Child's Nervous System (2019) 35:1117–1128
https://doi.org/10.1007/s00381-019-04182-4

REVIEW ARTICLE

Brain abscess in pediatric age: a review

Chiara Mameli[1] · Teresa Genoni[1] · Cristina Madia[1] · Chiara Doneda[2] · Francesca Penagini[1] · Gianvincenzo Zuccotti[1]

Received: 1 February 2019 / Accepted: 28 April 2019 / Published online: 6 May 2019

Abstract

Objective The purpose of the paper is to examine the current state of the art about epidemiology, diagnosis, and treatment of this infection.

Methods A review of the literature was performed through a PubMed search of original articles, case reports, and reviews using the key words "brain abscess," "cerebral abscess," "brain infection," "intracranial suppuration," "otogenic brain abscess," "otitis complications," and "sinusitis complications."

Results Pediatric brain abscess is a rare but serious infection, often involving patients with specific risk factors and burdened by a high risk of morbidity and mortality. Brain abscess incidence and mortality decreased over the years, thanks to improved antibiotic therapy, new neurosurgical techniques, and the wide spread of vaccinations. There are no guidelines for the adequate diagnostic-therapeutic pathway in the management of brain abscesses; therefore, conflicting data emerge from the literature. In the future, multicentric prospective studies should be performed in order to obtain stronger evidences about brain abscesses management. Over the next few years, changes in epidemiology could be observed because of risk factors changes.

Keywords Brain abscess · Intracranial infection · Children · Central nervous system infections

Introduction

Brain abscess (BA) is a focal central nervous system infection involving the cerebral parenchyma. This condition is infrequent in the adult population and even rarer in pediatric patients [65], but the risk is higher in some patient groups. Over the last decades, BA incidence decreased in some countries thanks to a reduction in predisposing factors, such as untreated otorhinolaryngological infections and uncorrected congenital heart defects; at the same time, other BA-associated conditions like immunosuppression (mainly due to untreated human immunodeficiency virus (HIV) infection and transplants) have gained greater importance [67].

Despite the advances in the diagnosis and treatment, BA remains a disease with significant morbidity and mortality, both in adults and children [65].

In this paper, we review and discuss the epidemiology, pathogenesis, diagnosis, and treatment of BA in the pediatric population.

Epidemiology and risk factors

Thanks to the health care quality improvement, in twentieth century, BA has become a rare disease with an overall incidence of 0.3–1.8 per 100,000 inhabitants per year [19, 28, 37, 48, 50, 51].

The incidence of BAs in children and adolescents is difficult to determine. Few studies have specifically explored the incidence of BAs in the pediatric population: Most of them are small case series or monocentric retrospective studies, almost exclusively focused on the situation in industrialized countries.

Overall, about 25% of BAs occur in children [64]. Recent studies show a considerable variability about which pediatric age is most frequently affected; this may be explained by the fact that some of them consider both adults and children, other report either the median age or an age interval; therefore, a comparison is difficult. Based on these reports, BA seems to occur most often between 4 and 10 years of age [19, 39, 56].

✉ Chiara Mameli
chiara.mameli@unimi.it

[1] Department of Pediatrics, V. Buzzi Childrens' Hospital, University of Milan, Milan, Italy

[2] Pediatric Radiology and Neuroradiology Unit, Children Hospital V. Buzzi, Milan, Italy

In Europe pediatric BA, prevalence ranges from 1.2% of cases in the under 7 years of age group of an Irish monocentric study [60], to a British monocentric study reporting 32% of cases in the 0–19 group [13]. The significant difference between these studies is probably explained by the two different age groups considered and the different inclusion criteria, with the first study considering only patients who underwent a surgical drainage, so pediatric BA—treated more conservatively—may be underestimated.

During the neonatal age, BAs are even rarer, but they are associated with a high risk of severe complications and mortality [14–38].

An unexplained male predilection was reported in the pediatric population [11, 64].

In developing countries, as expected, the incidence of BAs is higher. In fact, in these countries, different types of pathogens are encountered, and the transmission of pathogens is increased due to deficient infrastructure; malnutrition leads to amplified severity of common infections, and there is a lack of resources to treat this condition. BAs are reported to account for 8% of all intracranial mass lesions, and up to 50% occurred in population aged 0–20 years [22, 43, 48]. The smallest incidence was reported in the South-East Asian country Taiwan where only 5.4% of patients with BA were children.

Pediatric studies published in the last decade show that BAs are often associated with predisposing conditions in 56–86% of cases [8, 19, 39, 52, 56, 64].

Risk factors can be divided in acute events and chronic conditions. The first are mostly ear, sinus, and dental infections (frequently related to poor dental hygiene or dental procedures), neurosurgical procedures, and head trauma. An infrequent but typical cause of trauma in children are injuries with sharp toys or pencils [5]. Among chronic conditions, there is often the presence of a pulmonary circulation shunt, which could allow septic microemboli from distant foci of infection (endocarditis, osteomyelitis, pulmonary, and skin infections) to reach the brain without being stopped by pulmonary phagocytic filter; this may happen in carriers of congenital heart defects (CHD) [68] and pulmonary arteriovenous fistulas as in hereditary haemorrhagic telangiectasia [23].

