may require higher doses of alkali

Table 4 Genetic causes of different types of renal tubular acidosis

Gene involved	Inheritance	Location of gene	RTA type caused	Affected protein	Main clinical feature
SLC4A1 gene	AD AR	17q21-q22	Type 1 RTA	AE1	Type 1 RTA, hereditary spherocytosis
CA2 gene	AR	8q21.2	Type 1 RTA, type 3 RTA	CA II	Osteopetrosis, brain calcification, RTA
ATP6V1B1	AR	2q13	Type 1 RTA	H^+-ATPase	Sensorineural deafness
ATP6V0A4		7q33-q34			
SLC4A2 gene	AR	7q36.1	Type 2 RTA	AE2	PBC
SLC4A4 gene	AR	4q13.3	Type 2 RTA	(NBC)	Ocular abnormalities
SLC2A2 gene	AR	3q26.2	Type 2 RTA	GLUT2	Fanconi-Bickel syndrome, NIDDM
CLCN5 gene	X-linked recessive	Xp11.23	Type 2 RTA	H^+/Cl^- exchanger	Dent disease type 1, HHR
OCRL1 gene	X-linked recessive	Xq26.1.	Type 2 RTA	OCRL enzyme	Dent disease, type 2, LOCRS
NR3C2 (*MR*) gene	AD	4p	Type 4 RTA	MLR NRC	PHA1, hyperkalemia, salt wasting & hypotension
SCNN1A, *SCNN1B*, and *SCNN1G* genes	AR	SCNN1A (12p3). SCNN1B, & SCNN1G located in (16p12-p13)	Type 4 RTA	ENaC	Liddle syndrome, sodium loss from the kidneys and other organs, including the sweat glands, salivary glands, and colon

AD: Autosomal dominant; AE1: Anion exchanger 1 protein; AE2: Anion exchanger 2 protein; AR: Autosomal recessive; CA II: Carbonic anhydrase II; ENaC: Epithelial sodium channels located on the luminal membrane of the collecting tubule; GLUT2: Glucose transporter 2; HHR: Hereditary hypophosphatemic rickets; OCRL: Lowe oculocerebrorenal syndrome; MLR NRC: The mineralocorticoid receptor (or MR, MLR, MCR), also known as the aldosterone receptor or nuclear receptor subfamily 3, MR: Mineralocorticoid receptor, group C; NBC: Sodium bicarbonate cotransporter, which regulates bicarbonate secretion, absorption, and intracellular pH. NIDDM: Noninsulin-dependent diabetes mellitus, PBC: Primary biliary cirrhosis; PHA1: Primary pseudohypoaldosteronism type 1; RTA: Renal tubular acidosis.

Table 5 Comparison of different imaging modalities in nephrocalcinosis due to RTA

Modality	Advantages	Limitations
X-ray	Readily available; Cost-effective; Quick initial assessment; Suitable for detecting large, dense stones	Limited sensitivity for smaller or radiolucent stones; No detailed anatomical information
Ultrasound	Can be used to assess kidney size, shape, and echogenicity; Non-invasive; Real-time imaging; Widely available; Initial assessment of kidney stones and medullary cyst	Reduced sensitivity for smaller or deeply located calcifications; Limited anatomical details
CT	Excellent spatial resolution; Detailed cross-sectional images; Highly sensitive for detecting kidney stones and calcifications; Assesses impact on kidney function and urinary tract	Involves exposure to ionizing radiation; Contrast agents may be contraindicated in some patients; Not suitable for all patients due to contrast use
MRI	No ionizing radiation; Detailed images of the extent of calcification and surrounding soft tissue damage; Multiplanar imaging capability; Can provide information on tissue characteristics and perfusion	It may not be as readily available as other modalities; Limited sensitivity for detecting small or faint calcifications

CT: Computed tomography; MRI: Magnetic resonance imaging.

than those with heterozygous *SLC4A1* gene mutations[84]. A sustained-release granular form of potassium citrate and bicarbonate can be used in a 1:2 ratio to maintain normal serum bicarbonate levels[85]. This action improves urinary citrate, reduces the rate of nephrolithiasis, and ensures adequate growth in children[2]. Potassium citrate and additional potassium chloride are supplied as needed to correct hypokalemia. Thiazide diuretics, particularly hydrochlorothiazide, have been used to treat renal hypercalciuria and reduce the risk of nephrolithiasis[86]. The calcium/creatinine ratio can detect hypercalciuria and hypocitraturia, which may indicate inadequate correction of acidosis. In some cases, surgery may be necessary to remove kidney stones. Screening for sensorineural hearing loss during childhood is essential, and any issues should be monitored and treated accordingly[87].

When managing type 2 RTA, the primary goals are treating the root cause, correcting acidosis, promoting growth, and preventing bone deformities. These goals are typically achieved through oral bicarbonate supplements to compensate for urinary bicarbonate losses, with high doses of alkalies (10-15 mEq/kg/d)[88]. Depending on the severity, additional

measures may be necessary to address potassium and electrolyte imbalances. Potassium is administered at a dose of 1-5 mEq/kg/d, phosphate at a dose of 20-40 mg/kg/d, sodium at a dose of 3-5 mEq/kg/d, and magnesium at a dose of 25-50 mg/kg/d. Children with type 2 RTA usually require higher doses of bicarbonate therapy than those with type 1 RTA to maintain bicarbonate levels around the kidney threshold. In some cases, a potassium-sparing diuretic may be prescribed[3]. Vitamin D is vital in promoting calcium absorption and bone health. In type 1 RTA, the kidneys struggle to activate vitamin D, so active vitamin D supplementation in the form of calcitriol 20-40 ng/kg/day, combined with regular monitoring of urinary calcium levels and annual renal ultrasounds, is necessary to prevent nephrocalcinosis and osteoporosis[89]. Vitamin D supplementation may be unnecessary for type 2 RTA, as vitamin D activation is unaffected. However, vitamin D deficiency can induce type 2 RTA[90]. Nutritional intake should be monitored by specialized nutritionists, as children with RTA often have compromised nutritional status due to poor nutrient intake, polyuria, polydipsia, and increased sodium and nutrient loss. It is recommended to consume calorie-dense foods rich in potassium and phosphorus, along with sufficient fluids. Patients with RTA should consume less acidic foods, such as animal meat, and more alkaline-based foods, such as vegetables and fruits[1].

The treatment for type 3 RTA involves using alkaline therapy and addressing any specific underlying causes. In type 4 RTA, management requires controlling the underlying reason for the mineralocorticoid disorder. This may involve treating conditions like hyperaldosteronism or evaluating medication use[91]. Daily intake of 0.1 mg of fludrocortisone can effectively manage hyperaldosteronism-associated hyperkalemia. However, this is not generally recommended due to the high risk of hypertension, edema, and heart failure. Patients with hyperkalemia can effectively manage their condition by limiting their dietary potassium intake to 40 to 60 mEq daily and using diuretics such as loop or thiazide when necessary[92].

Nephrocalcinosis management in RTA should be tailored to each patient's specific condition, medical history, and the underlying cause of RTA. Since it is a progressive condition, it is crucial to start strategies to prevent, diagnose, and treat RTA-associated nephrocalcinosis early[93]. These early strategies and interventions can help control nephrocalcinosis and prevent it from producing severe complications. Encouraging adequate fluid intake can help dilute the urine, prevent the concentration and crystallization of calcium and other minerals in the urine, and reduce the risk of calcium deposition in the kidneys[24]. It is crucial to keep urinary calcium levels below < 0.1 mmol (< 4 mg)/kg and oxalate < 0.5 mmol (< 45 mg)/1.73 m^2 within 24 h of urine collection. Additionally, it is vital to keep urinary citrate levels above 1.9 mmol (365 mg)/1.73 m^2 in males and 1.6 mmol (310 mg)/1.73 m^2 in females within 24 h of urine collection[94].

Dietary adjustments should be made based on the type of RTA to prevent and treat nephrocalcinosis. Limiting calcium and oxalate intake is recommended to reduce the formation of kidney stones[95]. A low-sodium diet can also help decrease urinary calcium excretion, but sodium salts like sodium bicarbonate and citrate may increase calcium excretion and worsen stone disease[96]. Therefore, potassium bicarbonate or potassium citrate may be better alternatives, especially for patients with active calcium stone disease. In type 1 RTA, minimizing urinary potassium loss and correcting hypokalemia can alleviate or even reverse nephrocalcinosis, lowering the rate of calcium kidney stones and potentially correcting osteoporosis[97]. Reducing acidic and oxalate-rich foods like spinach, rhubarb, and beets can also be beneficial, but it is essential to consult a healthcare professional to avoid nutrient deficiencies[98]. Regular exercise and maintaining a healthy weight are also crucial in improving kidney function and reducing the risk of kidney stones. Lastly, avoiding passive smoking is essential in preventing nephrocalcinosis in children with RTA, as smoking can harm the kidneys[99].

Reviewing the medication chart, specifically for type 1 RTA, is important. Medications that can worsen nephrocalcinosis, such as carbonic anhydrase inhibitors, should be assessed and adjusted if needed[100]. Conversely, certain medications may help manage nephrocalcinosis depending on its severity and cause. For instance, thiazide diuretics can minimize calcium excretion in the urine, which could benefit specific cases of nephrocalcinosis[101]. Potassium-sparing diuretics, like amiloride, may help maintain blood potassium levels, especially when taking thiazide diuretics[102]. Pain management may be necessary for those experiencing kidney stone-related pain. Non-steroidal anti-inflammatory drugs or opioids are standard options for pain relief[103].

Regular monitoring of kidney function, electrolyte levels, and urinary calcium excretion is crucial for detecting any complications early, evaluating the effectiveness of the treatment, and identifying any progression of nephrocalcinosis [104]. Nephrocalcinosis can increase the likelihood of developing kidney stones, so preventive measures like dietary adjustments, increased fluid intake, and medication (such as potassium citrate) may be advised[66]. Genetic counselling can help provide information about inheritance patterns, assess the risk to family members, and guide family planning decisions for hereditary forms of RTA[105].

Prognosis of renal calcification in patients with RTA

The outlook for renal calcification in patients with RTA can differ depending on factors such as the type of RTA, underlying cause, extent of calcification, and treatment effectiveness. The type of RTA can impact the prognosis and management of renal calcification. For instance, type 1 RTA is usually linked with nephrocalcinosis and kidney stones[1]. Early detection of renal calcification and proper RTA management are crucial for a better prognosis. Treating the underlying acid-base imbalance, alkaline therapy, and controlling calcium excretion can help slow down the progression of nephrocalcinosis and prevent further kidney damage[106]. Nephrocalcinosis increases the risk of kidney stone formation, leading to recurrent kidney stone episodes and potential complications if not managed effectively. Preventive measures such as dietary adjustments, fluid intake, and medication can help reduce the risk of stone formation[107]. The extent of nephrocalcinosis and its impact on kidney function are vital in determining the prognosis. Extensive nephrocalcinosis can sometimes lead to chronic kidney disease and its associated complications. Identifying and treating the underlying cause of RTA and nephrocalcinosis are crucial[108]. For example, in type 1 RTA, potassium citrate or bicarbonate supplementation can help correct the acidosis and prevent stone formation. In type 2 RTA (proximal RTA), treatment may involve addressing the underlying cause, such as a genetic disorder or specific medications. Other medical

conditions or comorbidities can also impact the prognosis of nephrocalcinosis in RTA patients[109]. Managing these conditions alongside RTA and nephrocalcinosis is essential for overall health and outcomes. Regular monitoring and follow-up with healthcare providers are necessary for patients with RTA and renal calcification. Periodic evaluation of kidney function, imaging studies (*e.g.*, ultrasound and CT scans), and urine analysis can help assess the progression of the condition and guide treatment adjustments if needed[110]. The prognosis can vary significantly among individuals due to individual variability. It is important to recognize that early and comprehensive medical management is essential to optimize outcomes. Regular follow-up with healthcare providers, adherence to treatment plans, and lifestyle modifications can help improve the long-term prognosis for patients with nephrocalcinosis and RTA[111].

Limitations of the study

Several potential limitations could impact the reliability and generalizability of the study findings. There might be a limited number of studies and data available on renal calcification in children with RTA due to the relative rarity of this condition. This can reduce the included studies' sample size and statistical power, making it challenging to draw robust conclusions. In addition, the studies included in the review have differences in methodologies, patient populations, and definitions of renal calcification. This heterogeneity can make it challenging to compare and synthesize the results. We should also consider that RTA is not a single condition but rather a group of disorders with different underlying causes and manifestations. We should consider the variability in RTA types, their treatment approaches, and their potential impact on renal calcification. There is also a lack of longitudinal data and control groups in some studies, which limits our ability to fully understand the progression and impact of renal calcification on children with RTA. Furthermore, many studies included in the review may have been conducted in specific populations, which can limit the generalizability of the findings to other populations. Another significant limitation of the study is that we included studies published in English, which could result in the omission of important studies and potentially bias the results.

CONCLUSION

Our comprehensive review of the current literature underscores the significance of renal calcification as a critical concern for children with RTA. Our analysis reveals that renal calcification is a prevalent issue among children with RTA, with varying degrees of risk associated with different RTA types. Notably, type 1 RTA is frequently linked to nephrocalcinosis, emphasizing the importance of early detection and tailored management strategies for affected patients. While we acknowledge the limitations within the reviewed studies, such as the small number of available studies, methodological heterogeneity, and potential publication bias, they collectively emphasize the critical role of timely diagnosis and appropriate RTA management in reducing the risk of renal calcification and its associated complications. In particular, alkaline therapy remains a cornerstone treatment, effectively addressing the acid-base imbalance and minimizing the formation of kidney stones. To advance our understanding and guide clinical practice further, it is evident that future research efforts should focus on larger sample sizes, longitudinal data, and more rigorous methodologies. These endeavors will undoubtedly contribute to a more nuanced comprehension of the intricate relationship between RTA and renal calcification. By doing so, we can better inform treatment and prevention strategies, ultimately enhancing the long-term outcomes and quality of life for children affected by this condition.

ACKNOWLEDGEMENTS

We thank the anonymous referees and editors for their valuable suggestions.

FOOTNOTES

Author contributions: Al-Biltagi M developed the idea, collected the data, and wrote and revised the manuscript; Saeed NK, Bediwy AS, Hasan S, and Hamza MB collected the data and revised the manuscript from the laboratory aspect; Elbeltagi R collected the data, wrote the method section, and revised the manuscript.

Conflict-of-interest statement: All the authors declare that they have no conflict of interest to disclose.

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S-Editor: Liu JH

L-Editor: Wang TQ
P-Editor: Cai YX

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World Journal of Clinical Pediatrics

Submit a Manuscript: https://www.f6publishing.com

World J Clin Pediatr 2023 December 9; 12(5): 310-318

DOI: 10.5409/wjcp.v12.i5.310

ISSN 2219-2808 (online)

ORIGINAL ARTICLE

Case Control Study

Brain metabolic profile assessed by magnetic resonance spectroscopy in children with Down syndrome: Relation to intelligence quotient

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Specialty type: Pediatrics

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C
Grade D (Fair): D
Grade E (Poor): 0

P-Reviewer: Kaufman AS, United States

Received: July 17, 2023
Peer-review started: July 17, 2023
First decision: August 31, 2023
Revised: September 18, 2023
Accepted: September 28, 2023
Article in press: September 28, 2023
Published online: December 9, 2023

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Abstract

BACKGROUND

Down syndrome (DS) is one of the most common causes of intellectual disability. Children with DS have varying intelligence quotient (IQ) that can predict their learning abilities.

AIM

To assess the brain metabolic profiles of children with DS and compare them to standard controls, using magnetic resonance spectroscopy (MRS) and correlating the results with IQ.

METHODS

This case-control study included 40 children with DS aged 6-15 years and 40 age and sex-matched healthy children as controls. MRS was used to evaluate ratios of choline/creatine (Cho/Cr), N-acetyl aspartic acid/creatine (NAA/Cr), and myoinositol/creatine (MI/Cr (in the frontal, temporal, and occipital lobes and basal ganglia and compared to controls and correlated with IQ.

RESULTS
Children with DS showed significant reductions in NAA/Cr and MI/Cr and a non-significant reduction in Cho/Cr in frontal lobes compared to controls. Additionally, we observed significant decreases in NAA/Cr, MI/Cr, and Cho/Cr in the temporal and occipital lobes and basal ganglia in children with DS compared to controls. Furthermore, there was a significant correlation between IQ and metabolic ratios in the brains of children with DS.

CONCLUSION
Brain metabolic profile could be a good predictor of IQ in children with DS.

Key Words: Children; Down syndrome; Magnetic resonance spectroscopy; Metabolic profile; Intelligence quotient

Core Tip: This study compared the brain metabolic profiles of children with Down syndrome (DS) using magnetic resonance spectroscopy to healthy controls. The results showed significant reductions in specific metabolic ratios (N-acetyl aspartic acid/creatine and myoinositol/creatine) in the frontal lobes of children with DS compared to controls, as well as decreases in these ratios in the temporal and occipital lobes and basal ganglia. The study also found a significant correlation between intelligence quotient (IQ) and metabolic ratios in children with DS. These findings suggest that brain metabolic profiling could be a valuable predictor of IQ in children with DS.

Citation: El Feil NS, Elmahdy HS, Elmahdy RA, Aboelezz AAE, Dawoud HS, Al-Beltagi M. Brain metabolic profile assessed by magnetic resonance spectroscopy in children with Down syndrome: Relation to intelligence quotient. *World J Clin Pediatr* 2023; 12(5): 310-318
URL: https://www.wjgnet.com/2219-2808/full/v12/i5/310.htm
DOI: https://dx.doi.org/10.5409/wjcp.v12.i5.310

INTRODUCTION

Down syndrome (DS) is the most prevalent chromosomal disorder in humans and one of the leading causes of intellectual disability. It arises from the presence of an additional chromosome 21[1]. Children with DS exhibit various physical dysmorphic features affecting nearly every part of their bodies[2]. DS is a systemic disorder that impacts all body systems, particularly the central nervous system. Individuals with DS experience cognitive impairment and a range of conditions related to speech, language, and motor functions. They also face an elevated risk of early-onset dementia and Alzheimer's disease (AD)[3]. Two hypotheses have been proposed to elucidate the pathogenesis of DS: Developmental instability resulting from chromosomal imbalance loss and the gene-dosage effect[4]. According to the gene-dosage effect hypothesis, the genes located on chromosome 21 are overexpressed in the cells and tissues of DS patients, contributing to various phenotypic abnormalities[5].

Magnetic resonance (MR) spectroscopy (MRS) is an analytical technique used to quantify metabolites. Unlike conventional MR imaging (MRI), MRS provides physiological and chemical information rather than anatomical details[6]. Proton MRS (1 H-MRS) is widely employed to characterize brain neurochemical changes associated with health and disease. N-acetyl aspartic acid (NAA) is a derivative of aspartic acid primarily synthesized and stored in neurons. Therefore, it is a marker for neuronal density and viability[7]. As a neuronal marker, the concentration of NAA decreases in conditions such as extensive brain lesions, dementia, hypoxia, or multiple sclerosis, where neuronal destruction occurs[8]. Total creatine (Cr) reflects the amount of phosphocreatine and Cr present in neurons and glial cells. It appears as a prominent peak at 3.0 ppm in MR spectra, with an additional peak for Cr possibly visible at 3.94 ppm[9]. Cr remains relatively constant in the brain's energetic cellular metabolism and is often used as a reference metabolite for *in vivo* MRS. For instance, it is frequently employed in the calculation of metabolite ratios such as choline (Cho)/Cr, NAA/Cr, and myoinositol (MI)/Cr[10].

Cho serves as an indicator of cellular proliferation and cell membrane integrity. Increased choline levels reflect heightened synthesis and degradation of cell membranes[11]. MI functions as a marker primarily synthesized in glial cells. Elevated MI levels are often observed in cerebral diseases associated with significant gliosis[12]. Metabolic abnormalities, specifically elevated MI levels, have been observed throughout development in mouse models of DS and the brains of children and adults with DS. However, there is a scarcity of studies investigating brain metabolism during early childhood[13].

The intelligence quotient (IQ) is critical in assessing the neurological and cognitive development of children with DS. It may also reflect their physical and somatic growth, as documented by Kłosowska *et al*[14]. Therefore, establishing a connection between the brain's metabolic profiles and IQ in children with DS could provide insights into the underlying reasons for this relationship and aid in developing strategies to improve their IQ. Limited research has been conducted on elucidating metabolic changes in the developing brains of children with DS. Hence, this study aims to evaluate the brain's metabolic profile using MRS in children with DS, comparing it with normal controls and examining the correlation

between this metabolic profile and IQ.

MATERIALS AND METHODS

This case-control study was conducted between April 2019 and April 2021, involving a patient group of 60 children with DS. Out of these, 40 children completed the study. We also included a control group of 40 healthy children, matched in age and sex. The age range of the participating children was between 6 and 15 years. We recruited the children from the Outpatient Clinic of the Genetics Unit, Pediatric Department, at Tanta University in Egypt. The diagnosis of DS was based on clinical findings and confirmed through karyotyping. A comprehensive medical history was obtained, including demographic data, prenatal, natal, postnatal, family, and developmental history. Thorough clinical and psychiatric evaluations were performed as well. All patients underwent thyroid function tests, echocardiography, and glycated hemoglobin (HbA1c) measurements. We utilized the Stanford-Binet Intelligence Scales, Fifth Edition, to assess the IQ of the study groups. Cases with diseases that could potentially influence the results or pose risks during the MRS procedure were excluded. Exclusion criteria encompassed complex congenital heart disease, congenital neurological abnormalities, a history of perinatal asphyxia, suspected metabolic disease, epilepsy, attention deficit hyperactivity disorder, autistic spectrum disorders, and conditions that precluded MRI scans, such as the presence of metal devices like pacemakers, defibrillators, orthodontic braces, implants, or severe claustrophobia. Patients with known endocrine disorders like hypothyroidism or diabetes mellitus were excluded from the study. Ethical approval for this research was obtained from the Faculty of Medicine Ethics Committee, Tanta University. Written informed consent was acquired from the legal guardians of both patients and controls before the imaging procedure. The study adhered to the principles of the Declaration of Helsinki and good clinical practice. No adverse physiological effects resulting from the main magnetic field are known. Furthermore, no unexpected risks emerged during the research.

MRS study

The MRS studies were conducted at the Radiology Department of Tanta University in Egypt. A 1.5 Tesla system (Signa; GE Medical Systems, Milwaukee, WI, United States) with a quadrature head coil was used for all MRI and 1H-MRS procedures. Before the examination, the children were sedated using chloral hydrate at 25-100 mg/kg (maximum 2 g).

Initially, a conventional MRI scan was performed, followed by placing the voxel at various positions. Water suppression and the point-resolved spectroscopy methods were then employed, with a Time to Echo of 135 msec and a Repetition Time of 1500 msec. The NAA, Cho, MI, and Cr spectra were analyzed, and ratios for Cho/Cr, NAA/Cr, and MI/Cr were calculated in the frontal, temporal, occipital lobes, and basal ganglia. These ratios were compared between the patients and controls. NAA serves as an indicator of neuronal integrity, with its peak occurring at 2.02 ppm. Cho reflects cell turnover, with its highest point at 3.22 ppm. Cr is involved in cellular metabolism and peaks at three ppm. Normally, no lipid or lactate peak is observed in the brain; even if present, they overlap at 1.33 ppm[15].

Oxygen saturation, heart rate, and temperature were continuously monitored during the scan, and a skilled pediatrician was present for all examinations. The total examination time for each child did not exceed one hour. The child lay supine with their head positioned in the head coil, which was surrounded by a lunar pillow to minimize the sound from the magnetic field. Subsequently, the patient and coil were moved into the magnetic bore.

Statistical analysis

The study's power level was estimated using The Power and Precision V3 program (http://www.Power-Analysis.com, Englewood, New Jersey). The collected data were organized, tabulated, and subjected to statistical analysis using the SPSS version 19. For parametric variables, the mean and standard deviation were calculated. A comparison of mean values between the cases and controls was conducted using an unpaired Student's *t*-test, assuming equal variance in the two populations. Nonparametric variables were analyzed by calculating the number and percentage. The chi-square test was employed to compare different observations of categorical variables. Pearson's correlation coefficient was utilized to examine the association between two variables. A P value less than 0.01 was considered statistically significant after applying the Bonferroni correction of multiple comparisons to avoid any spurious significance and to mitigate the risk of Type I errors associated with multiple comparisons.

RESULTS

Table 1 illustrates the study's demographics. Sixty children with DS were initially recruited for the study, but 20 were excluded due to missed follow-up, inability to participate, or refusal to do an MRI. Ultimately, the study included 40 children with DS and 40 healthy children who completed the study. There were no significant differences in age, sex, and mean IQ between the excluded and included children with DS. Table 1 presents the demographic data of the included children. The patient group had an age range of 6-15 years, with a mean of 10.85 ± 2.7, while the control group ranged from 5-17 years, with a mean of 10.70 ± 2.6. Among the children with DS, 28 were males, and 12 were females, resulting in a male-to-female ratio of 1.4:1. The control group consisted of 24 males and 16 females, with a male-to-female ratio of 1.5:1. There were no significant differences in age and sex between the two groups. All included children with DS had the non-disjunction type of DS. The IQ was significantly lower in children with DS (68.45 ± 6.11) compared to the controls (96.73 ± 2.68), with a P value < 0.001.

Table 1 Demographic data and intelligence quotient of children with Down syndrome and their controls

	DS (*n* = 40)	Controls (*n* = 40)	*P* value
Age (yr, mean ± SD)	10.85 ± 2.72	10.70 ± 2.64	0.87
Sex, *n* (%)			0.24
Male	28 (70%)	26 (65%)	
Female	12 (30%)	14 (35%)	
IQ (mean ± SD)	68.45 ± 6.11	96.73 ± 2.68	0.001[1]

[1]*P* < 0.01 is significant.

DS: Down syndrome; IQ: Intelligence quotient.

Table 2 presents the metabolic profile of the studied groups. It revealed a significant reduction in NAA/Cr and MI/Cr ratios (*P* value < 0.001) and a non-significant reduction in the Cho/Cr ratio in the frontal lobe of children with DS compared to the controls. Furthermore, children with DS exhibited non-significant reductions in NAA/Cr (*P* < 0.05), Cho/Cr, and MI/Cr ratios in the temporal and occipital lobes compared to the control group. The occipital lobe showed the highest significant reduction in MI/Cr ratio (*P* value < 0.001). In addition, the basal ganglia exhibited the most substantial reduction in NAA/Cr, Cho/Cr, and MI/Cr ratios in children with DS compared to the control group.

Figures 1-3 display the correlation between IQ and various metabolic ratios. There was a statistically significant positive correlation between IQ and NAA/Cr ratio in the frontal lobe and Cho/Cr ratio in the temporal lobe among children with DS. Conversely, a statistically significant negative correlation existed between IQ and Cho/Cr ratio in the occipital lobe among children with DS, as shown in Table 3. The IQ was primarily influenced by NAA/Cr in the frontal lobe, Cho/Cr in the temporal lobe, and Cho/Cr in the occipital lobe in order of significance. Regression analysis for frontal NAA/Cr and IQ demonstrated a *P* value of < 0.001. However, the multivariate analysis presented in Table 4 showed that frontal Naa/Cr and temporal Cho/Cr had the most significant correlation with IQ.

DISCUSSION

The current study demonstrated a significant reduction in IQ among children with DS (55-75) compared to normal children. This is consistent with previous research, including Rachidi and Lopes's[3] study, which indicated that cognitive impairment is consistently observed in all individuals with DS. Most children and adults with DS exhibit mild to moderate intellectual disability, with an average IQ score of around 50 and individual values ranging from 30 to 70. Approximately 10% of individuals with DS fall within the low average borderline range of intellectual disability, while a minority have severe intellectual disability. The exact mechanisms underlying brain development in DS remain poorly understood. Still, multiple volumetric MRI studies have been conducted to gain further insights into the brain characteristics of individuals with DS. Several neuroimaging studies have reported reductions in total brain volume, as demonstrated by Beacher *et al*[16] in 2010, who observed volume reductions in the cerebrum, cerebellum, hippocampus, brain stem, and frontal lobes.

Our study calculated ratios for Cho/Cr, NAA/Cr, and MI/Cr in the frontal, temporal, occipital lobes, and basal ganglia, comparing the patient and control groups. We found a significant reduction in NAA/Cr and MI/Cr ratios in the frontal lobe, with a non-significant reduction in Cho/Cr among children with DS compared to the control group. This finding aligns with the study by Smigielska-Kuzia and Sobaniec[15], who investigated 34 children (14 with DS and 20 healthy children) and reported decreased Glx/Cr, NAA/Cr, Cho/Cr, and MI/Cr in patients with DS, with the first two markers showing a statistically significant difference. Lamar *et al*[17] also found a reduction in the absolute concentration of NAA in the frontal, temporal, and occipital lobes in patients with DS and AD. However, Shonk *et al*[18] detected elevated MI in adult patients with DS and AD compared to DS patients without AD. This difference could be attributed to our study's age range (6-15 years), as AD development may be associated with aging in DS.

Additionally, we observed a significant reduction in NAA/Cr, Cho/Cr, and MI/Cr ratios in the temporal lobe of children with DS compared to the control group. This finding agrees with Śmigielska-Kuzia *et al*[19] in 2010, who conducted a study on 40 children (20 with DS and 20 healthy children) and reported a statistically significant decrease in NAA/Cr, Cho/Cr, MI/Cr, and GABA/Cr.

Furthermore, a significant reduction in NAA/Cr, Cho/Cr, and MI/Cr ratios in the basal ganglia was observed in children with DS relative to the control group. This finding is consistent with a previous report by Fruen and Lester[20] in 1990, which described an increased MI/Cr ratio in adults with DS. The increased MI levels in brain tissue may be attributed to an extra *SLC5A3* gene in trisomic 21 cells, responsible for inositol transporter synthesis. These co-transporters regulate MI concentration in DS cortical cells. The results of the Fruen and Lester's[20] study and our study suggest that individuals with DS, whether demented or not, exhibit altered neuron-glial metabolism (reduced NAA and increased MI). Lin *et al*[21] found that this metabolic shift was more pronounced in DS individuals with dementia compared to those without dementia.

Table 2 Brain metabolite ratios of children with down syndrome and controls

Brain metabolite ratios (mean ± SD)	DS (*n* = 40)	Controls (*n* = 40)	*P* value
Frontal lobe			
NAA/Cr	1.19 ± 0.44	1.788 ± 0.273	0.001[1]
Cho/Cr	1.03 ± 0.40	1.08 ± 0.187	0.473
MI/Cr	0.56 ± 0.21	1.50 ± 0.47	0.001[1]
Temporal lobe			
NAA/Cr	1.26 ± 1.19	1.75 ±0.21	0.011
Cho/Cr	0.71 ± 0.30	1.07 ±0.16	0.001[1]
MI/Cr	0.41 ± 0.19	1.40 ±0.56	0.001[1]
Basal ganglia			
NAA/Cr	1.21 ± 0.55	1.78 ± 0.19	0.001[1]
Cho/Cr	0.68 ± 0.33	1.06 ± 0.17	0.001[1]
MI/Cr	0.35 ± 0.17	1.50 ± 0.54	0.001[1]
Occipital lobe			
NAA/Cr	1.72 ± 0.49	1.92 ± 0.34	0.033
Cho/Cr	0.83 ± 0.35	0.99 ± 0.14	0.011
MI/Cr	0.44 ± 0.17	1.48 ± 0.54	0.001[1]

[1]*P* < 0.01 is significant.
Cho: Choline; Cr: Creatine; DS: Down syndrome; MI: Myoinositol; Naa: N-acetyl aspartate.

Table 3 Correlation between intelligence quotient and the brain metabolite ratios in children with down syndrome

Correlations with IQ	*r*	*P* value
F NAA/Cr	0.533	< 0.001[1]
F Cho/Cr	-0.210	0.193
F MI/Cr	-0.259	0.107
T NAA/Cr	0.215	0.182
T Cho/Cr	0.330	0.037
T MI/Cr	-0.018	0.913
BG NAA/Cr	0.100	0.541
BG Cho/Cr	0.105	0.518
BG MI/Cr	0.008	0.961
O NAA/Cr	0.091	0.578
O Cho/Cr	-0.346	0.029
O MI/Cr	0.215	0.184

[1]*P* < 0.01 is significant.
BG: Basal ganglia; Cho: Choline; Cr: Creatine; DS: Down syndrome; F: Frontal; IQ: Intelligence quotient; MI: Myoinositol; NAA: N-acetyl aspartate; O: Occipital; T: Temporal.

In the occipital lobe, we found a significant reduction in NAA/Cr, Cho/Cr, and MI/Cr ratios among children with DS compared to the control group. This is consistent with a case-control study by Shonk and Ross[22] in 1995, which included 23 young DS patients without dementia, revealing elevated MI levels. They also reported one patient with DS and dementia who exhibited high MI but decreased NAA in the occipital cortex and parietal white matter. The decreased NAA findings align with our study, although our results differ from theirs regarding MI. This discrepancy could be attributed to age differences. NAA indicates brain maturation, dendritic and synaptic development, and oligodendroglial

Table 4 Multivariate analysis of the brain metabolite ratios that significantly affect intelligence quotient in children with down syndrome

	Unstandardized coefficients		Standardized coefficients	*t* value	*P* value
	B	SE	Beta		
F NAA/Cr	10.123	2.260	0.726	4.480	< 0.001[1]
T Cho/Cr	10.950	3.347	0.541	3.272	0.002[1]
O Cho/Cr	5.695	3.391	0.324	1.679	0.102

[1]*P* < 0.01 is significant.

Dependent variable: IQ; Cho: Choline; Cr: Creatine; F: Frontal; IQ: Intelligence quotient; NAA: N-acetyl aspartate; O: Occipital; T: Temporal.

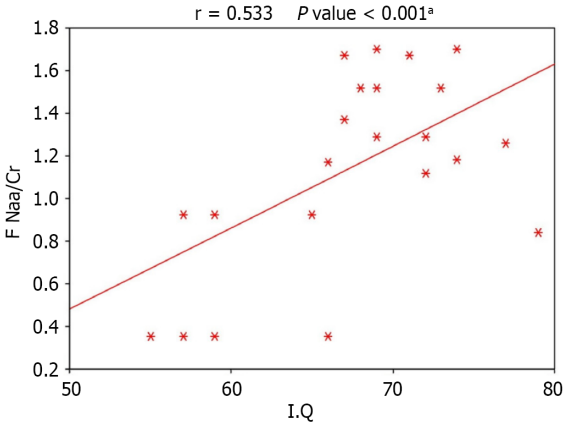

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Figure 1 Correlation between intelligence quotient and N-acetyl aspartate/creatine ratio in the frontal lobe of the Down syndrome group. IQ: Intelligence quotient; NAA/Cr ratio: N-acetyl aspartate/creatine ratio.

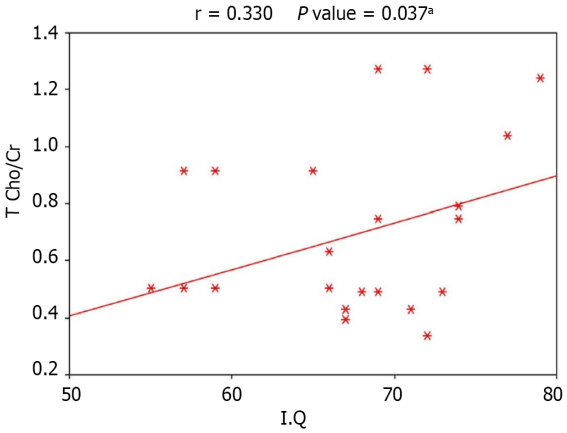

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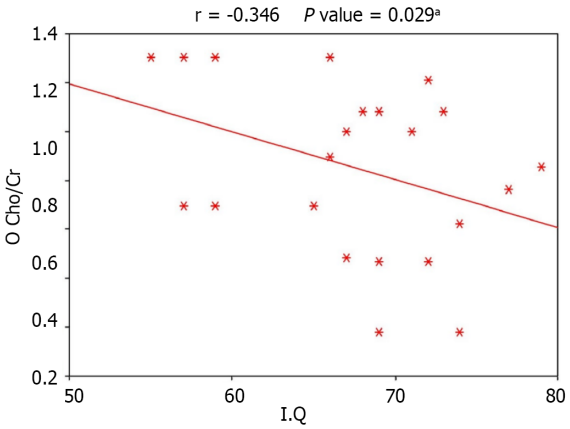
Figure 2 Correlation between intelligence quotient and choline/creatine ratio in the temporal lobe of the Down syndrome group. Cho/Cr: Choline/creatine; IQ: Intelligence quotient.

proliferation and differentiation (Kato *et al*[23], 1997). Previous studies in adults with DS have reported lower NAA ratios compared to healthy controls[18,21]. The observed decrease in NAA/Cr ratios in different brain regions among children with DS in our study suggests reduced brain maturation in these individuals.

Our research demonstrated that frontal NAA/Cr had the most significant correlation with IQ, followed by T Cho/Cr, while O Cho/Cr had the least effect. To the best of our knowledge, only one previous study utilized MRS to evaluate brain metabolites in children with DS. Due to the scarcity of studies in the literature, we could not find extensive data for comparison.



DOI: 10.5409/wjcp.v12.i5.310

Figure 3 Correlation between intelligence quotient and choline/creatine ratio in the occipital lobe of the Down syndrome group. Cho/Cr: Choline/Creatine ratio, DS: Down Syndrome, IQ: Intelligence quotient.

Limitation of the study

The study is subject to certain limitations, including a relatively small sample size and being conducted at a single center. Our study is mainly exploratory and should be followed by confirmatory studies to validate the observed associations. It would also be valuable to examine the correlation between the metabolic profile and the patient's medical conditions, parents' educational levels, and developmental milestones. Assessing any changes in the metabolic profile resulting from occupational and behavioral therapy could provide insights into improving IQ and promoting self-independence in children with DS. It is recommended to conduct future studies with larger sample sizes to better understand the DS brain's intricacies. Moreover, longitudinal studies involving adolescents and adults with DS, both with and without dementia, would be beneficial in monitoring metabolite changes and their impact on the mental health of patients with DS, particularly those who develop early-onset dementia. In addition, we would like to emphasize that the correlation of IQ to metabolic ratios in the brain does not imply causality. Correlations only establish relationships. We also acknowledge that our study design did not include a separate group of low-functioning children without DS for direct comparison. We will consider this point in the coming research. Adding such a group would have provided a valuable reference point for evaluating whether the observed differences in brain metabolic profiles and their correlation with IQ are specific to DS or could apply to low-functioning children in general.

CONCLUSION

The brain's metabolic profile in children with DS exhibits differences compared to typically developing children. Additionally, specific brain areas show positive and negative correlations between IQ and specific metabolic ratios. Thus, the brain's metabolic profile could serve as a predictor of IQ in children with DS.

ARTICLE HIGHLIGHTS

Research background

Down syndrome (DS) is the most prevalent chromosomal disorder in humans and one of the leading causes of intellectual disability. Magnetic resonance (MR) spectroscopy (MRS) is an analytical technique used to quantify metabolites. Proton MRS (1 H-MRS) is widely employed to characterize brain neurochemical changes associated with health and disease. N-acetyl aspartic acid (NAA) is a derivative of aspartic acid primarily synthesized and stored in neurons. Therefore, it is a marker for neuronal density and viability.

Research motivation

Establishing a connection between the brain's metabolic profiles and intelligence quotient (IQ) in children with DS could provide insights into the underlying reasons for this relationship and aid in developing strategies to improve their IQ.

Research objectives

We aimed to evaluate the brain's metabolic profile using MRS in children with DS, comparing it with that of normal controls and examining the correlation between this metabolic profile and IQ.

Research methods

The study was a case-control study that included sixty children with DS and forty healthy controls. IQ was assessed using Stanford-Binet Intelligence Scales, Fifth Edition. A conventional MR imaging scan followed by point-resolved spectroscopy was performed for all the participants.

Research results

Children with DS showed significant reductions in NAA/creatine (Cr) and myoinositol (MI)/Cr and a non-significant reduction in choline (Cho)/Cr in frontal lobes compared to controls. Additionally, we observed significant decreases in NAA/Cr, MI/Cr, and Cho/Cr in the temporal and occipital lobes and basal ganglia in children with DS compared to controls. Furthermore, there was a significant correlation between IQ and metabolic ratios in the brains of children with DS.

Research conclusions

Brain metabolic profile could be a good predictor of IQ in children with DS.

Research perspectives

To generalize our results, the authors must include a larger sample size and perform a multicentre study. We also need to include another group with low IQ for different reasons to investigate the unique features of brain metabolic profiles in children with DS.

ACKNOWLEDGEMENTS

We thank the parents and children who participated in this study. We also thank the editors and the reviewers for their efforts to improve the quality of the study.

FOOTNOTES

Author contributions: Dawoud HS provided the research idea and initiated the study design; El-Feil SE and El Mahdy HS collected the patients and their information; Aboelezz AA was responsible for statistical analysis; Elshafey RA was responsible for the technical part of the study; Also, Elshafey RA oversaw imaging and data analysis; Al-Biltagi M analyzed the data and revised the manuscript. All the authors revised and agreed on the final version of the manuscript.

Institutional review board statement: We performed the study according to the latest version of Helsinki's Declaration. The Institutional Ethical and Research Review Board of Faculty of Medicine, Tanta University, approved the study.

Informed consent statement: All parents, guardians, or next of kin signed informed consent for the minors to participate in this study.

Conflict-of-interest statement: The authors declare no conflict of interest for this article.

Data sharing statement: Data are available upon reasonable request.

STROBE statement: The authors have read the STROBE statement, and the manuscript was prepared and revised according to the STROBE statement.

Country/Territory of origin: Egypt

ORCID number: Mohammed Al-Beltagi 0000-0002-7761-9536.

S-Editor: Lin C
L-Editor: A
P-Editor: Zhang XD

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World Journal of Clinical Pediatrics

Submit a Manuscript: https://www.f6publishing.com

World J Clin Pediatr 2023 December 9; 12(5): 319-330

DOI: 10.5409/wjcp.v12.i5.319

ISSN 2219-2808 (online)

ORIGINAL ARTICLE

Retrospective Study

Clinical factors predicting rotavirus diarrhea in children: A cross-sectional study from two hospitals

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Specialty type: Gastroenterology and hepatology

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Dauyey K, Kazakhstan; Viswanathan VK, United States

Received: July 19, 2023
Peer-review started: July 19, 2023
First decision: August 31, 2023
Revised: September 7, 2023
Accepted: September 25, 2023
Article in press: September 25, 2023
Published online: December 9, 2023

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Abstract

BACKGROUND

Rotavirus is still a significant contributing morbidity and mortality in pediatric patients.

AIM

To look at clinical signs and symptoms and laboratory findings that can predict rotavirus gastroenteritis compared to non-rotavirus gastroenteritis.

METHODS

This was a cross-sectional study with medical records obtained from December 2015 to December 2019. Inclusion criteria for this study include all hospitalised pediatric patients (0-18 years old) diagnosed with suspected rotavirus diarrhea. The receiver operating curve and Hosmer-Lemeshow test would be used to assess the final prediction findings' calibration (goodness of fit) and discrimination performance.

RESULTS

This study included 267 participants with 187 (70%) rotavirus-diarrhea cases. The patients were primarily male in both rotavirus (65.2%) and non-rotavirus (62.5%) groups. The median age is 1.33 years old (0.08-17.67 years old). Multivariate analysis shows that wet season (OR_{adj} = 2.5; 95%CI: 1.3-4.8, P_{adj} = 0.006), length of stay (LOS) ≥ 3 days (OR_{adj} = 5.1; 95%CI: 1.4-4.8, P_{adj} = 0.015), presence of abdominal pain (OR_{adj} = 3.0; 95%CI: 1.3-6.8, P_{adj} = 0.007), severe dehydration (OR_{adj} = 2.9; 95%CI: 1.1-7.9, P_{adj} = 0.034), abnormal white blood cell counts (OR_{adj} = 2.8; 95%CI: 1.3-6.0, P_{adj} = 0.006), abnormal random blood glucose (OR_{adj} = 2.3; 95%CI: 1.2-4.4, P_{adj} = 0.018) and presence of fecal leukocytes (OR_{adj} = 4.1, 95%CI: 1.7-9.5, P_{adj} = 0.001) are predictors of rotavirus diarrhea. The area under the curve for this model

is 0.819 (95%CI: 0.746-0.878, *P* value < 0.001), which shows that this model has good discrimination.

CONCLUSION
Wet season, LOS ≥ 3 d, presence of abdominal pain, severe dehydration, abnormal white blood cell counts, abnormal random blood glucose, and presence of fecal leukocytes predict rotavirus diarrhea.

Key Words: Rotavirus; Pediatric; Gastroenteritis; Diarrhea; Indonesia

Core Tip: Rotavirus gastroenteritis accounted for 19.11% of diarrheal deaths worldwide in 2019 and is still a leading cause of morbidity and mortality, especially in children under five. This cross-sectional study involving 267 children found that wet season (OR_{adj} = 2.5; 95%CI: 1.3-4.8, P_{adj} = 0.006), length of stay ≥ 3 d (OR_{adj} = 5.1; 95%CI: 1.4-4.8, P_{adj} = 0.015), presence of abdominal pain (OR_{adj} = 3.0; 95%CI: 1.3-6.8, P_{adj} = 0.007), severe dehydration (OR_{adj} = 2.9; 95%CI: 1.1-7.9, P_{adj} = 0.034), abnormal white blood cell counts (OR_{adj} = 2.8; 95%CI: 1.3-6.0, P_{adj} = 0.006), abnormal random blood glucose (OR_{adj} = 2.3; 95%CI: 1.2-4.4, P_{adj} = 0.018) and presence of fecal leukocytes (OR_{adj} = 4.1, 95%CI: 1.7-9.5, P_{adj} = 0.001) are predictors of rotavirus diarrhea.

Citation: Indrawan M, Chendana J, Handoko TGH, Widjaja M, Octavius GS. Clinical factors predicting rotavirus diarrhea in children: A cross-sectional study from two hospitals. *World J Clin Pediatr* 2023; 12(5): 319-330
URL: https://www.wjgnet.com/2219-2808/full/v12/i5/319.htm
DOI: https://dx.doi.org/10.5409/wjcp.v12.i5.319

INTRODUCTION

Rotavirus gastroenteritis accounted for 19.11% of diarrheal deaths worldwide in 2019 and is still a leading cause of morbidity and mortality, especially in children under five. Surveillance data from 2008-2018 showed that 40.78% of all diarrheal diseases in children in Southeast Asia were attributable to rotavirus infection[1]. The fecal-oral transmission from person-to-person contact or ingestion of fecally contaminated food and water commonly leads to a rapid spread among communities, especially in developing countries[2].

When diagnosing gastroenteritis, it is necessary to analyse fecal specimens using widely available assays because rotavirus-caused gastroenteritis cannot be clinically distinguished from that caused by other enteric pathogens[3]. However, because the findings do not change clinical management, which primarily depends on effective rehydration therapy, rotavirus is not routinely tested for in patients with gastroenteritis[4]. Despite its worldwide prevalence, detecting rotavirus in stool samples is still a logistical and financial challenge in developing countries[5].

Considering the disease burden, it is essential to know reliable clinical signs and symptoms and other non-confirmatory laboratory tests that clinicians can use to guide their treatment. Hence, this study aims to look at clinical signs and symptoms and laboratory findings that can predict rotavirus gastroenteritis compared to non-rotavirus gastroenteritis.

MATERIALS AND METHODS

This study was cross-sectional, with medical records obtained from December 2015 to December 2019 from Siloam General Hospital and Siloam Hospital Lippo Village (SHLV). Patients covered by Indonesia's national health insurance can receive care at Siloam General Hospital, a teaching hospital. SHLV, on the other hand, primarily consists of patients who are self-paying or have private insurance. Inclusion criteria for this study include all hospitalised pediatric patients (0-18 years old) diagnosed with suspected rotavirus diarrhea, defined as the passing of ≥ 3 watery or loose stools each day [6]. Children who have previously experienced significant immunosuppression due to prolonged steroid usage or illnesses like the human immunodeficiency virus or primary immunodeficiency were excluded from this study. Another exclusion criterion was the presence of concurrent infections such as urinary tract infections or pneumonia. The sample size calculation used the following formula:

$$N = \frac{z^2(pq)}{e^2} \quad (1)$$

Where N is the sample size, z denotes the standard error, which was 1.96, p was the estimated prevalence in the population, q was 100-p, and e was the acceptable sample error set at 6% in this study. The prevalence of pediatric rotavirus diarrhea in Indonesia is 37.5% to 53.5%[7]. Hence, the minimum sample size required was 265 children.

We collected demographic data such as age, gender, and nutritional status. Clinical signs such as temperature upon arrival, vital signs, clinical manifestations (abdominal pain, respiratory symptoms, dehydration status according to World Health Organization (WHO)[6], duration and frequency of symptoms (diarrhea, vomiting, fever), length of stay (LOS),

treatment given during hospitalisation [intravenous (IV) rehydration and any antibiotics], rotavirus vaccination status, as well as the seasons during which the children contracted diarrhea. The need for IV rehydration represented severe dehydration in this study. Meteorology Climatology and Geophysics Council's data in 2017 were used to determine the seasons where October – February was the rainy season, and the rest was the dry season in Tangerang[8]. We adhered to WHO 2006 growth chart for children below five years, while the Centers for Disease Control and Prevention 2000 growth charts were used for children aged 5-18 years old to classify nutritional status[9]. We did not collect any data on zinc used for diarrhea as all children were given zinc for diarrhea as per standard protocol in our hospitals. Lastly, we collected laboratory findings such as complete blood count, serum electrolytes, random blood glucose, erythrocyte sedimentation rate (ESR), and urinary ketone for dehydration markers and fecal leukocytes[10]. We present laboratory values dichotomously (normal *vs* abnormal values) for multivariate analysis and in numerical forms for descriptive purposes. The reference range will be based on our population study's mean or median age group.

