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MINIREVIEWS

New device to implement the adenoma detection rate

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Abstract

It is well-known that colonoscopy is considered the gold standard for colon cancer prevention. Although performed by experienced endoscopists, the matter remains of polyps missed during this examination. The reasons may include the size, shape and location of the lesions. Many colorectal cancer screening programs have been proposed to increase the adenoma detection rate. The substantial difference between these methods is whether the improvement in vision, particularly the detection of irregularities of the mucosa, is inside the endoscope electronic components (magnification, wide-angle vision, narrow band imaging, flexible spectral imaging colour enhancement, i-Scan) or outside the same, by the use of specific caps (EndoCuff, EndoVision, EndoRings). Endocuff is a plastic device mounted at the end of the scope with a constant vision field of the entire colon. The aim of this study is to explore the potential clinical and technical benefits of Endocuff.

Key words: Adenoma detection rate; Cap-assisted colonoscopy; Colorectal cancer; Endocuff-assisted colonoscopy; Standard colonoscopies

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Core tip: One of the main goals of colonoscopy screening is to identify polypoid lesions, which are precursors of colorectal cancer. Once identified, the polypoid lesions need to be removed whenever possible. Throughout the years, many prototypes of colonoscopes, magnification techniques, and different devices such as caps have been developed for colonoscopy screening. Endocuff is a new device used to improve adenoma detection rates during colonoscopy. Based on the findings of many studies, Endocuff seems to be of great help in increasing the detection of colonic polyps, with no significant complications associated with its use.

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INTRODUCTION

Colorectal cancer (CRC) is one of the most frequently observed cancers, and screening programs, including the adenoma detection rate (ADR), play an important role in reducing its incidence. There are many screening methods such as withdrawal time and technique, second evaluation of the right colon, patient positional changes, gastrointestinal assistant participation during colonoscopy, water-aided technique, optimisation of bowel preparation, and antispasmodic administration[1].

Colonoscopy is globally recognised as the gold standard for CRC screening. A widely used indicator to emphasise "good colonoscopy" is the ADR, which refers to the number of patients out of every 100 undergoing first-time colonoscopy who have at least one adenoma removed[2]. Several studies showed that the prevalence of adenomas in asymptomatic adults vary from 25% to 40%[3-6]. Based on these findings, in 2014, a joint task force of the American College of Gastroenterology and the American Society of Gastrointestinal Endoscopy recommended an ADR benchmark of 25% for all patients (30% for men and 20% for women)[7]. ADR has been considered as the major quality measure predicting subsequent CRC incidence and mortality[8].

Over the years, several accessories have been developed in order to obtain a more accurate visualisation of the colon, facilitating and increasing the identification of polypoid lesions. Recently, one such new device called Endocuff has been developed.

The aim of this review is to identify the studies comparing Endocuff-assisted colonoscopy to standard colonoscopy considering the ADR as the end-point by searching through MEDLINE/PubMed and abstracts presented at international meetings, from January 2014 until January 2017. In particular, the following key-words were searched: "adenoma detection rate", "Endocuff" and "Endocuff-assisted colonoscopy".

TECHNICAL CHARACTERISTICS, METHODS OF USE AND INDICATIONS

The Endocuff™ Vision (ARC Medical Design and Norgine) is a new device created with the intent to improve the endoscopic view. It is a soft plastic cap of 2 cm in length, consisting of a cylindrical core in propylene endowed with small flexible finger-like projections made of a thermoplastic elastomer fixed to the core[9,10]. The first version of Endocuff™, dated in 2012 with the Food and Drug Administration approval, presented one proximal and one distal row of finger-like projections. On the contrary, the latest version, named Endocuff Vision™, has only one proximal row of more rounded finger-like projections in order to eliminate mucosal lacerations that were observed in the first model[11] (Figure 1). This device presents different colour-coded sizes (blue, green, purple, and orange) depending on the various colonoscopy compatible, both for paediatric than for adults instruments.

The device is for single use and is not recyclable. The usage is very simple, as it uses the distal end of the endoscope (Figure 2), which virtually coincides with the end of the tip of the colonoscope. Here, lubricants are not used due to their high risk of displacement from the scope during the procedure.

There are two principal indications for use: (1) keeping the suitable depth of endoscope's view field; and (2) helping the endoscope with being inserted into the gastrointestinal tract. During colon intubation, this accessory is practically invisible, and the projections do not interfere with the introduction. On the contrary, during the tool retraction, this device flattens folds, in particular of the sigmoid colon, and flexures of bowels (Figure 3).

Pioche *et al*[12] conducted a simulated pilot study which included an animal colorectal model used for learning and 32 endoscopists as follows, 16 Japanese and 16 visitors, in order to verify the Endocuoff's effectiveness in identifying the polypoid lesions. The model was specifically designed with the "packaging" of 13 polyps located in various locations, including those behind the folds. Endoscopists had a different degree of experience and worked randomly, either by performing standard colonoscopies (SC) or Endocuff-assisted colonoscopy (EAC). Their results showed that EAC detected more polyps compared to SC (mean lesions: 9.9 *vs* 7.5, $P = 0.03$) and that the use of this device was independent of the various endoscopic medical expertise levels[12].

CONTRAINDICATIONS

Reported contraindications in the usage of Endocuff Vision™ are: (1) known colonic strictures; and (2) active inflammatory disorders (acute infective colitis, colonic Crohn's disease, ulcerative colitis, and acute diverticulitis)[11]. Moreover, this device was not designed with the objective of deep ileal intubation, and it is strongly discouraged for complex sub-mucosal dissection (such as ESD, Endoscopic Submucosal resection).

ANALYSIS OF STUDIES AVAILABLE IN THE LITERATURE

The first report on the use of this accessory was

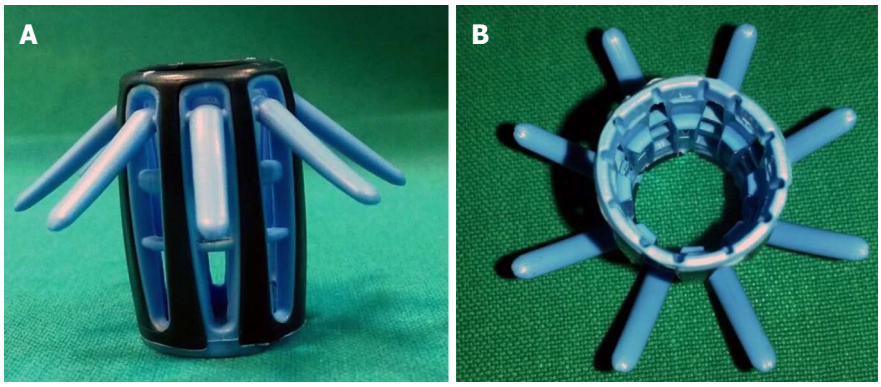

Figure 1 Endocuff's view: (A) lateral; (B) from above.

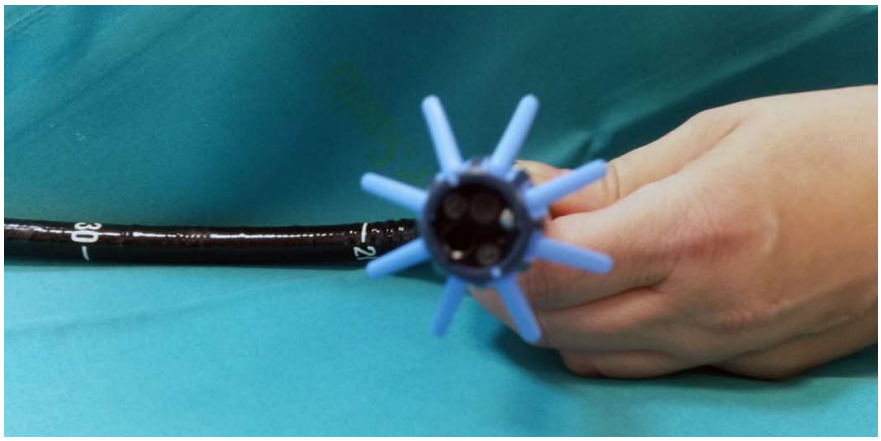

Figure 2 Endocuff Vision™ mounted at the tip of the colonoscope.

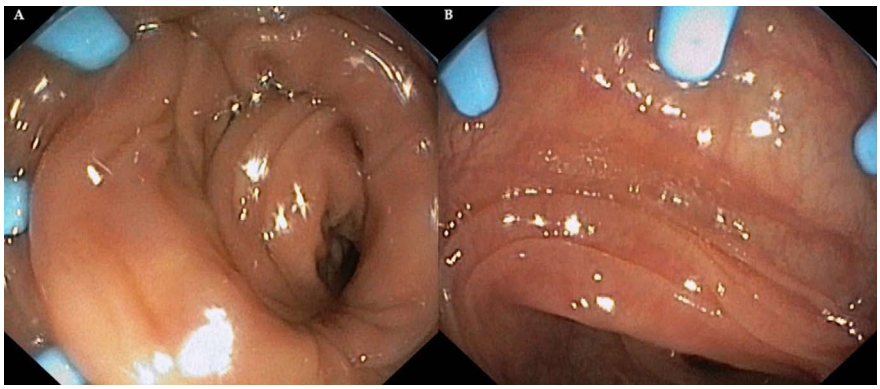

Figure 3 Endoscopic view of colonoscope retraction in which it's possible to note the flatting folds.

published in 2012 by Sanders and Tsiamoulos *et al*[9] of St Mark's Hospital in London. This was a single-centre, retrospective study with a small number of cases. The authors reported their experience with endoscopic cuff-assisted endoscopic mucosal resection (EMR) (5 patients) and control post scars-EMR (7 patients) for large flat/sessile sigmoid colon polyps. All the lesions were located in the sigmoid sigma, and no adverse events were seen.

Reviewed available studies focusing on EndoCuff-assisted colonoscopy are reported in Table 1. It was excluded from the analysis of the data, an ongoing study, promoted by Bevan *et al*[11]. It is a is a prospective, multicenter, randomised controlled trial comparing the ADR in patients undergoing EAC with SC. This study will be held at seven hospitals and will include the enrolment of 1772 patients[11].

REPORTED COMPLICATIONS

As observed in a recent meta-analysis[13], four studies[10,14,17,20] reported complication rates in the EC groups. The most frequent complication was superficial mucosal injury of negligible clinical significance that was found in 27 patients. Patient discomfort resulted in the removal of the cap in 23 cases, following which it was possible to complete the procedure. Another common complication was the loss of the device during the examination of 6 patients. In all these cases, the accessory was removed, and the study was complete. No perforations were reported[13]. Tsiamoulos *et al*[17] described elective removal in 4 cases due to sigmoid diverticulitis and 1 due to anal discomfort. Cattau *et al*[21] signalled one loss of the cap and one incomplete examination due to advanced diverticulosis. De Palma

Table 1 Studies focusing on EndoCuff-assisted colonoscopy

Ref.	Year	No. of patients (EAC)	No.of patients (SC)	Adenoma detection rate (%) (EAC)	Adenoma detection rate (%) (SC)	ADR significance
Floer *et al*[14]	2014	238	229	35.4	20.7	$P < 0.0001$
Lenze *et al*[15]	2014	50	//	34	//	//
Marsano *et al*[16]	2014	165	153	46.6	30	$P = 0.002$
Tsiamoulos *et al*[17]	2014	133	133 (pre-cuff period) 133 (post-cuff period)	68.98	55.13 61.74	//
Sawatzki *et al*[18]	2015	104	//	47	//	//
Chin *et al*[19]	2015	93	193	44.1	27.3	$P = 0.01$
Van Doorn *et al*[20]	2015	530	533	52	52	$P = 0.92$
Biecker *et al*[10]	2015	245	253	56	42	$P = 0.001$
Cattau *et al*[21]	2015	329	329	49.7	46.4	$P = 0.392$
Shah-Ghassemzadeh *et al*[22]	2015	219	230	62.1	49.13	$P = 0.0057$
Bhattacharyya *et al*[23]	2016	266	265	63	60.9	NS
Cavallaro *et al*[24]	2016	445	403	53	46	$P < 0.05$
De Palma *et al*[25]	2017	137	137	26.9	26.3	$P = 0.002$

EAC: Endocuff-assisted colonoscopy; SC: Standard colonoscopy; NS: Not significant; ADR: Adenoma detection rate.

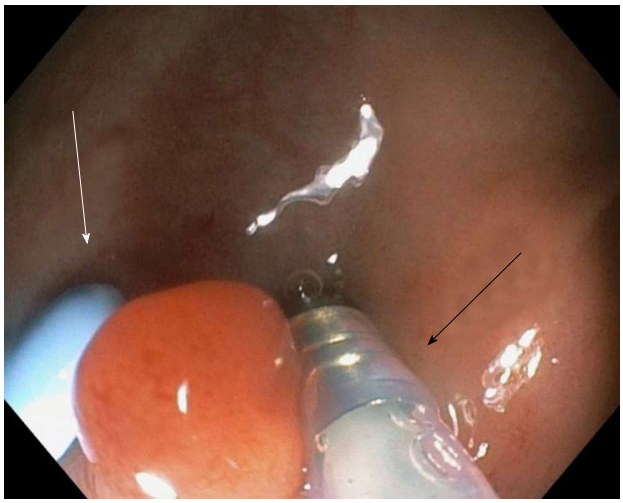

Figure 4 Endoscopic removal of a sessile polyp of the sigmoid colon, in which it's possible to see the Endocuff's flat (white arrow) and injection needle (22 G, Micro-Tech, Nanjing Co, Ltd) (black arrow).

et al[25] reported nine complications: 2 cases of device loss during the withdrawal and 7 cases of mucosal erosions, of which in 1 case was necessary sclerosis with adrenaline.

OUR INITIAL EXPERIENCE

The regional program for the CRC screening is operating at our Hospital. After the adhesion of the population to faecal occult blood test (FOBT), colonoscopy is mandatory. Colonoscopies, all conducted until the cecum, were performed using Endocuff Vision™ by expert operators with conventional colonoscopes (CF-Q165L, CF-H1285L, Olympus Optical, Hamburg, Germany). The bowel preparations used were the standard large-volume polyethylene glycol electrolyte solutions prepared the previous day or the split-dose regimens, depending on the time of the examination. Thirty patients (F 18, M 12) with a mean age of 67 years (range: 50-75 years), who underwent first-time screening colonoscopy, were studied. A total of 45 polyps were removed, 36 sessile (80%) and 9 pedunculated (20%). The sigma was involved in nearly half of the cases (45.7%). During our initial experience, we found polypoid lesions localised especially in the sigmoid colon that could be easily removed (Figure 4). No major adverse events were recorded, except for two cases of superficial "scratch-like" mucosal lesions of no clinical significance that occurred in the case of rigid colon due to inflammation (mild diverticulitis).

CONCLUSION

Prompt diagnosis of precancerous polyps during colonoscopy is extremely important in order to reduce CRC rate, especially in asymptomatic patients. During colonoscopy, the rate of colonic polyps missed varies from 6% to 27%[26]. It is known that the most effective way to estimate the adenoma miss rate, and consequently improve the ADR, is represented by the "back-to-back colonoscopy" technique performed in two consecutive same-day procedures in the same patient[27]. However, we cannot ignore this may double the potential complications, such as the risk of perforation.

The first study of this method using EndoCuff has been conducted by De Palma *et al*[25] in a single-centre randomised back-to-back-study. The participants underwent two colonoscopies, with and without the use of the device. The authors concluded that these kinds of examinations allow finding lesions missed by other procedures, but on the other hand, a limitation raised being the endoscopists not blinded for the presence of Endocuff[25]. From these studies emerge that the use of transparent plastic caps attached to the tip of the colonoscope can increase the ADR, with a mechanical mechanism of flattening the folds and the consequent increase of the visual field. This technique is known as cap-assisted colonoscopy (CAC). However,

several works show conflicting results with respect to improvement in adenoma detection by CAC. In particular, the ADR was not significantly improved in 6 studies analysed in a meta-analysis including 16 RCTs that compared CAC to standard colonoscopy[28].

As for the CAP, our results were not in agreement in defining the EAC superiority over SC. In fact, in three studies, there was no statistical significance between the two groups (EAC *vs* SC)[20,21,23]. As the Table 1 shows, this device can enhance the ADR.

The most frequently observed complication was the removal of Endocuff's due to the discomfort of the patient (24 times), followed by the loss of the device during the examination (9 times). No major complications were reported.

In Italy, CRC is one of the most frequently found cancers. At our local hospital, we started regional screening program for this kind of tumor from January 2012 onwards. In our country, the device has been registered in the database of medical devices of the Ministry of Health on January 29, 2016[29].

Our early experiences with EAC on a small population show that Endocuff can identify and facilitate polypectomy, especially in floppy folds of sigma, allowing better stabilization of endoscope in front of the polyp. Among 30 patients, we found 2 cases (6.6%) of insignificant superficial mucosal lacerations, probably related to the lack of experience with this accessory.

Some major limitations are represented by special circumstances such as sub-colonic strictures and acute inflammation of the mucosa (diverticulitis and inflammatory bowel diseases).

Unfortunately, when a person is subjected to colonoscopy for the first time, it is impossible to know any underlying diseases. Therefore, in some cases, it becomes necessary to remove the device in order to complete the procedure safely.

In conclusion, the results of EAC are still evolving. This accessory appears safe and useful in increasing the detection of the number of polyps and subsequently, the detection rate of adenomas. We recommend that Endocuff should be further investigated in other larger trials.

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MINIREVIEWS

Screening of celiac disease in Down syndrome - Old and new dilemmas

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Abstract

Celiac disease (CD) is a common and well defined autoimmune disorder caused by gliadin and related proteins of wheat, rye, and barley. Epidemiologic studies confirmed that CD is highly associated with other autoimmune diseases and with Down syndrome (DS). The symptomatic form of CD in patients with DS is more frequent than asymptomatic forms. However, growth impairment, anemia, intermittent diarrhea, and constipation are symptoms and signs typically of children with DS without CD. Late identification of the disease can lead to various complications, sometimes even very severe. Therefore, systematic screening for CD is essential in the management of children and adolescents with DS. Many medical organizations recommend screening in this group of patients. However, current policy statements vary in their recommendations for screening and there is still a need for establishing uniform diagnostic criteria.

Key words: Down syndrome; Celiac disease; Children; Screening; Practice guideline

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Core tip: Celiac disease (CD) is more common in children with Down syndrome (DS) than in general population. Recommendations for screening for DS and CD remain controversial and we still lack standard evidence-based guidelines. This review, based on existing reports, indicates the need for establishing uniform and immediately applicable diagnostic criteria.

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INTRODUCTION

Down syndrome (DS) is a chromosomal disorder caused by trisomy and other aberrations of chromosome 21[1]. This syndrome was first described by Langdon

Down[2] in 1886, while in 1959, French pediatrician and geneticist. Lejeune published a paper in which he identified trisomy 21 as its genetic cause[3]. It occurs with a prevalence of 1:733, therefore representing the most common chromosomal disorder and one of the leading causes of mental retardation[4]. DS is characterized by many typical somatic and visceral malformations. People with this syndrome are prone to autoimmune and other diseases, such as hearing and vision problems, immune dysfunction, obstructive sleep apnea, Alzheimer disease-like dementia, megakaryoblastic leukemia, hypothyroidism, diabetes mellitus (DM), and celiac disease (CD)[1,4].

CD is an autoimmune disorder induced by gluten-containing food from seeds of wheat, rye, and barley[5]. It can develop at any age as a result of an inherited (polygenic) disposition and exposure to gluten. Research carried out during the last two decades has shown that a central role in the occurrence of the disease is played by MHC class Ⅱ HLA antigens: HLA-DQ2 and HLA-DQ8[6]. The absence of HLA-DQ2 and HLA-DQ8 has a strong negative predictive value for CD[7]. Therefore, the question remains, why only a small percent of patients develops CD while approximately 40% of the population carries HLA-DQ2/DQ8 alleles and is exposed to gluten without developing a disease.

Even though enteropathy is the primary characteristic of the disease, CD may involve other extraintestinal organs[8]. Based on clinical, serological and histological variations, CD may be classified into two basic types: symptomatic and asymptomatic. Within symptomatic form of the disease, there are forms with classical and atypical clinical picture[9]. Classical form of CD occurs in infants and toddlers (9-36 mo) and it is characterized by gradual, rarely sudden onset of the disease. It is presented with a chronic diarrheal disorder, anorexia, vomiting, abdominal distension and pain, and in the most severe cases, with celiac crisis[10]. In the past two decades, the classical clinical manifestations in patients became less common, and we can see the emergence of a growing number of cases with the atypical form of CD (1:8 in general population)[11]. Among adolescents and adults, disease presents in atypical form, with absent or mild gastrointestinal symptoms, and with more common extraintestinal manifestations, such as sideropenic anemia resistant to oral therapy with iron, delay in longitudinal growth, marked thinness, chronic fatigue, osteopenia and osteoporosis, enamel hypoplasia, arthralgia, myalgia, epilepsy, ataxia, polyneuropathy, vitiligo, alopecia, dermatitis herpetiformis, *etc*[12].

Autoimmune diseases are ten times more common in patients with CD compared to general population. Such diseases include type 1 DM, autoimmune thyroid disease, Sjögren's syndrome, Addison's disease, chronic active hepatitis (elevated transaminases), primary biliary cirrhosis, IgA nephropathy, and juvenile chronic arthritis. Almost the same prevalence of the disease is also found in some chromosomal aberration disorders, such as Turner syndrome, Williams syndrome, and DS[13,14].

Diagnosis of CD is based on histological analysis of duodenal biopsies, HLA testing for HLA-DQ2 and HLA-DQ8, and detection of specific autoantibodies (mostly immunoglobulin A tissue transglutaminase - anti-TG2 and/or anti-endomysial antibodies - EMA). Gliadin antibody test and IgG class anti-TG2 antibody does not have the same specificity and clinical relevance. Use of a gluten-free diet is an effective treatment for CD as it has been shown to decrease the severity of clinical symptoms and reduce the risk of complications[6-8,15].

CD AND DS

Association between CD and DS was first described in 1975, by Bentley *et al*[16]. Since then, many papers were published in Europe, reporting the prevalence of CD in DS patients to be from 0-18.6%[17-28] (Figure 1), which is far more prevalent than CD in general population (1% in Western countries)[29].

Similar prevalence of CD among DS patients were found in the United States - 3.8% and 10.3%[30,31], Australia 3.9%[32], Argentina - 3.6%[33], and Brazil - 5.6%[34]. The reported rates are probably overestimated because most of the authors did not perform small bowel biopsy in all DS patients with positive serology[20,23,25-27,31-34]. Variability in prevalence may have been caused by differences in type of antibody used for screening, different cohort sizes (25-1453), variable age stratification and applied criteria for CD diagnosis. Most of the studies were conducted on patients receiving care from local medical centers, and only a few studies were conducted at the level of the region or a country[18,20,24,32]. Furthermore, in the majority of children, the authors did not perform testing for HLA-DQ2 and HLA-DQ8 recommended by European Society for Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) criteria[15].

In their study, Pavlovic *et al*[17] did not find CD in any of 82 children with DS. This can be explained by age of children (8 mo to 8.6 years), but further serological monitoring of these children would probably show the presence of the disease in this group of patients. Higher prevalence was found only in two previous smaller series from Sweden; Jansson and Johansson[23] screened 65 DS patients and they found CD prevalence of 16.9% while Carlsson *et al*[24] reported the similar prevalence of 18.6% (8/43). These regional differences raise the question about the relationship of environmental factors and ethnic influence.

Compared to the general population, the symptomatic form of CD is more frequent in DS children than asymptomatic form[35]. However, about one-third of DS patients with CD have no gastrointestinal symptoms[20]. In children with DS and symptomatic form of CD, growth failure, anemia, intermittent diarrhea, vomiting, and constipation are described as the most common manifestations of the disease[36]. Their significance

Figure 1 Prevalence of celiac disease in children with Down syndrome in Europe.

in clinical practice is not entirely obvious, bearing in mind the occurrence of the same symptoms and signs in children with DS, but without CD. Because of intellectual disability, DS patients may also be unable to accurately describe their symptoms. Growth failure as the manifestation of CD has little significance in children with DS, considering that the associated malformations, such as congenital heart defects and hypothyroidism, may also have the same effect[37]. Late identification or missed diagnosis of CD in DS patients can lead to failure to thrive, anemia, osteoporosis, and lymphoma[14,15].

WHEN AND HOW SHOULD WE SCREEN?

The screening is planned on the basis of prevalence of the disease, sensitivity and specificity of tests, complications or comorbidities of the disease, effectiveness of the therapy (gluten-free diet), and costs. Swigonski *et al*[38] believe that the consistent use of serological screening for CD might not be entirely justified, primarily for economic reasons. Kolek *et al*[19] suggest CD screening only in patients with symptoms (loose stool, constipation, abdominal discomfort), but not in patients without symptoms. Mackey *et al*[39] suggested routine follow-up testing at least every 3 years for all children with DS, and yearly CD screening for patients who are serology positive and biopsy-negative.

Despite some common diseases associated with DS have clear screening guidelines, *e.g.*, thyroid function, screening for CD remains controversial still lacking standard evidence-based guidelines (Table 1).

The healthcare guidelines for patients with DS developed by the American Academy of Pediatrics (AAP)[40] published in 2001 and Down's Syndrome Medical Interest Group United Kingdom and Ireland[41] did not made any recommendations for CD screening, even though they advised thyroid screening tests annually (risk of thyroid disease is 15%). Ten years later, AAP changed its position and advised screening for CD in the presence of symptoms, such as protracted constipation, slow growth, unexplained failure to thrive and anemia[42]. American Gastroenterological Association suggested that antibodies testing for CD is justified in patients with symptoms, but not those without symptoms and that HLA testing is appropriate only when the diagnosis based on other tests is not clear[44]. The recent recommendations by National Institute for Health and Care Excellence consider serological testing for CD in DS patients with IgA anti-TG2 as the first line of screening, and IgA EMA only if IgA anti-TG2 is weakly positive[45]. These recommendations do not imply HLA testing in the initial diagnosis of CD. The European Down Syndrome Association recommends blood tests for anemia, thyroid disease, CD and autoim-

Table 1 Health care guidelines for people with Down syndrome

Association	Screening for other diseases	CD screening	CD antibodies	Further CD antibodies testing	HLA testing
United Kingdom Down's Syndrome Medical Interest Group[41]	Thyroid function	No	No	No	No
American Academy of Pediatrics[42]	Thyroid function, anemia	Symptomatic patients	IgA, IgA anti-TG2	No	No
American Family Physician[43]	Thyroid function, diabetes mellitus	Not for adult	No	No	No
American Gastroenterological Association[44]		Symptomatic patients	IgA anti-TG2, IgA EMA	No	If other tests is not clear
National Institute for Health and Care Excellence[45]		In all patients	IgA anti-TG2	No	No
European Down Syndrome Association[46]	Thyroid function, anemia, immunological defects	In all patients	IgG, IgA AGA, IgA anti-TG2, IgA EMA	Annually	No
Down's Syndrome Medical Interest Group[47]	Thyroid function	At 2-3 yr in all patients	IgA EMA	No	No
North American Society for Pediatric Gastroenterology, Hepatology and Nutrition[48]		After 3 yr in all patients	IgA, IgA anti-TG2	Some years	If IgA anti-TG2 negative
European Society for Pediatric Gastroenterology, Hepatology and Nutrition[15]		After 2 yr in all patients	IgA anti-TG2 if HLA positive	Every 2 to 3 yr in DQ2 or DQ8 positive children	Yes

CD: Celiac disease; EMA: Antiendomisium antibodies; AGA: Antigliadin antibodies; anti-TG2: Tissue transglutaminase antibodies; IgA: Immunoglobulin A; IgG: Immunoglobulin G.

mune disorders at 12 mo, and yearly thereafter, until old age in all patients[46]. The Down's Syndrome Medical Interest group[47] recommends lifetime annual thyroid screening, and one-time screening for CD between ages 2 and 3, although North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN) reports that the youngest child with both DS and CD diagnosed through screening was 3.2 years old. On the other hand, NASPGHAN has suggested that CD screening of children with DS once in a lifetime is not enough and that periodic screening should be done[48]. Finally, according to the latest recommendations of the ESPGHAN from 2012, human leukocyte antigen HLA-DQ2 and HLA-DQ8 typing should be the first line of screening[15]. In patients who are HLA-DQ2 and HLA-DQ8 negative, further serological testing is unnecessary. If the patient is DQ8 and/or DQ2 positive, then an anti-TG2 IgA test and total IgA determination should be performed. If antibodies are negative, repeated testing for CD-specific antibodies is recommended every 2 to 3 years. Although HLA typing is relatively expensive and not always feasible, finally, it likely seems to be a cost-effective procedure because the significant proportion of patients can be excluded from further antibodies testing.

CONCLUSION

DS patients have increased the risk of congenital malformations and a higher incidence of CD. Current evidence has important implications to support obligatory screening for CD in DS patients. Currently, many policy statements vary in their recommendations, and there is a need for further harmonization. The strategy should aim at early diagnosis and treatment of the condition in order to prevent the development of osteoporosis and lymphoma, as the most severe complication of this disease.

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MINIREVIEWS

Practical approach to the patient with acute neuromuscular weakness

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Abstract

Acute neuromuscular paralysis (ANMP) is a clinical syndrome characterized by rapid onset muscle weakness progressing to maximum severity within several days to weeks (less than 4 wk). Bulbar and respiratory muscle weakness may or may not be present. It is a common neurological emergency which requires immediate and careful investigations to determine the etiology because accurate diagnosis has significant impact on therapy and prognosis. Respiratory failure caused by neuromuscular weakness is considered as more critical than lung disease because its development may be insidious or subtle until sudden decompensation leads to life threatening hypoxia. Also, the arterial blood gas finding of severe hypoxemia, hypercapnia, and acidosis may not be apparent until respiratory failure is profound. Hence, the requirement for respiratory assistance should also be intensively and promptly investigated in all patients with neuromuscular disease. The disorder is classified based on the site of defect in motor unit pathway, *i.e.*, anterior horn cells, nerve root, peripheral nerve, neuromuscular junction or muscle. Identification of the cause is primarily based on a good medical history and detailed clinical examination supplemented with neurophysiologic investigations and sometimes few specific laboratory tests. Medical history and neurological examination should be focused on the onset, progression, pattern and severity of muscle weakness as well as cranial nerves testing and tests for autonomic dysfunction. Associated non neurological features like fever, rash or other skin lesions etc. should also be noted. Globally, Guillain-Barré syndrome is the most frequent cause of ANMP and accounts for the majority of cases of respiratory muscles weakness associated with neuromuscular disorders. Newly acquired neuromuscular weakness in intensive care unit patients consist of critical illness polyneuropathy, critical illness myopathy and drug induced neuromuscular weakness which may arise as a consequence of sepsis, multi-organ failure, and exposure to certain medications like intravenous corticosteroids and neuromuscular blocking agents.

Key words: Neuromuscular weakness; Paralysis; Approach; Nerve; Muscle

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Core tip: Acute neuromuscular paralysis is a clinical syndrome characterized by rapid onset muscle weakness progressing to maximum severity within several days to weeks. It is a neurological emergency which requires immediate and careful investigations to determine the etiology because accurate diagnosis has significant impact on therapy and prognosis. Disorder is classified based on the site of defect in motor unit pathway, *i.e.*, anterior horn cells, nerve root, peripheral nerve, neuromuscular junction or muscle. Identification of the cause is primarily based on a good medical history and detailed clinical examination supplemented with neurophysiologic investigations and sometimes few specific laboratory tests. Medical history and neurological examination should be focused on the onset, progression, pattern and severity of muscle weakness as well as cranial nerves testing and tests for autonomic dysfunction.

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INTRODUCTION

Acute neuromuscular paralysis (ANMP) is a common neurological emergency and can be defined as a clinical syndrome characterized by rapid onset muscle weakness progressing to maximum severity within several days to weeks (less than 4 wk)[1,2]. ANMP carries high mortality when it leads to bulbar palsy, respiratory muscle weakness or autonomic dysfunction. The disorder is caused by defect somewhere in the pathway of motor unit (MU), *i.e.*, anterior horn cells, nerve root, peripheral nerve, neuromuscular junction or muscle (Figure 1). Immediate and careful evaluation to determine the etiology is crucial as the accurate diagnosis has significant implications on management and prognosis. Identification of the cause is primarily based on a good medical history and detailed clinical examination supplemented with neurophysiologic investigations and sometimes few specific laboratory tests.

The requirement for respiratory assistance should also be intensively and promptly investigated in patients with neuromuscular disease. Respiratory failure caused by neuromuscular weakness is considered as more critical than lung disease because its development may be insidious or subtle until sudden decompensation leads to life threatening hypoxia[2,3]. Also, the arterial blood gas finding of severe hypoxemia, hypercapnia, and acidosis may not be apparent until respiratory failure is profound[2,3].

Globally, Guillain-Barré syndrome (GBS) is the most frequent cause of ANMP and accounts for the majority of cases of respiratory muscles weakness associated with neuromuscular disorders[3-5]. Newly acquired neuromuscular weakness in intensive care unit (ICU) patients consist of critical illness polyneuropathy (CIP), critical illness myopathy and drug induced neuromuscular weakness which may arise as a consequence of sepsis, multi-organ failure, and exposure to certain medications like intravenous corticosteroids and neuromuscular blocking agents[1,2,6]. The disorders under the spectrum of ANMP are wide and based on the site of MU affection, ANMP can be classified as anterior horn cell disorder, polyradiculoneuropathy, peripheral neuropathy, disorders of myoneural junction and primary muscle diseases (Table 1).

Table 1 Differential diagnosis of acute neuromuscular paralysis

Anterior horn cell disorders
Poliomyelitis
West Nile virus
Peripheral neuropathy/polyradiculopathy
GBS
Porphyria
Diptheria
CMV polyradiculopathy
Lyme neuroborreliosis
Toxins (heavy metals, *e.g.*, arsenic, mercury, hexacarbon, drug intoxication, organophosphate, Buckthorn)
Critical illness polyneuropathy
Tick paralysis
Vasculitic neuropathy
Neuromuscular junction disorder
MG
Lambert-Eaton syndrome
Neuroparalytic envenomation (*e.g.*, tick and snake bites)
Botulism
Organophosphate and carbamate
Hypermagnesemia
Prolonged neuromuscular blockade
Overdose of anticholinesterases
Muscle disease
Periodic paralysis (hypokalemic: Hereditary and secondary, hyperkalemic)
Hypophosphatemia
Critical illness myopathy
Polymyositis, dermatomyositis, infectious myositis (*e.g.*, dengue myositis)
Acute rhabdomyolysis

Adapted from Maramattom *et al*[2]. GBS: Guillain-Barré syndrome; CMV: Cytomegalovirus; MG: Myasthenia gravis.

ANTERIOR HORN CELL DISORDER

Polio virus and West Nile virus (WNV) infections are two important causes of infection-associated acute muscular paralysis that primarily affect anterior horn cells. Poliovirus poliomyelitis is no longer prevalent nowadays. Afghanistan and Pakistan are two polio endemic countries[7-9]. WNV introduced to the United States in 1999 and has become endemic in North America and emerged as the commonest cause of epidemic meningoencephalitis. Presently, WNV is the leading cause of arboviral encephalitis in the United States[10].

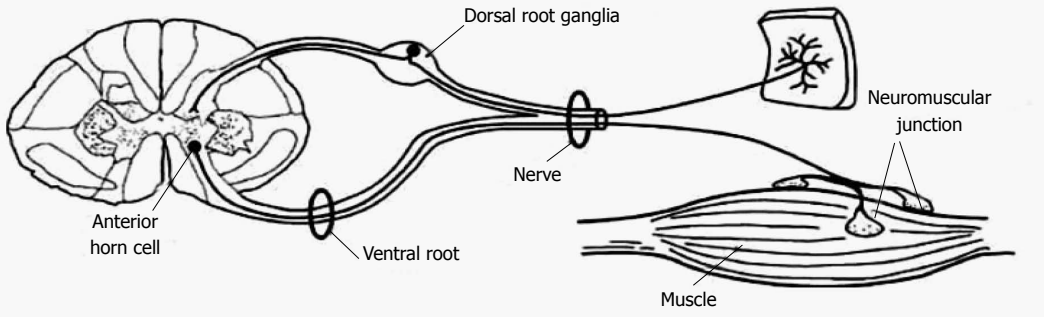

Figure 1 Schematic diagram showing the motor unit pathway.

Polio virus poliomyelitis

Poliomyelitis is a highly infectious disease caused by a virus belonging to the Picornaviridae family[9]. The clinical manifestations are varied, ranging from mild cases of respiratory symptoms, gastroenteritis, and malaise to severe forms of paralysis. These have been categorized into asymptomatic cases (90%-95%), mild illness or abortive poliomyelitis (4%-8%), aseptic meningitis (1%-5%), and paralytic poliomyelitis (0.1%-2%)[9]. Paralytic poliomyelitis is the most severe form presents as excruciating episodes of pain in back and limbs followed by motor weakness[9]. Weakness is rapid or gradual, asymmetric, predominantly proximal, and most commonly involves legs followed by the arms, abdominal, thoracic or even bulbar muscles. Respiratory failure may ensue in some patients either due to medullary involvement or phrenic or intercostal nerve paralysis[10]. Recovery may be complete in some patients but if the motor weakness persists beyond one year, lifelong disability occurs.

WNV associated paralysis

Acute, flaccid, and asymmetric motor weakness mimicking poliovirus may occur due to WNV[10]. Approximately 80% of WNV infections are asymptomatic, and 20% result in a self-limited disease referred to as West Nile fever. Less than 1% of patients develop neuroinvasive disease including meningitis, encephalitis, and acute flaccid paralysis or poliomyelitis[10]. As in poliovirus poliomyelitis, bulbar and respiratory muscles involvement may occur. Although anterior horn cells are primarily get affected, inflammatory changes may also involve muscles, peripheral nerves, spinal roots, spinal sympathetic neurons and ganglia. Rarely, WNV has been associated with demyelinating polyneuropathy similar to GBS.

The occurrence of meningoencephalitis, asymmetric pattern of weakness, normal sensory examination, lymphocytic pleocytosis in the cerebrospinal fluid (CSF) and reduced or absent compound muscle action potentials (CMAPs), preserved sensory nerve action potentials (SNAPs), and neurogenic electromyography (EMG) in a segmental pattern are core features that distinguish poliovirus or WNV paralysis from GBS[9]. Diagnosis is confirmed by detection of WNV-specific IgM antibody in CSF and serum nucleic acid amplification test is required in immunocompromised patients when antibody development is delayed or absent[9]. There is no specific treatment available for poliovirus and WNV poliomyelitis and management is primarily supportive care[10].