Goodkin et al., describing twentieth century BA trends at Children's Hospital Boston, found that congenital heart disease, otitis, and sinusitis decreased as a cause of intracranial infection [26]. Other more recent studies show the same trend in developed countries, thanks to early CHD correction and appropriate antimicrobial therapy [64]; they remain a significant problem in the developing world [68].

Another important predisposing condition are immunosuppressive states, which can be rare like X-linked agammaglobulinemia [31] or of increasing incidence like those associated with a solid-organ or hematopoietic stem-cell transplantation [6] and with HIV infection [25, 67].

BA can also be a rare complication of meningitis, particularly in neonates [59]. Other risk factors are described, in particular, the presence of foreign bodies in the airways [17], congenital dermal sinuses [47], and esophageal procedures [41]. Infancy (age < 6 months) and male sex are also predisposing factors [19, 26, 52, 56].

The presence of single nucleotide polymorphisms of ICAM-1 and MCP-1 genes has also been described as a risk factor for developing cerebral abscesses [44].

Finally, BA as a complication of acute bacterial sinusitis can be associated to a low socio-economic status even in developed countries [63].

Pneumococcal vaccination is changing BA etiology, with initial reports of a reduced incidence of *S. pneumoniae* [56].

Etiopathogenesis

A brain infection develops into a capsulated pus collection inside the cerebral parenchyma within 14 days, evolving from early cerebritis to late capsular stage [7].

In 40–50% of cases, pathogens reach the brain via a contiguous site, such as during middle ear, mastoid and paranasal sinus infections, or through a skull discontinuity due to head trauma or neurosurgery. In 30–40% of cases, they spread through blood flow from a distant focus of infection (e.g., dental abscess, endocarditis, lung, or cutaneous infections). The remaining cases are of unknown origin [67].

The location of the abscess depends on the origin of the primary infection. The most frequent site is the frontal lobe (secondary to frontal or ethmoidal sinusitis or dental infection), followed by parietal and temporal lobes (acute otitis media, mastoiditis, sphenoidal sinusitis) and less frequent sites such as cerebellum and brainstem, from otogenic or hematogenous origin [8, 56, 64].

Multiple abscesses occur in 19–33% of total BAs [15, 52, 56], often related to hematogenous spread, and they follow the distribution of the middle cerebral artery.

Bacteria are by far the most common pathogens in immunocompetent patients. A meta-analysis that included 6663 adult and 1023 pediatric BAs—reported between 1935 and 2012—in which pus or blood cultures were performed showed that children shared similar etiology with adults, with pediatric cultures positive for *Streptococcus* spp. in 36% of cases, followed by *Staphylococcus* spp. (18%) and gram-negative enteric bacteria (*Proteus* spp., *Klebsiella pneumoniae*, *Escherichia coli*, and *Enterobacteriae*) in 16% of cases [10]. *Streptococcus* spp. is commonly associated with sinusitis, otitis media, and endocarditis (the latter with the *S. viridans* group); a recent case series suggests a possible rise in the incidence of BA due to group A streptococcus [12].

Staphylococcus spp. (mainly *aureus and epidermidis)* infections are related to head trauma, surgery, or skin infections.

Neonatal BA can arise from *Citrobacter* or *Proteus* meningitis, less frequently from *Escherichia coli* and *Serratia marcescens* [26, 59].

Pneumococcal vaccination may contribute in future years to a variation in BA incidence and etiology, as it is beginning to be reported in some countries [52, 56].

Finally, unusual pathogens like fungi, parasites, and mycobacteria accounted for less than 2% of total cases, but this percentage was probably underestimated because many of the analyzed studies considered only bacterial BA [10]. BAs from opportunistic microorganisms are usually multiple. They can occur in HIV-positive children with a low CD4 count; the most common pathogens are *Toxoplasma* (although cerebral toxoplasmosis is less frequent than in adults), *Nocardia* and *Mycobacterium* spp [25]. Fungal abscesses (mainly *Aspergillus* or *Candida*) typically affect solid organ transplants recipients or children treated for leukemia [36].

Clinical features

Clinical features depend on BA number, site, size, the involvement of the surrounding area, and the microorganisms responsible for the infection [34, 56]. The median duration from the onset of symptoms to the diagnosis is 7–11 days [39, 56], but the presentation can vary from indolent to very rapid.

Patients are commonly symptomatic; signs and symptoms can be divided in general and neurological. Fever is frequent, often associated with neurological symptoms in isolation or combination, such as new onset headache (typically associated with vomiting), seizures, hemiplegia, cranial nerve palsies and altered level of consciousness ranging from drowsiness to coma [15, 52, 64]. Neonates can have a bulging fontanel and/or an increase of the cranial circumference [39, 56].

The clinical triad historically associated with BA (fever, headache, neurological deficits) is only present in a small percentage of cases in more recent retrospective studies [19, 52, 64]. Frontal abscesses can be symptomatic only when they reach large dimensions [65].

Diagnosis

Blood tests (in particular leukocyte count, C-reactive protein, erythrocyte sedimentation rate, and blood cultures) are the first and easiest examinations to perform urgently, to evaluate the possible presence of altered inflammatory markers secondary to the infection and find any hematogenous dissemination of the microorganism.

Moreover, in the presence of signs and symptoms of neurologic involvement, a lumbar puncture is useful to evaluate chemical-physical alterations of the cerebrospinal fluid (CSF) and to perform a CSF culture to find a specific etiology, even if the risk of finding negative samples is high [15, 26, 28, 39, 56, 62]. However, it is important to underline that a lumbar puncture should not be routinely performed and is contraindicated in the case of non-communicating obstructive hydrocephalus and brain shift, which can be consequences of the mass effect of the BA [16]. Therefore, computed tomography (CT) is often the first imaging performed urgently, followed by a magnetic resonance (MR) to confirm the diagnosis and deepen the characterization of the abscess [19, 62].

The etiological diagnosis can be obtained with the culture of the pus extracted from the abscess; the sample can be obtained thorough stereotactic biopsy or aspiration rather than a craniotomy with excision [3, 11, 15, 24, 26, 46, 52, 64], even though in some cases neurosurgery is not indicated and therapy should be undertaken and continued empirically, with monitoring of clinical and radiological improvement [11, 29, 52, 62].

Blood and CSF samples

Despite the presence of the infection, the probability of finding normal inflammatory markers could be high. Indeed, Udayakumaran et al. [68] report only a 20% of pediatric cardiogenic BAs with altered blood tests (leukocyte count, CRP, ESR). Regarding the evaluation of white blood cells, normal values are reported in about one fourth of cases by Atiq et al. [3], in about two-thirds of cases by Shachor-Meyouhas et al. [64] and in half of adult patients by Helweg-Larsen et al. [28]. In the presence of altered white blood cell count, leukocytosis is more frequently found than leukopenia [9, 10]. A normal value of CRP is described in about one third of cases presented by Raffaldi et al. [56] and Helweg-Larsen et al. [28] and in 17% of patients with intracranial suppurations (BA and subdural empyemas) presented by Cole et al. [15], with most of these cases concerning single or even multiple BAs.

Even in cases when a lumbar puncture can be performed, results obtained with the chemical-physical examination (white blood cell count, glucose, and protein content) can show a great variability [24, 39, 56]. However, considering the mean and median values reported in some studies, it is possible to underline the more frequent presence of leukocytosis, hyperproteinorrachia, and normal or reduced glucose values [24, 28, 39, 56]. Normal CSF analyses are described in 30% of cases by Shachor-Meyouhas et al. [64] and in 16% of patients in the systematic review by Brouwer et al. [10].

Cultural samples

Because of the wide range of micro-organisms that can be involved in the infection, cultures (for aerobic and anaerobic bacteria, *Mycobacterium*, fungi, protozoa), Gram and special stains (for fungi, *Mycobacterium*, *Nocardia*) and polymerase chain reaction should be performed on blood, CSF and pus of

the cerebral abscess (stereotactic biopsy or aspiration and specimens from craniotomy) [1, 3, 4, 9, 11, 15, 24, 26, 28, 39, 52, 62, 64].

With regard to the isolation of micro-organisms from blood and CSF samples, the available data are contrasting. Raffaldi et al. [56] report a rate of positive blood cultures of 22.7%; a slightly higher rate is described by Lee et al. [39], with blood culture positivity in 28.6% of cases. On the contrary, lower rates are reported by Canpolat et al. [11], with a 100% of blood culture negativity in patients who did not undergo surgery, Auvichayapat et al. [4], with only 2.8% of blood growth, and Cole et al. [15], with 16% of positive blood cultures.

Positive CSF culture rates vary in the literature, with a 2.8% rate of micro-organisms growth described by Auvichayapat et al. [4], a 24% and 33.3% shown in the studies by Raffaldi et al. and Lee et al. [39, 56], respectively, reaching a value of 44% in the report by Cole et al. [15].

The rate of micro-organism isolation from abscess samples is about 60–80%, with polymicrobial involvement in about 20–30% of cases [8, 11, 15, 19, 26, 28, 60]. However, some studies in literature [39, 52] report abscess culture positivity in less than half of cases.

Imaging

Frequently, the first type of imaging performed is a computed tomography (CT) [19, 39, 56, 64], as this is available as urgent and it is able to clarify the characteristics of the suspected lesion; according to what is reported by the ESCMID guidelines in 2016 [69], it is often performed before lumbar puncture in the case of a patient presenting with Glasgow Coma Scale < 10, focal neurological deficits, new-onset seizures, and severe immunocompromised state.

In the study by Felsenstein et al. [19], magnetic resonance (MR) is suggested as the gold standard imaging for the diagnosis, as in all the patients whose first imaging was MR, the BA was detected; they also recommend its use in the follow-up.

The superiority of MR compared to CT is due to its better resolution, the lower toxicity of the contrast used, and the ability to identify lesions at risk of complications precociously [67]. Moreover, with the use of spectroscopy and diffusion-weighted (DW) techniques, MR has high values of sensitivity and specificity in the differential diagnosis with cystic or neoplastic lesions [45, 53, 58].

The typical radiologic aspect of a pyogenic BA is a necrotic center with low signal at the DW-MR and a T2-hypointensity with enhancement for the peripheral capsule (Fig. 1); fungal abscesses show a hypointense center in T2-weighed images (Fig. 2) and have a variable expression in DW-MR; tubercular abscesses show hypointensity in T2-weighed images and a capsule enhancement, that is absent for the center [61].

Finally, a recent study by Liu et al. [40], performed on rat brains, has showed that a new MR technique, based on bacterial chemical exchange saturation transfer (bacCEST), is useful in detecting BAs (caused by *Staphylococcus aureus*) and monitoring the infection during the follow-up.

Further investigations

An otolaryngology evaluation with paranasal sinus and middle ear imaging should be taken into consideration [29, 35], because otogenic and sinogenic infections are one of the most frequent primary *foci* in patients with a diagnosis of BA [3, 19, 26, 52, 56, 62] and, in some cases, symptoms of sinusitis may be poor or misdiagnosed [61].

Similarly, a cardiologic evaluation with an echocardiogram should be performed because of the high risk of association with CHD or cardiac infections [3, 19, 26, 52, 56, 62].

Odontogenic origin of the infection is not particularly frequent [24, 26, 56, 62]; however, a dental origin should be suspected and a dental evaluation should be performed in case no other focus is found, oral flora is isolated from the abscess, an oral infection is found, or an oral intervention has been performed [42].

Finally, the use of ultrasound, X-ray, or CT scan could be useful to find other possible sources of infection, such as pulmonary arteriovenous malformations [66], lung infections or malformations, bone, abdominal, or skin infections [20].

Figure 3 shows a hypothesis of diagnostic and therapeutic flow chart in case a BA is suspected.

Treatment

There is a lack of international guidelines about the proper management of BAs; therefore, in a consensus document in 2010, Arlotti et al. [2] provided recommendations about infection treatment that can be either only medical or both medical and surgical.

According to these recommendations, medical treatment alone may be considered in patients without severe neurological impairment at admission (GCS > 12), with a small abscess (< 2.5 cm) or with multiple abscesses, with a diagnosed etiology and in case of contraindications to surgery; moreover, antibiotics represent an adjuvant therapy after surgery for large BAs or BAs causing mass effect [2].

Case series of pediatric patients (Table 1) show how the percentage of parenchymal BAs not treated with neurosurgical intervention varies, ranging from 0% [3, 24, 64] to more than two-thirds of cases, as described for instance by Jain et al. in a cohort of patients with otogenic BAs (neurosurgery performed in 36.1% of cases, but modified radical mastoidectomy in all the patients) [48]. Not all the studies show the

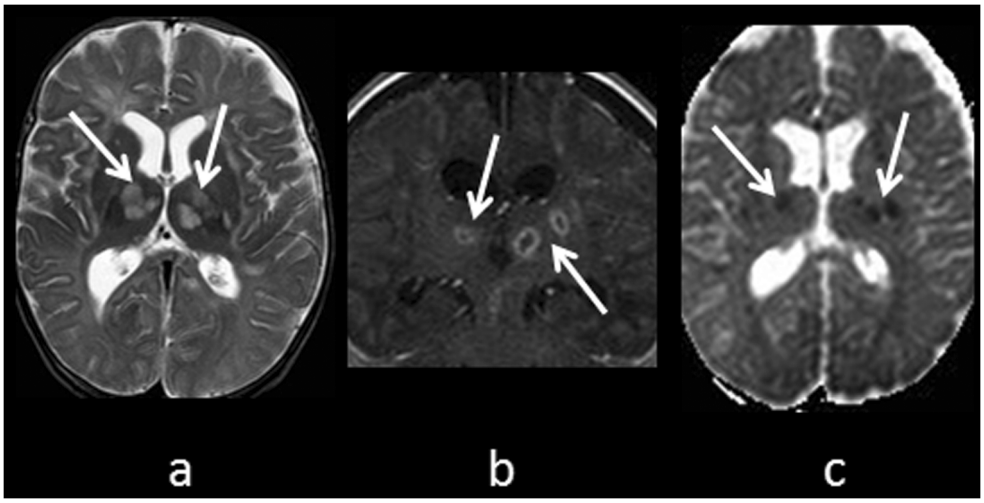

Fig. 1 Brain abscesses from *beta-hemolytic streptococcus* infection. MR imaging study in a 13-day-old baby affected by multiple small brain abscesses from *beta-hemolytic streptococcus* infection. **a** Axial T2 and **b** coronal contrast enhanced T1-weigthed sections showing multiple round shape lesions in basal ganglia region bilaterally, characterized by iso-hyperintense T2-weighted signal (arrows) and contrast enhancing regular rim with uniform hypointense core on T1-weighted image (arrows); **c** the apparent diffusion coefficient (ADC) axial map demonstrates uniformely reduced value within the core of the lesions, compatible with pus accumulation (arrows)

specific indications for the choice of a conservative strategy, but, when reported, they usually meet the criteria recommended by Arlotti et al. [67]. Additionally, Raffaldi et al. [10] describe the frontal lobe as the most frequently involved site in patients treated conservatively. Moreover, a lower tendency to a conservative approach is reported before 1980 [24].

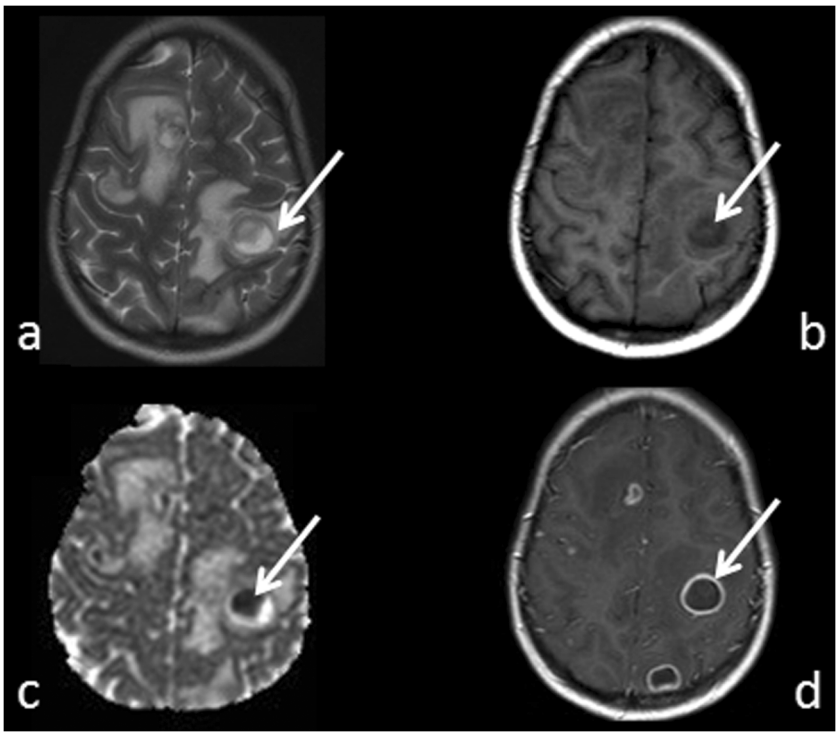

Fig. 2 Brain abscesses from *aspergillus fumigatus* infection. MR imaging study in a 13-year-old girl affected by multiple fully developed brain abscesses from *aspergillus fumigatus* infection. The heterogeneous content of the abscesses is the main feature helping in differentiating from bacterial-pyogenic abscesses. **a** Axial T2 and **b** T1-weigthed sections showing multiple brain focal lesions, the larger one (arrows) characterized by regular iso-hypontense T2-weighted rim and containing amorphous material in an eccentric nodule; **c** the corresponding apparent diffusion coefficient (ADC) map demonstrating reduced value (solid nature) in the eccentric nodule with adjacent crescent shape area of ADC increase (fluid nature), suggesting the nature (probable fungine) of the nodule; in **d** the contrast enhanced T1-weighted axial scan shows remarkable signal increase within the abscess rim, but not in the eccentric amorphous nodule that appears to be attached to the abscess wall. The presence of an eccentric solid nodule of low ADC value and amorphous material may help in differentiating a fungine from a bacterial-pyogenic abscess

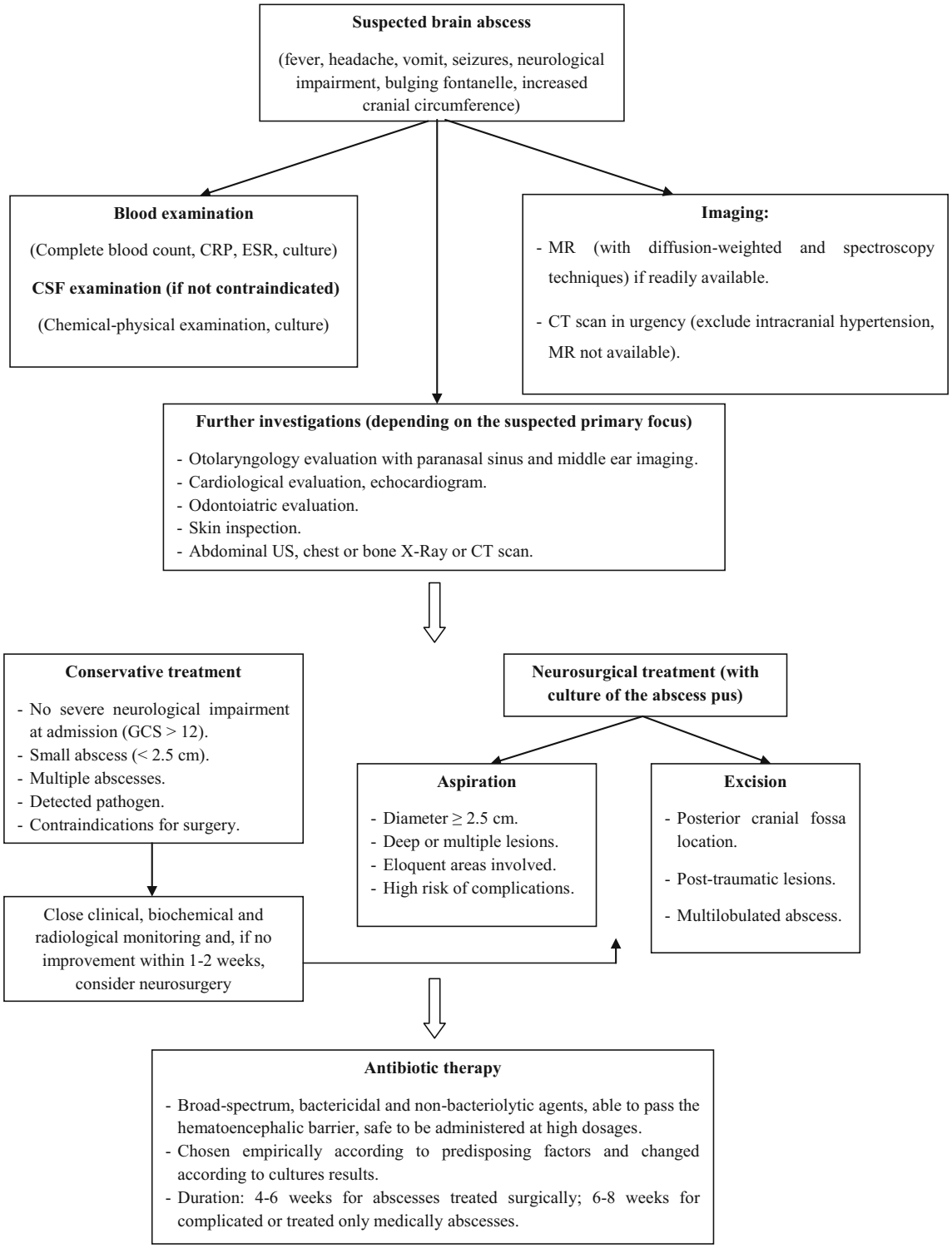

Fig. 3 Flow-chart for the management of suspected brain abscess. CRP C-reactive protein, CSF cerebrospinal fluid, CT computed tomography, ESR erythrocyte sedimentation rate, GCS Glasgow Coma Scale, MR magnetic resonance, US ultrasound,

Antibiotic therapy should be started empirically and then adjusted according to the results of the cultures [42]. The choice of empiric therapy should rely on the predisposing conditions and consequently on the micro-organism thought to be involved, should be directed towards bactericidal and nonbacteriolytic agents, using molecules that can pass the blood-brain barrier (lipophilic, with low molecular mass and low plasma protein binding) and sufficiently safe to be administered at high dosages even for a long time [49, 66, 67].

Table 1 Management of pediatric parenchymal brain abscesses

	Surgical intervention		Medical treatment			
	Neurosurgical intervention	Type of abscess	Antibiotics alone	Type of abscess treated only medically	Empiric antibiotic therapy	Duration of antibiotic therapy
Sahbudak Bal et al. 2018 [62]	*N* = 83.3% (93.3% burr hole – 6.7% craniotomy)	Not known	*N* = 16.7%	- Multiple abscesses	- Third generation cephalosporins with vancomycin; vancomycin and meropenem	- At least 6 weeks
Raffaldi et al. 2017 [56]	*N* = 76% (85% drainage – 11.7% resection – 3.3% other surgical intervention)	- Single abscess (78.3%) in the frontal lobe (33.3%) - Diameter of 3 ± 1.6 cm [0.5–6 cm]	*N* = 24%	- Single abscess (57.9%) in the frontal lobe (21%) - Diameter of 1.7 ± 0.9 cm [0.3–3 cm]	- IV: third generation cephalosporins alone or with metronidazole or with metronidazole and vancomycin or teicoplanin; third generation cephalosporins with different drugs - Oral: Amoxicillin-clavulanate	- Mean: 59.5 ± 28.4 [15–159] days of overall therapy - Mean: 65.3 ± 21.2 [30–119] days for medical treatment alone - Mean: 57.8 ± 30.2 [15–159] days for patients undergone surgical intervention - Mean: 42.4 ± 18.3 [5–120] days iv
Jain et al. 2017 [29][a]	*N* = 36.1% (neurosurgical drainage)	Poor response to treatment, enlarging abscesses with mass effect, risk of intraventricular rupture	*N* = 63.9%	Not known	- IV: ceftriaxone, vancomycin, metronidazole	- 4–6 weeks iv
Brizuela et al. 2017 [8]	*N* = 89.5%	Not known	*N* = 10.5%	Not known	- Vancomycin and meropenem; ceftriaxone and metronidazole with or without vancomycin	- Median: 56 [42–60] days of overall therapy - Median: 42 [35–56] days iv
Acar et al. 2016 [1]	*N* = 83.9% (73% aspiration – 27% resection) [*N* = 15.4% (concomitant mastoidectomy)]	Aspiration was preferred for multiple abscesses and eloquent brain areas involved	*N* = 16.1%	Not known	- IV: third generation cephalosporins with vancomycin and metronidazole; vancomycin and meropenem - Oral: Ciprofloxacin	- Median: 73 [28–540] days
Özsürekci et al. 2012 [52]	*N* = 76% (40% aspiration – 36% resection)	Not known	N = 24%	- Small size, multiple lesions, deep location, and good clinical response to medical therapy	- Third generation cephalosporins with vancomycin and metronidazole; penicillin G or ampicillin-sulbactam with chloramphenicol and/or metronidazole, with or without amikacin	Not known
Cole et al. 2012 [15]	*N* = 88% (60% burr hole aspiration – 13% stereotactic surgery – 7% endocopic aspiration – 20% craniotomy)	Not known	*N* = 12%	Single abscess but high risk for surgery	- Third generation cephalosporins alone or with metronidazole, with or without amoxicillin or another drug; meropenem, rifampicin, clindamycin[b]	- Mean: 14.9 weeks of overall therapy - Mean: 9 weeks if medical therapy alone

Table 1 (continued)

	Surgical intervention		Medical treatment			
	Neurosurgical intervention	Type of abscess	Antibiotics alone	Type of abscess treated only medically	Empiric antibiotic therapy	Duration of antibiotic therapy
						- Mean: 16.9 weeks if previous surgery - Mean: 9.7 weeks iv
Sachor-Meyouhas et al. 2010 [64]	*N* = 100% (70% burr hole drainage – 30% craniotomy)	Not known	*N* = 0%		- Chloramphenicol and cloxacillin or penicillin; third generation cephalosporins with metronidazole and/or vancomycin; meropenem alone or with vancomycin or trimethoprim/sulphamethoxazole	- 85.2% 6 weeks - 14.8% 3–4 weeks
Kao et al. 2008 [30]	*N* = 80%	Not known	*N* = 20%	Small abscess, good response to medical therapy, refusal of surgery	Not known	- Mean: 60 ± 30 [35–105] days for medical treatment alone - Mean: 46 ± 11 [28–63] days for patients undergone surgical intervention
Gelabert-González et al. 2008 [24]	N = 100% (7.2% aspiration – 92.8% craniotomy)	Not known	N = 0%		- Third generation cephalosporins with vancomycin and metronidazole	- Median: 6 weeks [4–12]
Auvichayapat et al. 2006 [4]	*N* = 85.3% (59.4% aspiration – 6.3% excision – both 34.3%)	Not known	*N* = 14.7%	Not known	Not known	Not known
Atiq et al. 2006 [3]	*N* = 100% (100% burr hole)	Diameter > 2 cm	N = 0%		- Metronidazole, third generation cephalosporins, cloxacillin, benzylpenicillin	- 14–40 days
Goodkin et al. 2004 [26][d]	*N* = 77% (93% aspiration – 7% resection)	Not known	*N* = 22%	Multiple abscesses, sepsis or shock with MOF, single and small abscess (diameter < 2 cm)	Not known	Not known

IV intravenous, *MOF* multi-organ failure, *N* number

[a] All of the patients underwent radical mastoidectomy

[b] Used for parenchymal abscesses and subdural empyemas

[c] Not specified if empiric or specific antibiotic therapy

[d] One patient was not treated with antibiotic

In pediatric patients, the most common combination of intravenous antibiotics is a third-generation cephalosporin together with metronidazole and in some cases vancomycin [5, 9–11, 19, 20, 24, 37, 44, 46–48, 50]. Some studies [9, 37, 50] also report the possible use of meropenem alone or in combination with other drugs and other studies [9, 12, 50] describe a wider use of chloramphenicol in the past. Moreover, Krzysztofiak et al. [68] show the effective use of linezolid in pediatric patients, with the evidence of clinical and radiological improvement. Finally, a recent review of fungal brain infections [70] reports that amphotericin B, voriconazole, and fluconazole are the most frequently antimycotic agents recommended.

Antimicrobial agents should be started intravenously and then can be switched to oral therapy, depending on clinical, biochemical, and radiological improvement [10]. Arlotti et al. [66] consider as adequate an overall treatment of 4–6 weeks for patients that have undergone surgical treatment and a parenteral therapy of 6–8 weeks for patients treated with just medical therapy or with complicated BAs. Felsenstein et al. [5] describe longer courses of antimicrobial therapy in children with immunodeficiency. Furthermore, it is worth noting that in the study by Raffaldi et al. [10], no significant difference was shown in duration of therapy between only-medically and surgically treated abscesses and, moreover, Cole et al. [37] describe a longer course of antibiotic treatment in patients that have undergone surgery.

There is indication for a short course of corticosteroids in the presence of edema, and their use is contraindicated in the absence of intracranial hypertension, because of the risk of delayed capsule formation, necrosis, and lower efficacy of antibiotics [49, 70].

In the absence of clinical and radiological improvement within 1–2 weeks, a neurosurgical intervention should be considered [66]. Depending on the characteristics, location, and number of the abscesses, there is the possibility to perform a stereotactic or endoscopic aspiration of the abscess rather than an open surgery (craniotomy with excision) [57]. Aspiration is frequently considered the gold standard neurosurgical treatment [21] and in a review by Ratnaike et al. [57], aspiration has been associated with a lower overall mortality rate when compared to excision.

Stereotactic aspiration is indicated in the case of abscesses $\geq$2.5 cm, deep or multiple lesions, eloquent areas involvement, and high risk of complications; excision can be indicated in the case of posterior cranial fossa location, post-traumatic lesions, multilobulated or superficial abscesses, and in the case of aspiration failure [2, 32, 54, 66].

In the case series of pediatric patients reported in Table 1, more than three-quarters of patients were treated with a neurosurgical intervention, with less-invasive techniques preferred over craniotomy, and similar data can be found in studies also involving adult patients over the years [4, 6, 7, 12, 13, 38, 70]. Lower percentages of neurosurgical treatments (aspiration or craniotomy) are described in the study by Jain et al. [29] in patients with intracranial complications of otitis media and in which, anyway, most patients underwent mastoidectomy.

Prognosis

Over the years, the mortality rate of BAs progressively decreased and data reported in the literature describe a current rate lower than 10% [1, 8, 10, 15, 19, 29, 30, 51, 52, 56, 62, 64, 69].

Higher percentages (11–25%) are reported by Gelabert-González et al. (10.7%), Auvyachapat et al. (10.7%), Atiq et al. (16%), and Goodkin et al. (24%) [3, 4, 24, 26].

The most frequent factors involved in higher rate of mortality are delayed presentation and diagnosis, severe neurological impairment, and development of complications [3, 4].

In the cases described so far, involving studies with both low and high mortality rates, death occurred more frequently in patients with lower Glasgow Coma Scale score, intraventricular rupture of the abscess [3, 19, 28, 55, 62] and severe underlining conditions, such as CHD, congenital or acquired immunosuppression, organ transplantation, tumors in treatment with chemotherapy, neonates born premature or with malformations [4, 8, 11, 19, 26, 64]. The only patient who died for a parenchymal abscess in the study by Cole et al. [15] had a primary immunodeficiency, and in the report by Acar et al. [1], of the two patients who died (6.4%), one had a concomitant tubercular infection in HIV and the other was immunosuppressed because of a liver transplantation. Moreover, the study by Felsenstein et al. [19] reports a younger age at presentation and a more immediate treatment (interpreted as a sign of severe clinical condition) as associated with poor outcome. On the contrary, Lee et al. [39] do not report association between outcome and factors such as neurological symptoms and level of consciousness at admission, presence of CHD, altered blood examination, and type of treatment.

A full recovery rate from the infection of about 60–70% is reported in the case of early diagnosis and proper therapy [10, 15, 19, 39, 56, 62, 64, 68]. However, a percentage of less than 50% of cases is described in other case series. These data may be explained by delayed intervention, the presence of higher number of patients with neurological impairment at admission, and severe predisposing conditions or the patient's choice to be followed in a specialized center [1, 3, 8, 11, 26, 30].

Regarding otogenic BAs, a systematic review by Duarte et al. [18] describes meningitis, cerebral herniation, and death as the most common acute complications. Clinical sequelae can be found in about 30% of patients and are mainly epilepsy, motor, visual and hearing deficits, hydrocephalus, and language impairment [1, 15, 26, 39, 56, 60, 62].

Conclusion

Pediatric BA is an infrequent disease, still burdened by high morbidity and mortality, despite the advent of advanced diagnostic and therapeutic procedures.

In the future, it would be interesting to evaluate changes in the epidemiology of brain infections, taking into account on one hand the progressive decrease of some predisposing factors, such as congenital heart disease (and immunosuppression induced by HIV infection), on the other hand the rise of antibiotic resistance, the decrease in vaccination coverage, and the growing number of patients with iatrogenic immunodeficiencies.

Multicentric prospective studies are needed, in order to achieve stronger evidence in particular on BA treatment.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

References

1. Acar M, Sutcu M, Akturk H, Muradova A, Hancerli Torun S, Salman N, Caliskan N, Izgi N, Somer (2016) Evaluation of Short-Term Neurological Outcomes in Children with Brain Abscesses. Turk Neurosurg. https://doi.org/10.5137/1019-5149.JTN.18672-16.1
2. Arlotti M, Grossi P, Pea F, Tomei G, Vullo V, De Rosa FG, Di Perri G, Nicastri E, Lauria FNJ, Carosi G, Moroni M, Ippolito G (2010) Consensus document on controversial issues for the treatment of infections of the central nervous system: bacterial brain abscesses. Int J Infect Dis 14(4): S79–S92
3. Atiq M, Ahmed US, Allana SS, Chisti KN (2006) Brain abscess in children. Indian J Pediatr 73(5):401–404
4. Auvichayapat N, Auvichayapat P, Aungwarawong S (2007) Brain abscess in infants and children: a retrospective study of 107 patients in Northeast Thailand. J Med Assoc Thail 90(8):1601–1607
5. Bank DE, Carolan PL (1993) Cerebral abscess formation following ocular trauma: a hazard associated with common wooden toys. Pediatr Emerg Care 9:285–288
6. Baytan B, Evim MS, Güler S, