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Review

Brain abscess of odontogenic origin in children: a systematic review of the literature with emphasis on therapeutic aspects and a new case presentation

Ascessi cerebrali di natura odontogena nei bambini: revisione sistematica della letteratura con attenzione agli aspetti terapeutici e presentazione di un nuovo caso clinico

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SUMMARY

Brain abscesses (BAs) are rare but life-threatening infections. BAs of an odontogenic origin should always be considered as a possible aetiological factor, especially when other infectious foci are not present. Clinical presentation in children may be ambiguous and pose a difficult differential diagnosis: the identification of causal bacteria can be difficult and odontogenic origin is often a diagnosis of exclusion. The aim of this paper was to systematically review the literature reports with particular emphasis on therapy and propose a diagnostic flow-chart for odontogenic brain abscess in children. A systematic literature review was performed on PubMed, Scopus and ISI Web of Science to identify cases of BAs in children and discuss clinical management: only human research articles, published in peer-reviewed English language journals, were included. Among 109 articles, 7 publications were selected for data analysis: clinical data could be extracted for only 8 subjects; different clinical approaches are descripted in the reports, even if therapy should be started as soon as possible to prevent rapid diffusion to the rest of the central nervous system. Due to their rarity and ambiguous clinical presentation in children, BAs of odontogenic origin are difficult to diagnose. A thorough oral-maxillofacial investigation should always be performed to exclude an oral origin.

KEY WORDS: Brain abscess • Oral abscess • Antibiotic therapy • Children

RIASSUNTO

Gli ascessi cerebrali (BA) sono infezioni rare, ma potenzialmente letali. L'origine odontogena degli ascessi cerebrali dovrebbe essere presa in considerazione soprattutto quando non sono presenti altri focolai infettivi. La presentazione clinica nei bambini può essere ambigua e potrebbe porre una diagnosi differenziale difficile: l'identificazione dei batteri causali può essere complessa e la conferma di un'origine odontogena dell'ascesso è spesso derivante da una diagnosi di esclusione. Lo scopo di questo articolo è quello di ottenere una revisione sistematica della letteratura con particolare attenzione alla terapia e proporre un diagramma di flusso diagnostico per l'ascesso cerebrale odontogeno nei bambini. È stata eseguita una revisione sistematica della letteratura su PubMed, Scopus e ISI Web of Science per identificare casi di BA nei bambini e discutere la loro gestione clinica: sono stati inclusi solo articoli su umani, pubblicati su riviste in inglese peer-reviewed. Tra 109 articoli, solo 7 pubblicazioni sono state selezionate per l'analisi dei dati: i dati clinici potevano essere estratti solo per 8 soggetti; nei rapporti vengono descritti diversi approcci clinici, tuttavia la terapia deve essere iniziata il prima possibile per impedire una rapida diffusione al resto del sistema nervoso centrale. A causa della loro rarità e della presentazione clinica ambigua nei bambini, le BA di origine odontogena sono difficili da diagnosticare. Un'analisi approfondita oro-maxillo-facciale dovrebbe sempre essere eseguita per escludere l'origine orale dell'ascesso.

PAROLE CHIAVE: *Ascessi cerebrali • Ascessi orali • Terapia antibiotica • Bambini*

Introduction

Brain abscesses (BAs) are focal infections that start as circumscribed cerebritis and evolve to necrosis with purulent exudate surrounded by a pseudo-capsule. BAs in the adult population have a higher rate in men than in women and have an incidence of approximately 1 in 100,000 new cases per year. Although more accurate diagnostic tools (CT and MRI) and the use of more powerful and targeted antibiotics have greatly improved prognosis, both quoad

vitam and quoad valetudinem, BAs are still extremely serious and life-threatening infections, with 0 to 24% mortality. The cause of BAs remains unknown in 15 to 30% of cases [1-3].

Twenty-five percent of all BAs occur in children, between 4 and 7 years, most often presenting with multiple abscesses (approximately 30% of cases) [4-6].