PERIPHERAL NEUROPATHY AND POLYRADICULONEUROPATHY

GBS

GBS is the most common and potentially life-threatening acute paralytic neuropathy worldwide with the reported annual incidence rate of 1-2 cases per 100000[11]. It is an acute-onset, rapidly progressive, immune-mediated symmetrical polyneuropathy with or without respiratory muscle involvement that often follows an antecedent infection. Two thirds of cases are usually preceded by systemic infection like upper respiratory tract infection or diarrhea[12]. *Campylobacter jejuni* is the most frequent antecedent infectious agent associated with subsequent development of the Guillain-Barré syndrome[13]. Epstein Barr virus, Cytomegalovirus (CMV), Mycoplasma, Human immunodeficiency virus are other common infectious agents that have been linked to GBS[13,14]. Studies have also documented the occurrence of GBS shortly after vaccinations or surgical procedures. Molecular mimicry between infectious antigen and surface components of peripheral nerve leads to activation of humoral and complement activation with membrane attack complex formation and nerve damage is the most accepted pathogenesis of disorder[15].

Any patient developing rapidly progressive, symmetrical limb weakness with/without sensory disturbances, hyporeflexia or areflexia and albuminocytological dissociation in CSF should first raise the diagnostic possibility of GBS. Neurological examination demonstrates proximal and often distal muscle involvement or sometimes limb weakness is global-both proximal and distal. Numbness, paresthesia and pain in the limbs are usual initial symptoms of GBS. The weakness progresses over a period of 12 h to 28 d before a plateau is reached and 80%-90% of patients with GBS become non-ambulatory during the

Table 2 Diagnostic criteria for Guillain-Barré syndrome

Features required for diagnosis
Progressive weakness in both arms and legs
Areflexia or hyporeflexia
Features that strongly support the diagnosis
Progressive motor weakness up to 4 wk
Relative symmetry of symptoms
Mild sensory involvement
Cranial nerve involvement, especially bilateral facial Weakness
Autonomic dysfunction
Pain
Albuminocytological dissociation in CSF
Electrodiagnostic features of demyelination
Features that should raise doubt about the diagnosis
Respiratory failure with limited weakness of limbs at onset
Severe sensory signs at onset
Bladder or bowel dysfunction at onset and persistence of dysfunction in the disease course
Fever at onset
Sharp sensory level
Slow progression with limited weakness without Respiratory involvement
Persistent asymmetry of motor weakness
Mono/polymorphonuclear leukocytosis in CSF

Adapted from Asbury *et al*[14]. CSF: Cerebrospinal fluid.

Table 3 Guillain-Barré syndrome Disability score[17]

0 Healthy state
1 Minor symptoms and capable of running
2 Able to walk 10 m or more without assistance but unable to run
3 Able to walk 10 m across an open space with help
4 Bedridden or chair bound
5 Requiring assisted ventilation for at least part of the day
6 Dead

illness[16]. Patients then have slow recovery phase that varies from weeks to months. Diagnostic criteria for the diagnosis of GBS as suggested by Asbury *et al*[14] and GBS Disability score are provided in Tables 2 and 3 respectively[14,17].

Respiratory insufficiency occurs in 25% of patients, and major complications, including pneumonia, sepsis, pulmonary embolism, and gastrointestinal bleeding, autonomic dysfunctions develop in 60% of mechanically ventilated patients[18]. Among the cranial nerves, the facial nerves are most commonly affected followed by bulbar and ocular motor nerves. Despite the appropriate treatment, mortality occurs in 4%-15% of cases and about 20% of severely-affected patients remain non-ambulatory after 6 mo of symptoms onset[18].

Based on the electrophysiological and pathological studies, GBS is classified into axonal and demyelinating subtypes[16,18]. Acute inflammatory demyelinating polyneuropathy is the most common GBS subtype, which is characterized pathologically by demyelination, lymphocytic infiltration, and macrophage-mediated clearance of myelin. The two axonal variant of GBS are acute motor axonal neuropathy (AMAN), characterized by pure motor neurological deficit, and acute motor sensory axonal neuropathy in which sensory fibers are also involved. However, detailed studies have suggested that mild sensory changes may occur in some patients with AMAN. The Miller Fisher syndrome is the least common type of GBS and appears to be more common among peoples who live in eastern Asia. It is characterized by a triad of ophthalmoplegia, ataxia, and areflexia. Facial and lower cranial nerve involvement, limb weakness, respiratory failure, and mild sensory involvement may occur in various combinations[16,18].

CSF examination in GBS typically reveals increased protein with normal CSF leukocyte count and termed as albumino-cytological dissociation. The protein concentrations are often normal in the first week, but increased in more than 90% of the patients at the end of the second week[16,18]. Increased CSF leukocyte count should raise the possibility of illness like leptomeningeal malignancy, Lyme's disease, WNV infection, HIV-related GBS, or poliomyelitis[18,19]. Electrophysiological studies have an important role in disease confirmation, subtype classification, and prognostication. Nerve conduction study of at least 4 motor nerves, at least 3 sensory nerves, F waves, and H reflexes provide sufficient electrodiagnostic information for the diagnosis of GBS[16,18]. Nerve conduction studies often reveal evidence of patchy demyelination, manifested as conduction block, slowed motor conduction velocities, prolonged distal latencies, and temporal dispersion of CMAPs (Figure 2). Similar to CSF analysis, electrodiagnostic testing may be entirely normal in the early phase of GBS. Inconsistent or absent F wave, prolonged F wave and distal motor latencies, reduced nerve conduction velocities, absent H response and abnormal upper extremity SNAP combined with a normal sural SNAP are the characteristic electrophysiological findings in early GBS[16,18].

Immunological treatment along with meticulous supportive care to prevent or manage complications is required[19-21]. Frequent monitoring of respiratory function by measurement of vital capacity, cardiac and hemodynamic monitoring, prophylaxis for deep vein thrombosis, management of bladder and bowel dysfunction, early initiation of physiotherapy, and pain management should be done. Intravenous immunoglobulin (IVIg) and plasma exchange (PE) are effective immunotherapies if given during the initial phase of disease. PE or IVIg is indicated in severely-affected patients with inability to walk unaided or GBS disability score $\geqslant$ 3. Immunotherapy should be started as soon as possible in these patients before irreversible nerve damage has taken place. Although equally effective, IVIg is preferred over PE because of its ease of administration and fewer side effects. It is unclear whether IVIg is effective in mildly-affected patients (GBS disability score $\leqslant$ 2) or in Miller Fisher syndrome. The recommended dose of IVIg is 0.4 g/kg

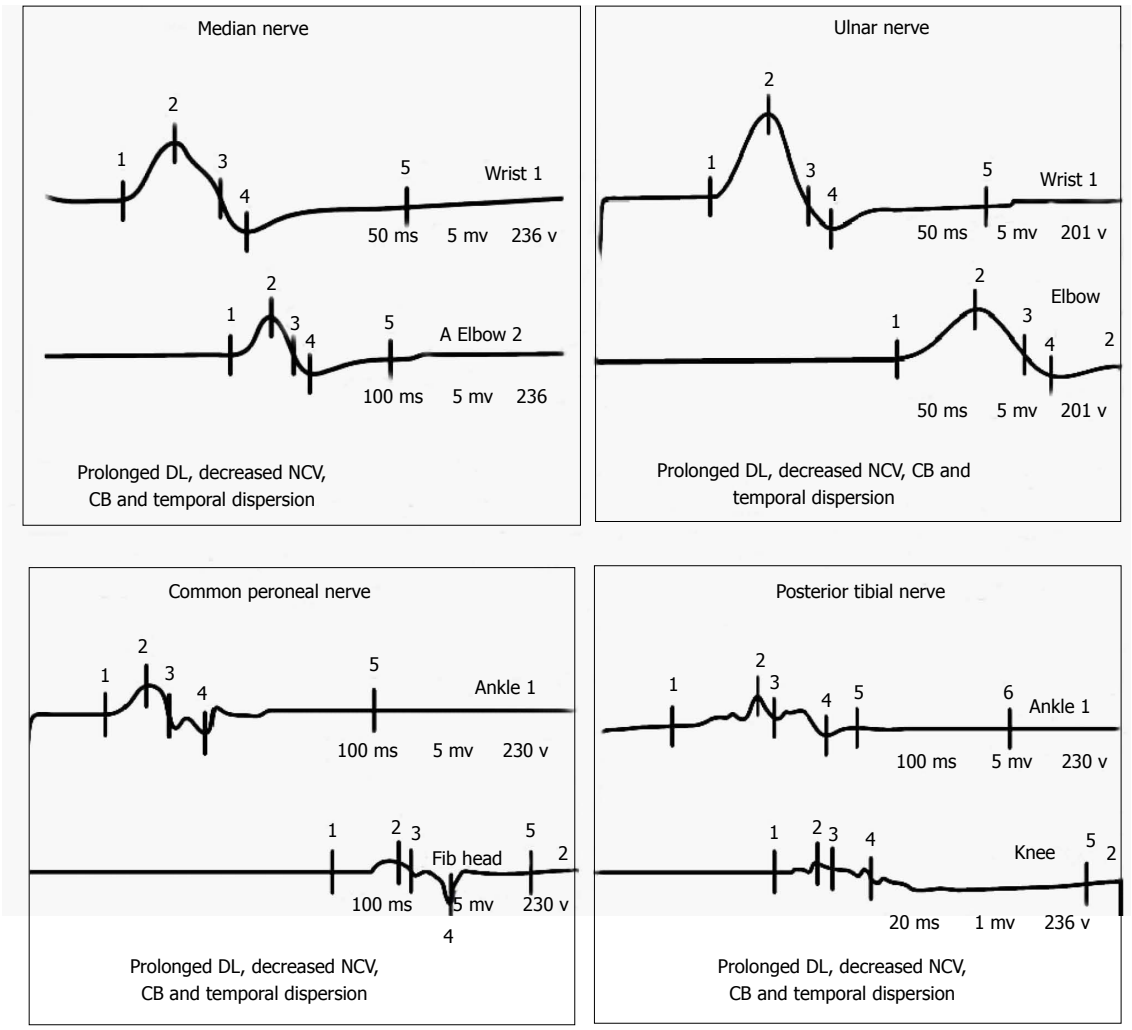

Figure 2 Motor nerve conduction study of a 24-year male patient presented with acute onset flaccid quadriparesis without sensory involvement. Nerve conduction study performed on day 2 shows typical findings of acquired demyelinating polyneuropathy. DL: Distal latency; NCV: Nerve conduction velocity; CB: Conduction block.

for 5 d and the usual regimen of PE is 5 times during 2 wk, with a total exchange of about 5 plasma volumes. In mildly-affected patients only 2 plasma volume may suffice and the dosage of IVIg conventionally administered (2 g/kg) may be suboptimal in some patients[18,19]. In clinical trials, no difference was found between IVIg and PE with respect to the improvement in disability grade after 4 wk, the duration of mechanical ventilation, mortality, or residual disability. The combination of PE and IVIg is not significantly better than PE or IVIg alone and oral or intravenous steroids are not beneficial[22]. About 10% of patients treated with IVIg or PE may deteriorate after initial improvement or stabilization and can be benefited by repeated treatment (2 g IVIg/kg in 2-5 d)[16-19].

Acute intermittent porphyria

Porphyrias are rare disorders of heme metabolism, characterized by a defect in an enzyme required for the synthesis of heme[23]. Acute intermittent porphyria (AIP) is an autosomal dominant disorder, results from a partial defect of porphobilinogen deaminase caused by a mutation in the hydroxymethylbilane synthase gene[23]. Neurological manifestations are characterized by acute polyneuropathy (predominantly motor), confusion, delirium, visual field defects, and seizures. Certain triggers like corticosteroids, other drugs, alcohol or fasting can precipitate an attack. The porphyric crisis typically begins with moderate to severe abdominal pain. Peripheral neuropathy is caused by axonal degeneration and predominantly affects motor nerves with minimal or no sensory involvement. Initially, weakness involves the proximal muscles of upper limbs[23]. Ankle jerk is frequently preserved. The polyneuropathy can affect cranial nerves and respiratory muscles requiring mechanical ventilation. Neuropsychiatric manifestations are common and seizures may occur in up to 20% of cases. Autonomic symptoms including tachycardia, cardiac arrhythmias, hypertension, constipation, and urinary retention are frequent and may lead to sudden death. The primary tool for diagnosis is measurement of porphyrin levels in urine, stool, and blood during an acutely symptomatic state. In an acute attack of AIP,

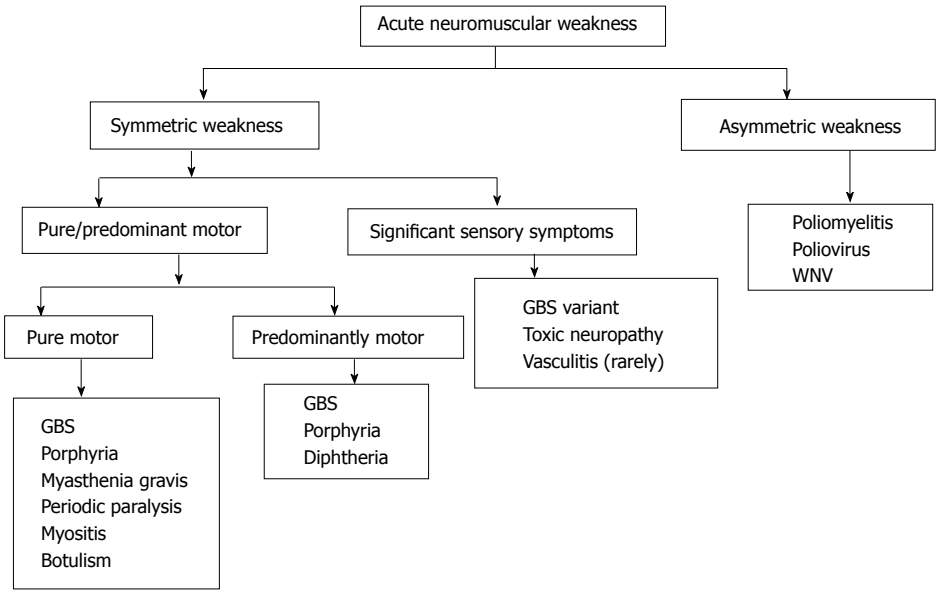

Figure 3 Althorithm: Practical approach to the patient with acute neuromuscular paralysis. GBS: Guillain-Barré syndrome; WNV: West Nile virus.

there is elevated urinary excretion of aminolevulinic acid (ALA), porphobilinogen (PBG), uroporphyrin, and coproporphyrin; erythrocyte PBG deaminase may be normal or decreased[23]. The urine turns dark when standing due to formation of porphobilin. The study of CSF is normal or may reveal slightly raised protein levels. Treatment is based on glucose supplementation, prohibition of drugs that may worsen an attack and hematin (4 mg/kg daily for 4 d) to inhibit synthesis of ALA synthetase[23]. Neuropathy begins to improve within days and may continue to improve over several days.

Diphtheria

Diphtheria is a contagious disease caused by toxin-producing strains of the bacterium *Corynebacterium diphtheriae*[24]. It is a biphasic illness with initial symptoms of fever, throat congestion, neck swelling and ipsilateral palatal weakness followed by diphtheric polyneuropathy. The latency in development of diphtheritic polyneuropathy varies from 18 to 46 d after the initial infection. It is an acute demyelinating polyneuropathy, occurs in about 20% of patients with diphtheria[24]. The classic features of include accommodation disturbances, convergence or pupillary light reflex disturbance, anisocoria, ptosis, mydriasis, malfunction of extraocular muscles and dysfunction of the other cranial nerves followed by quadriparesis[24]. Various combinations of these clinical manifestations may be seen. Respiratory muscle and diaphragmatic paresis leading to respiratory failure is a common life-threatening neurological complication. Improvement in cranial nerves occurs with evolving motor disturbance in the trunk and extremities. Autonomic dysfunction is common in diphtheritic polyneuropathy, with the incidence ranging from 36% to 100% in severe diphtheritic polyneuropathy[24]. Diphtheria antitoxin is ineffective if administered after one or two days of diphtheritic symptoms. Death from diphtheria occurs by autonomic dysfunction, cardiac arrhythmias, myocarditis, aspiration pneumonia or respiratory paralysis.

Lyme's disease and CMV related polyradiculoneuropathy

Lyme's disease is focally endemic in temperate climates of the northern hemisphere. It is the most common tick-borne disease in United States. It is a multistage and multi-system disease caused by Borrelia spirochetes, which are transmitted by ixodes ticks. It is focally endemic in temperate climates of the northern hemisphere. Early manifestations of the disease include fever, headache, fatigue, and a characteristic skin rash called erythema migrans. Weeks to months later, neurological or cardiac symptoms develop. Neurological manifestations are characterized by aseptic meningitis or fluctuating meningoencephalitis with cranial or peripheral neuropathies. Treatment is oral doxycycline or amoxicillin. Late or severe disease requires ceftriaxone or penicillin G. Single-dose doxycycline (200 mg orally) can be used as prophylaxis in selected patients. Preventive measures should be emphasized to patients to help reduce risk.

CMV polyradiculopathy is clinically characterized by lower extremity weakness, urinary retention, and sacral dysesthesias. It is an important cause of polyradiculitis in immunocompromised individuals including malignancies, organ transplant recipients and persons with acquired immunodefiency syndrome. CSF examination reveals pleocytosis. CMV polyradiculopathy is rapidly fatal without treatment. Detection of CMV in CSF is mandatory to confirm the diagnosis. Treatment with foscarnet or ganciclovir may improve or stabilize the condition.

Acute toxic polyneuropathies

Various environmental and industrial toxins including heavy metals, pesticides, organophosphates, and organic solvents can affect peripheral nerves. Although these toxins usually cause subacute or chronic neuropathy, acute polyneuropathy resembling GBS can also occur. Common toxins that can lead to acute neuropathy are described below.

Arsenic: Suicidal, homicidal or accidental ingestion of arsenic may lead to rapidly-evolving polyneuropathy 1-3 wk after acute poisoning. The neuropathy is of axonal type. Severe gastrointestinal symptoms including abdominal pain, diarrhoea, vomiting, and shock are other manifestations of acute arsenic poisoning. Urinary excretion of arsenic > 0.1 mg/L is abnormal and the levels can reach up to 1 mg/L after acute exposure. Once polyneuropathy has occurred it does not respond to chelating therapy with British anti-Lewisite agent.

Thallium: Patients with acute thallium poisoning present with abdominal pain, vomiting and diarrhea with later development of limb pain and paresthesia. Rapidly progressive muscle weakness develops soon, which is more prominent in distal muscles. Sensory impairment for pain is more markedly affected than other sensory modalities. Other neurological manifestations like cranial neuropathies, nystagmus, and optic neuritis may occur. Alopecia is another important clinical finding of thallium poisoning.

Organophosphate poisoning: Organophosphate compounds are widely used as pesticides and insecticides in agriculture and household. Organophosphorus poisoning may result from occupational, accidental or intentional exposure. Tri-ortho-cresyl phosphate is a common organophosphate compound leading to neurological disorders. Three typical patterns of neurological manifestations usually occur following organophosphates poisoning. Type 1 paralysis or acute cholinergic crisis occurs because of excessive muscarinic receptor stimulation by acetylcholine. Type 2 paralysis or intermediate syndrome usually appears 24-96 h after the apparent recovery from acute cholinergic phase. Dysfunction of neuromuscular junction caused by downregulation of presynaptic and postsynaptic nicotinic receptors is the proposed hypothesis in the pathogenesis of intermediate syndrome. The clinical features consist of proximal muscles weakness, neck flexors weakness, and respiratory paralysis. As the clinical manifestations occurred after the acute cholinergic phase but before organophosphate-induced delayed polyneuropathy, it is called "intermediate syndrome". Organophosphate-induced delayed neuropathy is a distal symmetric sensory motor (predominantly motor) axonal neuropathy, which occurs 2-5 wk after exposure. Cramping muscle pain in the lower limbs and paraesthesia occur, followed by progressive muscle weakness and diminished deep tendon reflexes.