The neutrophil-lymphocyte ratio (NLR) is obtained by dividing the total band and segmented neutrophil by the lymphocyte. In contrast, the monocyte-lymphocyte ratio is obtained by dividing the monocyte by the lymphocyte. Absolute neutrophil count is calculated with the formula as follows: (Total WBC × % [PMNs + bands]) ÷ 100.

While the absolute lymphocyte count is calculated with the formula: WBC count × 1000 × % lymphocyte. (NLR were obtained by dividing the total neutrophils by lymphocyte counts, and the same methodology was applied to obtain lymphocyte-to-monocyte ratio (LMR) and platelet-to-lymphocyte ratio (PLR)[11]. One or two ccs of peripheral venous blood samples were collected by antecubital venipuncture into vacutainer tubes (Becton Dickinson, Rutherford, NJ, United States) containing tri potassium ethylenediaminetetraacetic acid. The complete blood count was done within one to two hours after the blood samples were drawn, and the analysis was performed using the Advia 2120i automated analyser (Siemens Healthcare Diagnostics, Deerfield, IL, United States). Erythrocyte sedimentation rate levels were measured by TEST 1 (Alifax, Padova, Italy). The rotavirus analysis was done using immunochromatography (Alcore One-Step Rotavirust Test). Those who tested positive would be categorised as having rotavirus diarrhea, and those who tested negative would be categorised as having non-rotavirus diarrhea. Strict quality control procedures were adopted. All of the independent variables were chosen based on previous studies[7,12,13].

The data was processed using IBM SPSS 26.0 (Statistical Package for the Social Sciences, IBM Corp., Armonk, NY, United States). After a normality test, data with a normal distribution will be presented as mean and standard deviation. If not, the median and range will be applied. The Mann-Whitney-U test is used when the distribution of numerical data is non-normal, while the T-test is used when the distribution of numerical data is normal. Chi-square was used for bivariate analysis, and variables with p-values less than 0.25 would be used in multivariate logistic regression analysis. The receiver operating curve (ROC) and Hosmer-Lemeshow test would be used to assess the final prediction findings' calibration (goodness of fit) and discrimination performance. The area under the curve (AUC) is equal to 0.5 when the ROC curve represents chance, and it is equal to 1.0 when the ROC curve represents accuracy. A good calibration would be indicated by a *P* value > 0.05. The sensitivity and specificity of the various predictor variables in identifying non-severe and severe pneumonia were then calculated using the area under the curve. We also analysed casewise diagnostics to identify any outliers.

This study protocol was approved by the Committee on Ethics at the University of Pelita Harapan, Tangerang, Indonesia, with Code Ethic No. 430/FK-UPH/Ext./V/2019. The ethical board exempted informed consent due to the retrospective nature of our study. Identities were removed entirely, and data were analysed anonymously.

RESULTS

Descriptive characteristics

This study included 267 participants with 187 (70%) rotavirus-diarrhea cases (Table 1). The patients were primarily male in both rotavirus (65.2%) and non-rotavirus (62.5%) groups. The median age is 1.33 years old (0.08-17.67 years old), with the majority belonging to the 0-11 mo old category (34.5%). Most patients had good nutritional status in the non-rotavirus group (51.3%) and rotavirus group (53.5%). Most rotavirus cases occurred during the dry season (77.1%), while non-rotavirus cases occurred mainly in the wet seasons (37.8%) with an odds ratio (OR) of 0.49 [95% confidence interval (CI) 0.29-0.93, *P* value 0.01]. The majority of patients had a length of stay of ≥ 3 d in both groups (95% in the non-rotavirus group and 83.4% in the rotavirus group) (OR 0.27; 95%CI: 0.1-0.78, *P* value 0.02). Only one patient was put in the intensive care unit, belonging to the non-rotavirus group. In both groups, most patients are not vaccinated for rotavirus (86.3% in non-rotavirus diarrhea *vs* 94.7% in rotavirus diarrhea) with an OR of 0.35 (95%CI: 0.14-0.97, *P* value 0.04) (Table 1).

Clinical manifestations

The clinical manifestations vary between the two groups. Most patients presented with mild-moderate dehydration (67.4%) in rotavirus diarrhea, while most in the non-rotavirus group presented with no dehydration (43.8%). Fever mostly lasts less than three days for rotavirus diarrhea (55.1%), while fever lasts mostly ≥ 3 d in the non-rotavirus group (56.3%). The last difference in clinical manifestation between the two groups is in diarrhea duration, where in rotavirus diarrhea it lasts 2-4 d (51.3%) while it mostly lasts > 4 d (57.5%) in the non-diarrhea group. Meanwhile, in both groups, most patients suffer from more than five diarrhea episodes per day, 0-3 vomiting episodes, abdominal pain, and respiratory symptoms (Figure 1).

Table 1 Characteristics of the study population

Characteristics	Frequency		OR (95%CI)	*P* value
	Non-rotavirus	Rotavirus		
Gender				
Male	50 (29.1)	122 (70.9)	0.89 (0.52-1.53)	0.77
Female	30 (31.6)	65 (68.4)		
Age (mo)				
0-11	21	71	Ref	Ref
12-23	24	60	0.74 (0.38-1.46)	0.38
24-59	17	44	0.77 (0.37-1.61)	0.48
≥ 60	18	12	0.19 (0.08-0.47)	< 0.001
Nutritional status				
Severely underweight	10	34	1.39 (0.63-3.08)	0.4
Underweight	14	32	0.94 (0.45-1.94)	0.86
Normoweight	41	100	Ref	Ref
Overweight	7	6	0.35 (0.11-1.11)	0.08
Obese	8	15	0.77 (0.30-1.95)	0.58
Season				
Dry	32 (22.9)	108 (77.1)	0.49 (0.29-0.83)	0.01
Wet	48 (37.8)	79 (62.2)		
Hospitalisation				
In-patient	79 (29.7)	187 (70.3)	N/A	0.30
Intensive Care Unit	1 (100)	0 (0)		
Length of stay (d)				
< 3	4 (11.4)	31 (88.6)	0.27 (0.10-0.78)	0.02
≥ 3	76 (32.8)	156 (67.2)		
Clinical manifestations				
Diarrhea duration (d)				
< 2	2 (22.2)	7 (77.8)	Ref	Ref
2-4	32 (25)	96 (75)	0.86 (0.17-4.34)	1
> 4	46 (35.4)	84 (64.6)	0.52 (0.10-2.62)	0.72
Diarrhea frequency (d)				
< 3	4 (66.7)	2 (33.3)	Ref	Ref
3-4	32 (30.2)	74 (69.8)	4.63 (0.81-26.54)	0.08
> 5	44 (28.4)	111 (71.6)	5.05 (0.90-28.54)	0.07
Vomiting frequency (d)				
0-3	50 (36)	89 (64)	Ref	Ref
4-5	9 (20)	36 (80)	2.25 (1.00-5.04)	0.07
> 5	21 (25.3)	62 (74.7)	1.66 (0.91-3.04)	0.13
Fever duration (d)				
< 3	35 (25.4)	103 (74.6)	0.63 (0.38-1.01)	0.12
≥3	45 (34.9)	84 (65.1)		
Abdominal pain				

Negative	56 (25)	168 (75)	0.26 (0.14-0.52)	< 0.01
Positive	24 (55.8)	19 (44.2)		
Respiratory symptoms				
Negative	59 (28.8)	146 (71.2)	0.79 (0.43-1.45)	0.54
Positive	21 (33.9)	41 (66.1)		
Dehydration				
No dehydration	35 (46.7)	40 (53.3)	Ref	Ref
Mild-moderate	33 (20.8)	126 (79.2)	3.34 (1.85-6.10)	< 0.01
Severe	12 (36.4)	21 (63.6)	1.53 (0.66-3.55)	0.43
Treatment				
Antibiotic				
Negative	3 (1.7)	176 (98.3)	0.002 (0.001-0.01)	< 0.01
Positive	77 (87.5)	11 (12.5)		
IV rehydration				
Negative	19 (32.2)	40 (67.8)	1.15 (0.61-2.13)	0.80
Positive	61 (29.3)	147 (70.7)		
Rotavirus vaccination				
Negative	69 (28)	177 (72)	0.35 (0.14-0.97)	0.04
Positive	11 (52.4)	10 (47.6)		
Laboratory examinations				
Hemoglobin				
Normal	52 (28.1)	133 (71.9)	0.75 (0.43-1.32)	0.40
Abnormal	28 (34.1)	54 (65.9)		
White blood cell count				
Normal	50 (24.6)	153 (75.4)	0.37 (0.21-0.67)	< 0.01
Abnormal	30 (46.9)	34 (53.1)		
Basophils				
Normal	63 (31.5)	137 (68.5)	1.35 (0.72-2.53)	0.43
Abnormal	17 (25.4)	50 (74.6)		
Eosinophils				
Normal	23 (26.1)	65 (73.9)	0.76 (0.43-1.34)	0.42
Abnormal	57 (31.8)	122 (68.2)		
Band neutrophils				
Normal	66 (30.7)	149 (69.3)	1.20 (0.61-2.37)	0.72
Abnormal	14 (26.9)	38 (73.1)		
Segment neutrophils				
Normal	9 (18.8)	39 (81.3)	0.48 (0.22-1.05)	0.09
Abnormal	71 (32.4)	148 (67.6)		
Total neutrophils				
Normal	10 (20.4)	39 (79.6)	0.54 (0.26-1.15)	0.15
Abnormal	70 (32.1)	148 (67.9)		
Lymphocytes				
Normal	13 (26)	37 (74)	0.79 (0.40-1.58)	0.61

Abnormal	67 (30.9)	150 (69.1)		
Monocytes				
Normal	44 (32.1)	93 (67.9)	1.24 (0.73-2.10)	0.51
Abnormal	36 (27.7)	94 (72.3)		
Absolute lymphocytes count				
Normal	28 (23.5)	91 (76.5)	0.57 (0.33-0.98)	0.05
Abnormal	52 (35.1)	96 (64.9)		
Absolute neutrophils count				
Normal	40 (23.8)	128 (76.2)	0.46 (0.30-0.79)	0.007
Abnormal	40 (40.4)	59 (59.6)		
Neutrophils-to-lymphocyte ratio				
Normal	33 (29.5)	4 (57.1)	0.96 (0.57-1.63)	0.99
Abnormal	77 (29.6)	183 (70.4)		
Lymphocyte-to-monocyte ratio				
Normal	3 (42.9)	4 (57.1)	1.79 (0.40-8.15)	0.74
Abnormal	77 (29.6)	183 (70.4)		
Platelet-to-lymphocyte ratio				
Normal	6 (22.2)	21 (77.8)	0.64 (0.25-1.64)	0.47
Abnormal	74 (31)	165 (69)		
Erythrocyte sedimentation rate				
Normal	37 (31.1)	82 (68.9)	1.1 (0.65-1.86)	0.82
Abnormal	43 (29.1)	105 (70.9)		
Random blood glucose				
Normal	45 (24.6)	138 (75.4)	0.46 (0.26-0.80)	0.007
Abnormal	35 (41.7)	49 (58.3)		
Sodium				
Normal	42 (27.5)	111 (72.5)	0.76 (0.45-1.28)	0.37
Abnormal	38 (33.3)	76 (66.7)		
Potassium				
Normal	33 (29.5)	79 (70.5)	0.96 (0.56-1.63)	0.99
Abnormal	47 (30.3)	108 (69.7)		
Chloride				
Normal	42 (29.6)	100 (70.4)	0.96 (0.57-1.63)	0.99
Abnormal	38 (30.4)	87 (69.6)		
Urine and fecal tests				
Urinary ketone				
Negative	74 (29.8)	174 (70.2)	0.92 (0.34-2.52)	1.00
Positive	6 (31.6)	13 (68.4)		
Fecal leukocytes				
Negative	58 (25.9)	166 (74.1)	0.33 (0.17-0.65)	0.002
Positive	22 (51.2)	21 (48.8)		

N/A: Not applicable.

Treatment

98.3% of patients that are rotavirus positive did not receive antibiotics. In comparison, almost all (96.3%) patients who suffer from non-rotavirus diarrhea receive antibiotics with an OR of 0.002 (95%CI: 0.001-0.01, *P* value < 0.01). In both groups, most patients receive IV rehydration with no significant statistical difference (OR 1.15; 95%CI: 0.61-2.13, *P* value 0.08).

Laboratory parameters

Most laboratory parameters are within normal range except for decreased LMR and PLR in both groups, while ESR is slightly elevated. The potassium level is also slightly below the normal reference range, with a median of 4 mmol/L in both groups. Most urinary ketones are negative in both groups (92.5% in the non-rotavirus *vs* 93% in the rotavirus group). There is a significant difference in fecal leukocyte findings between both groups with an OR of 0.33 (95%CI: 0.17-0.65, *P* value 0.002) (Tables 1 and 2).

Multivariate logistic regression

Multivariate logistic regression analysis adjusted for variables with a p-value of < 0.25 is shown in Table 3. Multivariate analysis shows that wet season (OR_{adj} = 2.5; 95%CI: 1.3-4.8, P_{adj} = 0.006), LOS ≥ 3 d (OR_{adj} = 5.1; 95%CI: 1.4-4.8, P_{adj} = 0.015), presence of abdominal pain (OR_{adj} = 3.0; 95%CI: 1.3-6.8, P_{adj} = 0.007), severe dehydration (OR_{adj} = 2.9; 95%CI: 1.1-7.9, P_{adj} = 0.034), abnormal white blood cell counts (OR_{adj} = 2.8; 95%CI: 1.3-6.0, P_{adj} = 0.006), abnormal random blood glucose (OR_{adj} = 2.3; 95%CI: 1.2-4.4, P_{adj} = 0.018) and presence of fecal leukocytes (OR_{adj} = 4.1, 95%CI: 1.7-9.5, P_{adj} = 0.001) are predictors of rotavirus diarrhea. The Hosmer-Lemeshow test shows this model is a good fit with a p-value of 0.361. The AUC for this model is 0.819 (95%CI: = 0.746-0.878, *P* value < 0.001), which shows that this model has good discrimination (Figure 1).

DISCUSSION

Comparison with other studies

Rotavirus was shown to be the leading cause of morbidity and mortality in children, especially five years old and below [13]. Symptoms tend to be most severe in children between 3-24 mo old. However, in approximately 25% of rotavirus cases, severe disease occurs after two years of age. Serologic evidence of rotavirus infection can be virtually observed in all children aged 4-5[12]. Our results showed that our samples have a median age of 1.3 years old. In multivariate analysis, the wet season showed a significant association with rotavirus infection. A previous study showed that in the tropics, rotavirus infection tends to occur all year round compared to the seasonal pattern of infection in countries with temperate climates. However, factors other than temperature, such as rainfall and humidity, play a significant role in rotavirus incidence in the tropics. Due to the waterborne nature of rotavirus transmission, the outbreak pattern might be altered by precipitation levels[14]. In low-income areas, stagnant water sources and poor access to uncontaminated water and sanitation were hypothesised to pose a higher risk for rotavirus infection[15]. Study showed that monsoon season was significantly correlated with dehydrating rotavirus diarrhea among children aged 0-59 mo in South Asia[16]. Previous meta-analyses have also concluded that every 1'C increase in temperature is associated with a 4%-10% decrease in rotavirus infection incidence in the tropics. However, for every one-centimetre increase in mean monthly rainfall and 1% increase in relative humidity (22%), rotavirus incidence decreased by 1% and 3%, respectively. Based on the evidence, it was previously concluded that rotavirus incidence in the tropics was the highest during colder and drier times of the year[17].

Gastroenteritis is generally more severe in the rotavirus group than in the non-rotavirus sample. Length of stay was shown to be prolonged in children age below two years old with rotavirus gastroenteritis. Prolonged LOS, especially in pediatric patients, promote work absenteeism in 70% of parents and could negatively impact the quality of life[18]. Prolonged LOS ≥ 3 d is significantly associated with rotavirus gastroenteritis in this study.

Rotavirus has a broad spectrum of symptoms after 1 to 3 d of incubation, varying from subclinical illness to severe dehydration, shock and death. Rotavirus infection has a similar but more severe clinical manifestation than other gastrointestinal infections. Diagnosis of rotavirus gastroenteritis is commonly clinical based on the presence of vomiting and low-grade fever, followed by watery, non-bloody diarrhea. Moderate fever (temperature < 39°C) is found in approximately one-third of infected patients. Fever and vomiting frequently cease within 1 to 3 d. This finding explains our findings that prolonged fever and vomiting are not significantly associated with rotavirus gastroenteritis. Other physical findings such as abdominal cramping, fatigue and signs of dehydration might also occur during the 5 to 7 d disease course. Diagnosis can be further established by the absence of atypical features such as high-grade fever, which is more commonly present in bacterial gastroenteritis, projectile vomiting, bilious vomiting, blood or mucus in stool, persistent diarrhea for more than seven days, focal abdominal pain, absent bowel sound, and history of antibiotic use[4,19,20]. Presence of abdominal pain and severe dehydration was associated with rotavirus infection in this study. These findings correlate with findings from the previous study that rotavirus-positive subjects were more likely to present with severe dehydration and tend to require intravenous rehydration therapy than rotavirus-negative subjects[16]. However, the role of abdominal pain as a predictor of rotavirus infection is still controversial. Abdominal pain is hypothesised to be limited in rotavirus infection due to low inflammatory response demonstrated by minimal elevation of C-reactive protein or calprotectin levels as clinical markers of inflammation. Rotavirus replication appears to be limited exclusively in the villous epithelium of small intestines, and the diarrhea was considered malabsorptive secondary to enterocyte destruction. Despite non-specific symptomatology, severe abdominal pain and tenesmus tend to indicate large intestines

Table 2 Descriptive values of the laboratory findings

Variable	Reference range	Non rotavirus	Rotavirus
Hemoglobin (g/dL)	10.5-14.0	13.49 (± 16.0)	13.0 (± 11.3)
White blood cell count (10^9 L)	6.0-17.5	14.54 (4.21-42.07)	11.72 (2.86-38.6)
Basophils (%)	0-0.75	0 (0-1)	0 (0-1)
Eosinophils (%)	1-3	0 (0-5)	0 (0-5)
Band neutrophils (%)	3-5	3 (2-12)	3 (1-8)
Segment neutrophils (%)	54-62	62 (20-90)	51 (15-92)
Total neutrophils (%)	58-66	65 (23-93)	54 (18-95)
Lymphocytes (%)	25-33	27 (3-69)	37 (3-75)
Monocytes (%)	3-7	7 (3-13)	7 (1-15)
Absolute lymphocyte count	4000-10500	3354.6 (290.1-15356)	4232.8 (459-24532.2)
Absolute neutrophils count	1500-8500	8662 (1768.7-32814.6)	6100 (972.4-27898)
Neutrophil-to-lymphocyte ratio	Male: 1.48-6.37; Female: 1.22-5.59	2.5 (0-31)	2 (0-32)
Lymphocyte-to-monocyte ratio	Male: 11.12-26.82; Female: 16.08-28.18	4.29 (0.38-16.50)	5.29 (0.50-54)
Platelet-to-lymphocyte ratio	Male: 132.07-178.53; Female: 132.46-181.90	96.7 (20.5-722)	98 (15.89-969)
Thrombocyte count (μ/mm^3)	150000-350000	350000 (109800-1099000)	381000 (115000-1094000)
Erythrocyte sedimentation rate (mm/hour)	0-10	12 (2-215)	14 (1-68)
Random blood glucose (mg/dL)	60-100	94.5 (48-238)	85 (15-160)
Sodium (mmol/L)	134-143	136 (113-154)	135 (124-165)
Potassium (mmol/L)	4.1-5.3	4 (1.6-5.9)	4 (1.4-7.1)
Chloride (mmol/L)	98-106	100 (34.5-134)	101 (9.7-141)

Table 3 Results from multivariate logistic regression analysis for rotavirus diarrhea

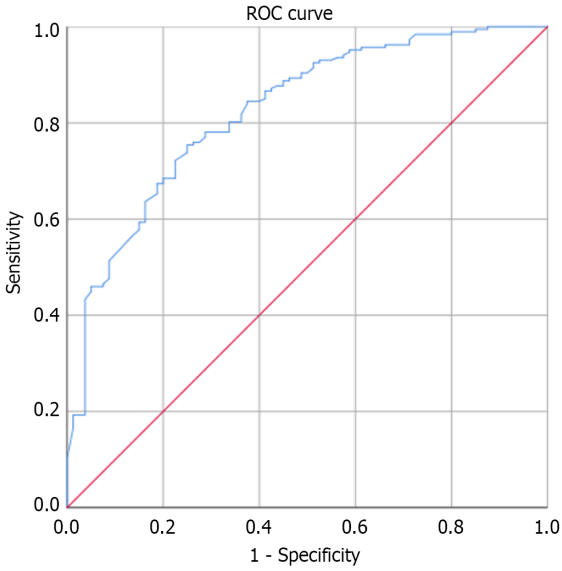
Values	OR_{adj} (95%CI)	*P* $value_{adj}$
Wet season	2.5 (1.3-4.8)	0.006
Length of stay ≥ 3 d	5.1 (1.4-4.8)	0.015
Fever lasts ≥ 3 d	1.9 (0.97-3.5)	0.06
Abdominal pain	3.0 (1.3-6.8)	0.007
Mild-moderate dehydration	1.2 (0.4-3.5)	0.75
Severe dehydration	2.9 (1.1-7.9)	0.034
Abnormal white blood cell counts	2.8 (1.3-6.0)	0.006
Abnormal absolute neutrophil counts	1.9 (0.9-3.8)	0.072
Abnormal random blood glucose	2.3 (1.2-4.4)	0.018
Presence of fecal leukocytes	4.1 (1.7-9.5)	0.001

CI: Confidence intervals; OR: Odds ratio, OR_{adj}: Adjusted odds ratio.

involvement[21,22]. Previous studies demonstrated that abdominal pain is particularly frequent in rotavirus-positive subjects or co-infection with rotavirus subjects. However, no significant association has been found in statistical analyses [23]. Ambiguous interpretation of abdominal pain by parents of young children during history taking could lead to a bias in pain assessment. This finding might explain the contradictory result regarding abdominal pain in this study.

Rotavirus diarrhea and laboratory values

In this study, rotavirus-positive patients demonstrated abnormal white blood cell counts and abnormal random blood glucose. However, previous studies showed no significant difference in white blood cell count between the rotavirus-



Area	95% CI	*P* value
0.819	0.746 - 0.878	< 0.001

DOI: 10.5409/wjcp.v12.i5.319

Figure 1 The receiver operating curve curve analysis.

positive and rotavirus-negative groups. These studies did not mainly compare rotavirus and the specific etiologic agent of gastroenteritis[24-26]. The wide causative range of non-rotavirus gastroenteritis might explain the different findings. Other more significant variables to be compared with rotavirus are indicators of metabolic acidosis secondary to fluid loss. A previous study showed that rotavirus-positive subjects had lower blood pH, higher base deficit, and lower bicarbonate[25]. Complete blood count examination appears to have minimal value in predicting rotavirus infection.

Rotavirus diarrhea and respiratory symptoms

Several reports have stated that respiratory symptoms might also occur during the rotavirus infection course. However, the mechanism that explains this finding is still controversial. Coincidental infection with respiratory viruses during rotavirus endemic season might manifest as respiratory symptoms. Previous studies have indicated that rotavirus might infect extra-intestinal organs during viremia, but there has not been sufficient evidence to prove its replication ability outside the intestine. Rotavirus antigens or RNA were detected in the spleen, heart, kidneys, testes, bladder, liver, cells or secretions from the respiratory tract, and endothelial cells[20,27]. Our result showed that respiratory symptoms do not predict rotavirus infection in children. Stool analyses in rotavirus-positive subjects are common without blood or white blood cells[20]. This result correlates with our findings that faecal leukocytes are a predictor of rotavirus infection. The presence of fecal leucocytes in rotavirus infection may indicate inflammatory processes in the intestines[28]. No other hematologic findings were significantly correlated with rotavirus infection in this study.

Limitation

This study has its limitations. Our research is a cross-sectional study to start with. As a result, we could not account for some factors that might affect the severity of rotavirus diarrhea, such as birth weight, source of water, and house-crowding status. Second, the study's focus on just two institutions raises the possibility that this study may not be generalisable to other centres. However, given the nature of the two different hospitals, we were able to include kids from a range of racial and ethnic backgrounds, assuring that both high- and low-income parents were represented in this study. Some variables have insufficient strength for analysis due to missing or unanalysed laboratory data. Third, we could not account for any temporal changes occurring in the four years of the study period. Any seasonality, changes in guidelines and diagnosis of rotavirus diarrhea, as well as immunization update may have altered the results of the study. Lastly, we did not analyse the antigenic properties of the rotavirus due to limited equipment and funding.