This age group might be particularly susceptible because the first phase of teeth exfoliation takes place in this period, and the remaining deciduous teeth are exposed to the oral cavity for several years, which makes them more vulnerable to tooth decay. Furthermore, in this age, children become more autonomous in dental brushing and do not always achieve optimal plaque control. The most frequently involved tooth seems to be the deciduous canine. The permanent bud is localised in a very cranial position in the maxilla ramus and can spread infection to the proximal maxillary and ethmoidal sinus [7 8]. For all these reasons, it is highly recommendable to have children visited by a dentist, on a regular basis, beginning at the age of 3.

Because BAs may be the result of dental infections, it is essential to perform careful clinical and radiological exam of the maxillofacial region whenever other infective sources are not detected.

In this paper, we present the results of a systematic literature review of odontogenic brain abscesses arising in childhood with emphasis on diagnosis and therapy, propose a clinical flow chart and describe a new representative case.

Materials and methods

The systematic search and review processes [9] were conducted on PubMed, ISI Web of Science and Scopus databases to identify articles concerning BAs in children until June 2017: we carried out a systematic search for the terms "brain abscess" and "odontogenic" which were combined with the operator 'AND'. The research was limited to children age using website limits. Two of the authors (C.L. and G.F.) independently examined all titles and abstracts retrieved and selected articles concerning with the selected topics. These included all types of human peer-reviewed research articles (i.e. case reports, cross-sectional, cohort, case-control or retrospective studies), published in English on peer-reviewed journals and describing or reporting clinical characteristics and management of odontogenic BAs in children. For a more comprehensive view on the topic, reviews, letters and commentary articles were also included. Exclusion criteria were: articles concerning odontogenic BAs in adults or reporting BAs in children not of ontogenic origin, and papers published in languages other than English. If there were no accordance on one paper, it was evaluated by a third reviewer (M.G.) for the final decision.

Results

The preliminary search retrieved 13 references in PubMed, 21 results in ISI web of Science and 75 in Scopus for a total of 109 articles. After exclusion of studies that did not meet the inclusion criteria and removal of duplicates, our search identified a total of 7 publications (Fig. 1) for review. The extracted data are reported in Table I.

Clinical data on 8 subjects, mean age 9 years (range 3-18), 5 males and 3 females could be extracted from the 7 papers. No diagnostic symptom could be identified, whereas radiological findings showed a predominance of frontal localisation (4 in the frontal lobe, 1 in the front/temporal and 1 in the temporal lobe). Therapeutical protocols will be described in the discussion section.

An interesting and representative new case is described in Figures 2 and 3: briefly, a 5-year-old boy, previously in good health, was hospitalised for suspected meningitis. He was confused and presented with fever, headache, vomit, neck stiffness and sight impairment. The medical history reported by his parents was non-contributory, except for the report of neglected recurrent dental abscesses mainly in the upper jaw. After examining the fundus oculi to exclude intracranial hypertension, rachicentesis was performed. No abnormal findings were detected in the cerebrospinal fluid, which appeared transparent, without sediment, and had normal chemical properties (glucose and proteins). In the following days, the culture was re-

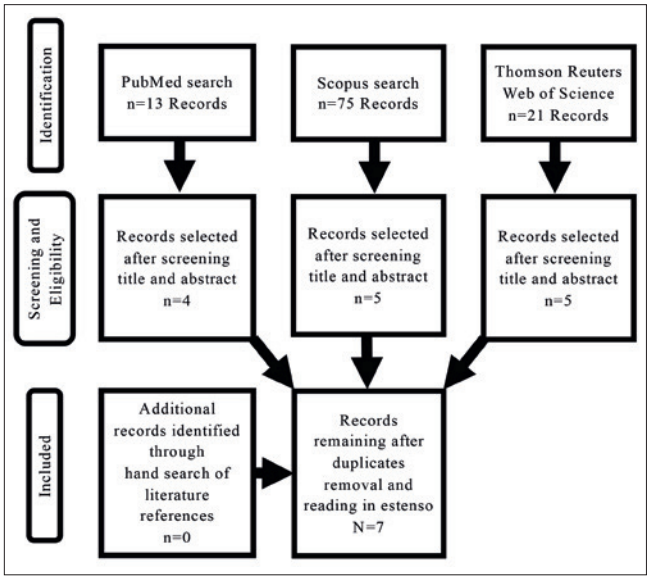

Fig. 1. The flow chart summarises the article search and revision strategy.

Table I. Clinical data on the 8 children.

References	Kanu OO, 2011 [19]	Maraki S, 2016 [27]	Hibberd CE, 2012 [11]	Solanki R, 2014 [26]	Vargas J, 2006 [21]	Moskovitz M, 2012 [22]	Canpolat M, 2015 [4]
Age	10	6	11	12	18	3	4 and 11
Sex	M	M	M	F	M	F	M
Presenting symptoms	Fever Recurrent headaches	Worsening Drowsiness Episodes of vomiting	Confusion/ Somnolence/ Behavioral disorders/ Dysphasia/ Unsteady ambulation/ Neck stiffness	Endocranial hypertension symptoms	Endocranial hypertension symptoms/ Behavioural disorders	Fever/ Vomiting/ Somnolence	Nausea/ vomiting/ headache / convulsion/fever/ alterated state of consciousness.
Clinical examination	No neurological symptoms/ Oral exam: cavities and periodontal disease (cavity of inferior premolar and high mobility of superior canine and inferior premolar)	Heart rate of 110 beats/minute, blood pressure 110/85 mmHg, oxygen saturation 97%. Afebrile, pale, with supple neck, dry mucous membranes, slightly decreased level of consciousness (Glasgow coma scale 12)	Oral exam: dental abscess of deciduous inferior molar 3 weeks before	CHD (Congenital Heart Disease)/ Fever/ Headache/ Vomiting/ Papilledema/ Poor oral hygiene	Headache/ Vomiting/ Aphasia/ Weakness of the left lower limb/ Behavioural disorders/ Fever/ Medical history of multiple periodontal treatments and extractions	Cyanotic Heart Disease/ Oral exam: cyanotic lips, left submandibular lymphadenopathy, gingivitis, poor oral hygiene, cavities, dental abscess with vestibular fistula from a deciduous molar	Normal neurological examination
Radiology	Frontal lesion with dura mater detachment and compression of frontal lobe	Chest radiograph normal. Sizable ring-enhancing lesion in the left frontal lobe (TC-SCAN). Brain oedema	Lesion of temporal lobe	Lesion of frontal lobe (size: 6x5 cm)	Lesion of left fronto-parietal lobe	Hypodense lesion of right medial and posterior region of the frontal lobe (size: 10x11 mm)	
Microbiology (culture)	Brain inflammatory exudate: no bacteria. Dental inflammatory exudate: *Staphylococcus aureus* sensitive to Ceftriaxon	*A. aphrophilus Catalase* and oxidase negative, and X and V factor independent Gram-negative coccobacillus. Isolate susceptible to ampicillin, amoxicillin plus clavulanic acid, cefuroxime, ceftriaxone, cefotaxime, imipenem, meropenem, clarithromycin, azithromycin, ciprofloxacin, levofloxacin, cotrimoxazole, tetracycline, and chloramphenicol	Brain inflammatory exudate: *S. anginosus*. Dental inflammatory exudate: *Streptococcus sp*	*Streptococcus oralis*	*Arcanobacterium haemolyticum*	*Streptococcus Intermedius*	Cultures sterile in 40%, *Peptostreptococcus*

continues ▶

Table I. *follows.*

References	Kanu OO, 2011 [19]	Maraki S, 2016 [27]	Hibberd CE, 2012 [11]	Solanki R, 2014 [26]	Vargas J, 2006 [21]	Moskovitz M, 2012 [22]	Canpolat M, 2015 [4]
Treatment	Craniotomy and drainage/ Antibiotic treatment (Ceftriaxone, Gentamycin, Metronidazole iv for 2 weeks and Cefpodoxime po for 3 week)/ Dental surgery	Frontoparietal (pterional) Craniotomy. (Metronidazole intravenous high-dose meropenem was administered as monotherapy for a total of 8 weeks)	Craniotomy and drainage/ Antibiotic treatment (Vancomycin, Ceftriaxone, Metronidazole and Phenytoin)/ Dental surgery	Drainage/ Antibiotic treatment (Empiric therapy: Ceftriaxon 500 mg ev, Amikacin 500 mg ev, Metronidazole 100 ml ev + support therapy. Targeted therapy: Vancomycin 30 mg/Kg per 12 h, than Levofloxacin 250 mg 2/die for 15 days)	Craniotomy and drainage/ Antibiotic treatment (Empiric therapy: Ceftriaxone 2 g/ day iv; Metronidazole 500 mg each 8 h ev; Targeted therapy: Penicillin G 24 mU /die ev for 21 days)	Pharmacological therapy (Dexamethasone 0.6 mg/Kg/die; Ceftriaxone 100 mg/Kg/die; Vancomycin 60 mg/Kg/die; Mannitol iv for 7 weeks; Metronidazole 30 mg/kg/day and Cefixime po for 3 months)/ Dental surgery	Surgical treatment: excision and drainage surgery. Medical treatment: antibiotic therapy for 6 weeks (ampicillin/sulbactam+amikacin+metronidazolo) 4y (Ceftriaxone+vancomicina+matronidazolo+rifampicina) 11y
Outcome	Good	Good	Residual comprehension problems	Good after 2 weeks of therapy	Good after 4 weeks	Good	No neurological sequelae in 1 patient, epilepsy and hemiparesis in the other.

vealed to be negative. Because of the history of recurrent dental abscesses, a CT scan of the skull and of the maxillofacial area was performed, revealing the presence of BAs in the right frontal and occipital lobes; the right maxillary and ethmoidal sinus were completely opaque, demonstrating a diffusion by contiguity of an inflammatory process from the upper maxilla (Fig. 2). Intraoral examination and panoramic radiograph of the jaws showed multiple infective foci (granulomas) and poor oral health status (Fig. 3). No other relevant head (middle ear, mastoid) or body foci were detected. After broad spectrum antibiotic therapy (ceftriaxone 100 mg/kg/day; gentamicin 3 mg/kg/day; metronidazole 10 mg/ kg/8 h; for 4 weeks) and the extraction of many dental roots (14 elements), the child was discharged with complete recovery. To date, four years later, the child shows no sequelae.

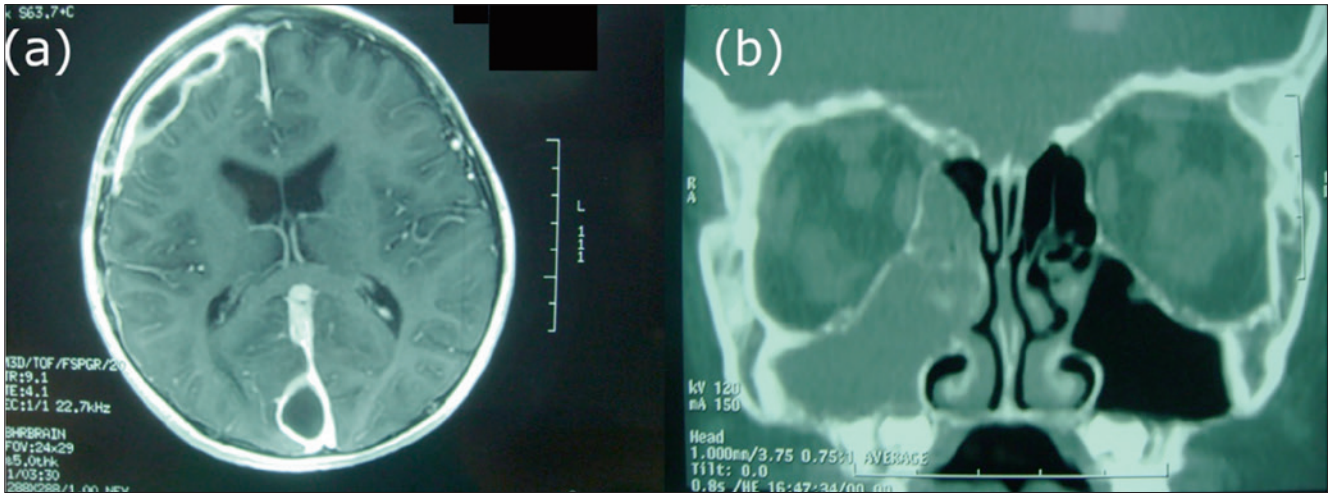

Fig. 2. A) Axial CT scan of the skull showing multiple brain abscesses in the frontal and occipital right parenchyma. **B)** Coronal CT scan of the mid-face showing the opacified right paranasal sinuses and the close relation with the brain (frontal fossa). In the case presented herein, diagnosis was driven by careful history and dental examination and was confirmed by CT scan, which showed diffusion of the infectious process to the brain.

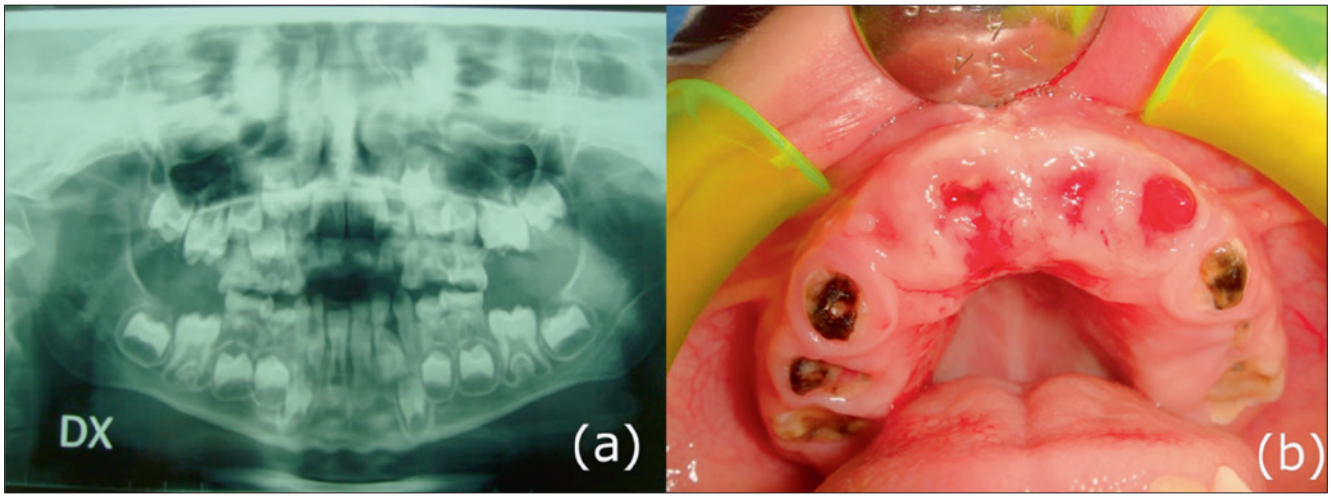

Fig. 3. A) Panorex shows poor oral health condition of the child. **B)** Intra-oral clinical presentation: numerous residual roots can be seen in the upper jaw.

Discussion

Brain abscesses are focal necrotic infections of the brain parenchyma which have a severe prognosis, both quoad vitam and quoad valetudinem, even if more effective antibiotic therapies are now available [1-6]. The literature reports highlight that about one-quarter of the BAs occur in children and, among these, the most affected age is between 4 and 7 years: in this regard, in our review a wide range of ages were found (3 to 18 years with a mean age of 8): such a wide age range should be carefully considered in the therapeutic approach and regimen [4-6].

Generally, BAs are favoured by immunosuppression and follow three main pathogenetic mechanisms: 1) haematogenous dissemination due to predisposing conditions (e.g., acute bacterial endocarditis, congenital heart defects with right to left shunt and by-pass of the pulmonary filter, bronchiectasis and other chronic septic foci); 2) direct inoculation during neurosurgical manoeuvres or brain trauma; and 3) spread by direct head, maxillofacial and ENT foci, of which odontogenic dissemination represents 3 to 10% of all cases [10 11].

Thrombophlebitis of the cavernous sinus due to thrombophlebitis of the facial (retromandibular) or ophthalmic veins has been advocated in the past as a major cause of the onset of BAs secondary to dental infections. More recently, Zhang and Stringer have demonstrated, in a study on cadavers, the presence of valves in the facial and ophthalmic veins; the increased risk of blood-borne brain infections from the oro-maxillo-facial area was thus attributed to the presence of diffuse facial anastomosis between the facial vein, pterygoid plexus, angular vein, ophthalmic vein and the cavernous sinus. Through these and other anatomical structures (maxillary and ethmoid sinuses), many infectious processes of the oral cavity (dental abscesses, periodontal osteomyelitis) can cause BAs [12].

Regarding the clinical features of BAs, there are several recognizable general and specific signs and symptoms that can indicate brain involvement. The most common general features of brain involvement are increased intracranial pressure, severe headache, nausea and vomiting, fever, convulsions, stiff neck, lethargy, aphasia, paresthetic crisis, behavioural changes and difficulty walking. Some cases have reported suture separation and bulging fontanelles. Specific brain involvement features are proportional to the involved parenchyma (e.g., cortical signs, bulb/pons nuclei involvement, cranial nerves). Paediatric presentation of BAs often does not encompass the classic triad of symptoms (fever, headache and neurological deficits) because symptoms can be nonspecific and mild [5].

The onset of mild and unspecific neurological symptoms can make differential diagnosis between meningitis and BAs difficult. Lumbar puncture can be of great diagnostic help; however, it can only be performed after exclusion of intracranial hypertension (in this regard, the fundus examination can show papilledema), otherwise transtentorial brain hernias can occur. In adults, intracranial hypertension was detected in 40 to 70% of BAs. In paediatric populations, this frequency is lower due to the possible distention of the skull [13-15]. If the lumbar puncture is negative, meningitis can usually be excluded. Therefore, a brain MRI should be performed to diagnose cerebritis or BAs.

There are four main phases that can be recognised in the pathogenesis of BAs: 1) early cerebritis, undifferentiated from the rest of the brain; 2) late cerebritis, with the onset of a reticular matrix (precursor of collagen) and the

development of a necrotic centre; 3) development of an early capsule with neo-vascularisation around a necrotic centre; and 4) late formation of the capsule characterised by a collagen capsule, necrotic centre and gliosis around the capsule [10].

In the case of history of recurrent dental abscesses and clinical examination that confirms the presence of numerous dental lesions, a CT scan can be performed to assess the presence of spread from oro-maxillo-facial structures. Microbiological investigations must be carried out on the blood, cerebrospinal fluid and exudate (drainage) together with imaging procedures. The diagnostic process we propose is summarised in a flow chart (Fig. 4).

The diagnostic corroboration of BAs of dental origin can be very complex because many potential sources of primary infection, even extraoral, should be considered. Thus, dental origin is often a diagnosis of exclusion. The diagnostic criteria [2] that should be collected to reach a diagnosis of BAs of odontogenic nature are as follows:

1) No other infection sources, particularly heart (endocarditis) and ENT diseases (recent sinusitis, otitis media, upper respiratory tract infections).
2) Microbiological evidence in brain exudate of bacteria pathogens normally found either in periodontal pockets, such as *Porphyromonas gingivalis*, *Prevotella intermedia*, *Aggregatibacter actinomycetemcomitans*, or in periapical foci, such as *Bacteroides species*, *Streptococcus, Fusobacterium, Peptostreptococcus, Actinomyces* and S*pirochaetes*, as well as the *Enterococcus faecalis* and *Candida albicans*, which are associated with persistent endodontic infections.
3) Presence of clinical and radiographic signs of dental infection that can cause acute or chronic abscesses.

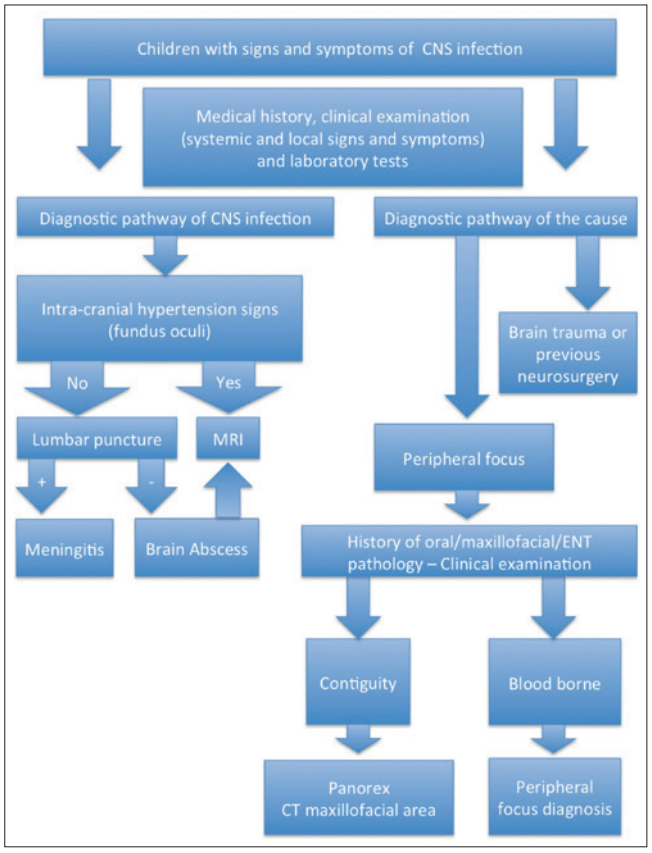

Fig. 4. Flowchart describing the clinical approach to children presenting with signs and symptoms of central nervous system (CNS) acute infection. (MRI: Magnetic Resonance Imaging; ENT: ear, nose and throat; CT: Computed Tomography).

According to a previous study, microbiological concordance between the oral cavity and the BA alone is not sufficient to diagnose odontogenic BA. The microbiological concordance could be due to chance, as there are many intraoral bacterial strains, BAs can occur spontaneously and dental infections (especially periodontal disease and periapical lesions) are common in adults [16]. Moreover, many studies have shown the occurrence of frequent bacteraemia of oral origin during the day, either as a result of masticatory acts, hygienic manoeuvres or therapeutic procedures.

Despite advanced microbiological culture and molecular biology techniques (PCR), microbiological diagnosis is not always successful. The literature regarding odontogenic BAs indicates that microorganisms from the oral cavity have been found in different areas of the brain parenchyma (in the fronto-parietal lobe, the pre-septal region, the occipital lobe, and the frontal and parietal lobe), either in single or multiple lesions [17].

The most commonly reported microorganisms are *Streptococci viridanti* (or *α-haemolitic*), *Bacteroides* and *Aggregatibacter actinomycetemcomitans* [1 3 18]. Viridans species can be isolated in the mouth or in other body sites and the most frequently encountered species in human pathology are *S. mutans*, *S. salivarius*, *S. sanguis*, *S. mitior* and *S. milleri*. The first four species can produce glucans that favour adherence to smooth surfaces, such as enamel or other structures (e.g., endocardium); *S. milleri*, however, does not produce glucans and has only been occasionally isolated from abscess lesions (periodontal abscesses, brain, bowel, etc.). The *S. milleri* group is now more properly called the Streptococci anginosus group. These bacteria are involved in various purulent infections, including abscesses in various parts of the body and are divided into three species: *S. anginosus*, *S. intermedius* and *S. constellatus*, which each have a different tissue tropism. In particular, a strong association between S. intermedius and BAs has been detected [16]. Identification of a single specific strain within the *S. anginosus* group cannot