Buckthorn poisoning: Buckthorn shrub is found mainly in Texas and Mexico. Ingestion of the green or ripe fruit of the buckthorn or tullidora shrub can cause a rapidly progressive, symmetric, progressive and severe axonal type neuropathy. Facial and pharyngeal weakness may also occur and neurological picture resembles GBS or other polyradiculoneuropathies.

Vasculitic neuropathy: Although, vasculitic neuropathies usually present in a subacute or chronic manner, sometimes aggressive vasculitic neuropathy may manifest acutely and resembles GBS[25]. Pseudo-conduction block in vasculitic neuropathy may be mistaken for conduction block typically seen in GBS. Presence of fever, history of multifocal involvement that very rapidly became confluent and pain accompanying focal weakness are important clinical features suggestive of vasculitic neuropathy. Nerve conduction studies in vasculitic neuropathy usually show only conduction block but no other features of demyelination. Also, conduction block disappears subsequently because axonal degeneration follows as a consequence of nerve infarct[25].

CIP

CIP is an acute reversible neuropathy that develops during the treatment of critically-ill patients and has an important impact on the outcome of patients in the ICU[26-28]. Difficulty in weaning from the mechanical ventilator in the absence of cardiopulmonary compromise and generalized muscle weakness in critically-ill patient should always lead to suspicion of CIP. It has been reported to occur in 70% of patients with sepsis and multiorgan failure[6,26]. Other causes of acute onset flaccid paralysis and areflexia in critically-ill patients needs to be ruled out before diagnosis of CIP is made. The severity of weakness ranges from moderate paresis to complete quadriplegia. The muscle weakness is predominantly distal and involves the lower limbs. The cranial nerves are usually spared, although facial weakness has been occasionally reported. Hyporeflexia or areflexia is common, although deep tendon reflexes may be normal in about one-third of the patients. The course of CIP is monophasic and self-limiting and shows significant recovery if the patient survives the underlying critical illness[26-28]. Sepsis, multi-organ dysfunction syndrome, multi-organ failure, female sex, use of corticosteroids, severe asthma, ionic abnormalities, malnutrition and immobility are frequently reported risk factors of CIP. Electrophysiological studies shows diminished compound motor and sensory nerve action potential amplitudes with normal conduction velocities suggesting axonal neuropathy. Needle EMG shows fibrillation potentials and positive sharp waves

suggesting denervation. Abnormal phrenic nerve conduction (bilateral reduced or absent diaphragmatic CMAP) is reported in about 50%-80% of patients. There is no specific treatment for CIP and management is primarily supportive[6,26,27].

DISORDERS OF NEUROMUSCULAR JUNCTION

Myasthenia gravis

Myasthenia gravis (MG) is the most common neuromuscular junction disorder featured by fluctuating motor weakness that has a predilection for the ocular and bulbar musculature. Incidence of MG has been reported to be 0.25-2 patients per 100000 populations[29]. It is an immune mediated disorder due to circulating antibodies directed against the postsynaptic acetylcholine receptors. Most common clinical manifestations include fatigue, diplopia, ptosis, dysphagia, difficulty in mastication, dysarthria, proximal and neck muscle weakness[29]. Involvement of respiratory muscles may lead to acute respiratory insufficiency. Although the subacute and chronic presentation is more common, a subset of patients with MG can present with ANMP. Diagnosis is essentially based on a positive edrophonium test, decremental response on repetitive nerve stimulation, and presence of serum acetylcholine receptor antibodies. About 85% of patients with generalized MG are seropositive for acetylcholine receptor antibodies. Patients with MG typically require admission to the ICU for myasthenic crisis or cholinergic crisis. The term myasthenic crisis refers to respiratory weakness in patients with acquired, autoimmune form of MG. The life-time risk of myasthenic crisis in patients with MG is about 20%-30% and it usually occurs during the course of first symptomatic presentation in the young and later in the course of the illness in elderly[29]. Two-thirds to 90% of patients with myasthenic crisis require intubation and mechanical ventilation. Most patients need immunosuppression, in addition to symptomatic therapy with acetylcholinesterase inhibitors. The most commonly used symptomatic drug in MG is pyridostigmine and also the faster acting neostigmine. Prednisolone and azathioprine are the first choice among immunosuppressants. Several second choice drugs like cyclosporine and mycophenolate mofetil are methotrexate may also be used. Thymectomy should be performed in MG with thymoma and in generalized, early-onset MG. For MG crisis and other acute exacerbations, IVIg and PE are equally effective and safe treatments. Whenever difficult to differentiate between myasthenic and cholinergic crisis, acetylcholinesterase inhibitors should be stopped and the patient should be observed in the ICU.

Botulism

Botulism is a food-borne illness caused by the exotoxin of *Clostridium botulinum,* which acts by blocking the presynaptic release of acetylcholine. The clinical manifestations usually begins 12-36 h after consumption of the tained food with bulbar symptoms, nasal intonation, blurred vision, ophthalmoplegia, fixed dilated pupils, and autonomic dysfunction including dry mouth, constipation, and urinary retention. The severity of muscle weakness is variable and may present with progressive descending flaccid paralysis and sometimes respiratory involvement. Deep tendon reflexes and gag reflex may be preserved except in cases of severe generalised weakness. Sensory symptoms are absent. The diagnosis should be suspected based on history of ingestion of improperly sterilized home-canned foods followed by the development of the clinical manifestations described above. It is confirmed by detection of toxin in serum, feces or contaminated food scraps and is supported by electrophysiological studies, which show small amplitude motor responses that increase in amplitude at high rates of repetitive nerve stimulation. Treatment involves administration of trivalent antitoxin to neutralize circulating neurotoxin in the serum. Mechanical ventilation may be required in severely-affected patients.

Snake bite and other neuroparalytic envenomation

Snake bite is common in the rural parts of developing countries and carries high mortality if not adequately managed. The venom of elapid snakes, cobra and krait are predominantly neurotoxic, causing a selective neuromuscular block. Post-synaptic neurotoxins in snake venom such as bungarotoxin and cobrotoxin bind to acetylcholine receptors at motor end plates, while presynaptic neurotoxins such as bungarotoxin, crotoxin, and taipoxin interferes the release of acetylcholine at the neuromuscular junction. The nerve conduction study plays an important role in supplementing the diagnosis of snake bite and may also help to differentiate it from other causes of neuromuscular paralysis. Cobra and krait venom affect mainly the ocular, bulbar, and respiratory muscles leading to respiratory failure. Early morning neuroparalytic syndrome or pseudomyasthenic syndrome commonly seen among farmers and slum dwellers is a presentation of the krait bite as their bites are generally painless. Timely administration of anti-snake venom serum and institution of supportive treatment is associated with good outcome.

The neurotoxin produced by the Rocky Mountain wood tick, Dermacentor andersoni causes rapidly progressive ascending paralysis that can lead to respiratory failure and death. Weakness usually starts after about 5-6 d after the insect has embedded itself into the skin. The toxin acts by inhibiting the release of acetylcholine from the presynaptic nerve terminal.

Drug-induced neuromuscular junction disorders

Several groups of drug including aminoglycosides, quinolones, polymyxin antibiotics, calcium-channel blockers, beta-blockers, quinidine, procainamide, and

neuromuscular blocking agents have been reported to produce or potentiate neuromuscular weakness[30]. Patients treated with high doses of nondepolarizing neuromuscular blocking agents such as vecuronium and pancuronium may have persistent weakness and difficult weaning from the ventilator even after drug has been stopped. At high doses, acetylcholinesterase inhibitors given to myasthenic patients can produce neuromuscular blockade and cause respiratory weakness. This overdose reaction is termed as cholinergic crisis and is characterized by nausea, diarrhea, miosis, bradycardia, muscle fasciculations, and hypersalivation[30].

MUSCLE DISORDERS

Periodic paralysis

Hypokalemic periodic paralysis is the classical and most common form of periodic paralysis. It is a calcium channel disorder manifests with acute muscle weakness that closely mimics GBS. Attacks usually begin in adolescence and are precipitated by exercise followed by rest, high carbohydrate and sodium content meals or sudden changes in temperature. The weakness evolves rapidly over minutes to several hours. Limbs are affected more than trunk and weakness is predominantly proximal. Deep tendon reflexes may be normal, decreased or absent. Ankle reflex is usually preserved even at the peak of weakness. Facial, ocular, bulbar, and respiratory muscles are rarely involved. Serum potassium levels are low. Hypokalemic periodic paralysis can be primary/hereditary (transmitted in an autosomal dominant pattern) or secondary caused by conditions such as thyrotoxicosis, barium poisoning, aldosteronism, and renal tubular acidosis. Treatment consists of large doses of oral potassium (0.25 mEq potassium chloride/kg) or potassium chloride intravenous solution in refractory cases and prevention with diet rich in potassium and low in carbohydrates and sodium. Acetazolamide can be used to prevent attacks. Hyperkalemic periodic paralysis is an autosomal dominant, inherited sodium channelopathy. It begins during childhood or the second decade of life and presents with crises of varying severity after exercise, cold, and fasting that usually last 1-2 h. The serum potassium level is high or borderline.

Polymyositis and dermatomyositis

Both polymyositis and dermatomyositis are inflammatory muscle disease which manifest in a subacute or chronic manner, although acute presentation can occur in rare cases[31]. In contrast to MG, extraocular muscles are never affected. Facial, bulbar, and respiratory muscles involvement is rare[31]. The clinical diagnosis of polymyositis and dermatomyositis is confirmed by elevated serum muscle enzyme concentrations, EMG, and muscle biopsy. In dermatomyositis, the inflammation is predominantly perivascular or in the interfascicular septae and around rather than within the fascicles; whereas in polymyositis, multifocal lymphocytic infiltrates surround and invade healthy muscle fibers. Prednisolone is the first-line drug and the addition of another immunosuppressive drug may be necessary in subjects who do not show improvement even after 3 mo of adequate dose of corticosteroids. In the first double-blind trial conducted for dermatomyositis, IVIg was reported to be effective in improving muscle strength and resolving the underlying immunopathology[32]. No controlled studies have been undertaken in polymyositis, but IVIg seems to be effective in about 70% of patients. Plasmapheresis was not found to be helpful in a double-blind, placebo-controlled study[33].

Several viruses (coxsackieviruses, infl uenza, parvoviruses, paramyxoviruses, CMV, Epstein-Barr virus, dengue) and bacteria (Borrelia burgdorferi, streptococci) have also been reported to be associated with acute myositis and muscle paralysis. Rhabdomyolysis trauma, sepsis, alcohol abuse, certain viral infections like influenza, dengue, *etc*. and various medications can lead to acute rhabdomyolysis. Rapid-onset muscle pain, swelling, tenderness, predominant proximal or generalized weakness, acute renal failure, myoglobinuria, and markedly raised serum ceatinine kinase are the core features. Sometimes weakness is severe enough to cause respiratory failure. Electromyography shows myopathic changes and spontaneous fibrillations. A muscle biopsy is confirmatory and shows massive muscle fiber necrosis and often numerous regenerating fibers with minimal inflammatory changes[33,34].

CONCLUSION

ANMP is a common neurological emergency and should be promptly investigated and treated. Sometimes, neurological examination in the emergency department or in ICU can be difficult. Combined clinical and electrophysiological assessment helps to locate the site of MU affection, *i.e.*, anterior horn cell, radical, nerve, muscle, and neuromuscular junction disorders. Algorithmic approach to a patient with acute neuromuscular weakness is shown in the Figure 3. Complications of critical illness, including critical illness neuropathy, critical illness myopathy and prolonged neuromuscular blockade, are now considered as the principal cause of new onset weakness in the seriously ill patients. These disorders should to be differentiated from other neurological conditions that may develop after admission to the ICU. A proper protocol based clinical and investigational approach is essential in every emergency department to manage such cases.

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ORIGINAL ARTICLE

Retrospective Study

Feasibility of initial endoscopic common bile duct stone removal in patients with acute cholangitis

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Author contributions: Kitamura K designed this study as well as collected and analyzed the data; Yamamiya A analyzed the data and drafted the manuscript; Kitamura K checked the manuscript and approved the final version; Yamamiya A, Kitamura K, Ishii Y, Mitsui Y, Nomoto T and Yoshida H participated in this study as either endoscopic operators or assistants.

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Abstract

AIM

To investigate the feasibility of initial endoscopic common bile duct (CBD) stone removal in patients with acute cholangitis (AC).

METHODS

A single-center, retrospective study was conducted between April 2013 and December 2014 and was approved by the Medical Ethics Committee at our institution. Written informed consent was obtained from each patient prior to the procedure. The cohort comprised 31 AC patients with CBD stones who underwent endoscopic biliary drainage (EBD) for naïve papilla within 48 h after AC onset. We retrospectively divided the participants into two groups: 19 patients with initial endoscopic CBD stone removal (initial group) and 12 patients with delayed endoscopic CBD stone removal (delayed group). We evaluated the feasibility of initial endoscopic CBD stone removal in patients with AC.

RESULTS

We observed no significant differences between the groups regarding patient characteristics. According to the assessments based on the Tokyo Guidelines, the AC severity of patients with initial endoscopic CBD stone removal was mild to moderate. The use of antithrombotic agents before EBD was less frequent in the initial group than in the delayed group (11% *vs* 58%, respectively; P = 0.004). All the patients underwent successful endoscopic CBD stone removal

and adverse events did not differ significantly between the groups. The number of endoscopic retrograde cholangiopancreatography procedures was significantly lower in the initial group than in the delayed group [median (interquartile range) 1 (1-1) *vs* 2 (2-2), respectively; $P < 0.001$]. The length of hospital stay was significantly shorter for the initial group than for the delayed group [10 (9-15) *vs* 17 (14-20), respectively; $P = 0.010$].

CONCLUSION

Initial endoscopic CBD stone removal in patients with AC may be feasible when AC severity and the use of antithrombotic agents are carefully considered.

Key words: Acute cholangitis; Common bile duct stone; Feasibility; Initial endoscopic common bile stone removal; Endoscopic retrograde cholangiopancreatography

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Core tip: Initial endoscopic common bile duct stone removal in patients with acute cholangitis (AC) may be feasible when AC severity and the use of antithrombotic agents are carefully considered.

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INTRODUCTION

Acute cholangitis (AC) is an acute inflammatory condition caused by a rise in bile duct pressure and biliary infection secondary to biliary obstruction[1]. Clinical findings include fever, abdominal pain and jaundice (Charcot's triad). Patients with severe AC present with septic shock and altered consciousness in addition to the classical signs of Charcot's triad (Reynolds' pentad).

First published in 2007, the Tokyo Guidelines for the management of AC (TG07)[2] were modified in 2013 to the updated version (TG13)[1]. The basic treatment for AC is conservative medical therapy with antimicrobial agents and biliary tract drainage.

According to the TG07, an additional endoscopic sphincterotomy (EST) is not necessary during initial biliary drainage. However, in the TG13, based on the clinical condition of the patient, initial common bile duct (CBD) stone removal with an additional EST may be performed. Furthermore, no consensus exists for when CBD stones should be removed in patients with AC. The aim of this study was to evaluate the feasibility of initial endoscopic CBD stone removal in patients with AC.

MATERIALS AND METHODS

This retrospective study was conducted at Showa University Hospital and was approved by the Medical Ethics Committee of our institution. The study was registered at the University Hospital Medical Information Network (UMIN) Clinical Trials Registry (registry number: 000020770). Informed written consent was obtained from each patient prior to the procedure.

Patients

Seven hundred thirty-seven patients underwent an endoscopic retrograde cholangiopancreatography (ERCP)-related procedure at our institution between April 2013 and December 2014. Among them, 164 patients underwent an emergency ERCP procedure. Following the exclusion of acute biliary pancreatitis ($n = 13$), altered gastrointestinal anatomy ($n = 9$), and other entities ($n = 111$), we analyzed the remaining 31 AC patients with CBD stones who underwent endoscopic biliary drainage (EBD) for naïve papilla within 48 h after AC onset.

We retrospectively divided the participants into two groups: 19 patients who underwent initial endoscopic CBD stone removal (initial group) and 12 patients who underwent delayed endoscopic CBD stone removal (delayed group) (Figure 1).

The delayed group was defined as patients who received EBD without CBD stone removal at first ERCP and underwent endoscopic CBD stone removal later.

Devices

ERCP was performed using a duodenoscope (JF-260V; Olympus Medical Systems Corp., Tokyo, Japan). The following devices were employed during the procedure: A sphincterotome with a tip length of 7 mm and a cutting wire length of 20 mm (Autotome RX44; Boston Scientific, Natick, MA, United States), a 0.035-inch guidewire (Jagwire; Boston Scientific), a balloon catheter for CBD stone removal (Multi-3V Plus; Olympus Medical Systems Corp., Tokyo, Japan), a biliary dilation balloon catheter designed to produce three distinct diameters at three separate pressures (CRE™ wire-guided biliary dilation balloon catheter; Boston Scientific), and a 5-Fr pigtail nasobiliary catheter (Create Medic Co. LTD., Tokyo, Japan) or a 7-Fr 10-cm Double Pigtail Stent delivery system Through Pass (Gadelius Medical K.K., Tokyo, Japan) as a drainage catheter and stent.

Endoscopic CBD stone removal

All ERCP procedures were performed by expert endoscopists. All patients provided written consent to undergo ERCP and were informed of the risks and benefits of the procedure. The patients who exhibited no evidence of altered consciousness or septic shock

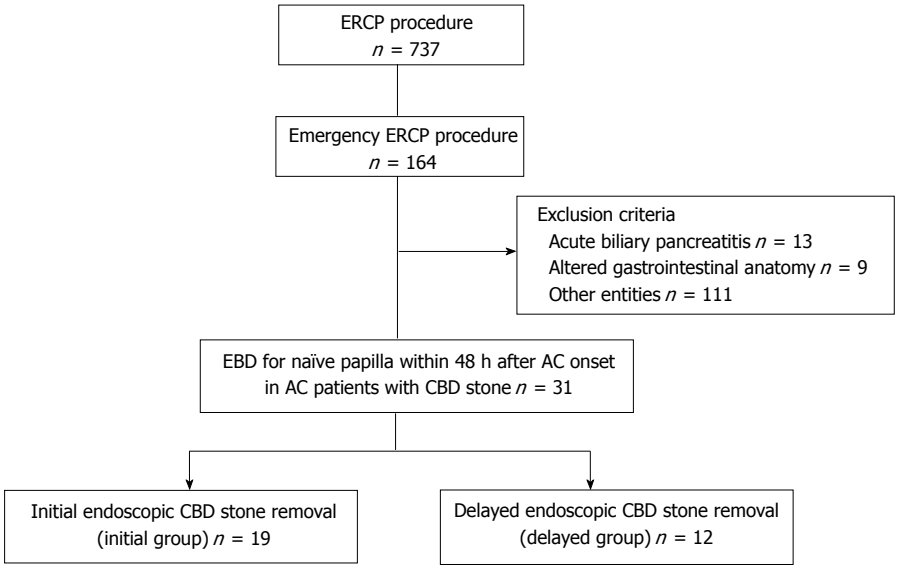

Figure 1 Flow diagram of patient selection process. ERCP: Endoscopic retrograde cholangiopancreatography; EBD: Endoscopic biliary drainage; AC: Acute cholangitis; CBD: Common bile duct.

received ERCP under sedation with benzodiazepines or pentazocine as analgesics. Wire-guided cannulation for selective bile duct cannulation and EST with a small or medium-sized incision of the papilla of Vater were primarily performed to remove the CBD stone. An Erbotom ICC200 (ERBE Elektromedizin GmbH, Tubingen, Germany) was used for the EST using the Endocut mode. The effect 3 current was set at an output limit of 120 W and the forced coagulation current was set at an output limit of 30 W. Patients with large CBD stones (*i.e.*, diameter of 13 mm or more) received endoscopic papillary large balloon dilation (EPLBD) with EST. A balloon catheter was used to remove the CBD stone. All patients received intravenous infusions of a protease inhibitor (gabexate mesilate - 600 mg or nafamostat mesilate - 60 mg) for approximately 12 h (beginning immediately after the ERCP procedures). All patients were administered antibiotics before the ERCP procedure, and antimicrobial therapy was continued until the cholangitis symptoms improved. The off-period for antithrombotic agents was based on the Japanese guidelines for gastroenterological endoscopy in patients undergoing antithrombotic treatment[3]. Based on the judgment of the endoscopist, either a 5-Fr drainage catheter or a 7-Fr 10-cm double pigtail stent was inserted for EBD.

Outcome measures

The primary outcome of this study was the success rate of initial endoscopic CBD stone removal in patients with AC. The secondary outcomes were the number of ERCP procedures, the incidence of adverse events, the duration of antibiotic administration, the length of hospital stay and hospital costs.

Post-ERCP pancreatitis was defined as the presence of abdominal pain lasting for more than 24 h after ERCP with serum amylase levels 3 times the upper limit of normal or higher and graded by CT when necessary[4]. Bleeding complications were classified as follows: Mild, with hemoglobin drop < 3 g without a need for transfusion; moderate, with transfusion (4 units or less) with no angiographic intervention or surgery; and severe, with transfusion (5 units or more) or additional intervention[4].

Statistical analysis

Continuous variables are expressed as the median with interquartile range (IQR). Statistical analyses were performed using JMP version 12 (SAS Institute Inc., Cary, NC, United States). Data were analyzed using the Mann-Whitney *U* and χ^2 tests. Differences of $P < 0.05$ were considered significant.

RESULTS

Patient characteristics

Patient characteristics are presented in Table 1. No significant differences between the groups were observed regarding age, sex, AC severity, CBD diameter, number of CBD stones, diameter of CBD stones, periampullary diverticulum, period until EBD, blood CRP level before EBD or positive blood cultures. The use of antithrombotic agents before EBD was less frequent in the initial group than in the delayed group (11% *vs* 58%, respectively; $P = 0.004$).

Success rate of endoscopic CBD stone removal

There was no significant difference between the groups regarding procedures involving the ampulla, such as EST or EPLBD, to remove CBD stones. All patients underwent successful endoscopic CBD stone removal using a balloon catheter (Table 2).

Table 1 Patient characteristics *n* (%)

	Initial group (*n* = 19)	Delayed group (*n* = 12)	*P* value
Age, median (IQR), yr	71 (62-80)	80 (74-84)	0.064[1]
Sex, male/female, *n*	11/8	6/6	0.667[2]
AC severity[3], mild/moderate/severe, *n*	11/8/0	5/4/3	0.072[2]
CBD diameter, median (IQR), mm	9 (8-10)	11 (8-13)	0.169[1]
Number of CBD stones, single/multiple, *n*	9/10	6/6	0.886[2]
Diameter of CBD stone, < 10 mm/≥ 10 mm, *n*	15/4	9/3	0.798[2]
Periampullary diverticulum	9 (47)	4 (33)	0.441[2]
Use of antithrombotic agents before EBD	2 (11)	7 (58)	0.004[2]
Period until EBD from AC onset, < 24 h/24-48 h, *n*	11/8	8/4	0.648[2]
Blood CRP level before EBD, median (IQR), mg/dL	3.9 (1.4-6.7)	5 (1.6-12.2)	0.429[1]
Positive blood culture, *n*/total	6/14 (43)	5/7 (71)	0.217[2]

[1]Mann-Whitney *U* test; [2]χ^2 test; [3]Tokyo Guidelines for the management of acute cholangitis (TG13). IQR: Interquartile range; AC: Acute cholangitis; CBD: Common bile duct; EBD: Endoscopic biliary drainage; CRP: C-reactive protein.

Table 2 Clinical outcomes *n* (%)

	Initial group (*n* = 19)	Delayed group (*n* = 12)	*P* value
Procedures for ampulla, EST/EPLBD with EST, *n*	18/1	10/2	0.296[1]
Use of balloon catheter for stone removal	19 (100)	12 (100)	
Successful CBD stone removal	19 (100)	12 (100)	
Number of ERCP procedures, median (IQR)	1 (1-1)	2 (2-2)	< 0.001[2]
Adverse events, pancreatitis/bleeding/perforation, *n*	0/0/0	0/1/0	0.201[1]
Duration of antibiotic administration, median (IQR), d	7 (5-8)	6 (5-7)	0.059[2]
Hospital stay, median (IQR), d	10 (9-15)	17 (14-20)	0.010[2]
Hospital costs, median (IQR), $	726 (579-1028)	988 (868-1033)	0.224[2]

[1]χ^2 test; [2]Mann-Whitney *U* test. EST: Endoscopic sphincterotomy; EPLBD: Endoscopic papillary large balloon dilation; CBD: Common bile duct; ERCP: Endoscopic retrograde cholangiopancreatography; IQR: Interquartile range.

Number of ERCP procedures

The number of the ERCP procedures performed was significantly lower in the initial group than in the delayed group [1 (1-1) *vs* 2 (2-2) for the initial and delayed groups, respectively; $P < 0.001$] (Table 2).

Adverse events

Adverse events did not differ significantly between the two groups. Post-ERCP pancreatitis or perforation did not occur in either group. Mild bleeding 4 d after ERCP occurred in 1 patient in the delayed group (Table 2).

Antibiotic administration

The duration of antibiotic administration did not differ significantly between the groups [7 (5-8) d *vs* 6 (5-7) d for the initial and delayed groups, respectively, $P = 0.059$] (Table 2).

Hospital stay

The length of hospital stay was significantly shorter for the initial group than that for the delayed group [10 (9-15) d *vs* 17 (14-20) d for the initial and delayed groups, respectively; $P = 0.010$] (Table 2).

Hospital costs

There was no significant difference in hospital cost between the groups [$726 (579-1028) *vs* $988 (868-1033) for the initial and delayed groups, respectively, $P = 0.224$] (Table 2).

DISCUSSION

This study suggested that emergency initial endoscopic CBD stone removal in patients with AC may be feasible when AC severity and the use of antithrombotic agents are carefully considered.

In 2013, the TG07 was modified to the updated version, TG13[1]. AC results from causes such as CBD stones, benign biliary tract strictures, biliary anastomotic strictures and malignant biliary tract strictures. Though a CBD stone is the most frequent etiology of AC, the incidences of AC due to malignant biliary tract stricture and sclerosing cholangitis have been increasing recently[5,6].

The major changes reflected in the TG13 were a rearrangement of the diagnostic items and the exclusion of abdominal pain from the diagnostic list. Cholangitis severity was categorized as grade Ⅰ (mild), grade Ⅱ (moderate) and grade Ⅲ (severe). Kiriyama *et al*[7] investigated the accuracy of the TG13. The sensitivity for AC severity is 91.8%, and the specificity for AC is 77.7%.

According to the TG13, appropriate treatment during the acute phase of AC is important because the mortality associated with AC is 2.7%-10%. Among 60842 AC cases extracted from the Japanese admini-

strative database according to the Diagnosis Procedure Combination system of Japan, the mortality was 2.7%[8]. The primary cause of death among patients with AC is multiple organ failure associated with irreversible shock[9].

The TG13 further recommends treatment based on AC severity. The initial treatment, which includes a full dose of antimicrobial agents, is provided for all patients with AC. For non-responders with mild and moderate AC, biliary drainage should be performed immediately. For patients with severe AC, appropriate organ support is required, and biliary drainage should be performed after hemodynamic stabilization has been achieved[10]. Biliary drainage includes percutaneous transhepatic biliary drainage, surgical biliary drainage, EBD and endoscopic ultrasonography-guided biliary drainage. EBD is recommended as the first choice because it is considered a minimally invasive biliary drainage technique[11-13].

There are several differences in EST between the TG07 and TG13. In the TG07, an additional EST is not necessary because EST is associated with serious complications, such as hemorrhage. AC alone is a risk factor for post-EST hemorrhage[14]. In particular, EST should be avoided in patients with severe AC because they often have blood-coagulation disorders. According to the TG13, EST may be indicated for the initial endoscopic CBD stone removal in patients with AC[1]. These recommendations suggest that the choice of performing an additional EST should be based on the patient's clinical condition[15].

Recently, studies evaluating initial endoscopic CBD stone removal in patients with AC have emerged in the literature. Eto *et al*[16] reported that the improvement rate of cholangitis was 90% and that the rate of complications was 10% (post-ERCP pancreatitis, hemorrhage, cholecystitis, or pneumonia). Notably, hemorrhage occurred in 2% of patients[16].

At our institution, patients with moderate and severe AC undergo emergency EBD. We also perform emergency EBD in patients with mild AC and high fever (> 38 ℃) or severe abdominal pain. When AC patients with CBD stones are administered antithrombotic agents, we consider the off-period of these drugs and perform additional EST according to the Japanese guidelines for gastroenterological endoscopy in patients undergoing antithrombotic treatment[3]. In this guideline, EST is classified in the high bleeding risk group. We have performed additional EST and CBD stone removal in patients with mild and moderate AC. Based on the guideline, we do not perform additional EST for the following patients: Those taking antithrombotic agents that require an off-period of more than 5-7 d; those taking more than 2 types of antithrombotic agents; and those with evidence of septic shock. Therefore, these patients received only EBD. In this study, the use of antithrombotic agents before EBD was less frequent in the initial group than in the delayed group (P = 0.004). Hemorrhage occurred in 1 patient from the delayed group, an older adult with underlying disease who was taking more than 2 types of antithrombotic agents. After the EBD and antithrombotic agent off-period, the patient underwent successful delayed CBD stone removal with EST. However, this patient developed a mild hemorrhage 4 d after the procedure.

In this study, emergency initial endoscopic CBD stone removal was feasible for patients with mild or moderate AC when the guidelines in the TG13 and the recommendations for the use of antithrombotic agents were strictly followed. The number of ERCP procedures was significantly less in the initial group than in the delayed group (P < 0.001) because the delayed group underwent ERCP for CBD stone removal after the severe AC had subsided or during the antithrombotic agent off-period. The length of hospital stay was significantly shorter for the initial group than for the delayed group (P = 0.010) with no significant differences regarding the number of adverse events observed between the two groups. Thus, initial endoscopic CBD stone removal in patients with AC may reduce the treatment-associated patient burden.

The limitations of this study are the single-center focus, the retrospective design and the small number of patients. Additional multicenter, randomized controlled trials are necessary to confirm the feasibility of emergency initial endoscopic CBD stone removal in patients with AC.

Emergency initial endoscopic CBD stone removal in patients with AC may be feasible when AC severity and the use of antithrombotic agents are carefully considered.

COMMENTS

Background

Initial endoscopic common bile duct (CBD) stone removal in patients with acute cholangitis (AC) may reduce the number of endoscopic retrograde cholangiopancreatography (ERCP) procedures performed and the length of hospital stay. However, there is no consensus on when CBD stones should be removed in patients with AC. The aim of this study was to investigate the feasibility of initial endoscopic CBD stone removal in patients with AC.

Research frontiers

The current standard for treating AC patients with CBD stones is a conservative medical approach with antimicrobial agents and biliary drainage. However, few studies have evaluated the timing of CBD stone removal in patients with AC.

Innovations and breakthroughs

The authors compared the clinical outcomes among patients with AC who underwent either initial endoscopic CBD stone removal or delayed endoscopic CBD stone removal. The number of ERCP procedures and the length of hospital stay were significantly reduced in the initial group compared to that in the delayed group.

Applications

Emergency initial endoscopic CBD stone removal in patients with AC may reduce subsequent patient burden associated with the treatment. However, multicenter, randomized, controlled trials are needed to confirm these findings.

Terminology

Endoscopic CBD stone removal is a stone removal method that utilizes the ERCP-related procedure with a duodenoscope.

Peer-review

Although this is a small study, it was well written.

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SYSTEMATIC REVIEWS

Diagnostic performance of high resolution computed tomography in otosclerosis

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Data sharing statement: Technical appendix, statistical code, and dataset available from the corresponding author at Dryad repository, who will provide a permanent, citable and open-access home for the dataset.

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Abstract

AIM

To determine the sensitivity and specificity of high resolution computed tomography (HRCT) in the diagnosis of otosclerosis.

METHODS

A systematic literature review was undertaken to include Level I-III studies (Oxford Centre for Evidenced based Medicine) that utilised HRCT to detect histology confirmed otosclerosis. Quantitative synthesis was then performed.

RESULTS

Based on available level III literature, HRCT has a relatively low sensitivity of 58% (95%CI: 49.4-66.9), a high specificity, 95% (95%CI: 89.9-98.0) and a positive predictive value of 92% (95%CI: 84.1-95.8). HRCT is better at diagnosing the more prevalent fenestral form of otosclerosis but remains vulnerable to inframillimetre, retrofenestral and dense sclerotic lesions, despite the advent of more advanced CT scanners with improved collimation.

CONCLUSION

Whilst the diagnosis of otosclerosis remains largely clinical, HRCT remains the gold standard imaging of choice for the middle ear and serves as a useful adjunct to the clinician, helping to delineate extent of disease and exclude other causes.

Key words: Otosclerosis; High resolution computed tomography; Otospongiosis; Retrofenestral; Sensitivity; Specificity; Fenestral; Computed tomography

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Core tip: Diagnosis of otosclerosis remains clinical and

high resolution computed tomography (HRCT) can be a useful adjunct when assessing the extent of disease and excluding other causes. HRCT of the temporal bones has a high specificity and low sensitivity and is particularly vulnerable to inframillimetre lesions.

Kanzara T, Virk JS. Diagnostic performance of high resolution computed tomography in otosclerosis. *World J Clin Cases* 2017; 5(7): 286-291 Available from: URL: http://www.wjgnet.com/2307-8960/full/v5/i7/286.htm DOI: http://dx.doi.org/10.12998/wjcc.v5.i7.286

INTRODUCTION

Otosclerosis is focal osseous dyscrasia of unknown aetiology which predominantly affects only the endochondral bone of the otic capsule in humans[1]. In the Caucasian population the estimated prevalence is between 0.3% and 0.4% but this is thought to be less in the Asian population[2,3]. However, there is a dearth of high level studies evaluating the incidence and prevalence of otosclerosis in the non-Caucasian population. Histopathologically normal endochondral bone of the otic capsule is replaced by disorganised foci of Haversian bone which ultimately becomes sclerotic and dense. Otospongiosis, the early or active phase of otosclerosis, is characterized by the presence of spongy irregular vascular foci of demineralised bone. This is followed by an otosclerotic or inactive phase where these diseased foci become less vascular, forming dense bone[4].

Otosclerosis can be divided into 2 types: Fenestral and retrofenestral, depending on the topography of the lesions. Fenestral lesions are in the lateral wall of the otic capsule, *i.e.*, the regions of the round and oval windows, promontory, and tympanic segment of the fallopian canal. The retrofenesteral type affects the labyrinthine capsule, including the pericochlear region, the semicircular canals, internal acoustic meatus, vestibule, and cochlear and vestibular aqueducts[5,6].

Diagnosis is based on a combination of medical history, physical examination, audiological testing and imaging. The clinical findings include conductive, mixed, or rarely, pure sensorineural hearing loss and vertiginous symptoms in the absence of middle ear inflammation[2,7,8]. Surgical or histological confirmation is important in correlating clinical findings.

High resolution computed tomography (HRCT) is the gold standard imaging modality in the diagnosis of otosclerosis; it detects pathologic bone lesions in and around the stapes footplate, cochlea, and labyrinth[9-11]. In active otospongiosis, disease foci are visualised on CT as areas of reduced bone density and appear as increased bony radiolucency in the otic capsule, typically at the fissula ante fenestram, just anterior to the oval window in the fenestral type of the disease. HRCT can also demonstrate disease within the peri-labyrinthine bone and the cochlea in the retrofenestral subgroup. CT highlights differences in the density of the capsule's outline, the so called double ring sign, which is a low density demineralised endochondral defect outlining the cochlea[7,9]. The density of disease foci increases in otosclerosis giving an appearance resembling normal otic capsule bone thereby complicating diagnosis and increasing the false negative rates[1,2,8].

HRCT may also be useful in distinguishing between otosclerosis and other pathological conditions such as tympanosclerosis, cholesteatoma, ossicular fixation and congenital malformations[9-11]. Its use in the preoperative stage for otosclerosis surgery remains debatable[12]. The aim of this study is to evaluate the sensitivity and specificity of HRCT in the diagnosis of otosclerosis using the best available evidence.

MATERIALS AND METHODS

A contemporary literature review regarding the use of HRCT imaging in the diagnosis of otosclerosis was undertaken. A PubMed, MEDLINE and Google Scholar database search using terms "high resolution computed tomography", "HRCT", "CT", "otosclerosis", "diagnosis", "sensitivity", "specificity" in all combinations was completed. Abstracts were reviewed independently by two authors and relevant articles were then evaluated. Inclusion criteria were Level Ⅰ-Ⅲ studies where a diagnostic work up consisting of history and otolaryngology examination; speech/pure tone audiometry; tympanometry; and imaging in the form of HCRT had been carried out. We also included other studies where a CT diagnosis of otosclerosis was confirmed histologically in the absence of clinical information. Exclusion criteria were level Ⅳ-Ⅴ evidence, studies where HRCT was used postoperatively and studies prior to 2000.

Level of evidence was assigned in accordance with the Oxford Centre for Evidence-based Medicine guidance, in a hierarchy of evidence strength from randomised controlled trials (level Ⅰ), cohort studies (level Ⅱ), case-control studies (level Ⅲ), case series (level Ⅳ) to expert opinion and, case reports (level Ⅴ) with suffixes "a" and "b" denoting a systematic review and an individual study respectively[13].

Statistical analysis

Statistical analysis was performed using MedCalc (Ostend, Belgium).

RESULTS

Figure 1 summarises the PRISMA systematic review flow diagram; the checklist is available as a supplementary file.

The 5 level Ⅲ studies (Table 1) had a combined pool of 206 ears and 130 patients. A HRCT bone protocol was utilised in all studies. Axial and coronal

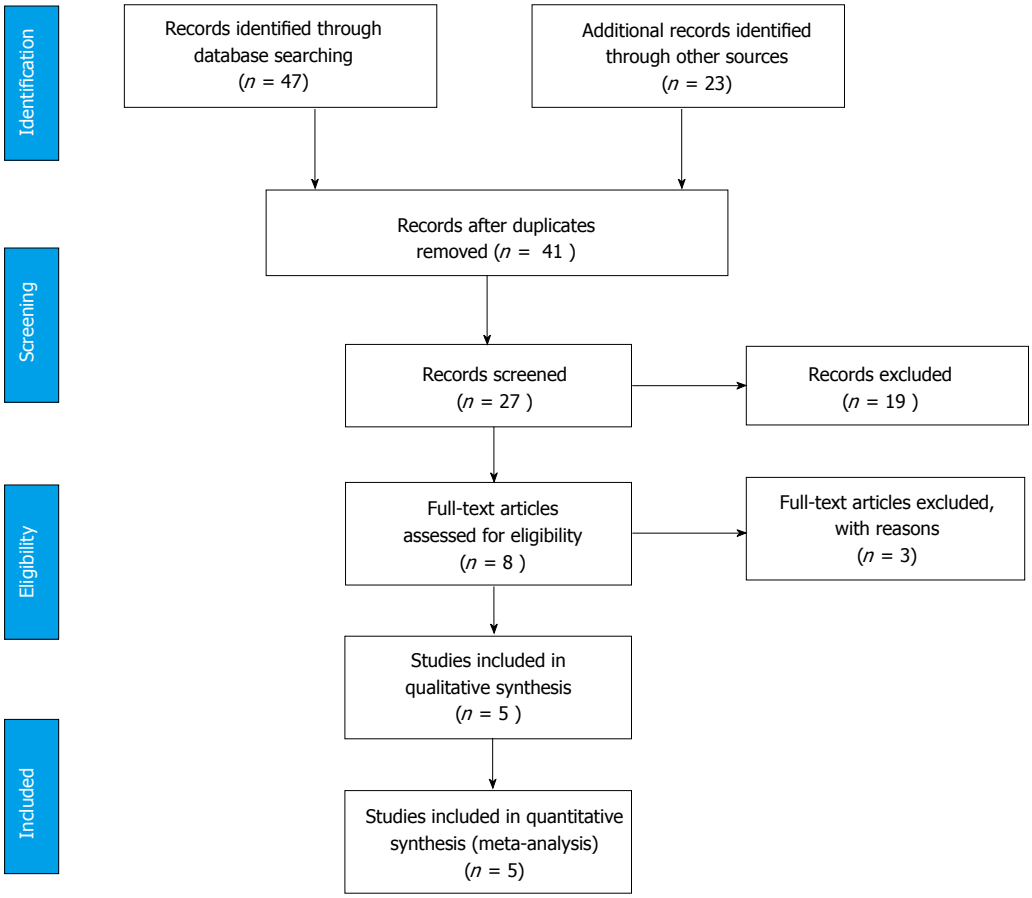

Figure 1 PRISMA flow diagram.

Table 1 Studies included in analysis

Ref.	Year	Level of evidence	No. of patients	Control group (*n*)	Sensitivity	Specificity
Grayeli *et al*[15]	2004	IIIb	10	33	70%	100%
Vicente *et al*[8]	2006	IIIb	54	22	87%	82%
Lee *et al*[2]	2009	IIIb	22	15	46%	100%
Zhu *et al*[14]	2010	IIIb	34	33	12%	100%
Quesnel *et al*[1]	2013	IIIb	10	36	80%	92%

reconstruction of the HRCT images with a slice thickness ranging from 0.6-2 mm were reviewed on a computerised picture archiving system and analysed in a blinded fashion by a radiologist, otologist or both. Otosclerotic foci were defined as hypodense lesions in the otic capsule or thickening/obliteration of the round and oval windows.

All analysed studies used control groups. The age and sex of the control group was not always included in the studies. There was a clear definition of control groups and we judged the risk of bias to be low, given that these included confirmed otosclerosis negative groups, vestibular schwannoma patients and contralateral ears in facial palsy patients.

Quantitative synthesis analysis demonstrated low sensitivity of 58% (95%CI: 49.4-66.9), a high specificity of 95% (95%CI: 89.9-98.0) and a positive predictive value of 92% (95%CI: 84.1-95.8). Negative predictive value was 71% (95%CI: 66.1-74.7) (Figure 2). The majority of the otosclerotic foci identified on CT were in the fenestral region and a combination of fenestral and retrofenestral foci was second most common.

Quesnel *et al*[1]'s study demonstrated an excellent correlation between CT imaging on a series of temporal bones with otosclerosis and corresponding histology slides of the same. The same study also concluded that CT can diagnose endosteal margin involvement (63% sensitivity) but cannot be relied upon to exclude it[1].

Lee *et al*[2]'s study specifically focused on a specific ethnic group (Taiwanese) with the ultimate objective of elucidating the tomographic findings of otosclerosis in that group.

In Zhu *et al*[14]'s study all positive results had a double ring sign on HRCT. This study was the outlier

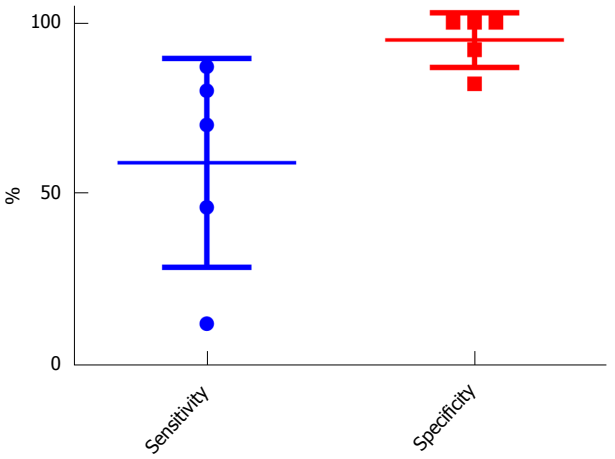

Figure 2 Box and Whisper Plot highlighting range of sensitivity and specificity.

by some distance and markedly affected the overall sensitivity of the pooled analysis. It is questionable that such a low diagnostic performance (4 of 34) should be possible and it is notable that some data was extrapolated as the primary aim of this study, like Zhu *et al*[14], was to assess the role of automated bone densitometry to diagnose otosclerosis. However, the study was retained within the analysis.

Quesnel *et al*[1] demonstrated a false positive rate of 8% (3/36) in their control group. These false positive cases which had appeared as hypodense lesions like otospongiotic foci were shown to be areas of increased connective tissue and vessels on histology. In another study a hypodense area in the anterior vestibule of 1 temporal bone in the control group was identified and judged to be a silent otosclerotic foci even though the subject was asymptomatic[8]. This was purely speculative and was not confirmed surgically.

A longer duration of disease was linked to multiple lesions in the otic capsule, false negative rates and larger preoperative air-bone gap (Vicente *et al*[8], 2006 and Lee *et al*[2], 2009).

DISCUSSION

In this review, we sought to elucidate the diagnostic performance of HRCT in otosclerosis using current level I-III studies. Numerous level IV and V papers have reported a wide-ranging sensitivity between 34% and 95%, with more recent studies suggesting values above 90%[10]. HRCT scans in otosclerosis are typically acquired using a bone algorithm with a slice thickness of 1 mm or less; slice thickness greater than 1 mm leads to increased false negative rates. Various studies have demonstrated that the sensitivity of HRCT is limited by inframillimetre and superficial foci, inactive disease, and density variations of less than 200 hounsfield units which are imperceptible to the naked eye[7,10].

The advent of improved CT scanning machines with improved collimation is thought to have raised the quality of the images available for analysis[1,2]. This, allied to the use of computerised workstations such as PACS for image analysis, has led to a higher diagnostic yield. Computerised workstations afford the ability to zoom in and scroll through images leading to a better appreciation of subtle abnormalities[16].

Overall, the analysed studies demonstrated a low sensitivity, high specificity and a high positive predictive value. However, there were wide confidence intervals particularly in the sensitivity, largely due to Zhu *et al*[14] study (12%). This study has limitations and has a particularly poor sensitivity in comparison to all other studies, possibly in part due to their primary aim being a densitometry study alongside with possible differing expertise levels. Other considerations include the disparate characteristics of the tested populations and the possible differences in the stages of the disease when the scans were performed. For instance, Lee *et al*[2]'s study (46% sensitivity) focused exclusively on a Taiwanese study group. With previous reports[17,18] suggesting a low sensitivity and incidence in other Asian ethnic groups it is impossible to ascertain whether the relatively low sensitivity in Lee *et al*[2]'s study is due to ethnic differences per se or is a manifestation of other factors such as patients presenting late in the otosclerotic phase. The rarity of the disease in Asians and the dearth of otologists with expertise in stapes surgery has led to a preference for non-surgical treatment amongst the greater proportion of patients with otosclerosis within the Taiwanese subgroup[2]. These factors are inevitably linked to the late presentation and arguably the low sensitivity on HRCT. Wider application of these findings is limited by the unique characteristics of the subgroup.

Quesnel *et al*[1] provide some useful insight into the relationship between HRCT and the size of disease foci. By matching presumed foci of otosclerosis identified on axial imaging with corresponding histology slides they demonstrate a sensitivity of 80%. The false negative results were due to the presence of an inframillimetres lesion which interestingly had not become clinically apparent. By correlating HRCT findings and histology, Quesnel *et al*[1] provide good evidence for the utility of HRCT in otosclerosis given that clinical/histopathological diagnosis is the gold standard in confirming pathology. Unfortunately their study is limited by a small sample size (18 ears) and the fact that the conditions under which the study was carried out are not easily reproducible clinically.

Our review shows that HRCT is better at identifying fenestral otospongiosis, thus confirming findings from previous studies. Identifying retrofenestral and endosteal margin involvement remains challenging notwithstanding that retrofenesteral otosclerosis is less common than fenesteral disease[8,10,14]. Studies have reported the limitations of HRCT in diagnosing retrofenestral otosclerosis with Dudau *et al*[19] sug-

gesting a sensitivity of 58%. The main areas of interest in retrofenesteral otosclerosis are the cochlear, pericochlear, and the areas anterior to the round window niche[1,15]. Clinically, the presence of cochlear disease has implications for planning treatment and counselling patients because of the risk of developing sensorineural hearing loss. This makes preoperative diagnosis useful.

Unfortunately, CT diagnosis remains problematic particularly where otospongiotic foci are small and where other conditions that demineralise the otic capsule such as osteogenesis imperfecta, Paget's disease or syphilis are considered[2,8]. These limitations are highlighted in Quesnel *et al*[1]'s study where CT had a sensitivity of 63% in identifying endosteal margin involvement.[1]The false negatives where due to inframillimetre disease. This illustrates that while HRCT can identify endosteal lesions it cannot be relied upon to conclusively rule it out.

Quesnel *et al*[1] and Vicente *et al*[8]'s studies identified abnormalities on HRCT in their respective control groups. Having dismissed findings of mild pericochlear lucency as a non-specific sign and therefore not necessarily suggestive of otosclerosis, Vicente *et al*[8] concluded that a hypodense focus anterior to the wall of the vestibule in one of the control ears was suggestive of silent otosclerosis. This taken in context with Quesnel *et al*[1]'s study where presumed area of otosclerotic foci on HRCT were shown to be areas of connective tissue and vessels on histology highlights the limitations of HRCT in diagnosing otosclerosis: Normal variants and other disease processes can appear as otosclerosis on HRCT[1,8]. Diagnosis of otosclerosis remains clinical and HRCT can play an ancillary role.

Study limitations

The studies included in our review used small sample sizes which makes them vulnerable to some of the limitations associated with such studies, *i.e.*, underpowered, with large confidence intervals and heterogeneity. In addition, we have pooled data from disparate groups which adds to the limitations of using small samples. This, however, must be taken in the context of an overall dearth in studies that are level Ⅲ or above whose primary aim is to investigate the utility of HRCT in diagnosing otosclerosis. Also, 2 of the 5 studies reviewed are retrospective and therefore prone to the shortcomings of such studies. Furthermore, because we have relied upon authors reporting of methodology and results for quality assessment and data extraction we cannot eliminate all bias.

The sensitivity and specificity of HRCT in diagnosing otosclerosis were not always the primary objective of all the studies included; in some studies, this was an indirect measure. For instance, in studies examining the utility of HRCT bone densitometry in otosclerosis (Grayeli *et al*[15] 2004 and Zhu *et al*[14] 2010). Zhu's study in particular demonstrates an outlying sensitivity that had to be extrapolated from their study. Had this study been excluded the sensitivity of this pooled dataset would be 71%. It is unusual to have such a low diagnostic performance and this may reflect patient factors, disease factors (*i.e.*, advanced disease) or local expertise factors. This demonstrates the inherent difficulty in pooling data from differing authors and studies and serves as a significant limiting factor in this analysis.

In conclusion, Based on current level Ⅲ evidence HRCT has a high specificity and positive predictive value and a relatively low sensitivity in diagnosing otosclerosis. HRCT has a high sensitivity in identifying the more prevalent fenestral subtype of otosclerosis, particularly lesions in the fissula ante fenestram.

Inframillimetres lesions, retrofenestral lesions and dense sclerotic lesions present a diagnostic challenge despite the advent of more advanced CT scanners and better understanding of otosclerosis as a disease process. Diagnosis of otosclerosis remains clinical and HRCT can be a useful adjunct especially when assessing the extent of disease and when excluding other causes.

COMMENTS

Background

Otosclerosis is focal bone dyscrasia of unknown aetiology which predominantly affects only the endochondral bone of the otic capsule in humans. Patients typically present with conductive hearing loss. The diagnosis of otosclerosis is based on a combination of medical history, physical examination, audiological testing and imaging.

Research frontiers

High resolution computed tomography (HRCT) of the temporal bones is the current imaging modality of choice in the investigation of otosclerosis. However, as demonstrated in this study and others, it has variable sensitivity and specificity.

Innovations and breakthroughs

This study highlights the value and limitations of HRCT in the diagnosis of Otosclerosis. Some studies in the literature are exploring the utility of cone beam computed tomography (CBCT) as an alternative to HRCT in the investigation of otosclerosis. However, these are in their infancy and time will tell whether CBCT supersedes HRCT as the modality of choice in imaging the middle ear.

Applications

HRCT is the gold standard imaging technique in investigating the middle ear. It may be useful in distinguishing between otosclerosis and other pathological conditions of the middle ear such as tympanosclerosis, cholesteatoma, ossicular fixation and congenital malformations

Peer-review

Otosclerosis is a bony dyscrasia of the inner ear otic capsule. HRCT has a significant role in imaging the labyrinthine and bony capsule of the temporal bone. The extent of otosclerosis into the cochlear capsule can be quantitatively evaluated using densitometric measurements. In this manuscript, the authors focused on the sensitivity and specificity of HRCT in the diagnosis of otosclerosis. This systematic review indicates that HRCT is a useful imaging method in diagnosis of otosclerosis [HRCT has a high specificity (98%) and low sensitivity (63%) in diagnosing otosclerosis], supported by level Ⅲ evidence. This review has some significance for clinicians and researchers working.

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CASE REPORT

Post traumatic dural sinus thrombosis following epidural hematoma: Literature review and case report

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Author contributions: Pescatori L and Tropeano MP designed work and wrote the manuscript; Mancarella C, Prizio E and Santoro G researched the bibliography; Domenicucci M have supervised and corrected the manuscript.

Institutional review board statement: This case report was exempt from the Institutional Review Board standards at Sapienza University of Rome.

Informed consent statement: The patient gave his written informed consent authorizing use and disclosure of his protected health information.

Conflict-of-interest statement: All the authors have no conflicts of interests to declare.

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Abstract

Dural sinus thrombosis following a head trauma is a rare condition, described in literature along with the lack of consensus regarding diagnosis and management. We present a case of a fifty-year-old man with a head injury and combined supratentorial-subtentorial epidural hematoma who was treated conservatively through the administration of low molecular weight heparin. The diagnosis and management of this condition are discussed based on a literature review. The early diagnosis may prevent potentially treatable poor outcomes.

Key words: Dural sinus thrombosis; Epidural hematoma; Low molecular weight heparin

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Core tip: Dural sinus thrombosis (DST) is a rare although serious clinicopathological entity that causes approximately 0.5% of all stroke cases. Head trauma may be identified as a possible cause of DST. The lack of consensus regarding the most appropriate therapeutic strategy prompted us to describe this unusual case of transverse sinus thrombosis caused by a combined supra-subtentorial haematoma. The absence of symptoms of the patient convinced us to assume a conservative behaviour which consisted in the administration of low molecular weight heparin after the computed tomography scan had

documented the stability of the extradural collection. Our strategy leads to the recanalization of the sinus.

Pescatori L, Tropeano MP, Mancarella C, Prizio E, Santoro G, Domenicucci M. Post traumatic dural sinus thrombosis following epidural hematoma: Literature review and case report. *World J Clin Cases* 2017; 5(7): 292-298 Available from: URL: http://www.wjgnet.com/2307-8960/full/v5/i7/292.htm DOI: http://dx.doi.org/10.12998/wjcc.v5.i7.292

INTRODUCTION

Dural sinus thrombosis (DST) is a rare although serious clinicopathological entity that causes approximately 0.5% of all stroke cases[1]. Superior sagittal sinus as well as transverse sinus are more affected than other dural sinuses[1]. Head trauma may be identified as a possible cause of DST. In particular, depressed skull fractures occurring at the site of the dural sinuses as well as epidural or subdural hematoma have been found to be associated with DST[2-6]. Here we describe the case of a man who reported the occlusion of the transverse sinus as the consequence of the development of a combined supratentorial-subtentorial epidural hematoma. The patient was treated conservatively through the administration of low molecular weight heparin (LMWH). We discuss the physiopathologycal hypothesis, the clinic-radiological aspects as well as the management options reviewing the literature.

CASE REPORT

This is the case of a fifty-year-old man who was hospitalized after being involved in a car accident in which he reported a concussive head trauma. Except for the trauma he did not have a significant history of illness. The patient was subjected to a brain computed tomography (CT) scan which showed the presence of a combined right supra-subtentorial hematoma (Figure 1). Clinical evaluation of the patient did not reveal any neurological signs except for a mild headache. Because of the site of the hematoma, an involvement of the transverse sinus was suspected. As a consequence a brain magnetic resonance imaging (MRI) with arterial and venous reconstruction was performed. The MRI confirmed the presence of the hematoma involving the supratentorial and the subtentorial compartment. Furthermore the venous study did not show any appreciable signal of blood flow within the right transverse sinus. This radiological finding was likely to be due to the occlusion of the sinus (Figures 2 and 3). Because of the absence of neurological signs as well as the patency of the contralateral dural sinuses system, a conservative management was adopted. A CT scan performed 48 h after the accident showed a slight increase in the size of the hematoma (Figure 4). As a consequence, administration of LMWH was delayed. By the 10th post-traumatic day two more brain CT scan had been performed which had shown the progressive decrease in the size of the hematoma (Figure 5). This reduction encouraged us to begin the administration of LMWH. On 15th post-traumatic day the patient was discharged at home. During the subsequent 23 d the patient did not experience any symptoms related to the trauma. On 24th post-traumatic day, he began to complain of mild headache, vertigo and nausea. Since the symptoms were not responsive to oral analgesics and antiemetic drugs, the patient came back to the Emergency Department of our Hospital. A new brain CT scan was performed. It showed a further reduction of the size of both hematomas. Given the clinical history, a new brain MRIs can with venous angiographic reconstruction was performed. The new MRI confirmed the further decrease in the size of the epidural hematomas. Angiographic reconstructions of the dural sinuses showed that, although characterized by a less intensity in comparison with the contralateral sinus, the blood flow signal within the previously occluded transverse sinus was now visible. These radiological findings were likely to be due to the partial recanalization of the sinus (Figure 6). Symptoms progressively disappeared and after a brief period of hospitalization the patient was discharged at home.