CONCLUSION

In this study, wet season, LOS ≥ 3 d, presence of abdominal pain, severe dehydration, abnormal white blood cell counts, abnormal random blood glucose and presence of fecal leukocytes predict rotavirus diarrhea. Since these parameters have good discrimination, these findings should alert clinicians to the presence of rotavirus diarrhea. Clinicians may use these parameters to further alert them to the possibility of rotavirus diarrhea in children and order tests more prudently as well as prescribing appropriate therapy.

ARTICLE HIGHLIGHTS

Research background

Rotavirus gastroenteritis accounted for 19.11% of diarrheal deaths worldwide in 2019 and is still a leading cause of morbidity and mortality, especially in children under five. Surveillance data from 2008-2018 showed that 40.78% of all diarrheal diseases in children in Southeast Asia were attributable to rotavirus infection.

Research motivation

Rotavirus diarrhea is still a leading cause of mortality among Indonesian children. However, since antigen detection is not affordable amongst many families, other cheap clinical proxies for rotavirus diarrhea must be determined.

Research objectives

This study aims to determine clinical and laboratory values that may serve as an indicator to raise clinicians' awareness about rotavirus diarrhea.

Research methods

This study was cross-sectional, with medical records obtained from December 2015 to December 2019 from Siloam General Hospital and Siloam Hospital Lippo Village. Inclusion criteria for this study include all hospitalised pediatric patients (0-18 years old) diagnosed with suspected rotavirus diarrhea, defined as the passing of ≥ 3 watery or loose stools each day. We collected demographic data such as age, gender, and nutritional status. Clinical signs such as temperature upon arrival, vital signs, clinical manifestations (abdominal pain, respiratory symptoms, dehydration status according to World Health Organization), duration and frequency of symptoms (diarrhea, vomiting, fever), length of stay (LOS), treatment given during hospitalisation [intravenous (IV) rehydration and any antibiotics], rotavirus vaccination status, as well as the seasons during which the children contracted diarrhea.

Research results

This study included 267 participants with 187 (70%) rotavirus-diarrhea cases. The patients were primarily male in both rotavirus (65.2%) and non-rotavirus (62.5%) groups. The median age is 1.33 years old (0.08-17.67 years old). Multivariate analysis shows that wet season (OR_{adj} = 2.5; 95%CI: 1.3-4.8, P_{adj} = 0.006), LOS ≥ 3 d (OR_{adj} = 5.1; 95%CI: 1.4-4.8, P_{adj} = 0.015), presence of abdominal pain (OR_{adj} = 3.0; 95%CI: 1.3-6.8, P_{adj} = 0.007), severe dehydration (OR_{adj} = 2.9; 95%CI: 1.1-7.9, P_{adj} = 0.034), abnormal white blood cell counts (OR_{adj} = 2.8; 95%CI: 1.3-6.0, P_{adj} = 0.006), abnormal random blood glucose (OR_{adj} = 2.3; 95%CI: 1.2-4.4, P_{adj} = 0.018) and presence of fecal leukocytes (OR_{adj} = 4.1, 95%CI: 1.7-9.5, P_{adj} = 0.001) are predictors of rotavirus diarrhea. The area under the curve for this model is 0.819 (95%CI: = 0.746-0.878, *P* value < 0.001), which shows that this model has good discrimination.

Research conclusions

In this study, wet season, LOS ≥ 3 d, presence of abdominal pain, severe dehydration, abnormal white blood cell counts, abnormal random blood glucose and presence of fecal leukocytes predict rotavirus diarrhea. Since these parameters have good discrimination, these findings should alert clinicians to the presence of rotavirus diarrhea. Clinicians may use these parameters to further alert them to the possibility of rotavirus diarrhea in children and order tests more prudently as well as prescribing appropriate therapy.

Research perspectives

More bigger and confirmatory studies are needed to confirm our findings.

FOOTNOTES

Author contributions: Octavius GS and Widjaja M designed the research study; Indrawan M, Chendana J, Handoko TGH, and Octavius GS performed the research; Indrawan M and Chendana J gathered and analyzed the data; Indrawan M, Chendana J, Octavius GS, and Handoko TGH wrote the draft; All authors have read, edited and approved the final manuscript.

Institutional review board statement: This study protocol was approved by the Committee on Ethics at the University of Pelita Harapan, Tangerang, Indonesia, with Code Ethic No. 430/FK-UPH/Ext./V/2019.

Informed consent statement: The ethical board exempted informed consent due to the retrospective nature of our study. Identities were removed entirely, and data were analysed anonymously.

Conflict-of-interest statement: All the authors declare that they have no conflict of interest.

Data sharing statement: Data is available upon reasonable request.

Country/Territory of origin: Indonesia

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S-Editor: Liu JH
L-Editor: A
P-Editor: Zhang XD

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World J Clin Pediatr 2023 December 9; 12(5): 331-349

DOI: 10.5409/wjcp.v12.i5.331

ISSN 2219-2808 (online)

SYSTEMATIC REVIEWS

Migration of the distal ventriculoperitoneal shunt catheter into the stomach with or without trans-oral extrusion: A systematic literature review and meta-analysis

Rajendra Kumar Ghritlaharey

Specialty type: Neurosciences

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Rajderkar DA, United States

Received: June 25, 2023
Peer-review started: June 25, 2023
First decision: August 17, 2023
Revised: September 4, 2023
Accepted: October 30, 2023
Article in press: October 30, 2023
Published online: December 9, 2023

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Abstract

BACKGROUND

Intra-gastric migration of the distal ventriculoperitoneal shunt (VPS) catheter clinically presenting with or without trans-oral extrusion is one of the rare complications of VPS catheter insertion.

AIM

To identify the demographics, clinical presentation, clinical findings, and results of surgical therapy offered for the treatment of intra-gastric migration of the distal VPS catheter, clinically presented with or without trans-oral extrusion.

METHODS

An online search was performed for the extraction/retrieval of the published/available literature pertaining to the above-mentioned VPS complication. Manuscripts were searched from PubMed, PMC (PubMed Central), ResearchGate, and Google Scholar databases using various terminology relating to the VPS complications. The first case of migration of a VPS catheter into the stomach was reported in the year 1980, and the data were retrieved from 1980 to December 2022. Cases were categorized into two groups; Group A: Cases who had migration of the distal VPS catheter into the stomach and clinically presented with trans-oral extrusion of the same, and Group B: Cases who had migration of the distal VPS catheter into the stomach, but presented without trans-oral extrusion.

RESULTS

A total of n = 46 cases (n = 27; 58.69% male, and n = 19; 41.3% females) were recruited for the systematic review. Group A included n = 32, and Group B n = 14 cases. Congenital hydrocephalus was the indication for the primary VPS insertion for approximately half of the (n = 22) cases. Approximately sixty percent (n = 27) of them were children ≤ 5 years of age at the time of the diagnosis of the

complication mentioned above. In seventy-two percent (n = 33) cases, this complication was detected within 24 mo after the VPS insertion/last shunt revision. Clinical diagnosis was evident for the entire group A cases. Various diagnostic modalities were used to confirm the diagnosis for Group B cases. Various surgical procedures were offered for the management of the complication in n = 43 cases of both Groups. In two instances, intra-gastric migration of the distal VPS catheter was detected during the autopsy. This review documented four deaths.

CONCLUSION

Intra-gastric migration of the peritoneal end of a VPS catheter is one of the rare complications of VPS catheter implantation done for the treatment of hydrocephalus across all age groups. It was more frequently reported in children, although also reported in adults and older people. A very high degree of clinical suspicion is required for the diagnosis of a case of an intra-gastric migration of the distal VPS catheter clinically presenting without trans-oral extrusion.

Key Words: Complication; Extrusion; Hydrocephalus; Migration; Protrusion; Stomach; Shunt revision; Ventriculoperitoneal shunt; Ventriculoperitoneal shunt complications

Core Tip: This systematic review included n = 46 cases of intra-gastric migration of the peritoneal end of a ventriculoperitoneal shunt (VPS) catheter. Thirty-two cases clinically presented with the peroral extrusion of the distal VPS catheter. The remaining n = 14 cases clinically presented with other symptoms but without peroral extrusion of the distal VPS catheter. Sixty percent were children ≤ 5 years of age at the time of diagnosis of VPS complication mentioned above. In more than two-thirds of cases, the VPS complication was evident within 24 mo after the primary VPS insertion/last VPS revision. The demographics, indications for the primary/initial VPS insertion, age distribution at the time of VPS insertion and diagnosis of the VPS complication, the interval, and the surgical procedures carried out by the various authors for the above-described VPS complication are described in the manuscript.

Citation: Ghritlaharey RK. Migration of the distal ventriculoperitoneal shunt catheter into the stomach with or without trans-oral extrusion: A systematic literature review and meta-analysis. *World J Clin Pediatr* 2023; 12(5): 331-349
URL: https://www.wjgnet.com/2219-2808/full/v12/i5/331.htm
DOI: https://dx.doi.org/10.5409/wjcp.v12.i5.331

INTRODUCTION

The treatment of hydrocephalus has evolved over centuries, but progress has occurred during the past few decades[1,2]. The ventriculoperitoneal shunt insertion is the commonly performed surgical procedure for treating hydrocephalus caused by various etiologies and is performed across all age groups[3-7]. Various complications occur in approximately one-fifth to four-fifths of the cases following the VPS insertion, and many of them require shunt revisions[5-9]. VPS revisions are needed more during the first 12 mo following the initial VPS placement[5,6,8]. VPS complications and shunt revisions are more frequently documented and required in children than adults[5,8]. Perforation of the hollow viscus viz gastrointestinal tract, urinary bladder, and uterus (female genital tract) by the peritoneal end of a VPS catheter is known, and it may occur with or without extrusion of the distal VPS catheter through the natural orifices[10-14]. Perforation of the large bowel by the peritoneal end of a VPS catheter and protrusion/extrusion of the same *via* the anal canal is commonly reported[10,11]. Migration of the distal VPS catheter into the stomach is a rare clinical entity[14]. The preferred reporting items for systematic reviews and metaanalyses (PRISMA) guidelines are followed for reporting this manuscript [15,16]. This manuscript is a systematic literature review of the n = 46 cases published (1980 to December 2022) on the management of the intra-gastric migration of the distal VPS catheter clinically presented with or without trans-oral extrusion[17-62]. Thirty-two cases had intra-gastric migration of the distal VPS catheter and clinically presented with trans-oral extrusion of the same[17-48]. Remaining n = 14 cases had intra-gastric migration of the distal VPS catheter but clinically presented without trans-oral extrusion of the distal VPS catheter[49-62].

MATERIALS AND METHODS

PubMed, PMC, ResearchGate, and Google Scholar databases were searched for retrieval of the published/available literature pertaining to the migration of the distal VPS catheter into the stomach with or without trans-oral extrusion. Various terminology relating to VPS complications were utilized during the online search. Some of the keywords employed during the online search were "trans-oral extrusion of distal VPS catheter", "per-oral/oral extrusion of distal VPS catheter", "intra-gastric migration of distal VPS catheter", "protrusion/extrusion of VPS catheter", "bowel

perforation by distal VPS catheter", and "rare complication of VPS catheter". The maiden case of migration of a VPS catheter into the stomach was reported by Nishijima *et al*[49] in 1980, and related literature/manuscripts were retrieved from 1980 to December 2022, and those were preferably available in the English language. Four cases (n = 2 duodenal and n = 2 jejunal) of bowel perforation (not gastric perforation) by the distal VPS catheter, clinically presented with trans-oral extrusion were also included in the present review. Cases/case reports retrieved during online search with incomplete details were excluded from the review. Cases are categorized into two groups, Groups A and Group B. Group A: Cases who had migration of the distal VPS catheter into the stomach and clinically presented with trans-oral extrusion of the same, and Group B: Cases who had migration of the distal VPS catheter into the stomach but clinically presented without trans-oral extrusion. The "Preferred Reporting Items for Systematic Reviews and MetaAnalyses" (PRISMA) guidelines are followed for reporting this systematic review. The selection of articles for systematic review was done by assessing the titles, abstracts, and full texts of the manuscripts. Literature selection and extraction of the desired information from the manuscripts were independently carried out by the author alone, as this is a single-author manuscript. The desired information retrieved from the published literature/case reports were the patient's age, sex, indication for the VPS insertion, interval from VPS insertion to the diagnosis of the complication, clinical characteristics, diagnostic modalities used, surgical procedures offered/performed, postoperative complications, and the outcome of surgical therapy. This manuscript is a systematic review of the published cases, and institutional ethical committee approval is not required.

RESULTS

A total of n = 46 cases of intra-gastric migration of the peritoneal end of a VPS catheter clinically presented with or without peroral extrusion were included for the systematic review and retrieved from the n = 46 manuscripts. The process of database search, screening, and selection of the manuscripts for the present systematic review is presented in a PRISMA flow diagram in Figure 1. Group A included n = 32 cases and details are provided in Table 1. Group B included n = 14 cases and details are provided in Table 2. The causes of hydrocephalus and indications for the primary VPS insertion for the entire case are detailed in Figure 2. Congenital hydrocephalus was the indication for the primary VPS insertion for approximately half of the (n = 22) cases. Figure 3 detailed the distribution of the age of the entire cases at the time of primary VPS insertion. The initial VPS catheter placement was done during infancy in two-thirds (n = 22) of Group A cases. The initial VPS catheter placement was done during infancy only in one-fourth (n = 4) of Group B cases. Figure 4 details the distribution of the age of the entire cases at the time of diagnosis of the above-mentioned VPS complication. Approximately sixty percent (n = 27) of them were children ≤ 5 years of age at the time of diagnosis of the complication mentioned above. Figure 5 details the interval from the primary/initial VPS insertion/last VPS revision to the diagnosis of the VPS complication mentioned above. In seventy-two percent (n = 33) cases, this complication was detected within 24 mo after the VPS insertion/last shunt revision.

The chief complaint and clinical finding for Group A cases was the trans-oral extrusion of the distal VPS catheter (Figure 6). In most cases, it was associated with a bout of vomiting of short duration. Mild abdominal pain/discomfort relating to the upper gastrointestinal (GI) tract was also documented in some cases. Clinical presentation in Group B cases was vague and not specific to the distal VPS catheter complication. Group B cases mostly had symptoms relating to the central nervous system (CNS) or upper GI tract. Clinical diagnosis was evident in the entire Group A cases due to the clinical finding of the presence of trans-oral extrusion/protrusion of the distal VPS catheter. Various diagnostic modalities (radiological and endoscopic) were used to confirm the diagnosis in Group B cases. Different surgical procedures were offered for the management of the above-mentioned VPS complication and are detailed in Figure 7. Removal of the entire VPS catheter/removal of part of the peritoneal /peritoneal catheter with or without external ventricular drainage (EVD) was preferred by the authors. In n = 2 Group B cases, an intra-gastric migration of the distal VPS catheter was detected during the autopsy. For one Group B case, the surgical therapy was not carried out, as his VPS catheter was not causing any problems. Percutaneous surgical removal of the entire or the distal VPS catheter with or without an EVD was a procedure of choice and was opted for n = 27 (n = 24 Group A and n = 3 Group B) cases. For the management of VPS complications mentioned above, formal laparotomy was carried out only in n = 11 (n = 7 Group A and n = 4 Group B) cases. The site of bowel perforation caused by the distal VPS catheter is detailed in (Figure 8A). In eighty-five percent of cases, the site of bowel perforation was the stomach. The site of bowel perforation was repaired only in n = 11 cases and is detailed in (Figure 8B). The review revealed n = 4 (8.69%) deaths, two from each group.

DISCUSSION

Perforation of the gastrointestinal tract, urinary bladder, and uterus by the distal VPS catheter is a known complication of the VPS placement carried out for the treatment of hydrocephalus, and most of them clinically present with the extrusion of the peritoneal part of a VPS catheter through the natural orifices[10-14]. Perforation of the large bowel by the peritoneal end of a VPS catheter and extrusion of the same *via* the anal canal is most common and is reported to occur in 0.1% to 2.5% of the cases[10,11]. Migration of the distal VPS catheter into the stomach is a rare clinical entity, and two-thirds of them presented with the trans-oral extrusion of the distal part of peritoneal catheter[17-62].

Summary of evidence

A total of n = 46 manuscripts including n = 46 cases of the above-mentioned VPS complication were reviewed for

Table 1 Demographics, clinical features, and outcome of the surgical procedures performed for the migration of the distal ventriculoperitoneal shunt catheter into the stomach with trans-oral extrusion (*n* = 32)

Ref.	Indication for VPS insertion	Age VPS insertion sex	Age trans-oral extrusion	Interval (mo)	VPS (R)	History GI Surg	Shunt tract infection	Peritonitis meningitis	CSF infection	Operative procedures executed	[1]Site repaired (Yes/No)	Complication	Outcome
Griffith *et al* [17], 1987	Hydrocephalus (Post infective)	9.6 yr Female	9.9 yr	3	Yes	Yes	No	No	No	Part of distal VPS catheter cut by child, proximal VPS catheter as EVD, delayed ventriculo-atrial shunt done	**Stomach (No)**	Yes	Death
Danismend *et al*[18], 1988	Hydrocephalus (Congenital?)	8 mo Female	18 mo	10	No	No	No	No	No	Removal of distal VPS catheter and Immediate ventriculo-atrial shunt done	Stomach (Yes)	Nil	R
Park *et al*[19], 2000	Hydrocephalus (Post-haemorrhagic)	12 mo female	5 yr	48	No	No	Yes	No	No	Removal of part of distal VPS catheter, Proximal VPS catheter as EVD, Delayed re-VPS/VPS (R) done	Stomach (No)	Nil	R
Jiménez Moya *et al*[20], 2001	Hydrocephalus (Brain tumor)	9.11 yr female	11.2 yr	2	Yes	Yes	No	No	No	Removal of entire VPS catheter, Delayed re-VPS insertion done	Stomach (NA)	Nil	R
Kothari *et al* [21], 2006	Hydrocephalus (Congenital)	1 mo male	18 mo	17	No	No	No	No	Yes	Removal of entire VPS catheter, Delayed re-VPS insertion done	Stomach? (No)	Nil	R
Odebode *et al* [22], 2007	Hydrocephalus (Congenital?)	9 mo female	15 mo	6	No	No	Yes	No	No	Removal of entire VPS catheter, Delayed re-VPS insertion done	Jejunum (Yes)	Nil	R
Berhouma *et al* [23], 2008	Hydrocephalus with NTD (Congenital)	9 mo male	2 yr	15	No	No	No	No	Yes	Removal of part of distal VPS catheter, Proximal VPS catheter as EVD	NA (No)	Yes	Death
Murali *et al* [24], 2008	Hydrocephalus (Congenital)	6 mo male	6 yr	66	No	No	No	No	No	Removal of part of distal VPS catheter, Proximal VPS catheter as EVD, Removal of cranial catheter failed	Stomach (No)	Nil	R
Sridhar *et al* [25], 2009	Hydrocephalus (Post infective)	2 mo female	8 mo	6	No	No	No	No	No	Removal of entire VPS catheter (re-VPS catheter insertion not required)	Stomach? (No)	Nil	R
Sinnadurai *et al* [26], 2009	Hydrocephalus (Cyst)	12 yr female	27 yr	2 wk	Yes	No	No	No	No	Removal of part of distal VPS catheter, Proximal VPS catheter as EVD, Delayed VPS (R) done	Stomach (No)	Nil	R
Low *et al*[27], 2010	Hydrocephalus (Post infective)	6 mo male	12 mo	6	**No**	Yes	No	No	No	Removal of entire VPS catheter, Insertion of EVD, Delayed re-VPS insertion done	Stomach (No)	Nil	R
Dua *et al*[28], 2011	Hydrocephalus with NTD (Congenital)	20 d male	8 mo	7	No	No	No	No	No	Removal of part of distal VPS catheter, Proximal VPS catheter as EVD, Delayed re-VPS insertion done	Stomach (No)	Nil	R
Agarwal *et al* [29], 2011	Hydrocephalus (Congenital)	4 mo male	12 mo	8	No	No	No	No	No	Removal of entire VPS catheter, Delayed re-VPS insertion done	NA (No)	Nil	R
Gupta *et al*	Hydrocephalus	6 mo male	4 yr	42	No	No	No	No	No	Removal of entire VPS catheter (re-VPS	Stomach (No)	Nil	R

[30], 2012	(Congenital)									insertion not required)			
Kundal *et al* [31], 2012	Hydrocephalus (Post infective)	6 yr male	7 yr	12	No	No	No	No	No	Removal of entire VPS catheter, Delayed re-VPS insertion done	NA (No)	Nil	R
Yilmaz *et al* [32], 2013	Hydrocephalus (Pseudotumor)	37 yr female	47 yr	120	No	Yes	No	No	No	Removal of entire VPS catheter (re-VPS insertion not required)	Stomach (Yes)	Nil	R
Gupta *et al* [33], 2014	Hydrocephalus (Congenital)	12 mo male	11 yr	7	Yes	No	No	No	No	Removal of entire VPS catheter (Previous VPS functioning well)	Stomach (No)	Nil	R
Mandhan *et al* [34], 2015	Hydrocephalus with NTD (Congenital)	Infant female	11 yr	53	No	Yes	No	No	No	Removal of entire VPS catheter (re-VPS insertion not done/required?)	Stomach (No)	Nil	R
Thiong'o *et al* [35], 2015	Hydrocephalus (Congenital)	10 d female	3 mo	2	No	No	No	No	No	Removal of entire VPS catheter, Insertion of EVD, Delayed re-VPS insertion done	**Stomach? (No)**	Nil	R
Sohal *et al*[36], 2015	Hydrocephalus (Congenital?)	NA male	11 mo	10 d	Yes	**Yes**	No	No	No	Removal of part of distal VPS catheter, Proximal VPS catheter as EVD, Delayed ventriculo-atrial shunt done	Stomach (No)	Nil	R
Ghritlaharey *et al*[37], 2015	Hydrocephalus (Post infective/Congenital)	12 mo female	24 mo	9	Yes	No	No	No	No	Removal of part of distal VPS catheter, Proximal VPS catheter as EVD, Delayed VPS (R) done	Stomach? (No)	Yes	R
Shah *et al*[38], **2016**	**Hydrocephalus (Congenital)**	**12 mo male**	**4** yr	12	**Yes**	**No**	**No**	**No**	**No**	**Removal of entire VPS catheter (re-VPS insertion not required)**	**Stomach (No)**	**Nil**	R
Sharma *et al* [39], **2017**	**Hydrocephalus (Congenital)**	**Neonate male**	**8 mo**	**7**	**No**	**No**	**No**	**No**	**No**	**Removal and re-positioning of distal VPS catheter into the peritoneal cavity**	**Stomach (No)**	**Nil**	R
Al Fauzi A *et al* [40], **2017**	**Hydrocephalus (Brain tumor)**	**4 yr male**	**5 yr**	12	**No**	**No**	**No**	**No**	**No**	**Removal of entire VPS catheter (re-VPS insertion not required)**	**Stomach (No)**	**Nil**	R
Reyes *et al*[41], **2017**	**Hydrocephalus (Post-haemorrhagic)**	**2 mo male**	**16 mo**	**8**	**Yes**	**No**	**No**	**No**	**No**	**Removal of entire VPS catheter, Immediate re-VPS insertion done**	**Stomach (No)**	**Nil**	R
Badri *et al*[42], **2018**	**Hydrocephalus (Congenital)**	**4** yr **male**	**4** yr	**1**	**No**	**No**	**No**	**No**	**No**	**Removal of distal VPS catheter, Immediate VPS (R) done**	**Duodenum (Yes)**	**Nil**	R
Romuald *et al* [43], **2018**	**Hydrocephalus (Congenital)**	**24 mo male**	**34 mo**	**10**	**No**	**No**	**No**	**No**	**Yes**	**Removal of entire VPS catheter, Insertion of EVD, Delayed re-VPS insertion done**	**Duodenum (Yes)**	**Nil**	R
Ezzat *et al*[44], **2018**	**Hydrocephalus (Congenital)**	**2 mo male**	**22 mo**	**20**	**No**	**No**	**No**	**No**	**No**	**Removal of entire VPS catheter, Cranial catheter as EVD? Delayed re-VPS insertion done**	**Stomach? (No)**	**Nil**	R
Bemora *et al* [45], **2019**	**Hydrocephalus (Post infective)**	**7 mo female**	**16 mo**	**9**	**No**	**No**	**No**	**No**	**NA**	**Removal of entire VPS catheter, Immediate re-VPS insertion done**	**Stomach (No?)**	**Nil**	R
Feeney *et al* [46], **2020**	**Hydrocephalus (Post trauma)**	**57** yr **male**	**58** yr	**11**	**No**	**No**	**No**	**No**	**Yes**	**Removal of distal VPS catheter, Proximal VPS catheter as EVD, Removal of proximal VPS catheter**	**Jejunum (No)**	**Nil**	R

										(re-VPS insertion not required)			
Calgaro *et al* [47], 2020	**Hydrocephalus (Congenital)**	**2 mo male**	**7 mo**	**5**	**No**	**No**	**No**	**No**	**NA**	**Removal of entire VPS catheter, Immediate re-VPS insertion done**	**Stomach? (No)**	**Nil**	R?
Najib *et al*[48], 2022	**Hydrocephalus with NTD (Congenital)**	**Neonate male**	**8 mo**	**7**	**No**	**No**	**No**	**No**	**No**	**Removal of part of distal VPS catheter and re-positioning of remaining distal catheter into the peritoneal cavity**	**Stomach (Yes)**	**Nil**	R

[1]Site: Site of perforation.

CSF: Cerebrospinal fluid; EVD: External ventricular drainage; GI Surg: Gastrointestinal/abdominal surgery; NA: Not available/details not available; NTD: Neural tube defect; R: Recovered; VPS: Ventriculoperitoneal Shunt; VPS (R): Ventriculoperitoneal Shunt revision.

systematic review[17-62]. Forty-four manuscripts are published in the English language[17-19,21-40,42-62]. Only *n* = 2 manuscripts published and available in languages other than English are also included in the review. For the above two manuscripts, the desired details are obtained by translating them into the English language using Google Translate[20, 41]. All the *n* = 46 manuscripts included in the review are already published, and none are conference proceedings or unpublished. All the *n* = 46 manuscripts included for systematic review are full-text articles[17-62]. Thirty-five manuscripts described/detailed the isolated case[17,19,23-30,32,33,37-43,45,46,48-54,56-62]. Two of the manuscripts included in the review are original articles[35,44]. For one case, the details were extracted from a manuscript published as a case series[31]. Eight manuscripts are published and available under the headings of medical images, letters to the editor, correspondence, and technical notes[18,20-22,34,36,47,55]. Four manuscripts included *n* = 5 cases of the above-mentioned VPS complications were excluded from review due to the incomplete desired information[63-66].

This review included *n* = 46 cases (*n* = 27; 58.69% were males and *n* = 19; 41.3% were females). It was evident more in males, with a male-to-female ratio of 1.42:1. Group A included *n*=32 cases (*n* = 20; 62.5% male, and *n* = 12; 37.5% females) while Group B included *n*=14 cases (*n* = 7; 50% male, and *n* = 7; 50% females).

The indication for the primary VPS insertion was congenital hydrocephalus for approximately half of the entire cases (*n* = 22) cases and approximately sixty percent (*n* = 19) of the Group A cases. Post-infective hydrocephalus was also one of the indications for VPS insertion in approximately one-fifth (*n* = 6) of the Group A cases. Normal pressure hydrocephalus (NPH), idiopathic intracranial hypertension, and intracranial aneurysm with or without hemorrhage were the indications for the primary VPS catheter insertion for fifty percent of the Group B cases.

Group A cases were much younger than the Group B cases at the time of initial VPS placement. Two-thirds (*n* = 22) of Group A and one-fourth (*n* = 4) of Group B cases were infants, at the time of initial VPS placement. Three-fourths (*n* = 9) of Group B cases were > 40 years of age, at the time of initial VPS placement. Group A cases were much younger at the time of the diagnosis of VPS complications as well. More than half (*n*=17) of Group A cases were children ≤ 2 years of age at the time of diagnosis of the VPS complication mentioned above. One-fourths (*n* = 4) of Group B cases were children ≤ 5 years of age at the time of diagnosis of the VPS complication mentioned above. Seventy-two percent (*n* = 23) of Group A cases were ≤ 5 years of age, while more than half (*n* = 8) of Group B cases were > 40 years of age. Age was not a bar for the intra-gastric migration of the distal VPS catheter. A trans-oral extrusion of the distal VPS catheter was infrequently reported after 15 years, and only three cases were reported after the age of 15 years. Probably one of the reasons may be the age difference at the time of primary VPS insertion for both the Group cases and the second reason may be the difference in the indication for the initial VPS catheter insertion. The probable reason for a greater number of intra-gastric migrations clinically presented as trans-oral extrusion of the distal VPS catheter in children than in adult/older population may be because the number of VPS placements carried out in infants and children are many folds more than

Table 2 Demographics, clinical features, and outcome of the surgical procedures performed for the migration of the distal ventriculoperitoneal shunt catheter into the stomach without trans-oral extrusion (*n* = 14)

Ref.	Indication for VPS insertion	Age VPS insertion sex	Age gastric migration	Interval (mo)	VPS (R)	History GI Surg	Shunt tract infection	Peritonitis meningitis	CSF infection	Operative procedures executed	[1]Site repaired (Yes/No)	Complication	Outcome
Nishijima *et al* [49], 1980	Hydrocephalus (NPH)	69 yr female	71 yr	27	No	No	No	Meningitis	Yes	Distal VPS catheter found within the gastric lumen (Autopsy finding)	Stomach (Autopsy)	-	Death
Oi *et al*[50], 1987	Hydrocephalus (posttraumatic)	12 mo male	3 yr	24	Yes	No	Yes	Meningitis	Yes	Removal of part of distal VPS catheter, Proximal VPS catheter as EVD, Delayed VPS revision done	Stomach (Glue)	Nil	R
Oshio *et al*[51], 1991	Hydrocephalus (Posttraumatic)	12 mo male	3 yr	24	No	No	Yes	Meningitis	Yes	Removal of part of distal VPS catheter, Proximal VPS catheter as EVD?, Delayed VPS revision done	Stomach (Glue)	Yes	R
Ho *et al*[52], 1992	Hydrocephalus (NPH)	68 yr male	72 yr	42	No	No	No	Meningitis	Yes	Distal VPS catheter found within the gastric lumen (Autopsy finding)	Stomach (Autopsy)	-	Death
Alonso-Vanegas *et al* [53], 1994	Hydrocephalus with NTD (Congenital)	Neonate female	4 mo	4	No	No	No	No	No	Removal of entire VPS catheter, Immediate ventriculo-atrial shunt	Stomach (Yes)	Nil	R
Christoph *et al* [54], 1995	Hydrocephalus (Congenital)	5 mo female	5 mo	1 d	No	Yes	No	No	No	Removal of distal VPS catheter from gastric lumen and converted as EVD, Delayed ventriculo-atrial shunt done	Stomach (NA)	Nil	R
Hart *et al*[55], 2001	Hydrocephalus (Congenital)	NA female	33 yr	NA	NA	No	No	No	No	Removal of distal VPS catheter from gastric lumen and relocation of distal catheter within the peritoneal cavity	Stomach (NA)	Nil	R
Masuoka *et al* [56], 2005	Hydrocephalus (Intracranial aneurysm)	47 yr male	51 yr	42	No	No	No	No	Yes	Removal of entire VPS catheter (re-VPS insertion not required)	Stomach (No)	Nil	R
Cheng *et al*[57], 2007	Hydrocephalus (Posttraumatic)	87 yr male	88 yr	8	No	No	No	No	Yes	Removal of entire VPS catheter (re-VPS insertion not done/required)	Stomach (Yes)	Nil	R
Cohen-Added *et al*[58], 2018	Hydrocephalus (Intracranial aneurysm)	65 yr male	72 yr	7 yr?	No	No	No	No	No	Surgical therapy not executed for intra-gastric migration of distal VPS catheter	Stomach (No)	--	R
Sidhu *et al*[59], 2019	Hydrocephalus (Intracranial aneurysm)	83 yr? male	84 yr	12?	No	Yes	No	No	No	Removal of entire VPS catheter (re-VPS insertion not required)	Stomach (NA)	Nil	R
Yala *et al*[60], 2019	Hydrocephalus (Intracranial aneurysm)	41 yr female	65 yr	36?	Yes	No	No	No	No	Removal of distal VPS catheter from gastric lumen and relocation of distal catheter within the peritoneal cavity	Stomach (Yes)	Nil	R
Chen *et al*[61], 2020	Hydrocephalus (Post infective)	44 yr female	54 yr	NA	Yes	No	No	No	Yes	Removal of entire VPS catheter, Placement of EVD, Delayed re-VPS insertion done	Stomach (Yes)	Nil	R

Scarascia *et al* [62], 2022	Hydrocephalus (IIH)	15 yr female	31 yr	16 yr?	No	No	No	No	No	Removal of entire VPS catheter (re-VPS insertion not done)	Stomach (Yes)	Yes	R?

[1]Site: Site of perforation.

CSF: Cerebrospinal fluid; EVD: External ventricular drainage; GI Surg: Gastrointestinal/abdominal surgery; IIH: Idiopathic intracranial hypertension; NA: Not available/details not available; NPH: Normal pressure hydrocephalus; NTD; Neural tube defect; R: Recovered; VPS: Ventriculoperitoneal Shunt; VPS (R): Ventriculoperitoneal Shunt revision.

done in adults and older age. Like the present findings, a recent review included *n* = 210 cases of the management of extrusion of the distal part of peritoneal catheter through the anal canal, also evidenced that in 73% of the cases, the age of the cases was ≤ 5 years of age[11]. For *n* = 19 of the Group A and *n* = 9 of the Group B cases, the details of the shunt type/which type of the VPS catheter implanted during the initial procedure was not available/not mentioned by the authors in the manuscripts[20,21,23-27,29-32,34,36,38,42,43,45,47,48,52,54,55,57-62]. "Chhabra slit n spring hydrocephalus VPS catheter" (Shahjahanpur, India) was used during the VPS implantation in *n* = 8 of the Group A cases[22,28,33,35,37,39,40,44]. For the remaining *n* = 4 Group A and *n* = 5 Group B cases, the shunt catheter used during VPS insertion were (1) Raimondi peritoneal catheter (*n* = 3); (2) Codman Hakim VPS system (*n* = 5); and (3) VPS catheter (Biomed valve, slit valve, silicon catheter, not spring type) (*n* = 1), respectively[17-19,41,46,49-51,53,56]. As in this review, in sixty percent (*n* = 28) cases, which type of VPS catheter implanted was not available, and therefore it is not clear whether any particular shunt catheter was responsible for the increased risk of gastric perforation.

For the entire Group A and Group B cases, the interval from the initial VPS insertion/VPS revision to the diagnosis of the VPS complication described above ranged from one day to 11 years. For the cases that had a history of VPS revision, for them, the interval was calculated from the date of the last VPS revision done. In seventy-two percent (*n* = 33) of the entire case, this complication was detected within 24 mo after the VPS insertion/shunt revision. In 60% (*n* = 28) of the entire case, it occurred within 12 mo of VPS insertion/last shunt revision. In one-fourths (*n* = 12) of the entire cases, it was detected within 6-months of VPS insertion/shunt revision. For Group A cases, the said complication was detected within a month to 24 mo in more than four-fifths (*n* = 27) of cases. For Group B cases, the complication was detected within a month to 24 mo in forty-three percent (*n* = 6) cases. In *n* = 5 of Group B cases, the interval from VPS insertion to the detection of the said VPS complication was 3 to 10 years. A recent systematic review (2022) of the *n* = 210 cases on the management of trans-anal extrusion of the distal VPS catheter also revealed that in 70% of the cases, it occurred within 12 mo after the VPS insertions[11]. Like the above finding, the present review also revealed that 60% of the entire cases and four-fifths of Group A cases were also diagnosed within 12 mo of the VPS insertion. In a recent systematic review (2022) of the *n* = 37 instances of the management of the perforation and intra-vesical (urinary bladder) migration of the distal part of the peritoneal catheter clinically presented with or without per-urethral extrusion identified that only onethird of the cases presented within 12 mo after the VPS insertion[12]. It means that urinary bladder perforation by the distal VPS catheter is a late complication than colonic or gastric perforation by the distal VPS catheter.

Peroral extrusion of the distal part of a VPS catheter was the chief complaint and clinical finding for Group A cases and it was evident in all the *n* = 32 cases reviewed. In the majority of the cases, the trans-oral extrusion of the distal VPS catheter was associated with a bout of vomiting of short duration. Mild abdominal pain/discomfort relating to the upper GI tract was also documented in some cases. A few Group A cases also had associated headaches and fever. Clinical presentation in Group B cases was vague, and not specific to the distal VPS catheter complication. The Group B cases mostly had symptoms relating to the CNS or gastrointestinal tract (GIT). Five cases presented with symptoms related to the CNS. Six cases presented predominantly with symptoms related to the upper GIT. Eight cases also had associated general symptoms like fever, weakness, and others.

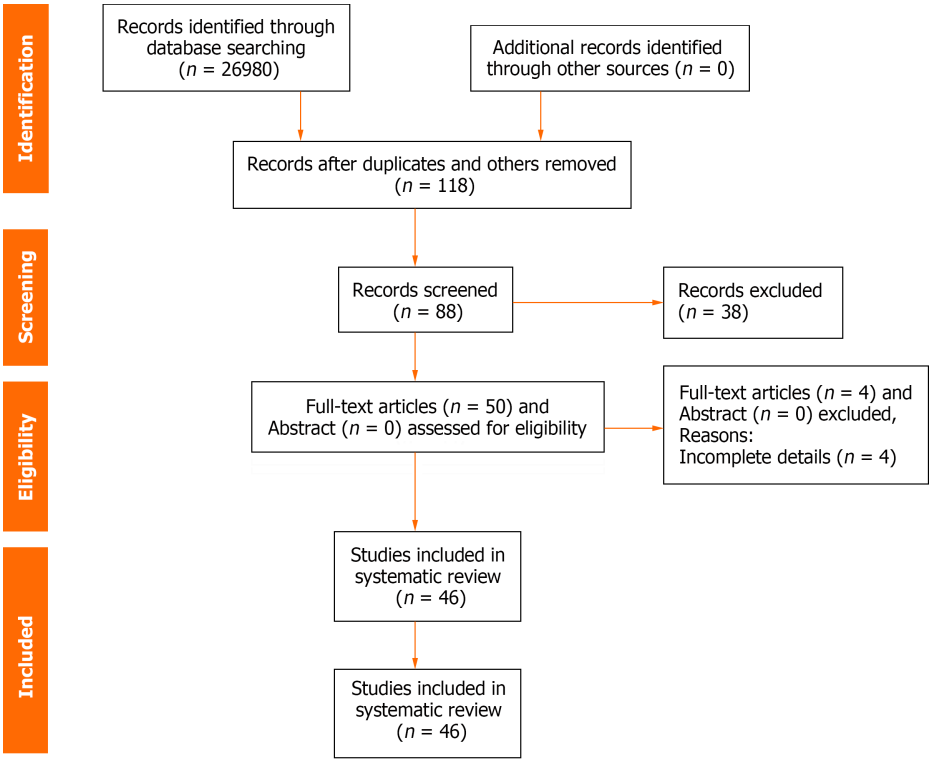

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Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram for manuscripts screening and selection for the systematic review of the management of migration of the distal ventriculoperitoneal shunt catheter into the stomach with or without trans-oral extrusion.

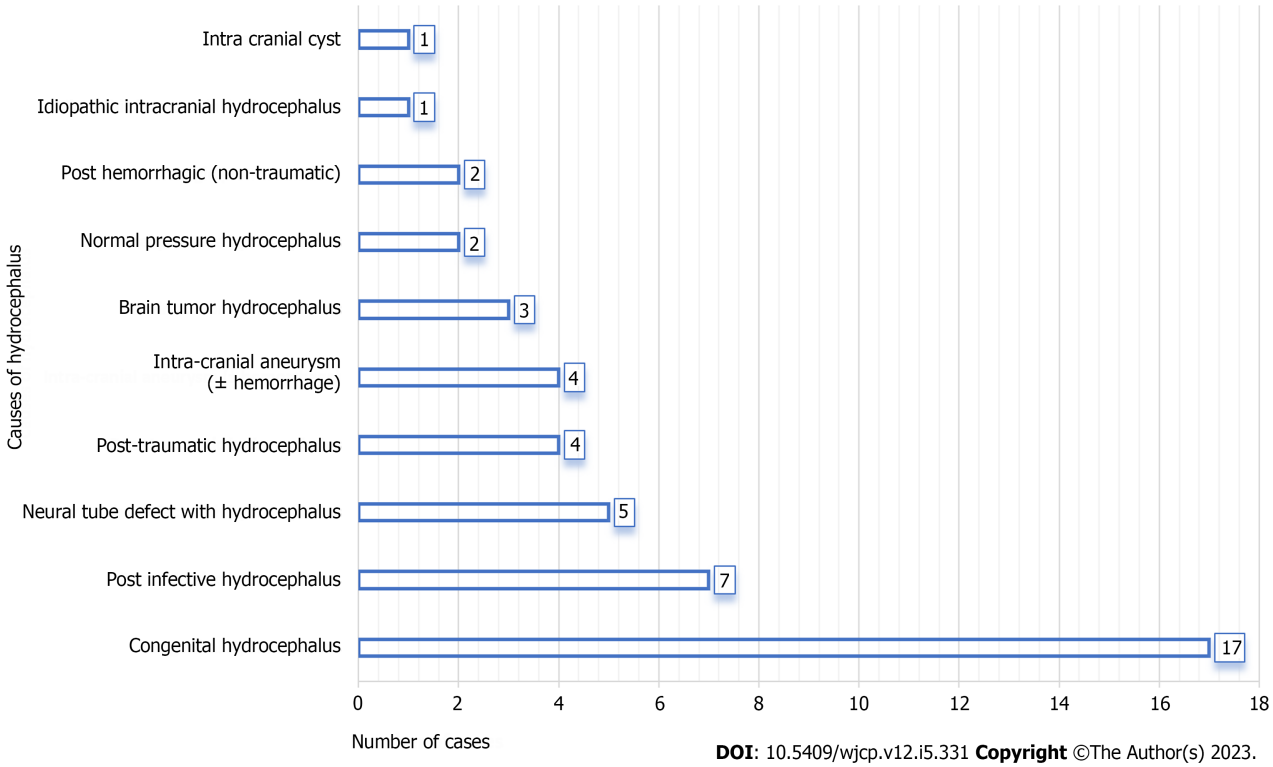

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Figure 2 Indication (causes of hydrocephalus) for primary ventriculoperitoneal shunt insertion for entire cases (*n* = 46).

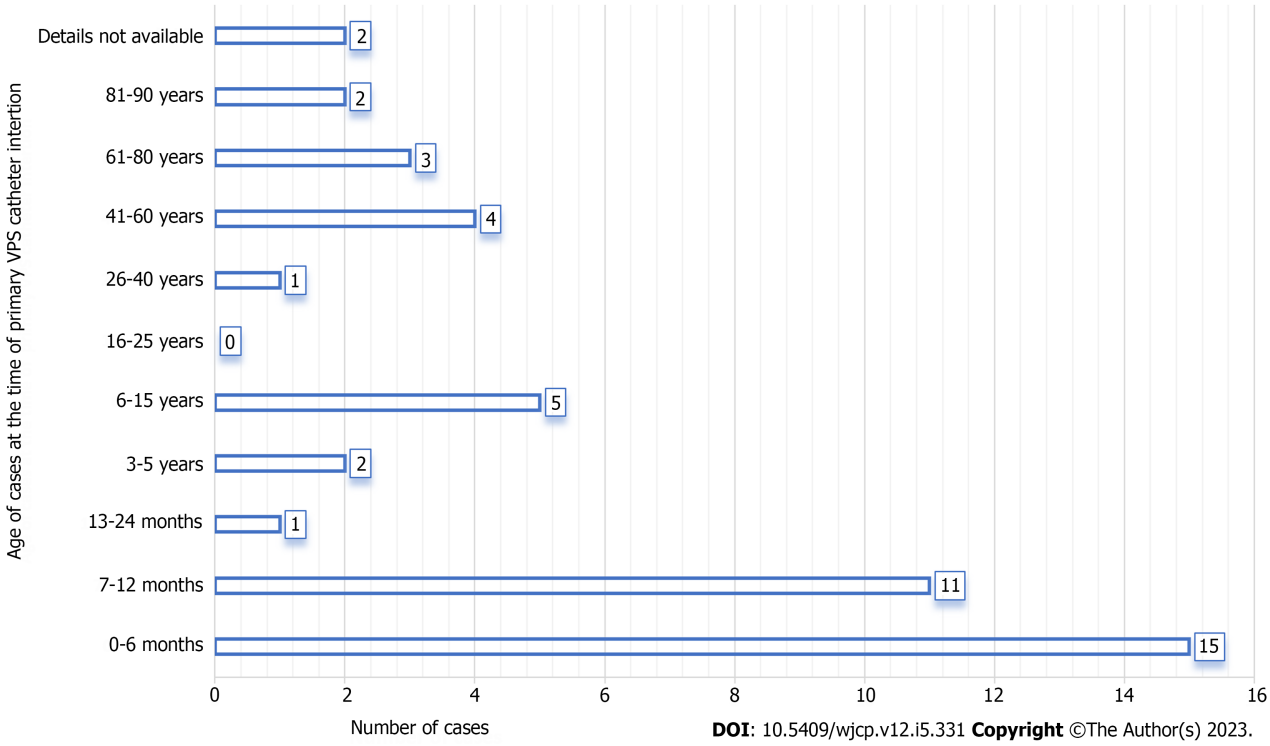

Figure 3 Age distribution (entire cases) at the time of primary ventriculoperitoneal shunt insertion (*n* = 46).

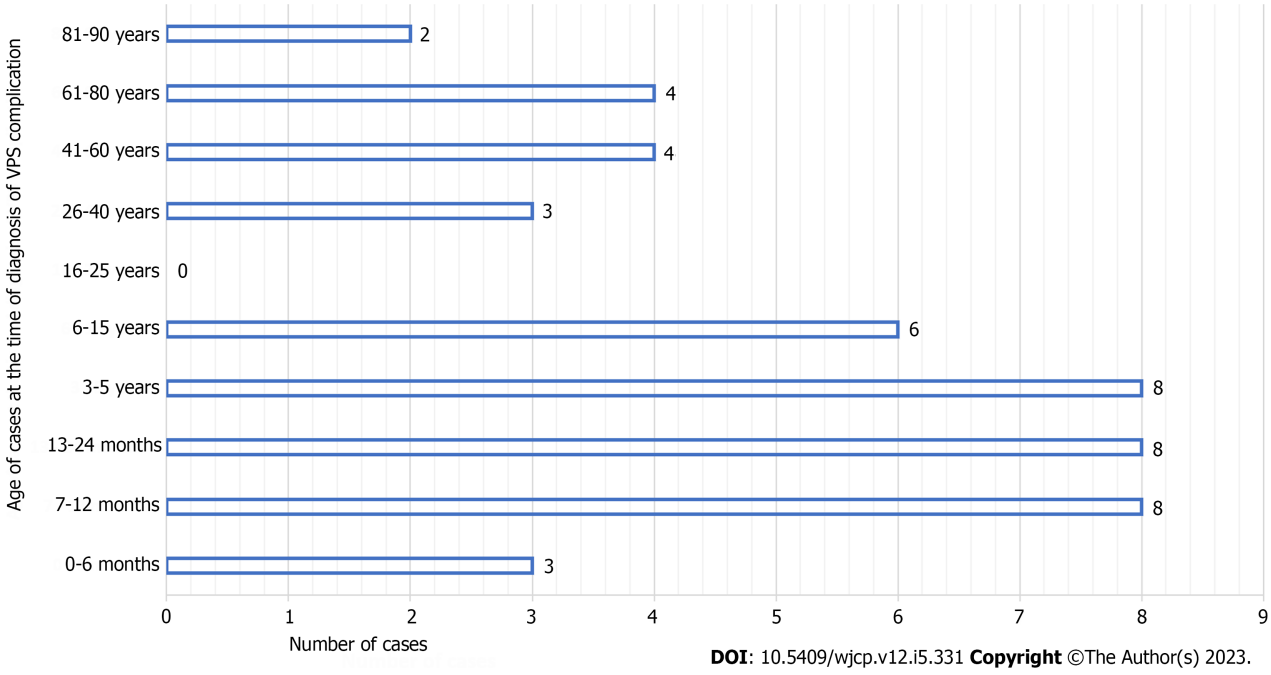

Figure 4 Age distribution (entire cases) at the time of diagnosis of migration of the distal ventriculoperitoneal shunt catheter into the stomach with or without trans-oral extrusion (*n* = 46).

In a 5-mo-old girl, an iatrogenic gastric perforation occurred during the initial/primary VPS insertion, but it was unnoticed. On the first postoperative day, the presence of a distal VPS catheter within the lumen of the stomach was detected, and it was treated successfully[54]. An 87-year-old man underwent investigation for upper GI bleeding/coffee-ground vomiting and the intra-gastric presence of his distal VPS catheter was detected during the upper GI endoscopy [57]. A 65-year-old woman was under investigation for iron deficiency anemia and the intra-gastric presence of her distal VPS catheter was detected during the upper GI endoscopic evaluation[60].

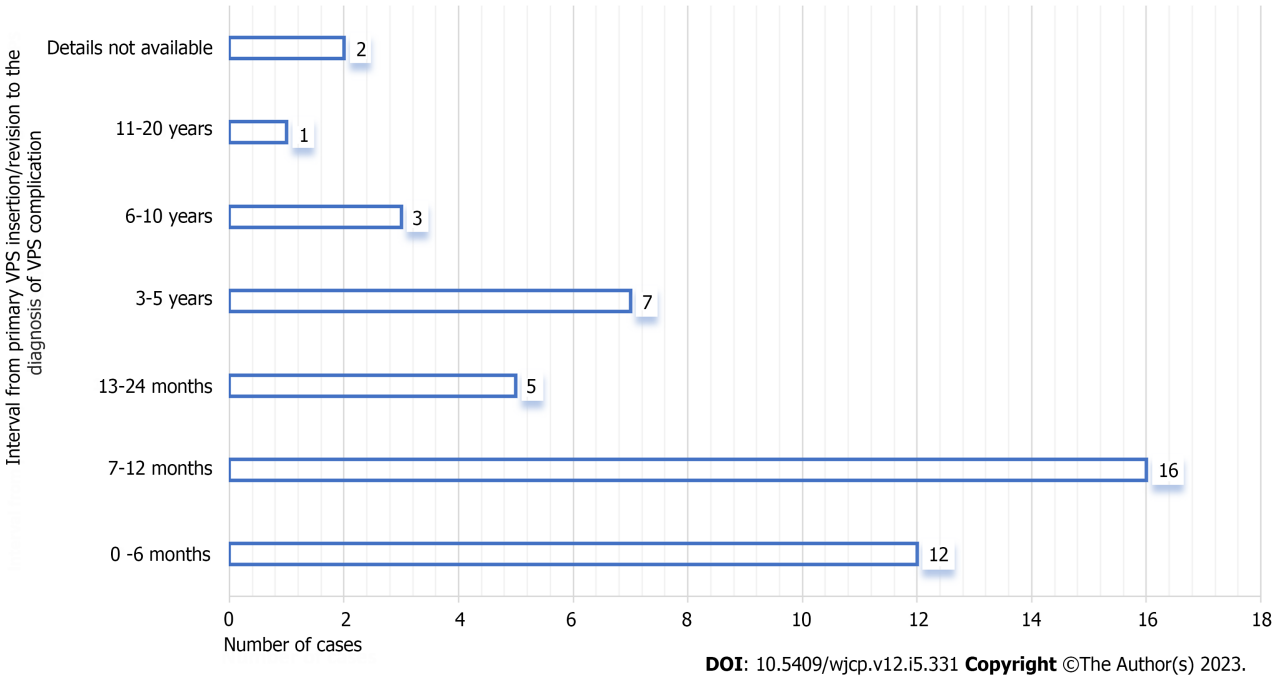

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Figure 5 Interval (entire cases) from primary ventriculoperitoneal shunt catheter insertion/revision to the diagnosis of migration of the distal ventriculoperitoneal shunt catheter into the stomach with or without trans-oral extrusion (*n* = 46).

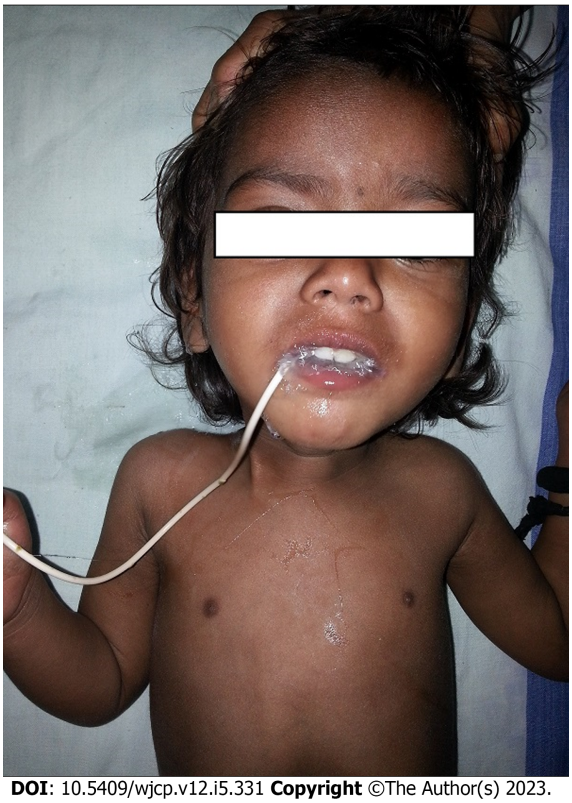

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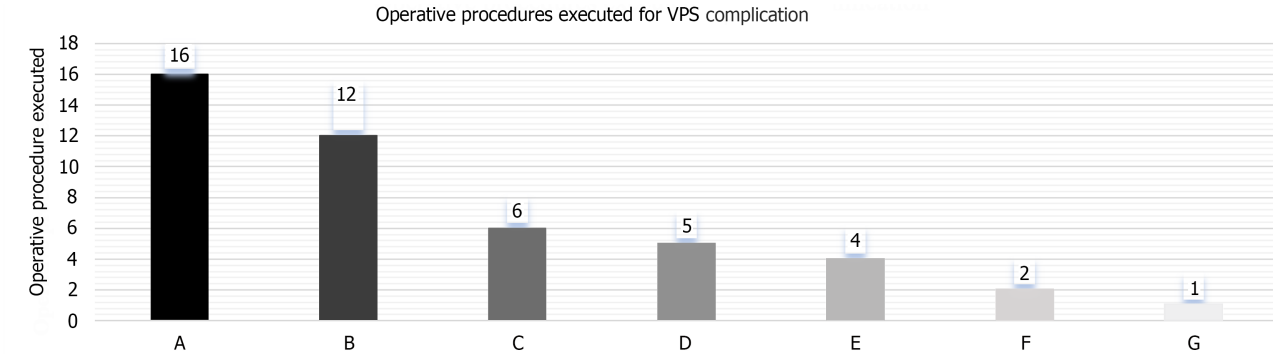
Figure 6 Clinical photograph of a 2 years-old-girl presented with trans-oral extrusion of the distal ventriculoperitoneal shunt catheter. This child was operated upon/managed by the author and published[37].

VPS catheter tract infection was not a frequent clinical finding. During the clinical examination, *n* = 4 (two from each Group) cases had features suggestive of shunt tract infection. Clinical features of peritonitis were not documented in any of the cases reviewed. The occurrence of peritonitis after the bowel/colon perforation by a distal VPS catheter is not a rule, and it was not reported in most cases. In a systematic review of trans-anal extrusion of the distal VPS catheter, peritonitis was documented only in 3.8% of the cases[11]. Possibly for similar reasons like colon perforation clinically



A = Removal of entire ventriculoperitoneal shunt (VPS) catheter
B = Removal of part of distal/distal VPS shunt catheter ± proximal VPS catheter/cranial catheter converted as external ventricular drainage
C = Removal of entire/distal VPS catheter and immediate re-VPS insertion/ventriculo-atrial shunt/VPS revision
D = Removal of entire VPS catheter + external ventricular drainage
E = Removal of part of distal VPS catheter and relocation of remaining distal VPS catheter into the peritoneal cavity
F = Autopsy findings
G = Surgical therapy not done/not offered for the intra gastric migration of the distal VPS catheter

DOI: 10.5409/wjcp.v12.i5.331

Figure 7 Operative procedures executed for the migration of distal ventriculoperitoneal shunt catheter into the stomach with or without trans-oral extrusion (*n* = 46).

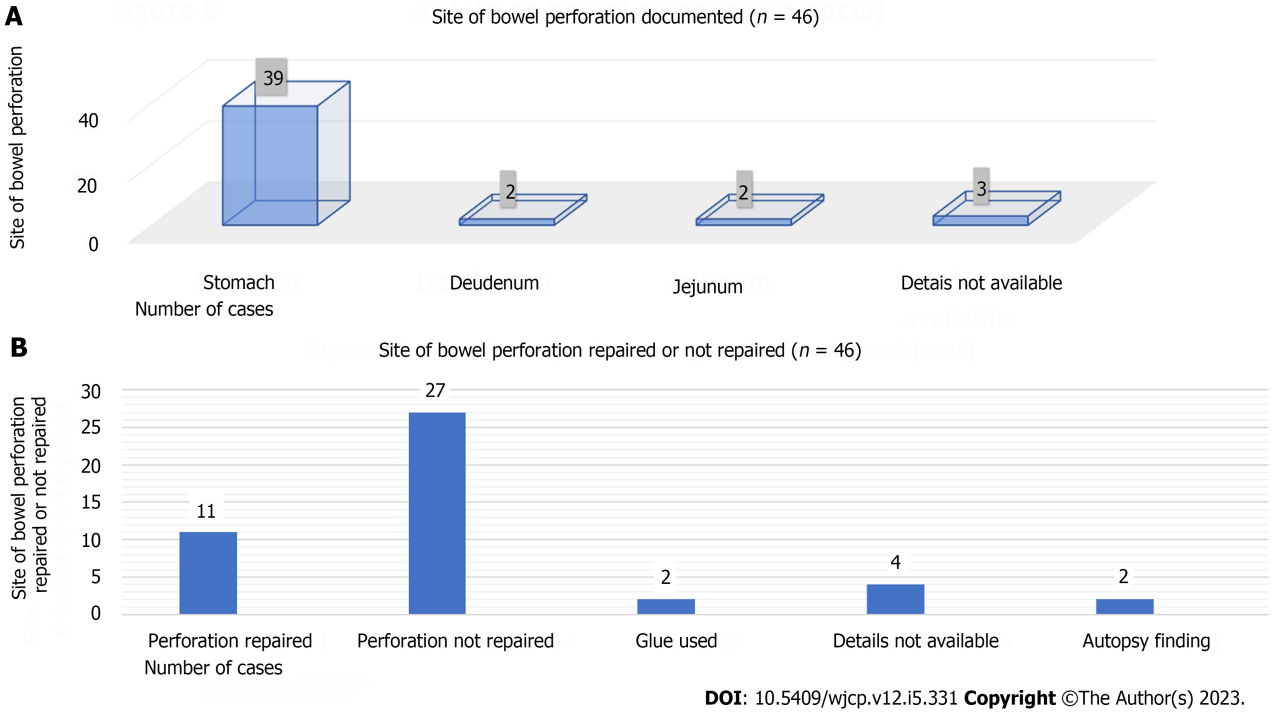


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Figure 8 The site of bowel perforation caused by the distal ventriculoperitoneal shunt catheter. A: Site of bowel perforation documented in the entire cases (*n* = 46); B: Site of bowel perforation repaired or not repaired (*n* = 46).

presented with per-rectal extrusion of VPS catheter, there was no peritonitis even though there was perforation and migration of distal VPS into the stomach in a present review. Clinical signs of meningitis were evident in *n* = 4 of Group B and none of the Group A cases. Cerebrospinal fluid (CSF) infection was documented in *n* = 11 cases. CSF infection was more frequently documented in Group B cases, as half of them had CSF infection. CSF infection was less frequent in Group A cases, as only *n* = 4 had CSF infection at the time of diagnosis of the VPS complication mentioned above.

The clinical diagnosis of peroral extrusion of the distal part of a VPS catheter was evident for the entire Group A cases. Various investigations were required for the diagnosis of Group B cases. Varieties of investigations were needed and carried out to confirm or exclude the continuity of the VPS catheter, the presence or absence of gas under the diaphragm, peritoneal fluid collections, and evaluation of the ventricular system. A skiagram of the head, abdomen, and chest was one of the commonly advised investigations. Cranial computed tomography (CT) scan was ordered in *n* = 15 cases (*n* = 10 for Group A and *n* = 5 for Group B) for the confirmation of the position of the ventricular catheter within the ventricle and the understanding of the hydrocephalus/ventricles[23,24,28,32,37,38,40,42,43,46,51,58,59,61,62]. CT scan of the abdomen was ordered for *n* = 9 cases[26,46,55,56,58,59,60-62]. It was only ordered for *n* = 2 of the Group A cases[26,46].

CT scan of the abdomen was ordered for *n* = 7 of the Group B cases for the confirmation of the intra-gastric position of the distal VPS catheter[55,56,58,59,60-62]. Shuntogram (*n* = 3) and dye studies (*n* = 3) were performed/done during the investigations[33,34,50,51,53]. Upper gastrointestinal endoscopic evaluation was carried out in *n* = 12 cases[19,32,34,38,55-62]. Eight of the Group B cases were evaluated by the upper GI endoscopy, which was helpful in the confirmation of the intra-gastric location of the distal VPS catheter[55-62].

Much progress has taken place not only in the field of better understanding of the etiopathogenesis of the hydrocephalus, but also in the field of physiology of CSF circulation, development of shunt devices/shunt systems, use of newer technology, perioperative and postoperative care, and management of the shunt related complications[67-69]. VPS catheter implantation is among the most frequently performed surgical procedures in the management of hydrocephalus, caused by various etiology, and performed across the globe for all ages. Many VPS-related complications also require shunt revisions[70-74]. The insertion of the peritoneal/distal VPS catheter within the peritoneal cavity for primary VPS insertion or shunt revision surgery can be done *via* mini-laparotomy, using a trocar or laparoscopic technique with the advantages and disadvantages of each of the surgical techniques[75-77]. A recent international survey carried out for the preference of the distal VPS catheter insertion within the peritoneal cavity found that most of the responded neurosurgeons preferred doing so via/through a mini-laparotomy, and it was frequently preferred by the surgeons over the laparoscopic methods[78].

Management of the intra-gastric migration of the distal VPS catheter with or without trans-oral extrusion is three-fold: (1) The removal of intra-gastric migrated distal VPS catheter; (2) treatment of the gastric perforation caused by the distal VPS catheter; and (3) shunt revision, if required. It differs from case to case, depending upon the presence or absence of shunt or shunt tract infection, CSF infection/meningitis, peritonitis, and the general condition of the patient. Various surgical procedures were offered for the management of the above-described complication in *n* = 43 cases of both Groups. One-third (*n* = 16) of the entire case was treated by the removal of the entire VPS catheter. One-fourth (*n* = 12) of the entire case was treated by the removal of the part of the peritoneal/distal VPS catheter with or without conversion to EVD. In six cases (*n* = 5 Group A and *n* = 1 Group B), the entire/distal VPS catheter was removed and shunt revision was carried out during the same operative procedure. In five cases (*n* = 4 Group A and *n* = 1 Group B), the entire VPS catheter was removed and an EVD was inserted. Four cases (*n* = 2 Group A and *n* = 2 Group B) were managed by the relocation of the distal/remaining distal VPS catheter within the peritoneal cavity. In two instances/cases, the intra-gastric presence of the distal VPS catheter was detected during the autopsy[49,52]. In one of the cases, the surgical therapy was deferred as he was clinically stable and did not have symptoms related to the intra-gastric migration of the distal VPS catheter[58]. Percutaneous surgical removal of the entire/distal VPS catheter with or without an EVD was the procedure of choice and was preferred in *n* = 27 (*n* = 24 Group A and *n* = 3 Group B) cases. Exploratory laparotomy was carried out for the management of the above-described distal VPS catheter complication in *n* = 11 (*n* = 7 of Group A and *n* = 4 of Group B) cases[18,22,32,39,41,42,43,53,54,59,61]. The laparoscopic technique was applied in *n* = 5 cases and was carried out in *n* = 4 Group B cases[34,55,57,60,62].

The functional status of the VPS catheter was not mentioned/not provided in the literature reviewed for *n* = 22 of Group A and *n* = 11 of Group B cases[17,19-23,26,27,30-32,34-36,41-49,51-54,57-62]. The distal end of the VPS catheter was draining CSF, confirming that the VPS catheter was functioning well in *n* = 6 of Group A and *n* = 2 of Group B cases, respectively[18,24,25,29,37,39,50,55]. The authors also documented that the VPS catheter was not functional, and it was not draining CSF at the distal end in *n* = 4 of Group A and *n* = 1 of Group B cases, respectively[28,33,38,40,56].

Crust formation at the tip of the distal VPS catheter was not detected/documented in any of the Group A cases managed for the transoral extrusion of the distal VPS catheter[17-48]. Crust formation at the tip of the distal VPS catheter was not detected/documented during the radiological/endoscopic evaluation and operative procedures executed for the management of intragastric migration of the distal peritoneal catheter/distal VPS catheter *n* = 11 of the Group B cases[50,51,53-57,59-62]. Only in one of the Group B cases, during the autopsy, a white stone-like structure was detected at the tip of the distal VPS catheter, although the other drainage holes/perforations of the distal VPS catheter were patent. The intragastric part of the distal VPS catheter was like a rigid coiled spring catheter[52]. In this case, the stone/crust formation at the tip of the distal VPS catheter that happened either before the intragastric migration or afterward was also not explained/not clear[52].

The literature review documented/revealed the use of the stomach as the site for the insertion of the distal VPS catheter for CSF diversion in the treatment of hydrocephalus[79-82]. In 1965, Alther described a direct insertion of the distal VPS catheter into the stomach through a Witzel-type fistula[79,80]. In 1972, Lamesch reported/published the use of a gastric tube for the insertion of a distal CSF shunt catheter in seven mongrel dogs. He experimented and performed ventriculogastrostomy by means of the creation of the pedunculated gastric pouch and insertion of the distal shunt catheter within the gastric pouch. In the same paper, he also reported the first successful result of a ventriculogastrostomy that was performed by him on a 3-year-old boy. The operation was performed by him on April 22, 1970. He further reported that the boy was doing well at the follow-up done 10 mo after the operation[80]. In 1975, Weiss *et al*[81] also reported ventriculogastrostomy as an alternative means for CSF diversion as a preliminary study. They experimented with the technique in eight of the mongrel dogs. They also performed ventriculogastrostomy on a 3-wk-old child for the treatment of hydrocephalus. In 1977, Duff *et al*[82] reported their experience with ventriculo-gastric shunts and the role of gastroscopy in shunt evaluation and revision. They reported their experience of ventriculo-gastric shunts, that was performed on six patients, and their age ranged from three weeks to nine years. Two of their cases developed distal shunt obstruction and were evaluated and successfully treated by means of gastroscopy.

The stomach was the site of perforation by the distal VPS catheter *n* = 25 of the Group A and all (*n* = 14) the Group B cases. The duodenum was perforated by the distal VPS catheter in two of the Group A cases[42,43]. The jejunum was perforated by the distal VPS catheter in two of the Group A cases[22,46]. The site of perforation by the distal VPS catheter was not mentioned/not provided in the manuscripts for three cases. Repair of the bowel perforation caused by the distal

VPS catheter is not always required. A systematic review of *n* = 210 cases of bowel perforation by the distal part of the VPS catheter clinically presented with the extrusion of the same *via* the anal canal revealed that colon/bowel perforation was repaired only in onefourth of the cases. In the remaining, threefourths cases, the colon/bowel perforation healed spontaneously, after the removal of the migrated/extruded VPS catheter[11]. In the present systematic review of *n* = 46 cases of gastric perforation by the distal VPS catheter only one-fourth (*n* = 11; *n* = 6 Group A and *n* = 5 Group B) of the cases, the perforation site was surgically repaired. In two cases, the perforation site was sealed by the fibrin glue application. In more than half (*n* = 27) cases, the gastric perforation caused by the distal VPS catheter was not repaired and healed spontaneously.

Shunt revision was also an integral part of the management of the intra-gastric migration of a distal VPS catheter clinically presented with or without peroral extrusion of the distal end of VPS catheter. In the present review of *n* = 46 cases of the trans-gastric migration of the distal VPS catheter, the details for *n* = 25 (*n* = 20 Group A and *n* = 5 Group B) cases are available regarding the shunt revision procedures. Delayed re-VPS insertion/VPS revision or VA shunt placement was preferred over the immediate shunt revision. The advantages of delayed reVPS insertion/VPS revisions or VA shunt insertion were that the optimal treatment was provided for meningitis/CSF infection, if present, and it was also possible to evaluate the cases for the requirement of shunt revision. Delayed re-VPS insertion/VPS revision or conversion to a VA shunt was carried out in *n* = 19 (*n* = 15 Group A and *n* = 4 Group B) cases. For the Group A cases; delayed re-VPS insertion in *n* = 11, VPS revision in *n* = 2, and VA shunt placement in *n* = 2, were preferred by the authors. In six (*n* = 5 Group A and *n* = 1 Group B) cases, the shunt revision procedure was executed immediately after removing the entire/distal VPS catheter. The authors performed an immediate re-VPS insertion in *n* = 3, VPS revision in *n* = 1, and an immediate VA shunt insertion in *n* = 2 cases. In the present review, authors also documented that re-VPS insertion/VPS revision or VA shunt insertion was not required in *n* = 10 (*n* = 7 Group A and *n* = 3 Group B) cases, neither during the immediate postoperative nor during the followup period.

The exact cause and mechanism of why and how the distal VPS catheter perforates the stomach, migrated within the stomach, and in some of them extruded trans-orally and not extruded in other cases. Possible factors that were responsible for the above in the present review were; the younger age of cases (infants and children younger than 5 years), redundant intra-peritoneal distal VPS catheter in children, history of VPS revisions, and history of abdominal/GI surgery. One-fourth (*n* = 11) underwent VPS revision in the past, and *n* = 8 of the cases had a history of abdominal/GI surgery in the past and were also the possible factors responsible for the migration of the distal VPS catheter into the stomach. The presence of meningitis (*n* = 4) and CSF infection (*n* = 11) in the present study was most probably the result of ascending infection, and may not be the factor responsible for the VPS complication discussed. The perforation of the gastric wall by the distal VPS catheter may be a result of the continuous friction effect. Once there is a small perforation, it is sealed off without producing clinical peritonitis. The distal VPS catheter is forced within the stomach due to the variation in the size of the stomach, the force of abdominal wall movements, and changes in the intra-abdominal pressure. Once it is within the stomach, why some of them extruded trans-orally is not very clear. Most probably, the presence of redundant extra length of the distal VPS catheter within the peritoneal cavity/stomach (especially in children) is responsible for the peroral extrusion of the distal part of a VPS catheter. The intra-gastric distal VPS catheter acts as a foreign body and is expelled per-orally by forceful regurgitation/vomiting. The combination of forceful upward movement of the stomach, increased intra-peritoneal pressure, and forceful abdominal wall movement during nausea/vomiting are responsible for the trans-oral extrusion/protrusion of the distal VPS catheter. The length of the distal VPS/peritoneal catheter is not much extra or redundant in adults and older people and may be the reason for the migration of the distal VPS catheter within the stomach only, and clinically not presenting as trans-oral extrusion of the same.

In the present review, a total of five cases documented complications that were detected during the immediate and late postoperative period. The complications revealed were brain stem herniation (*n* = 1), CSF infection (*n* = 2), meningitis (*n* = 1), and VPS catheter extrusion from the abdominal wound (*n*=1). During the management of the cases of the intra-gastric migration of the distal VPS catheter, this study revealed a total of four (8.69%) deaths, two from each Group[17,23,49,52]. In a 9.3-year-old girl, a VPS catheter was inserted for post-infective hydrocephalus. She also required a feeding gastrostomy for inadequate oral nutritional intake. Three months after VPS insertion, she presented with trans-oral extrusion of her distal VPS catheter, without the clinical features of peritonitis or meningitis, and her CSF also did not detect any organisms. Her VPS complication was treated with EVD and placement of a VA shunt. One month after the VA shunt insertion, she developed acute brain stem herniation and died of the same[17]. A two-year-old boy was diagnosed with congenital hydrocephalus and associated neural tube defect (NTD). His NTD was repaired and a VPS catheter was also placed at the age of 9 mo. Fifteen months after the VPS insertion at the age of two years, he presented with trans-oral extrusion of his distal VPS catheter, without the clinical features of meningitis and peritonitis. His VPS complication was treated with the removal of part of the peritoneal/distal VPS catheter and conversion of the proximal VPS catheter as an EVD. He had a CSF infection and developed ventriculitis that failed to respond well to the antibiotics, and finally died of the same during the treatment[23]. Two of the Group B cases died due to the intra-gastric migration of the distal VPS catheter and the related complication[49,52]. A 69 years-old female developed meningitis 7 mo after VPS insertion that was done for normal pressure hydrocephalus. She was treated conservatively and finally, she died of pneumonia 27 mo after the VPS insertion[49]. A 68-year-old man was diagnosed with NPH and a VPS catheter was implanted. His CNS condition deteriorated further. He was also detected with CSF infection and was treated with antibiotics and other supportive measures, but died of the same[52]. In the above two cases, the intra-gastric migration of the distal VPS catheter was detected during the autopsy[49,52].

Limitations

This systematic review revealed/obtained a limited number of published literature/manuscripts, and it is one of the limitations of this review. Four manuscripts that included five cases were excluded from review for various reasons[63-

66]. There was no uniformity in the treatment of the cases, treated by surgical techniques ranging from simple percutaneous removal of the entire/distal VPS catheter to exploratory laparotomy. For n = 4 (8.69%) cases, the entry site in the bowel by the distal VPS catheter is also not known/not available. The exact cause and the mechanism for the perforation of the stomach and intra-gastric migration of the distal VPS catheter is also not known.

CONCLUSION

Intra-gastric migration of the peritoneal end of a VPS catheter is one of the rare complications of VPS catheter implantation done for the treatment of hydrocephalus across all age groups. Intra-gastric migration with trans-oral extrusion of the distal VPS catheter was twice more commonly reported than the intra-gastric migration of the distal VPS catheter without trans-oral extrusion. It was more frequently reported in children, although also reported in adults and older people. Intra-gastric migration of the distal VPS catheter without transoral extrusion was more frequent in adults and older age groups. Formal exploration of the abdomen for the management of the VPS complication described above was neither done nor required in 70% of cases. In two-thirds of cases, the repair of the stomach/bowel perforation caused by the distal VPS catheter was not done and it healed after the removal of the distal shunt catheter from the stomach/bowel. A very high degree of clinical suspicion is required for the diagnosis of the intra-gastric migration of the distal VPS catheter, clinically presenting without trans-oral extrusion.

ARTICLE HIGHLIGHTS

Research background

Intra-gastric migration of the distal ventriculoperitoneal shunt (VPS) catheter clinically presenting with or without trans-oral extrusion is one of the rare complications of VPS catheter insertion.

Research motivation

To know more about the intra-gastric migration of the distal VPS catheter.

Research objectives

This systematic review of the literature aims to highlight the demographics, clinical characteristics, and outcome of the surgical procedures performed for the intra-gastric migration of the distal VPS catheter, clinically presented with or without trans-oral extrusion of the distal end of peritoneal/VPS catheter.

Research methods

An online search was carried out for extraction/retrieval of published literature about the intra-gastric migration of the distal VPS catheter. PubMed, PubMed Central, ResearchGate, Google Scholar, and Google Images databases were searched using various terminology relating to the VPS complications. Manuscripts were retrieved from 1980 to December 2022. The selection of literature for the present review was done by assessing the titles, abstracts, and full texts of the manuscripts.

Research results

A total of n = 46 cases of intra-gastric migration of the distal VPS catheter clinically presented with or without peroral extrusion were recruited for the systematic review and were retrieved from the n = 46 manuscripts. Approximately sixty percent of them were children ≤ 5 years of age at the time of diagnosis of the complication mentioned above. In seventy-two percent of cases, this complication was detected within 24 mo after the VPS insertion/last shunt revision. Removal of the entire VPS catheter/removal of part of the distal/distal VPS catheter with or without external ventricular drainage was preferred by the authors. Percutaneous surgical removal of the entire or the distal VPS catheter with or without external ventricular drainage was a procedure of choice and was opted for n = 27 cases. For the management of VPS complications mentioned above, formal laparotomy was carried out only in n = 11 cases. In eighty-five percent of cases, the site of bowel perforation was the stomach. The site of bowel perforation was repaired only in n = 11 cases.

Research conclusions

Intra-gastric migration of the peritoneal end of a VPS catheter is one of the rare complications of VPS catheter implantation done for the treatment of hydrocephalus across all age groups. It was more frequently reported in children, although also reported in adults and older people. Formal exploration of the abdomen for the management of the VPS complication described above was neither done nor required in 70% of cases. In two-thirds of cases, the repair of the stomach/bowel perforation caused by the distal VPS catheter was not done and it healed after the removal of the distal shunt catheter from the stomach/bowel.

Research perspectives

This systematic review revealed that the intra-gastric migration of the peritoneal end of a VPS catheter was more commonly reported in children than adults and older people. Intra-gastric migration with peroral extrusion of the distal

VPS catheter was twice as commonly reported than the intra-gastric migration of the distal VPS catheter clinically presented without peroral extrusion. A high degree of clinical suspicion is required for the diagnosis of cases of an intra-gastric migration of the distal VPS catheter clinically presenting without trans-oral extrusion. The exact mechanism for the intra-gastric migration of the peritoneal end of the VPS catheter is not known and requires some specific experimental studies.

FOOTNOTES

Author contributions: All authors have read and approved the final, revised manuscript.

Conflict-of-interest statement: All the authors declare that they have no conflict of interest.

PRISMA 2009 Checklist statement: The authors have read the PRISMA 2009/2021 Checklist, and the manuscript was prepared and revised according to the PRISMA 2009 Checklist.

Country/Territory of origin: India

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S-Editor: Liu JH
L-Editor: A
P-Editor: Cai YX

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World Journal of Clinical Pediatrics

Submit a Manuscript: https://www.f6publishing.com

World J Clin Pediatr 2023 December 9; 12(5): 350-358

DOI: 10.5409/wjcp.v12.i5.350

ISSN 2219-2808 (online)

SYSTEMATIC REVIEWS

Warburg effect mimicking inborn errors of metabolism in childhood hematologic malignancies: A case-based systematic review

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Specialty type: Pediatrics

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C, C, C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Jeong KY, South Korea; Sultana N, Bangladesh

Received: July 22, 2023
Peer-review started: July 22, 2023
First decision: September 4, 2023
Revised: September 9, 2023
Accepted: September 26, 2023
Article in press: September 26, 2023
Published online: December 9, 2023

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Abstract

BACKGROUND

Type B lactic acidosis and hypoglycemia can occur in various pediatric conditions. In young children with a history of fasting preceding these metabolic derangements, inborn errors of metabolism should be primarily considered. However, the Warburg effect, a rare metabolic complication, can also manifest in children with hematologic malignancies. Only a few reports of this condition in children have been published in the literature.

AIM

To identify the clinical course, treatment strategies, and outcomes of childhood hematologic malignancies with type B lactic acidosis.

METHODS

We performed a comprehensive search of the PubMed, Scopus, and Cochrane databases without any time restriction but limited to English language articles. The databases were last accessed on July 1st, 2023.

RESULTS

A total of 20 publications were included in the analysis, all of which were case reports or case series. No higher quality evidence was available. Among children with hematologic malignancies and Warburg effect, there were 14 cases of acute lymphoblastic leukemia and 6 cases of non-Hodgkin's lymphoma including our illustrative case. Lactic acidosis occurred in 55% of newly diagnosed cases and 45% of relapsed cases. The mean age was 10.3 ± 4.5 years, and 80% of cases were male. The mean serum lactate was 16.9 ± 12.6 mmol/L, and 43.8% of the cases had concomitant hypoglycemia. Lactic acidosis initially subsided in 80% of patients

receiving chemotherapy compared to 60% in the contrast group. The mortality rate of newly diagnosed cases was 45.5%, while the relapsed cases represented a 100% mortality rate. All 8 patients reported before 2001 died from disease-related complications. However, patients described in reports published between 2003 and 2023 had a 54.5% rate of complete remission.

CONCLUSION
This complication has historically led to fatal outcome; however, patients who received chemotherapy showed a more favorable response. Therefore, it is crucial to promptly initiate specific treatment in this context.

Key Words: Warburg effect; Lactic acidosis type B; Inborn errors of metabolism; Leukemia; Lymphoma; Children

Core Tip: In children with a history of fasting preceding lactic acidosis, inborn errors of metabolism (IEM) should be considered. However, we describe a case of 10-year-old boy with Burkitt leukemia who exhibited Warburg effect mimicking IEM. The most recent review on lactic acidosis in pediatric leukemia/lymphoma was published in the journal Cancer in 2001. All cases published to that date experienced worsening or recurrence of lactic acidosis, with a mortality rate of 100%. However, this updated systematic review has shown improved outcomes for children with this complication over the past two decades. Newly diagnosed patients and those who received chemotherapy displayed more favorable outcomes.

Citation: Permtawee K, Tengsujaritkul M, Choed-Amphai C, Chanthong S, Mankhemthong K, Sathitsamitphong L, Natesirinilkul R, Charoenkwan P. Warburg effect mimicking inborn errors of metabolism in childhood hematologic malignancies: A case-based systematic review. *World J Clin Pediatr* 2023; 12(5): 350-358
URL: https://www.wjgnet.com/2219-2808/full/v12/i5/350.htm
DOI: https://dx.doi.org/10.5409/wjcp.v12.i5.350

INTRODUCTION

Leukemia and lymphoma are the most common childhood cancers worldwide[1]. These hematologic malignancies have been known to develop several complications, such as tumor lysis syndrome, hyperleukocytosis, and superior vena cava syndrome[2]. In terms of metabolic derangements, hyperkalemia, hyperuricemia, hyperphosphatemia, and hypocalcemia commonly occur in patients with active disease. In a minority of cases, another form of metabolic complication in children with cancer is lactic acidosis[3].

Normal lactic acid production is mainly derived from glucose metabolism *via* the glycolytic pathway, and its utilization primarily occurs in the liver. When abnormal lactate accumulates in the body, it can lead to metabolic acidosis. A serum lactate between 2 mmol/L and 5 mmol/L represents hyperlactatemia, whereas lactic acidosis is commonly found when lactate levels are greater than 5 mmol/L[4]. Lactic acidosis usually occurs when there is an imbalance between oxygen delivery and oxygen demand in type A lactic acidosis. In contrast, type B lactic acidosis results from an impairment of oxidative phosphorylation, which is associated with various conditions, including inborn errors of metabolism (IEM), exposure to drugs toxins, and malignancies. The latter form, which is presented in patients with cancer, could be defined as the "Warburg effect".

Unlike normal cells, which primarily rely on mitochondrial oxidative phosphorylation to generate the energy required for cellular processes, most cancer cells instead rely on aerobic glycolysis[5]. Various factors influence this phenomenon such as oncogene activation, loss of function of tumor suppressors, and effects of transcription factors[6]. This is a rare and unusual metabolic complication in children with hematologic malignancies. Few pediatric case series and case reports of this condition have been published. A previous literature review in 2001 showed that cases with lactic acidosis were more commonly observed in relapsed disease with specific clinical manifestations related to bone marrow, hepatosplenic, or lymph node involvement, and were associated with a poor outcome[3]. However, we encountered a case of newly diagnosed Burkitt leukemia in a 10-year-old boy with hypoglycemia and lactic acidosis which mimicked an IEM disorder. The patient achieved complete remission after treatment with a combination of rituximab and multiagent chemotherapy. Furthermore, we performed an updated systematic review in order to identify the overall profile of clinical course, treatment strategies, and outcomes of childhood hematologic malignancies with type B lactic acidosis from recent decades.

Illustrative case

A 10-year-old boy presented with poor appetite and vomiting that had persisted for 2 d. The physical examination did not show any masses, lymphadenopathy, or hepatosplenomegaly. Complete blood count and peripheral blood smear were within normal limits. A critical blood sample demonstrated the following values: Sodium of 142 mmol/L (normal range: 136-143 mmol/L); potassium of 4.0 mmol/L (normal range: 3.8-4.9 mmol/L); chloride of 109 mmol/L (normal range: 101-107 mmol/L); HCO_3 of 9 mmol/L (normal range: 17-26 mmol/L); anion gap of 24 mmol/L (normal range: 10-

14 mmol/L); blood urea nitrogen of 17 mg/dL (normal range: 7.3-21 mg/dL); creatinine of 1.1 mg/dL (normal range: 0.31-0.61 mg/dL); venous pH of 7.3 (normal range: 7.35-7.45); base excess of -15.2 mmol/L [normal range: (-2)-(+2) mmol/L]; and glucose of 49 mg/dL (normal range: 70-100 mg/dL). Further laboratory studies showed increased serum lactate (3.7 mmol/L; normal range: 1-2 mmol/L), serum ketone (2.7 mmol/L; normal range: 0-1 mmol/L), uric acid (12.5 mg/dL; normal range: 3.4-7.0 mg/dL), and triglycerides (354 mg/dL; normal range: 0-200 mg/dL), while serum cortisol and blood ammonia were normal (20.9 μg/dL and 50 μmol/L, respectively).

Based on the patient's clinical signs and symptoms, wide anion gap metabolic acidosis with ketotic hypoglycemia, IEM especially gluconeogenesis defects, glycogen storage disorders, and organic acidemia were considered. Subsequently, a specific test for plasma amino acids was performed, but only a nonspecific increase in cystathionine of 8.1 nmol/mL (normal range: 0-3 nmol/mL) and β-aminoisobutyric acid of 598.0 nmol/mL (normal range: 0-2 nmol/mL), which is a product of pyrimidine metabolism, was demonstrated. Urine organic acid testing showed an increased excretion of lactic acid and 4-hydroxyphenylactic acid. These findings explained that lactic acidosis was the cause of the wide anion gap metabolic acidosis without any supporting evidence of those IEM.

During admission, the patient developed hypertension and seizure. Computed tomography scan of the brain was performed, which revealed posterior reversible encephalopathy syndrome. The results of the metabolic workup showed that he had hyperuricemia, hyperphosphatemia, hypocalcemia, and acute kidney injury, along with markedly elevated levels of lactate dehydrogenase. These abnormal findings were consistent with tumor lysis syndrome.

Further computed tomography scan of the chest and abdomen was performed to evaluate the cause of hypertension and metabolic derangement, which demonstrated a posterior gastric wall thickening, and infiltrative soft tissue thickening of peritoneum and omentum without hepatic involvement. In addition, lobulated multifocal hypo-enhancing lesions were found scattered throughout the bilateral enlarged renal parenchyma. The patient underwent esophagogastroduodenoscopy for gastric tissue biopsy, and histological pathology revealed a monotonous, intermediate-size lymphoid cells with starry sky appearance. These cells showed round nuclei with finely clumped chromatin and several paracentral nucleoli. Tingible body macrophages phagocyting apoptotic debris were also observed. The immunohistochemistry testing was positive for *CD20*, *CD79a*, *CD10*, *c-MYC*, and *Ki67* (> 95%), leading to the definitive diagnosis of Burkitt lymphoma.

After the procedure, the patient experienced disease progression characterized by progressive cytopenia with abnormal cells observed on peripheral blood smear. As part of disease staging, a bone marrow examination was performed, which revealed a lymphomatous involvement of 30%. The final diagnosis was Burkitt leukemia. A combination of rituximab and multiagent chemotherapy was administered following the St. Jude Mature B-Cell lymphoma and leukemia study III group c protocol. The patient responded well to the treatment, and the metabolic derangement was rapidly resolved. As of June 2023, the patient has been in complete remission for 1 year and 3 mo.

MATERIALS AND METHODS

Data sources and searches

Three authors (Permtawee K, Choed-Amphai C, and Chanthong S) independently conducted searches of the PubMed, Scopus, and Cochrane databases without any time restrictions. The following keywords were used for the search: "lactic acidosis"; "Warburg"; "pediatric"; "child"; "leukemia"; and "lymphoma". For PubMed, the specific search-term strategy was: ["acidosis, lactic" (MeSH Terms) or "acidosis" (All Fields) and "lactic" (All Fields) or "lactic acidosis" (All Fields) or "lactic" (All Fields) and "acidosis" (All Fields) or "warburg" (All Fields) or "warburg's" (All Fields)] and ["paediatrics" (All Fields) or "pediatrics" (MeSH Terms) or "pediatrics" (All Fields) or "paediatric" (All Fields) or "pediatric" (All Fields) or "child" (MeSH Terms) or "child" (All Fields) or "children" (All Fields) or "child's" (All Fields) or "children's" (All Fields)] and ["leukaemia" (All Fields) or "leukemia" (MeSH Terms) or "leukemia" (All Fields) or "leukaemias" (All Fields) or "leukemias" (All Fields) or "leukemia's" (All Fields) or ["lymphoma" (MeSH Terms) or "lymphoma" (All Fields) or "lymphomas" (All Fields) or "lymphoma's" (All Fields)] or ["haematologic malignancy" (All Fields) or "hematologic neoplasms" (MeSH Terms) or "hematologic" (All Fields) and "neoplasms" (All Fields) or "hematologic neoplasms" (All Fields) or "hematologic" (All Fields) and "malignancy" (All Fields) or "hematologic malignancy" (All Fields)]. Only articles published in English language were considered for selection.

Article selection

Inclusion criteria were as follows: Type B lactic acidosis in children with hematologic malignancies (including leukemia and lymphoma); and presence of data on clinical course, treatment strategies, and outcomes. Articles which did not meet these criteria were excluded. Summarization of the inclusion and exclusion criteria for this systematic review is presented in Table 1. The study followed the preferred reporting items for systematic reviews and meta-analysis 2020 guideline[7].

Data extraction

Extracted data included demographic and disease characteristics, laboratory parameters, clinical course, treatment strategies, and outcomes.

Data analysis

A qualitative systematic analysis was conducted using descriptive statistics. Due to differences among individual cases and small sample sizes, a meta-analysis could not be performed.

Table 1 Inclusion and exclusion criteria

Criteria
Inclusion
Children, 0 to 18 yr
Diagnosis of hematologic malignancy, including leukemia and lymphoma
Presence of lactic acidosis
Availability of clinical course, treatment, and outcome data
Exclusion
Adults, > 18 yr
Diagnosis of other solid tumors
Presence of other causes of metabolic acidosis without lactic acidosis
Incomplete information regarding clinical courses, treatment, and outcomes

RESULTS

Search results and article inclusion

A total of 115 publications were obtained through the search. Thirty-five abstracts were screened. The publications were limited to English language articles that provided detailed information about the clinical courses of type B lactic acidosis in children with leukemia or lymphoma resulting in the inclusion of 18 articles. A further two publications were discovered from manually searching the references of prior articles (Figure 1). The 20 included publications were case reports and case series, and there was no higher quality evidence available for this rare complication. These could be categorized into three groups according to cause of type B lactic acidosis, including Warburg effect, thiamine deficiency, and medications. Table 2 summarizes the clinical and laboratory parameters, treatments, and outcomes of the previously reported cases[3,8-26].

Demographic and disease characteristics

Among the pediatric cases with hematologic malignancies and the Warburg effect, there were 14 of acute lymphoblastic leukemia (ALL), including 7 with B-ALL, 4 with T-ALL, and 3 with unknown cell type, as well as 6 cases of non-Hodgkin's lymphoma (NHL), which consisted of 5 of Burkitt leukemia/lymphoma and 1 of T-NHL. Lactic acidosis occurred in 11 cases with newly diagnosed leukemia/lymphoma (55%), while the remaining cases had relapsed disease (45%). The mean age of the patients was 10.3 ± 4.5 years, and 80% of the cases were male.

Clinical manifestations and laboratory parameters

The most common clinical manifestations were dyspnea (44.4%), symptoms related to cytopenia (38.9%), fever (27.8%), weight loss (27.8%), and splenomegaly (27.8%). Hepatic involvement, which included patients with hepatomegaly, impaired hepatic synthetic function, cholestasis, or imaging-proven infiltrative disease, was found in 62.5% of cases (10 out of 16 patients). Renal involvement, which was defined as patients with imaging-proven infiltrative disease, occurred in about half of the cases (8 out of 14 patients). Patients with renal failure that might have resulted from other specific causes, such as tumor lysis syndrome, were excluded. The mean serum lactate was 16.9 ± 12.6 mmol/L, and 43.8% of the cases had concomitant hypoglycemia.

Treatment strategies

Almost all cases received sodium bicarbonate infusion (85%) in addition to general management protocols such as delivery of intravenous fluids and glucose. Renal replacement therapies, including continuous renal replacement therapy and peritoneal dialysis, were provided in only 20% of cases. Chemotherapy was given to three-quarters of the patients as a specific treatment.

Clinical courses and outcomes

Lactic acidosis initially subsided in about 80% of patients receiving chemotherapy compared to 60% in the contrast group. Furthermore, patients treated with chemotherapy had a more favorable response (complete remission of 40% *vs* 0%, respectively). The disease status may also affect the long-term outcome. The mortality rate of patients with newly diagnosed hematologic malignancies and lactic acidosis was 45.5%, while the relapsed patients had a 100% mortality rate. Warburg effect accounted for 23.1% of the causes of death. This review also highlighted that patients in the last two decades have experienced better outcomes than those in the previous review. Prior to 2001, patients diagnosed with leukemia or lymphoma-associated lactic acidosis had extremely poor outcomes. Six out of eight cases died from the disease-related conditions, while the other two cases experienced uncontrolled infections. However, publications between 2003 and 2023 revealed that 54.5% of cases achieved complete remission. In the minority of cases, patients with type B

Table 2 Demographics, treatments, and outcomes of previously reported children with leukemia/lymphoma and type B lactic acidosis

Ref.	Primary diagnosis	Age in yr, Sex	Clinical manifestation	Initial lactate in mmol/L	Blood glucose in mg/dL	Hepatic involvement	Renal involvement	Treatment	Clinical course	
									Lactic acidosis	Outcome
Type B lactic acidosis-Warburg effect										
Field *et al* [8]	Relapsed ALL	4, M	Bleeding, hepato-splenomegaly	20.2	NR	Yes	NR	Bicarbonate, radiotherapy, chemotherapy	Improved but recurred	Death from disease
	ALL	8, M	NR	9.9	NR	NR	NR	Bicarbonate, chemotherapy	Improved but recurred	Death from infection
Coleman *et al*[9]	Relapsed T-ALL	2, M	Lymphadenopathy, splenomegaly, dyspnea	24.6	74	No	NR	Bicarbonate, thiamine, insulin, methylglyoxal	Improved but recurred	Death from disease
Ali *et al* [10]	Relapsed B-ALL	12, M	Poor appetite, weight loss, abdominal pain	12.0	NR	No	Yes	Bicarbonate, chemotherapy	Improved but recurred	Death from infection
Révész *et al*[11]	Relapsed Burkitt lymphoma	8, M	Seizure, altered mental status, dyspnea, polydipsia, polyuria	24.0	93	No	Yes	Bicarbonate, thiamine, chemotherapy, radiotherapy	Improved but recurred	Death from disease
Sillos *et al* [3]	Relapsed T-ALL	11, F	Altered mental status	10.8	47	Yes	No	Bicarbonate, CRRT, chemotherapy	Improved but recurred	Death from disease
	Relapsed T-ALL	17, M	Altered mental status, dyspnea, edema	16.0	132	No	No	Bicarbonate	Worsened	Death from disease
	T-NHL	18, F	Fever, weight loss, lymphadenopathy, splenomegaly, dyspnea	15.4	44	Yes	No	Bicarbonate, chemotherapy	Resolved but recurred	Death from disease
Hayek and Srinivasan [12]	B-ALL	7, M	Anemia, lymphaden-opathy, hepatosplen-omegaly	8.4	96	Yes	Yes	Bicarbonate, PD, chemotherapy	Resolved after chemotherapy	CR
Rastogi *et al*[13]	Burkitt lymphoma, HIV	11, M	Fever, hepatospleno-megaly, periorbital and pedal edema	4.2	26	Yes	NR	Bicarbonate, glucagon	Improved	Death from disease
Luscri *et al* [14]	Relapsed B-ALL	7, M	Fever, ascites, dyspnea	5.5	33	Yes	NR	Bicarbonate, CRRT	Worsened	Death from LA, disease
Kulkarni *et al*[15]	Burkitt lymphoma	12, M	Dyspnea, hepato-megaly, abdominal pain	21.0	Normal	Yes	Yes	Bicarbonate, chemotherapy	Resolved after chemotherapy	CR
Terpe *et al* [16]	B-ALL	11, M	Nausea, dyspnea, lymphadenopathy, abdominal pain, pancytopenia	21.0	48	Yes	Yes	Bicarbonate, chemotherapy	Worsened	Death from LA, ACS
Gökçe *et al*[17]	B-ALL	13, M	Weight loss, nausea, bone pain	62.0	97	Yes	Yes	Bicarbonate, chemotherapy	Resolved after chemotherapy	CR
Schuh *et al* [18]	Relapsed B-ALL	12, M	Fever, abdominal pain, bicytopenia	14.8	80	Yes	Yes	Chemotherapy	Worsened	Death from disease
Narayani *et al*[19]	ALL	2, M	Fever, pancytopenia	13.5	96	NR	No	Bicarbonate, chemotherapy	Resolved after chemotherapy	CR
Khera *et al* [20]	T-ALL	11, F	Poor appetite, weight loss, nausea, dyspnea, bicytopenia	20.0	104	No	No	Bicarbonate, chemotherapy	Resolved after chemotherapy	CR
O'Rourke *et al*[21]	Burkitt leukemia	13, M	NR	NR	Low	NR	NR	Chemotherapy	Worsened	Death from LA

Hui *et al* [22]	Relapsed B-ALL	17, F	Poor appetite, weight loss, bicytopenia	15.0	NR	NR	No	Bicarbonate CRRT	Improved	NR
This study	Burkitt leukemia	10, M	Poor appetite, nausea, vomiting	3.7	49	No	Yes	Rituximab, chemotherapy	Resolved after chemotherapy	CR
Type B lactic acidosis-thiamine deficiency										
Oriot *et al* [23]	Relapsed ALL, on TPN without vitamin	3, M	Altered mental status, fever, dyspnea, hepato-megaly	30.0	43	Yes	No	Bicarbonate, PD, thiamine	Resolved	CR
Svahn *et al* [24]	B-ALL, on TPN without vitamin	0.9, F	Altered mental status	18.6	NR	NR	NR	Bicarbonate, multivitamin including thiamine	Resolved	CR
Didisheim *et al*[25]	ALL, post-sepsis	13, M	Fever, abdominal pain, hypotension	19.6	NR	NR	NR	ECMO, thiamine	Resolved	CR
Type B lactic acidosis-medication (s)										
Smolka *et al*[26]	Relapsed B-ALL, pneumonia (antibiotics including linezolid)	9, F	Altered mental status, dyspnea	19.0	NR	Yes	NR	Bicarbonate, withdraw linezolid	Improved	CR

ACS: Abdominal compartment syndrome; ALL: Acute lymphoblastic leukemia; CR: Complete response; CRRT: Continuous renal replacement therapy; ECMO: Extracorporeal membrane oxygenation; F: Female; LA: Lactic acidosis; M: Male; NR: Not reported; PD: Peritoneal dialysis.

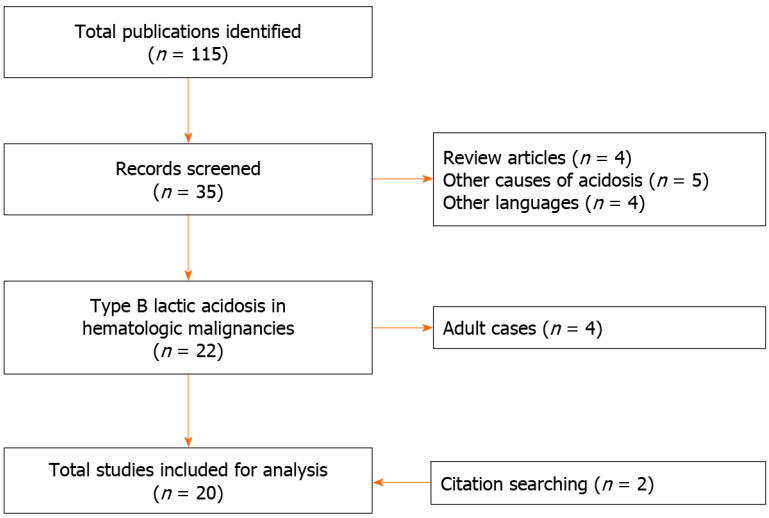

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Figure 1 Preferred reporting items for systematic reviews and meta-analysis flowchart for study selection.

lactic acidosis from thiamine deficiency and linezolid treatment had excellent outcomes, with a 100% complete remission rate.

DISCUSSION

In the pediatric population, especially young children, an IEM disorder should be considered as a potential differential diagnosis in patients with a history of fasting or poor intake followed by hypoglycemia, and lactic acidosis with or without ketosis. The specific disorders of carbohydrate metabolism that can present with hyperlactatemia include glycogen storage diseases, gluconeogenesis defects, and organic acidemia. Findings from personal history taking, family history taking, and physical examination should be evaluated. Another crucial investigation in these diseases is a critical blood sampling taken during hypoglycemia episodes and including analysis of lactate, ammonia, blood gas analysis, insulin, cortisol, and ketones. Additional plasma amino acid and urine organic acid tests should be performed depending on the clinical suspicion[27,28]. After a comprehensive evaluation in our case, there was no evidence to support these

diseases. However, the patient later developed clinical symptoms of hypertensive emergency, tumor lysis syndrome and cytopenia, which led to the final diagnosis of Burkitt leukemia.

Type B lactic acidosis is an uncommon complication in patients with cancer, although there are several precipitating causes such as thiamine deficiency and medications. Cancer itself can lead to this form of metabolic acidosis. The proposed pathophysiology of this condition was first described by Warburg[29] in 1925. Since then, several studies have explored cancer metabolism and Warburg effect, which can be summarized into four main functions, as follows: Cell signaling; rapid adenosine triphosphate synthesis; biosynthesis; and tumor microenvironment[5]. Contrary to the publications on adult cases, the most recent review of lactic acidosis in pediatric leukemia and lymphoma was published in 2001 [3]. Sillos *et al*[3] summarized a total of 9 pediatric cases of hematologic malignancies with lactic acidosis, comprising 2 with lymphomas (1 Burkitt lymphoma and 1 T cell-non-Hodgkin's lymphoma) and 7 with ALLs. All cases experienced worsening or recurrence of lactic acidosis, and the outcome was extremely poor, with a 100% mortality rate. However, this updated review demonstrated that outcomes have improved in the last two decades, possibly due to increased understanding of disease pathophysiology, advances in treatment, and improvements in supportive care. Patients with newly diagnosed leukemia/lymphoma and those who received a specific treatment with chemotherapy appeared to have a better outcome. These findings also differ from those in the adult population. In the past decade, adults with hematologic malignancies who experienced lactic acidosis still had a mortality rate of more than 80%[30,31]. Despite the same pathophysiology of this complication in the pediatric and adult populations, disease status and response to treatment may explain the dismal outcome in adults. According to the United States' surveillance, epidemiology, and end results program database, survival rates according to age of diagnosis (all patients) at 17 years, 20 years, and 70 years were 75%, 48%, and 15%, respectively. Different treatment regimens and responses were determined to have played significant roles in this survival cliff drop-off[32]. This systematic review is limited by the rarity of this complication, with only a few case reports and case series available.

When compared to the other pediatric reports, our case presented with only nonspecific symptoms (a less common clinical manifestation). The patient had hypoglycemia with slightly elevated serum lactate levels, which is usually described as hyperlactatemia. However, further comprehensive investigations were performed and demonstrated that hyperlactatemia was the only remaining cause of the wide anion gap metabolic acidosis in this patient. One of the different management approaches used for this patient was administration of rituximab, a monoclonal antibody to *CD20*, which elicited a rapid response when combined with conventional chemotherapy. The lactic acidosis was abruptly resolved, and the patient has remained in complete remission.

CONCLUSION

Historically, Warburg effect in childhood hematologic malignancies has led to absolute fatal outcome, but over the past two decades about half of the cases have achieved complete remission. Specific treatment should be promptly initiated in this context. Furthermore, our case illustrates this uncommon metabolic derangement in childhood Burkitt leukemia. While IEM are one of the causes of metabolic acidosis in young children, Warburg effect in hematologic malignancies should also be considered in older children.

ARTICLE HIGHLIGHTS

Research background

Type B lactic acidosis is a rare metabolic complication in children with hematologic malignancies which can mimic inborn errors of metabolism (IEM). There have been few pediatric case series and case reports published on this specific condition. Moreover, the most recent review was conducted over two decades ago, in 2001.

Research motivation

The illustrative case of a 10-year-old boy with Burkitt leukemia who exhibited Warburg effect mimicking IEM was the basis of our systematic review. The previous review of this metabolic complication showed an extremely poor outcome. In recent years, however, advancements in cancer treatments may have led to the overall improvement in the clinical course.

Research objectives

To identify the clinical course, treatment strategies, and outcomes of childhood hematologic malignancies with type B lactic acidosis.

Research methods

We performed a comprehensive search of the PubMed, Scopus, and Cochrane databases without any time restrictions to identify children with leukemia/lymphoma and type B lactic acidosis. The publications considered for inclusion were limited to English language articles.

Research results

Lactic acidosis initially subsided in 80% of patients receiving chemotherapy compared to 60% in the contrast group. The mortality rate of newly diagnosed cases was 45.5%, while the relapsed cases had a 100% mortality rate. All 8 cases reported before 2001 died from disease-related complications, while cases reported between 2003 and 2023 showed a 54.5% rate of complete remission.

Research conclusions

Historically, this complication has led to fatal outcome; however, patients who received chemotherapy showed a more favorable response. Therefore, it is crucial to promptly initiate specific treatment in this context.

Research perspectives

This systematic review has revealed an improvement in the clinical course and outcomes compared to the past. Future studies in this context might include a larger scale of cases involving multicenter research. Retrospective study on prognostic factors or therapeutic research in the era of immunotherapy and targeted therapy could also be performed in this population.

ACKNOWLEDGEMENTS

The authors would like to express their gratitude to Ms. Somjai Sittiprechachan for her contribution to the care of our patient.

FOOTNOTES

Author contributions: Permtawee K, Tengsujaritkul M and Choed-Amphai C drafted the manuscript; Permtawee K, Tengsujaritkul M, Choed-Amphai C, Chanthong S, Mankhemthong K, Sathitsamitphong L, Natesirinilkul R and Charoenkwan P participated in patient management and data collection; Permtawee K, Choed-Amphai C and Chanthong S contributed to the systematic review; All authors contributed to the article and approved the submitted version.

Conflict-of-interest statement: All the authors declare that they have no competing interests.

PRISMA 2009 Checklist statement: The authors have read the PRISMA 2009 Checklist, and the manuscript was prepared and revised according to the PRISMA 2009 Checklist.

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S-Editor: Qu XL
L-Editor: A
P-Editor: Yuan YY

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World Journal of Clinical Pediatrics

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World J Clin Pediatr 2023 December 9; 12(5): 359-364

DOI: 10.5409/wjcp.v12.i5.359

ISSN 2219-2808 (online)

CASE REPORT

Situs inversus totalis in an asymptomatic adolescent - importance of patient education: A case report

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Specialty type: Pediatrics

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: MD XM, China

Received: June 6, 2023
Peer-review started: June 6, 2023
First decision: August 30, 2023
Revised: September 9, 2023
Accepted: September 26, 2023
Article in press: September 26, 2023
Published online: December 9, 2023

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Abstract

BACKGROUND

Situs inversus totalis (SIT) may be an incidental finding in asymptomatic children. Patients may not understand the implications of this condition and the importance of relaying the diagnosis to their healthcare providers.

CASE SUMMARY

We report an asymptomatic seventeen-year-old adolescent with previously-diagnosed SIT who presented for a routine well-child visit. During history taking, he denied any past medical conditions, including cardiovascular conditions. Only when physical exam revealed point of maximal impulse and heart sounds on the right side, did he convey that he had been diagnosed with SIT incidentally at age of 12 years. He was not aware of associated conditions or the potential implications of his diagnosis, nor did he realize it is pertinent medical history to be relayed to healthcare providers. Chest X-ray confirmed dextrocardia and abdominal X-ray showed right-sided stomach. Abdomen sonogram showed left-sided liver and right-sided spleen. Echocardiogram showed normal valvular structure and function. A comprehensive discussion was provided to address the patient's lack of understanding that SIT is a medical diagnosis with potential implications.

CONCLUSION

While SIT is rare and mostly asymptomatic, affected patients may not comprehend the importance of the diagnosis and its potential ramifications. Recognition of the patient's lack of awareness allows the healthcare provider to educate the patient and hopefully can prevent potential medical and surgical complications.

Key Words: Situs inversus; Dextrocardia; Adolescent; Education; Case report

Core Tip: Situs inversus totalis (SIT) is a rare and mostly asymptomatic condition. This care report describes a previously-diagnosed seventeen-year-old adolescent who presented for a routine healthcare visit. During history taking, he denied any past medical conditions, including cardiovascular issues, until physical exam showed heart sounds on the right. He then revealed that he had been diagnosed with SIT incidentally at age 12, but did not realize that it is a significant condition. Patients with SIT may not understand the importance of the diagnosis and its potential ramifications. Healthcare workers must recognize that this lack of understanding of their diagnosis exists and educate them. Our patient was counseled that his diagnosis, although asymptomatic, should be relayed to healthcare teams.

Citation: Hayashi LC, Acharya R. Situs inversus totalis in an asymptomatic adolescent - importance of patient education: A case report. *World J Clin Pediatr* 2023; 12(5): 359-364
URL: https://www.wjgnet.com/2219-2808/full/v12/i5/359.htm
DOI: https://dx.doi.org/10.5409/wjcp.v12.i5.359

INTRODUCTION

Situs inversus totalis (SIT) is a rare congenital anomaly in which the abdominal and thoracic organs are transposed across the sagittal midline with complete mirror-image reversal of laterality[1]. Situs solitus totalis is the term used to describe the normal left-right asymmetry with respect to midline in the arrangement of internal organs. Situs ambiguous, also called heterotaxy syndrome, involves a disturbance in the usual left-right distribution of the thoraco-abdominal organs which does not entirely correspond to the complete mirror image, unlike in SIT[2]. An example would be isolated dextrocardia, in which the heart has reverse orientation without concomitant laterality shift of thoracoabdominal organs. In some of these ambiguous cases, normally asymmetric structures like the lung (2 left lobes *vs* 3 right) and kidneys (different vascular branching patterns) tend toward symmetry[2]. SIT refers to complete, 180 degree reversal of left-to-right orientation, such that the heart, stomach and spleen are located on the right side, liver on the left side, and the paired lungs and kidneys also display reversal of left-right characteristics[1]. However, given that most of these cases are discovered incidentally during the work-up for another condition and are mostly asymptomatic, patients and their families may not realize the importance of this condition. Here, we report such a lack of awareness in a 17-year-old male with SIT who presented for a routine health care examination visit in a primary care provider's office.

CASE PRESENTATION

Chief complaints

Patient is a 17-year-old male who presents to the adolescent clinic in the southeastern United States for a sports physical examination and well-child visit.

History of present illness

Patient is accompanied by his mother, who is from South America and does not speak English. Patient and mother report that he is "completely healthy with no medical conditions." He exercises regularly for 90 min daily, encompassing both strength training and cardiovascular fitness.

History of past illness

The patient initially reports no medical history, including when directly asked about cardiac conditions or symptoms of chest pain, shortness of breath, dyspnea at rest or on exertion, palpitations, ascites, or leg edema. However, when physical exam revealed right-sided heart sounds, the patient revealed that he had been diagnosed incidentally at the age of 12 years following an X-ray performed for unrelated abdominal pain. He subsequently had two appointments with a cardiologist in South America with no reported symptoms or complications. Since moving to the United States two years ago, he has not had medical care. He denies history of sinopulmonary infections or decreased olfaction. When asked why the patient and mother did not disclose this diagnosis when queried about cardiac conditions, their answer was that it was not important information since he is healthy and SIT does not affect him; their understanding was that he did not have a disease, just a mirror-image flip and was essentially normal. The patient and his mother were surprised by these questions and were unaware that this condition may be associated with other syndromes or that there may be potential ramifications for his medical treatment in the future.

Personal and family history

The patient's personal and family history were otherwise unremarkable for cardiovascular conditions or sudden deaths.

Physical examination

Physical examination revealed stable vital signs with manual blood pressure 120/74 mmHg (< 95th percentile for age, height and gender), pulse 86 beats per minute, temperature 96.2° F, and body mass index of 24.5 kg/m^2. Cardiovascular examination was significant for point of maximal impulse palpated on the right at the 5th intercostal space at the midclavicular line. Rate and rhythm were regular with no murmurs, rubs or gallops. Skin had two benign-appearing dark nevi with well-defined borders (approximately 2-3 mm) along posterior axillary line bilaterally. There were no surgical scars detected. Abdominal examination was significant for inferior border of liver palpated 2 cm beneath left costal margin. There were normal bowel sounds with no rebound or guarding.

Laboratory examinations

Investigations showed borderline decreased high-density cholesterol of 27 mg/dL (23-92 mg/dL), and otherwise unremarkable lipid studies. Complete blood count showed hemoglobin of 16 g/dL. Renal and hepatic function was normal.

Imaging examinations

Chest X-ray showed dextrocardia with situs inversus (Figure 1). Abdominal radiograph showed stomach on the right upper quadrant (Figure 2). Transthoracic echocardiogram showed heart located in the right chest with cardiac apex pointing to the right. There was atrial situs inversus with atrio-ventricular concordance and ventriculo-arterial concordance. The pulmonary veins drained normally to the right sided morphologic left atrium. The superior and inferior vena cava drained normally to the left sided morphologic right atrium. There was normal valvular structure and function. Abdominal sonogram report from South America mentioned liver on the left, spleen on the right, and mirror image configuration of aorta and inferior vena cava.

FINAL DIAGNOSIS

The final diagnosis was SIT with dextrocardia.

TREATMENT

No specific treatment for this condition was necessary.

OUTCOME AND FOLLOW-UP

Given that the patient was asymptomatic with otherwise stable chest X-ray and normal echocardiogram, no further workup was deemed necessary. The main intervention consisted of counseling the patient and his mother about SIT, including how it is a medical condition that should be included when relaying his history. The patient was asked to follow up at next well-child visit for routine check-up. It was suggested that no scheduled follow up with cardiology is necessary unless symptoms arise.

DISCUSSION

In this report, we describe an asymptomatic adolescent male with a history of incidentally found SIT who, upon relaying his medical history, initially denied cardiac conditions, including when directly asked about congenital heart conditions. The patient was unaware that SIT is a diagnosis that should be communicated to his providers as part of his history. It was only when heart sounds were auscultated on his right side that he mentioned his diagnosis. He explained that from his understanding, SIT would not impact his health. He was unaware that it may be associated with other syndromes and was thus confused when further questioned about symptoms that could be associated with SIT. It is critical to educate these patients about their condition and potential implications. This case report is the first to our knowledge to highlight the lack of patient understanding of their SIT diagnosis and to focus upon the importance of patient education.

Reverse orientation of thoracoabdominal organs was first documented in human beings in the 17th century[3]. In 1888, the condition was documented with illustrations of physical exam findings. Finally, in 1897, Vehsemeyer was the first to demonstrate transposition by X-ray, which in addition to ultrasound has since been the diagnostic method of choice[4]. The incidence of SIT has been reported to be 1:6500 to 1:25000[1].

Laterality is established in utero around day 22 when embryological cardiac tubes rotate rightward, known as looping [5]. The apex of the heart migrates to the left thorax over the following two weeks, such that the heart is located on the left side of the chest[6]. Dextrocardia is a heart with the apex directed to the right[7]. When the abnormal rotation of the cardiac tubes leftward is also accompanied by a similar rotation of the lungs and visceral organs, SIT results. The embryological cascade which dictates laterality is believed to involve over a hundred genes, including those coding for signaling, cell adhesion and motor peptides. While most cases of abnormal laterality are sporadic, there are also

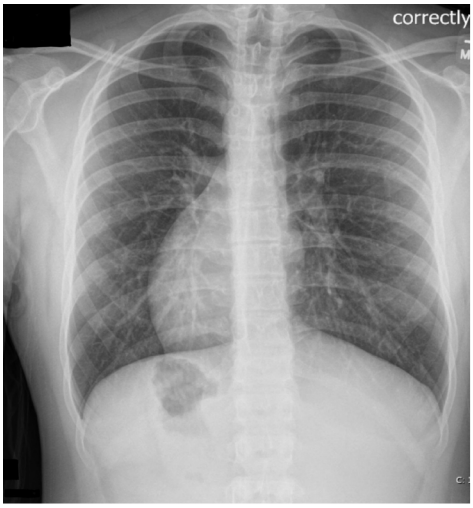

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Figure 1 Chest X-ray reveals dextrocardia with situs inversus. Heart size and hila are normal. Stomach gas is noted in the right upper quadrant.

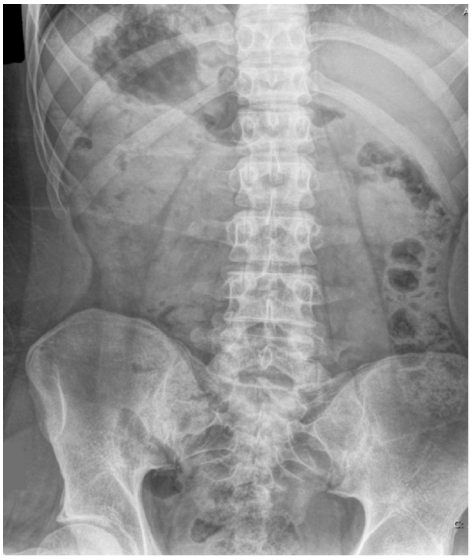

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Figure 2 Situs inversus is seen with stomach in the right upper quadrant. There is no evidence of abnormal bowel dilation or obstruction. There is moderate amount of fecal matter noted in the colon and rectum.

hereditary cases[8].

It is important to note that SIT may occur with other anomalies or as a part of broader syndromes. The most common is primary ciliary dyskinesia, also known as immotile cilia or Kartagener syndrome, which can involve a triad of situs inversus, bronchiectasis and sinusitis. About half of the individuals with a diagnosis of Kartagener's syndrome have SIT. The underlying dysmotility in cilia and flagella results in recurrent sinopulmonary infections, anosmia and infertility in males[9].

Rates of congenital heart disease increase with left-right malformation. Cardiac anomalies occur in 3%-9% of patients with SIT and 80% with situs ambiguous, compared to 0.6% without a laterality condition[10]. Up to 25% of patients with situs ambiguous may not be diagnosed until adulthood, especially those with mild cardiac abnormalities[1]. Caval vein disorders are also common, which may lead to higher rates of deep vein thrombosis[11]. When situs ambiguous disrupts splenic development, it can cause either asplenia (double right-side anatomy or right isomerism) or polysplenia (double left-side anatomy or left isomerism)[12]. Asplenia is associated with severe cardiac and pulmonary abnormalities, leading to a mortality rate up to 80% in the first year[13,14]. It is important to take a careful history about syndromic or congenital heart disease symptoms and following up the abnormal physical examination findings with imaging to differentiate among these laterality diagnoses.

Our patient falls into the majority of SIT patients who are asymptomatic with an incidental diagnosis. Even though he was previously diagnosed, he did not realize this information is pertinent medical history and was unaware that his presentation could be part of a broader syndrome.

An understanding of their disease is of especial importance in pediatric adolescent patients as they transition to adult care. Of the handful of studies that address this topic in adolescents with congenital heart conditions, participants have shown a poor understanding of their disease. One study in adolescents (median 13 years of age) with a wide spectrum of heart disease (not including SIT), illustrated that 78% of participants did not know the medical name of their condition and 36% had a poor understanding or wrong concept about their disease. There was no association between understanding and severity of the congenital heart disease but there was a positive correlation between understanding and increasing age[15]. Another study (median age 17 years of age) replicated a poor knowledge, including < 50% correctly knowing name of their heart defect (also not including SIT), reasons for follow-up, effects on competitive sports and future implications[16]. These studies illustrate an incomplete knowledge that, if addressed, could help adolescents take greater responsibility for their own health.

Having an understanding of SIT and communicating the diagnosis is of particular importance in emergent settings such as acute abdomen, since SIT patients may have atypical symptom locations[17]. Patients who present with left sided abdominal pain in the setting of appendicitis are more likely to have delayed diagnosis and treatment[18]. One report described a 46-year-old with a family history of SIT who presented with left upper quadrant pain[19]. Because the patient volunteered the SIT family history, clinical suspicion for SIT was high and thus atypical differential diagnoses were considered. Indeed, the work-up revealed both a new SIT diagnosis and acute cholecystitis, which might have otherwise been misdiagnosed and mistreated as gastritis. Another report described a patient who was diagnosed incidentally during exploratory laparotomy in the setting of trauma[20]. Visceral surgery in SIT patients poses a unique challenge; the common guidance for surgery in SIT patients includes diligent preoperative planning and selection of experienced surgeons who can adapt to technical modifications for the reverse anatomy[21].

Our case report illustrates a poor understanding of SIT in a previously-diagnosed adolescent. Given the patient was a new international patient to our clinic, his previous medical records from South America were unavailable. We were thus relying on his and his mother's history, in which they failed to convey his SIT diagnosis until it was revealed by physical exam. He subsequently showed a lack of knowledge about the disease or its potential implications. After our patient had a stable X-ray and echocardiography to rule out congenital abnormalities, he was deemed clear for sports and counseled about his condition. This surprise diagnosis in an outpatient setting had little health consequence, but could have added confusion and costly time to diagnosis or surgical challenges in the context of urgent care or trauma.

The main limitation of this case is that the patient had an incentive to present himself as a healthy individual with no medical conditions, since he was seeking medical clearance for high school sports. It is possible this led him to downplay his diagnosis; yet it is also possible that he truly had an inaccurate understanding of his disease. If this misperception is genuine, it may be that his previous cardiologist's reassurances that SIT is not immediately life-threatening led to this patient's idea that it is not a medical disease. To fully understand the extent of incomplete comprehension about SIT within asymptomatic patients, more research is needed in pediatric patients outside of the medical-clearance context.

Because SIT is so rare and most physicians will encounter only a few cases in their careers[4], the medical profession has not recognized this lack of awareness within adolescent SIT patients, let alone SIT patients in general. There are currently no guidelines about how to counsel patients with this condition. This case report highlights a knowledge gap within the medical literature on the extent to which patients with SIT understand their disease. Further research on this topic may help guide clinical practice in counseling patients with SIT and enable patients, especially adolescents, to safeguard their health.

CONCLUSION

SIT is a congenital anomaly with potential health implications. This case report highlights the poor understanding of the disease in a previously diagnosed adolescent and the importance of patient education. For an adolescent approaching adulthood, it is of particular importance that he comprehend and can communicate his own medical history, especially with a diagnosis of SIT. This understanding can help avert diagnostic and therapeutic confusion, especially in the setting of trauma or emergent surgeries, where a thorough review of past medical records is not always feasible. The patient was counseled that his SIT diagnosis, although asymptomatic, must be relayed to future healthcare teams as it could affect his medical care.

FOOTNOTES

Author contributions: Hayashi LC and Acharya R were involved in the acquisition of the clinical data, analysis, writing, interpretation and revision.

Informed consent statement: Informed consent was obtained from the parent of the patient by Dr. Acharya for publication of the information.

Conflict-of-interest statement: Both authors report no relevant conflicts of interest for this article.

CARE Checklist (2016) statement: The authors have read the CARE checklist, and the manuscript was prepared and revised according to the CARE checklist.

Country/Territory of origin: United States

ORCID number: Lauren C. Hayashi 0009-0001-1678-2567.

S-Editor: Lin C
L-Editor: A
P-Editor: Yuan YY

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