be achieved with routine microbiological technique. Only molecular biology techniques, such as PCR, can identify the single sub-species. In children, *Staphylococcus aureus* is the most frequently involved microorganism, followed by the *Bacteroides*, *Clostridium, Proteus, Pseudomonas* and *Haemophilus species* [19]. In this regard, several studies have highlighted that many dental procedures (e.g., extractions, alveolar surgery, periodontal therapy, injection of local anaesthetic and dental hygiene) can cause bacteraemia; even minimally invasive procedures can cause transient bacteraemia. In a study by Roberts et al. (1997) conducted on children, transient bacteraemia was detected in 38.5% of cases after tooth brushing, whereas more invasive procedures (such as tooth extractions) resulted in a massive general circulation of microorganisms [20]. In most individuals, however, the immune system eliminates and controls the numerous microorganism intrusions that occur during the day. Therefore, the duration of bacteraemia, an individual's predisposition or a particular bacteria virulence are necessary for the onset of a distant infection [11]. These findings led to a change in the antibiotic prophylaxis protocols for oral surgery procedures to indicate precise procedures and patient types with particular risk factors (e.g., prosthetic valves, carriers of prostheses, previous infective endocarditis) [18].

Among different systemic factors, such as immunosuppression, diabetes, congenital heart disease represents the most important predisposing factor for BAs in childhood [4 22]. Other individual predispositions, such as arteriovenous malformations (AVMs), can contribute to developing BAs. Inherited bleeding telangiectasia (HHT), or Rendu-Osler-Weber syndrome, is an autosomal dominant disorder that is a predisposing factor for the onset of BAs. Recurrent episodes of spontaneous epistaxis, skin telangiectasia and mucous and visceral AVMs are its major clinical features and may involve the pulmonary circulatory system, liver, brain, spinal and other systems [23]. It is estimated that BAs occur in approximately 5 to 10% of patients with HHT; bacteraemia, especially of dental origin, plays a decisive role in the pathogenesis of BAs in patients with HHT. HHT, similar to some cardiac and pulmonary arteriovenous malformations, promotes haematogenous dissemination of septic emboli to the CNS, most likely because it facilitates the bypass of pulmonary capillary filtration (and thus avoids the action of reticuloendothelial system cells). Furthermore, patients with HHT may have a mild immunodeficiency condition [24].

The treatment of BAs consists of local infection control (antibiotic therapy with or without surgical drainage) and therapy of the focus that caused the BA (e.g., oral rehabilitation) [2 3 16 25]. A combined pharmacological-surgical approach is usually preferred, but it is still a matter of debate in the literature because medical management of the disease is sufficient to resolve the problem in some situations. Some clinical variables, such as the size of the abscess, location, origin, virulence of microorganisms, presence of multiple abscesses, patient response to antibiotic therapy and degree of perilesional oedema, can influence the therapeutic approach. Antibiotic therapy alone is preferred in cases of abscesses with a diameter of < 2 cm, high density lesions, multiple abscesses and systemic conditions that make surgery dangerous.

Drainage is the most common surgical approach, as it presents an opportunity to perform bacterial culture and antibiogram and helps to decompress intracranial hypertension. More rarely, craniotomy and excision are suggested for large abscesses (> 2.5 cm) that behave as a space-occupying process [24 26 27].

Although Evidence Based Medicine (EBM) clinical protocols for children are not available [Randomised Controlled Trials (RCTs) are not carried out], data emerging from the literature suggest that the combination of ceftriaxone 100 mg/kg/day, gentamycin 3 mg/kg/day (or vancomycin 60 mg/kg/day) and metronidazole 10 mg/kg/8 h for 4 weeks is the most used pharmacological protocol. Table I summarises the case reports of BAs of odontogenic origin in paediatric patients. A craniotomy with drainage of the abscess was practiced in three of the 7 children, while the other children, as in the case we present herein, received only antibiotics and resolution of the generating focus. In our case, the small dimensions of the BAs together with the easily resolution of the infective oral focus drove us to a more conservative therapy as suggested by Frazier [5], with the complete recovery of the child.

Conclusions

Due to their rarity and ambiguous clinical presentation in children, BAs of odontogenic origin are difficult to diagnose. A thorough oral-maxillofacial-ENT investigation should always be performed to exclude the oral origin.

Conflict of interest statement

None declared.

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