DISCUSSION

DST is a rare although serious clinicopathological entity that causes approximately 0.5% of all stroke cases. The signs and symptoms are extremely varied and non specific. Cerebral sinus thrombus formation due to head injury has been postulated to be caused by a sinus endothelial injury, thrombus extension from scalp abrasions, or damage to the emissary veins[7]. Sinus thrombosis can often occur with thrombosis of the cerebral veins, leading to cytotoxic and vasogenic edema[8]. The sinus thrombi lead directly to the decreased absorption of cerebrospinal fluid because of the increased sinus venous pressure, resulting in intracranial hypertension. Patients with cerebral sinus thrombosis most often present with severe headache that can be gradual or acute in nature. Patients can also have symptoms of increased intracranial pressure, including nausea and vomiting. Some patients have seizures. In 1946, Ecker described the first case of head injury associated with DST. Since then, other trauma-induced DSTs have been reported in cases of head injuries[5,9,10]. Ochagavia announced that the incidence of DST was 4% after penetrating head trauma[10]. However, Stiefel *et al*[11] reported that he found DST with an incidence of 6.8% in the pediatric age group. There are two series on post traumatic DST in children but sporadic case reports in adults and in

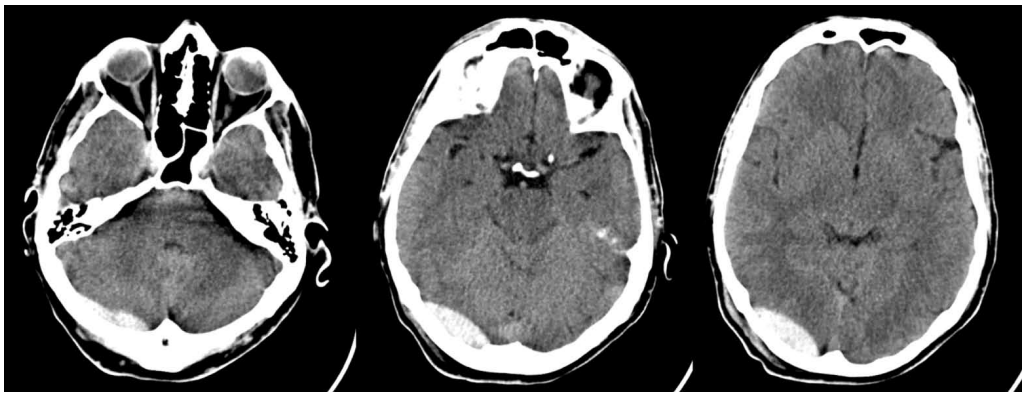

Figure 1 First computed tomography scan performed after the trauma. It shows the presence of a combined supra-subtentorial epidural hematoma.

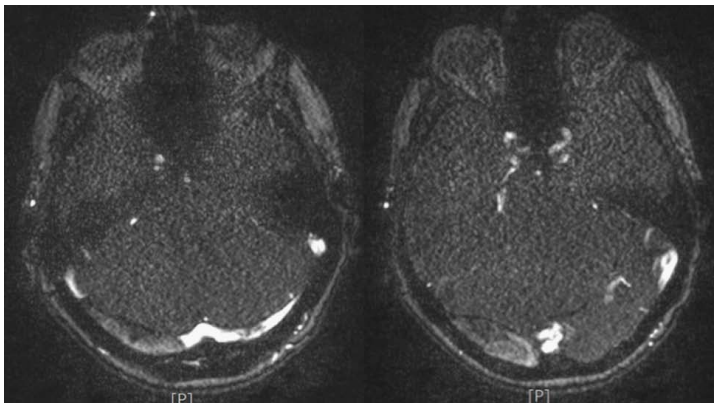

Figure 2 Angio-magnetic resonance imaging documenting the absence of the blood signal within the sinus as well as the epidural hematoma compressing the cerebellum and the sinus wall.

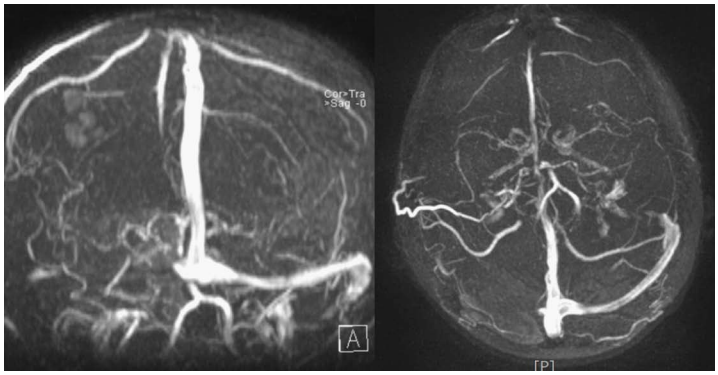

Figure 3 Angio-magnetic resonance imaging three dimensional reconstruction of the dural sinus system. It is not possible to appreciate any signal within the right transverse sinus as it happens for dural sinus occlusion. Notice the patency of the contralateral dural sinus complex.

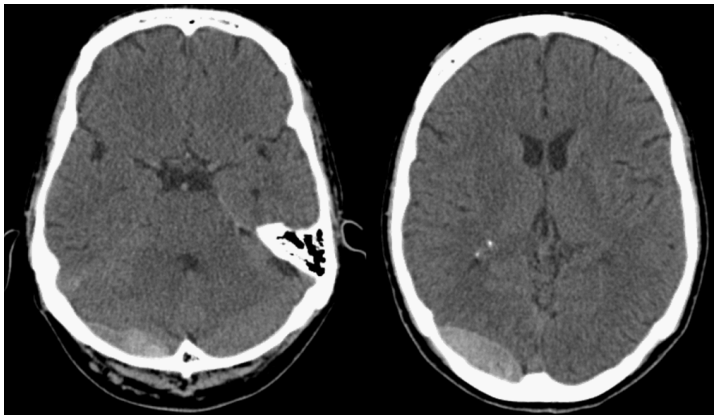

Figure 4 Computed tomography scan performed 48 h after the trauma. An increase of the size of the ematoma was identified by the radiologist. As a consequence we decided to postpone the administration of low molecular weight heparin.

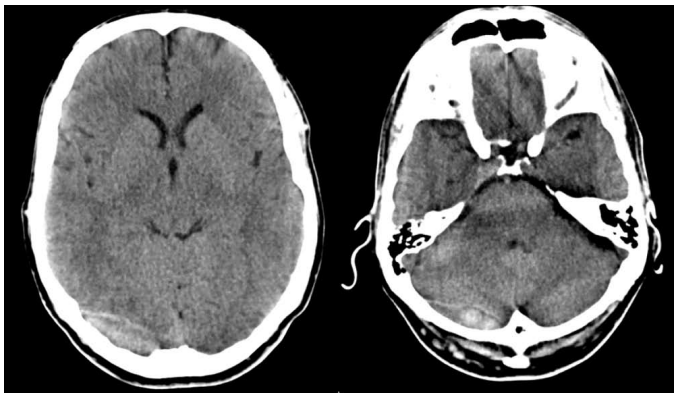

Figure 5 By the 10th post-traumatic day two more brain computed tomography scan had been performed showing the partial reabsorption of the hematoma. From this moment the administration of low molecular weight heparin heparin began.

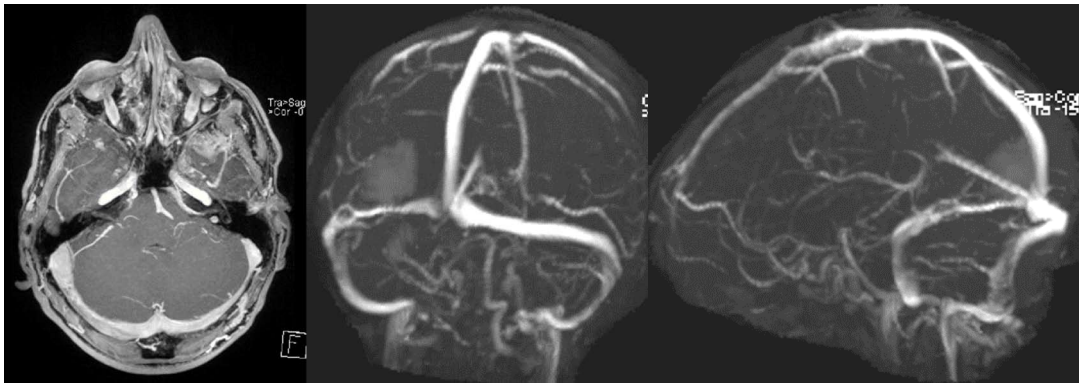

Figure 6 Brain magnetic resonance imaging with angiographic reconstruction of the venous system performed on 24th post-traumatic day after the onset of posterior cranial fossa symptoms. Magnetic resonance imaging shows the partial recanalization of the right transverse sinus as well as the almost complete reabsorption of the epidural hematoma.

Table 1 Summary of reported cases with cerebral sinus thrombosis due to head injury in the last 30 years

Ref.	Age, sex	Symptom	Skull fracture	Intracranial lesion	Treatment	Follow-up
Hesselbrock *et al*[8]	44, M	IICPS, seizure	?	Contusion	Supportive	Unknown
Taha *et al*[22]	5 (3M/2F) children	Various	3 cases	Contusion	Supportive	4 RC 1 no RC
Ochagavia *et al*[10]	27, M	Herniation due to IICPS	-	Edema	-	dead
Ferrera *et al*[17]	24, M	IICPS	+	Venous infarct	Surgery	Unknown
Stiefel *et al*[11]	8 (5F/3M) children	IICPS	All cases	-	-	6 RC 1 no RC 1 dead
Meena *et al*[9]	40, M	IICPS, seizure, hemiparesi	-	-	AC	Unknown
Satoh *et al*[21]	2, F	IICPS	-	-	Supportive	RC
Brors *et al*[13]	32, M	Cranial nerve palsy	+	Contusion	AC	RC
Erdogan *et al*[16]	1, M	IICPS	-	Venous infarct, SH	Supportive	Unknown
Owler *et al*[4]	18, M	IICPS, hemiparesi	-	Venous infarct	Supportive, surgery	Unknown
Sousa *et al*[19]	7, F	IICPS	-	-	supportive	Unknown
Muthukumar *et al*[25]	7, F	IICPS	+	-	AC	Unknown
Saad *et al*[20]	10, F	IICPS	-	-	AC	Unknown
Yuen *et al*[23]	4, F	IICPS	+	-	Supportive	RC
Dalgiç *et al*[15]	35, M	IICPS	-	-	AC	RC
	25, M	Facial palsy	+	EH	AC	No RC
Caplan *et al*[14]	27, M	IICPS, paraesthesias	+	Contusion	AC	Unknown
Bakar *et al*[12]	18, M	IICPS	+	Edema	Surgery	Unknown
Beer-Furlan *et al*[26]	3, M	IICPS	+	EH	Surgery	Dead
Lebowitz *et al*[18]	6, M	IICPS	-	SH	AC	No RC
Yun *et al*[24]	10, M	IICPS	+	EH	Supportive	RC
Our case	50, M	IICPS	-	EH	Supportive, AC	RC

M: Male; F: Female; IICPS: Increased intracranial pressure; EH: Epidural hematoma; RC: Recanalization; SH: Subdural hematoma; AC: Anticoagulation.

children have been published[4,6,12-25]. Overall, there are 32 cases including 22 children and 10 adults (Table 1). The higher number of children can be explained by the fact that the venous collateral system is not completely mature in their cerebrum. In only 3 cases (1 adult and 2 children) there was an epidural hematoma (EH). It was always associated with skull fracture. Our case is the first case reported, to our knowledge, in which the epidural hematoma was not associated to skull fracture and had a supra and subtentorial localization. In our case, although it is difficult to establish if the occlusion of the sinus was owed to the extrinsic compression of the hematoma on the sinus wall or to the development of a thrombus within the sinus, it is possible that both the phenomenon contributed to the occlusion through a cause-effect process. The extrinsic compression of the hematoma probably caused a deceleration of the blood flow within the sinus. As a consequence, according to the principles of blood stasis, modifications of the vascular wall and blood rheology enunciated by Virchow, it is likely that a thrombus within the transverse sinus developed. The initial imaging study in the evaluation of patients with possible DST is usually a brain CT scan. Magnetic resonance imaging, as well as MR angiography and venography, provide us with the most sensitive tools for detecting DST. The combination of these imaging modalities constitutes the study of choice in the diagnosis of DST. In fact the images shown by our MRI are compatible with an occlusion of the transverse sinus. There is no consensus on the overall treatment concerning surgical, radiosurgical, endovascular or conservative treatment. Identification and treatment of the underlying causes should represent the first step in the treatment of dural sinus occlusion. In case of extrinsic compression such as depressed skull fractures as well as epidural or subdural hematoma surgical removal of the identified source of compression has been advocated by several authors[12,14], even if only 1 case of post-traumatic DST related to EH, reported in literature, was underwent to surgical treatment[26]. In our case, despite the presence of the epidural hematoma without mass effect as well as the occlusion of the sinus, the complete absence of neurological symptoms encouraged us to adopt a conservative behaviour. Despite the role of antithrombotic therapy has been widely examined and several studies have been published in this sense, its use in post-traumatic DST still remain controversial, because of increased risk for venous hemorrhagic infarction[26]. A meta-analysis conducted by Coutinho *et al*[27] which included 2 randomized controlled studies investigating the role of unfractionated heparin as well as LMWH, concluded that the anticoagulant treatment can be considered safe and is associated with a better overall outcome in patients affected with DST. The EFNS guideline on the treatment of cerebral venous and sinus thrombosis in adult patients conducted by Einhäupl *et al*[28] in 2010 concludes that patients with cerebral sinus thrombosis without contraindications for anticoagulant should be treated either with body weight-adjusted subcutaneous LMWH or with dose adjusted intravenous heparin. In addition the study concluded that the use of LMWH should be considered safe despite the presence of intracranial haemorrhage. Although conscious of current literature, we decided to postpone the administration of subcutaneous LMWH because of the growth of the epidural hematoma that had been shown by a control CT scan performed 48 h after trauma. Once seriated CT scan demonstrated the progressive reduction in the size of the hematoma subcutaneous LMWH heparin was administered and continued after discharge. LMWH pharmacologically doesn't possess thrombolytic action; given this the main purpose of their administration is to prevent recurrent thrombosis and appositional thrombus growth. Data collected from different studies confirm that DST patients display a high spontaneous and intrinsic thrombolytic potential, with recanalization rates of 60% during the first 20 d as happened in our case. Thereafter, recanalization rates increase insignificantly[26]. The second MRI with angiographic and venous reconstruction performed during the second hospitalization showed that the blood flow within the transverse sinus had reappeared. The administration of LMWH as well as the progressive reabsorption of the epidural hematoma are related to the recanalization of the transverse sinus. The consequent reorganization of the venous blood flow within the dural sinus system was may explain the physiopathology of the posterior cranial fossa symptoms characterized by vertigo and headache.

DST is a rare although serious condition described in literature along with a lack of consensus regarding diagnosis and management. Most reports show good outcome and recovery, but DST might be related to a poor recovery and even lead to death. DST may be caused by post-traumatic depressed skull fractures or intracerebral hematomas compressing the sinus wall and altering the blood flow within the sinus until thrombosis, so additional diagnostic investigations should be performed in terms of DST in head trauma cases that have other risk factors. The administration of anticoagulant therapy still remains controversial but in association with the progressive reabsorption of the hematoma it could allow the recanalization of the dural sinus.

COMMENTS

Case characteristics

A fifty-year-old man was hospitalized after being involved in a car accident in which he reported a concussive head trauma.

Clinical diagnosis

Except for a mild headache, the patient didn't show neurological signs.

Differential diagnosis

Haemorrhage, concussion injury, cerebral contusion.

Laboratory diagnosis
All labs were within normal limits.

Imaging diagnosis
Computed tomography (CT) scan showed the presence of a combined right supra-subtentorial hematoma, while the magnetic resonance imaging scan showed the occlusion of the transverse sinus.

Treatment
Once seriated CT scan demonstrated the progressive reduction in the size of the hematoma subcutaneous heparin or low molecular weight heparin was administered and continued after discharge.

Related reports
Dural sinus thrombosis (DST) following a head trauma is a rare condition, described in literature along with the lack of consensus regarding diagnosis and management.

Term explanation
Dural venous sinus thrombosis is a subset of cerebral venous thrombosis. It is the presence of a blood clot in the dural venous sinuses that causes approximately 0.5% of all stroke cases. The symptoms depend mainly on which sinus is involved.

Experience and lessons
In case of head trauma the DST should always be considered. This entity is often underestimated. Recognizing this condition can prevent misdiagnosis and suggest the best treatment option. The administration of anticoagulant therapy could allow the recanalization of the dural sinus.

Peer-review
This is a rare and interesting case, which could highlight a differential diagnosis for clinical doctors.

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CASE REPORT

Rare case of cryptogenic brain abscess caused by *Raoultella ornithinolityca*

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Abstract

Cerebral abscess is a potentially fatal neurosurgical condition, despite improvements in technology, new antimicrobial agents and modern neurosurgical instruments and techniques. I report the case of a 64-year-old woman, affected by a right frontobasal brain abscess, compressing the homolateral frontal horn of lateral ventricle, with a second mass partially occupying the right orbital cavity. She presented also with inflammatory sinusopathy involving the right maxillary, ethmoid and frontal sinuses. After 14 d of clinical observation and antimicrobial therapy, the patient received a computed tomography scan, which showed growth of the cerebral mass, with a ring of peripheral contrast enhancement and surrounding edema. She promptly underwent neurosurgical treatment and recovered well, except for the sight in her right eye, which remained compromised, as before the operation. This is believed to be the first case of cryptogenic cerebral abscess caused by *Raoultella ornithinolityca* isolated from the brain, with more than 1-year follow-up.

Key words: Brain abscess; Headache; *Raoultella ornithinolityca*; Visual loss

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Core tip: Brain abscess is a focal intracranial infection that evolves in a collection of pus. It could have cryptogenic origin in 10%-35% of cases. I present a 64-year-old woman affected by a frontal brain abscess that was surgically treated, from which *Raoultella ornithinolytica* (*R. ornithinolytica*) was isolated. The patient, after > 1 year, is doing well, except for her right eye that had already lost its visual power before surgery. This is believed to be the first case of cryptogenic cerebral abscess caused by *R. ornithinolytica*.

Luongo M. Rare case of cryptogenic brain abscess caused by *Raoultella ornithinolityca*. *World J Clin Cases* 2017; 5(7): 299-302 Available from: URL: http://www.wjgnet.com/2307-8960/full/v5/i7/299.htm DOI: http://dx.doi.org/10.12998/wjcc.v5.i7.299

INTRODUCTION

Brain abscess is a focal intracranial infection characterized as an area of cerebritis that evolves in a collection of pus surrounded by a vascularized capsule. Organisms can reach the central nervous system by spreading from a contiguous source of infection, hematogenous dissemination, or trauma, but there are cryptogenic brain abscesses in 10%-35% of cases. The frontal lobe is the predominant site of cerebral abscess in patients with paranasal sinusitis. *Raoultella ornithinolytica* (*R. ornithinolytica*) is an encapsulated Gram-negative bacterium and member of the Enterobacteriaceae. Human infections caused by *Raoultella* are rare. I describe a case of cryptogenic cerebral abscess caused by *R. ornithinolytica*, with good recovery after > 1 year after surgery.

CASE REPORT

A 64-year-old woman was admitted to our hospital for fever and headache. She was hospitalized in the Infectious Disease Department for observation and study. Chest X-ray and abdominal ultrasound examination were normal. Magnetic resonance imaging (MRI) with gadolinium revealed a right frontobasal brain abscess, compressing the homolateral frontal horn of the lateral ventricle, with a second mass partially occupying the right orbital cavity (Figure 1A). She presented also with inflammatory sinusopathy involving the right frontal, ethmoid and maxillary sinuses. After 14 d of clinical observation and intravenous broad-spectrum antibiotic therapy, nasal culture was performed on day 14 of hospitalization, which showed evidence of low levels of *Candida albicans*. Ophthalmological consultation revealed visual loss from her right eye, and contrast computed tomography (CT) showed an increase in abscess size, so the patient underwent prompt surgery with right frontobasal craniotomy (Figure 1B). Thanks to neuronavigation and under operative microscopy, the abscessual capsule was opened widely, in order to drain its content, and it was coagulated to avoid damage to nervous structures, given that the cerebral parenchyma in the right orbit appeared to be involved in an inflammatory reaction. Some of the mass content was sent for microbiological examination in Bactec broth and, 8 d after surgery, *R. ornithinolytica* was isolated by conventional microbiological tests. On the basis of an antibiogram, determined according to the European Committee on Antimicrobial Susceptibility Testing, and after consulting an infectious diseases specialist, the patient started intravenous therapy with metronidazole and ceftriaxone, four times and twice daily, respectively (Table 1). She received a basal CT scan that showed no residual or recurrent brain abscess.

Her general clinical conditions were improved but, on day 30 in hospital (approximately 2 wk after surgery) she developed right-side pneumonia with pleural effusion, caused by *Klebsiella pneumoniae*, which was treated by intravenous ceftriaxone and ciprofloxacin twice daily, together with amphotericin B and amikacin once daily (Table 1). During the last month she was free from antimicrobial therapy, without infectious problems, but it was necessary to correct persistent hypokalemia, presented by the patient from the first time. The patient was discharged after approximately 3 mo of hospitalization and she is currently well.

DISCUSSION

R. ornithinolytica is an encapsulated, aerobic, non-motile, blood-borne Gram-negative bacterium belonging to the Enterobacteriaceae, which is frequently misidentified as *Klebsiella* spp. It was first described by Sakazaki *et al*[1] in 1989 and it can be isolated from aquatic environments, insects, fish and brackish water. It can cause fish poisoning because of its capacity to produce histamine and it can cause headache, flushing, abdominal cramps, pruritus, and rarely, bradycardia, bronchospasm and hypotension. Over the years, *R. ornithinolytica* has emerged as an infrequent cause of human infections, with about 10 cases reported linking the bacterium to bacteremia, sepsis, and soft tissue and other infections, as described by Nakasone *et al*[2] in their article about a case of community-acquired urinary infection.

An important study on clinical characteristics of *R. ornithinolytica* bacteremia focused on its unfavorable outcomes, compared to bacteremia caused by other *Raoultella* spp. The study analyzed 16 patients (11 male and 5 female) over 10 years, with a mean age of 55.7 years; all but one had an underlying malignant condition and seven had infections associated with the biliary tract. They found that the overall mortality of *R. ornithinolytica* bacteremia could be compared to that of *Klebsiella* spp., and it was reported to be 20%-25%. In addition, suggested an increased risk of *R. ornithinolytica* bacteremia in patients affected by underlying malignant conditions extending to the biliary tract[3]. Even though some cases of biliary tract infection, urinary infection and bacteremia have been reported, there is not much information about clinical features and outcomes of *R. ornithinolytica*. A recent review by Seng and colleagues discusses the largest series reported to date of 86 cases from four French universities over 12 years (with half of cases in 2015), and emphasizes different important characteristics such as a high rate of hospital-acquired infection (49%). Besides comorbidity and risk factors previously reported such as solid tumor, post-urethra trauma, and post invasive procedures, Seng *et al*[4] found that half of the patients had diabetes or immunodeficiency, and they described infections not previously reported, including pleural effusion, meningitis and cerebral

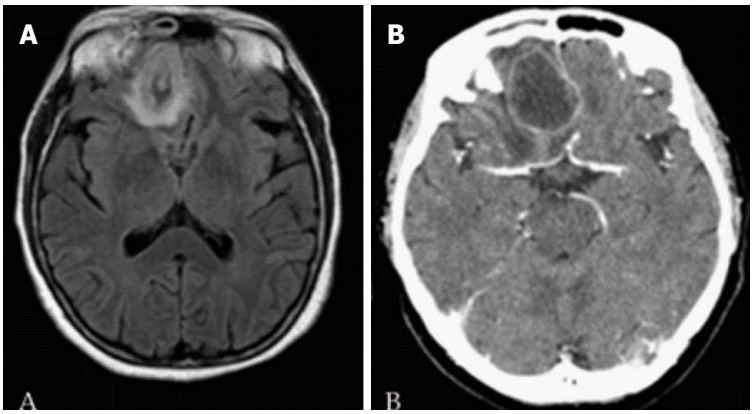

Figure 1 Preoperative images. A: Magnetic resonance imaging with gadolium showing right frontobasal brain abscess and a second mass occupying the right orbit; B: Contrast-enhanced computed tomography scan.

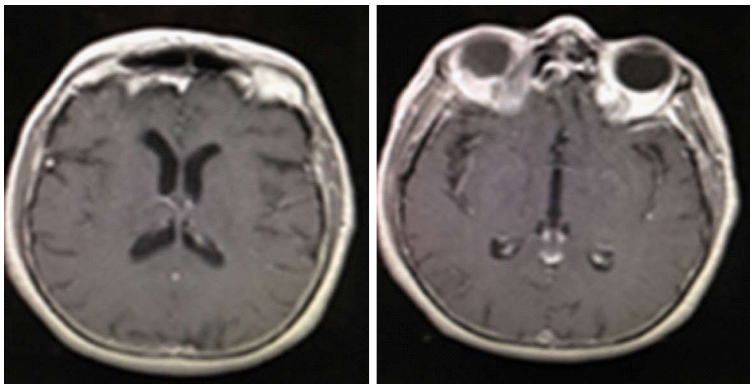

Figure 2 Magnetic resonance imaging performed 14 mo after surgery.

Table 1 Scheme summarizing the antimicrobial drugs assumed by the patient during the hospitalization

Drug	Dosage	Administration route	Duration of therapy, d	Frequency of administration, d
Ceftriaxone	2 g	Intravenous	50	2
Amphotericin b	50 mg	Intravenous	20	1
Amikacin	500 mg	Intravenous	12	1
Ciprofloxacin	200 mg	Intravenous	11	2

abscess. The cerebral abscess described by Seng *et al*[4] was secondary to a craniotomy for head trauma and not spontaneous as in the present case[4].

The frontal lobe is the predominant site in patients with brain abscess secondary to paranasal sinusitis, so I thought that the cerebral abscess in my patient was secondary to sinusopathy, but nasal culture only isolated a low number of *C. albicans*. The patient has diabetes and experienced pleural effusion caused by *K. pneumoniae* during hospitalization, > 2 wk after surgery, so this case was not related to any condition previously described.

In summary this is the report of a rare case of brain abscess caused by *R. ornithinolytica* that was successfully treated by intravenous antibiotics and prompt surgical intervention. This is believed to be the first cryptogenic brain abscess caused by *R. ornithinolytica*, with MRI showing complete surgical removal and no recurrence after > 1 year (Figure 2). It could be important to focus attention on this bacterium in order to understand better and eventually prevent occurrence of this potentially fatal condition.

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COMMENTS

Case characteristics

A 64-year-old woman with inflammatory sinosupathy and, a few days later, visual loss in the right eye.

Clinical diagnosis

Fever and headache with visual disturbance.

Differential diagnosis

Central nervous system inflammatory conditions, cerebral abscess, meningitis, and brain tumor.

Laboratory diagnosis

Nasal culture and microbiological examination of the surgically removed cerebral

mass.

Imaging diagnosis
Magnetic resonance imaging with gadolinium revealing the presence of a right frontobasal brain abscess and a second mass partially occupying the right orbital cavity.

Pathological diagnosis
Some of the mass content was sent for microbiological examination and *Raoultella ornithinolytica* was isolated by conventional microbiological tests.

Treatment
Right frontobasal craniotomy was performed and the abscessual capsule was opened widely and coagulated. On the basis of an antibiogram and after consulting an infectious diseases specialist, the patient started intravenous therapy with antibiotics.

Related reports
R. ornithinolytica is a Gram-negative bacterium belonging to the family Enterobacteriaceae that is frequently misidentified as *Klebsiella* spp.. It has potent virulence and is rare in clinical situations but results in a high risk of bacteremia in patients affected by underlying malignant conditions extending to the biliary tract.

Term explanation
R. ornithinolytica brain abscess is a rare condition because, over the years, the bacterium has mainly been responsible for infrequent but important human urinary tract infections.

Experience and lessons
Brain abscess caused by *R. ornithinolytica* is a rare condition to be aware of in daily clinical practice in order to understand, prevent and treat it, through a combination of prompt surgical intervention and intravenous antibiotics.

Peer-review
This is a very interesting presentation about a rare etiology for brain abscess. It is a case that reminds us to be aware of this condition in the daily practice. The paper is well structured and written.

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CASE REPORT

Is dengue emerging as important cause of acute liver failure in endemic regions?

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Abstract

Dengue virus infection continues to be major public health problem in large part of world. The epidemiology of dengue viral infection is becoming increasingly complex and has substantially changed over almost past six decades not only in terms of prevalent strains and geographical locations but also in terms of disease severity and atypical presentations. Though liver is the most common organ affected but is generally asymptomatic. We present a case of infant with severe dengue who died of fulminant hepatic failure and showed pan lobular necrosis on post mortem liver biopsy. The case is being presented to highlight life threatening complication of dengue in young children, and dengue viral infection as a cause of acute liver failure in endemic areas. Thus dengue fever should also be considered as one of the differential diagnosis in children presenting with fever and fulminant hepatic failure in endemic regions.

Key words: Dengue viral infection; Acute liver failure; Panlobular hepatic necrosis; Hepatomegaly; Transaminitis

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Core tip: Dengue infection has more severe manifestation in young children and it should be considered as a cause of acute liver failure in children residing in endemic area.

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INTRODUCTION

Dengue virus (DENV) infections continue to be a major public health problem in large parts of the world[1]. It is one of the most important causes of febrile illness in endemic regions. DENV affects various organs during the period of viremia including liver and brain. Liver is the most common organ affected but is generally asymptomatic. Liver involvement ranges from derangement of liver enzymes, increased bilirubin to clinical jaundice and acute liver failure rarely. DENV is known to cause severe manifestation in infants. Virus virulence factor and detrimental host response are responsible for severe manifestations of dengue.

We present a case of infant with severe dengue who died of fulminant hepatic failure and showed pan lobular necrosis on post mortem liver biopsy. The case is again a reminder of life threatening complication of dengue in young children, and DENV as a cause of acute liver failure in endemic areas.

CASE REPORT

A 3-mo-old male, presented, with jaundice and frank bleeding from multiple sites (gastrointestinal, nasal, skin). Child was relatively asymptomatic 1 wk back then developed high grade fever with running nose. On 3rd day of illness, child had one episode of seizure followed by altered sensorium which persisted beyond postictal period. He was documented to be afebrile for 2 d before developing frank bleeding, abdominal distension and worsening of sensorium. On examination, child was sick looking with pallor, deep icterus and rapid pulse. Abdominal examination revealed hepatomegaly with liver 8 cm below the costal margin with sharp border and mild tenderness.

The differential diagnosis of acute infective viral hepatitis, complicated malaria, leptospirosis, severe dengue was kept and investigations ordered. Baseline investigations are shown in Table 1.

Child met the criteria for acute liver failure defined by the Pediatric Acute Liver Failure study group as there was no past history of chronic liver disease, his coagulopathy was not corrected after giving vitamin K and he was in hepatic encephalopathy with deranged PT/INR. Child was managed with supportive care (vitamin K, fresh frozen plasma infusion for coagulopathy), broad spectrum antibiotic, monitoring for electrolyte abnormality and hypoglycaemia and management of raised intracranial pressure. Despite these measures, there was progressive deterioration in clinical condition with requirement for mechanical ventilation. Child succumbed to the illness, 12 h after admission due to massive bleed and refractory shock, in the setting of fulminant hepatic failure.

The post-mortem liver biopsy showed multilobular and pan lobular hepatic necrosis with predominant involvement of centrilobular and midzonal regions with relative sparing of zone 1 (Figure 1). Thus, final diagnosis of severe dengue fever[1] with acute liver failure was made.

DISCUSSION

Dengue has recently emerged as the most rapidly spreading arboviral disease with an estimated 390 million dengue infections annually[2]. The pattern of dengue fever in Indian subcontinent has changed substantially in the last 60 years shifting from sporadic epidemic disease to an endemic one. With the endemicity, the disease severity has changed and atypical presentations like acute liver failure, myositis, hemophagocytic syndrome myositis are increasingly being reported[3].

Dengue fever has a spectrum of clinical manifestations ranging from self-limited illness to fulminant course resulting in death. Younger age is a risk factor for severe manifestation of dengue. Virus virulence factor and detrimental host response are responsible for severe manifestations of dengue. Pathogenesis of the different manifestations of dengue virus infections in humans is still an area of research. The spectrum of clinical manifestation of dengue involves relatively benign subclinical infection or dengue fever to life-threatening dengue haemorrhagic fever, and dengue shock syndrome (DSS). Differential targeting of specific vascular beds may cause localized vascular hyperpermeability seen in DSS. Hepatic involvement is usually subclinical but dengue virus is known to have hepatotoxic effect. Derangement of liver enzymes and jaundice may be seen and rarely it may cause acute liver failure. In presence of detrimental host response like young age as in our case, the rare manifestations of dengue are increasingly being recognized in endemic areas.

With considerable decrease in the prevalence of hepatitis B due to universal immunization and hepatitis A due to improved sanitation dengue has emerged as an important cause of acute liver failure in children especially during epidemics[4].

Hepatic involvement in dengue fever presents with liver enlargement and elevated transaminases[5,6]. In most of the studies, elevation in AST is more than ALT. The increased AST/ALT ratio seen in dengue fever is rarely observed in Hepatitis A, B or C viruses induced acute hepatitis[7]. The mortality rate is reported to be 50% to 66% in childhood dengue infection associated ALF[8].

The pathogenesis of hepatic injury in dengue infection remains elusive however it is believed to be multi factorial and various factors implicated include direct viral injury, dysregulated immune response and hypoxic/ischemic injury. The frequent use of acetamino-

Table 1 Baseline investigation of the infant with acute liver failure caused by Dengue infection

Investigation	Result	Reference range
Hb	8.4 g/dL (haematocrit 25.9%)	10.0-13.2 g/dL
Total leukocyte count	14000/mm^3	6-17.2 × 10^3/uL
Differential count	Neutrophil (N) 68, Lymphocyte (L) 25	N 15-45, L-47-77
Platelet	98 × 10^3 cells/mm^3	1.5-4.5
Peripheral smear	No malarial parasite, no atypical cell, microcytic hypochromic picture	
ALT	3853 IU	13-45 IU/L
AST	20861 IU	9-80 IU/L
Total bilirubin	8.28 mg/dL	< 1.2 mg/dL
Direct bilirubin	4.59 mg/dL	< 0.2 mg/dL
Total protein	4.02 g/dL	
Alkaline phosphatase	171 IU	80-280 IU
Prothrombin time	56.4 s	11.5-15.3
Control	12.4 s	
CRP	90 mg/L	0-5 mg/L
Renal function test	Urea 121.6 mg/dL	7-20 mg/dL
	Creatinine -0.3	0.2-0.4 mg/dL
Infective etiology work up	LDH antigen for malarial parasite - negative	
	Chikungunya PCR - negative	
	Hepatitis A IgM, anti hepatitis E IgM - negative	
	Hepatitis B surface antigen - negative	
	Hepatitis C IgM - negative	
	Dengue NS-1 antigen and IgM antibody - positive	
	(serum capture enzyme linked immunosorbent assay)	
	Leptospira IgM - negative	

ALT: Alanine transaminase; AST: Aspartate transaminase.

Table 2 Differential diagnosis in cases presenting with fever and acute hepatic failure[12]

	Acute viral hepatitis	Complicated malaria	Leptospirosis	Dengue associated ALF
High grade fever	Absent	Present	Present	Present
Haematocrit	Normal	Normal	Falls	Raised
Platelet	Normal	Decreased	Normal	Decreased
SGOT	Raised	Normal	Normal	Raised
SGPT	Raised	Normal	Normal	Raised
SGOT/SGPT	Raised	Normal	Normal	Markedly raised
Hypoalbuminemia	Not seen in acute viral hepatitis may be seen in acute on chronic cases	Absent	Absent	Present especially in DHF due to plasma leakage[11]
Renal function test	Deranged	Normal	Normal	Deranged in DHF and DSS due to hypotension
Plasma leak	Absent	Rare	absent	Present
Peripheral smear	-	Malaria Parasite	-	-

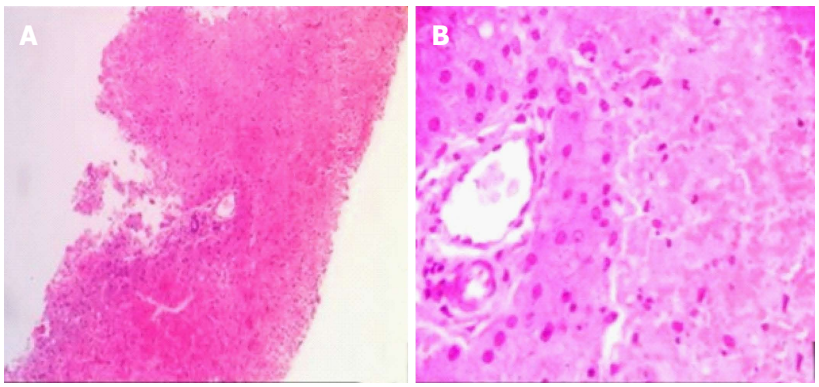

Figure 1 Liver biopsy showing multilobular and pan-lobular hepatic necrosis (A, HE × 200); Higher magnification shows relative sparing of zone 1 hepato-cytes (B, HE × 400).

phen in dengue may add to liver injury in susceptible individual[9].

Liver biopsy in fatal cases of dengue points to Hepatocytes and Kupffer cells as prime targets for dengue virus infection[10].

Several hepatic histological changes have been reported in dengue infection[9]. This includes fatty change (micro vesicular), Kupffer cells hyperplasia, and destruction, hepatic necrosis, Councilman bodies and infiltrates at the portal tract consisting of mainly

mononuclear cells. The midzonal area is most commonly involved followed by the centrilobular area. This may be due to higher susceptibility of the hepatocytes in midzonal area to anoxia but preferential targeting of the midzonal hepatocytes by dengue virus may also be a possibility.

The magnitude of liver involvement in acute phase of dengue may be missed as DENV hepatic involvement and its manifestations peaks around day 6-7 of illness[11].

The possible pointers to hepatic involvement in early phase include extreme nausea and vomiting with laboratory tests showing very high levels of AST with rise in serum bilirubin and alkaline phosphatase. Such presentation should raise the suspicion of impending liver failure (Table 2).

Primary dengue infection may lead to pan lobular hepatic necrosis. In dengue, endemic regions, dengue fever should be one of the differential for fever with fulminant hepatic failure in children.

COMMENTS

Case characteristics

A three-month-old child with fulminant hepatic failure.

Clinical diagnosis

Child was clinically diagnosed as dengue induced acute liver failure with evidence of coagulopathy and encephalopathy.

Differential diagnosis

The differential of acute liver failure in such young infant will be infective or metabolic causes. For the indexed patient infective causes were considered as the first possibility. Malaria, chikungunya, leptospirosis, hepatitis A and E were ruled out.

Laboratory diagnosis

Dengue NS1 Ag and IgM were positive by serum capture enzyme linked immunosorbent assay.

Pathological diagnosis

Panlobular hepatic necrosis caused by dengue virus infection.

Treatment

Child received vitamin K, fresh frozen plasma, broad spectrum antibiotic and 3% NaCl for raised intracranial pressure.

Related reports

Please provide other contents related to the case report to help readers better understand the present case.

Experiences and lessons

Dengue may have fulminant course in young children. The prognosis will be worse in presence of pan lobular necrosis.

Peer-review

The main highlight of the case is presence of dengue induced pan lobular necrosis in such a young infant. The main limitation of the report is inability to explain reasons behind such fatal complication of dengue virus in such patients.

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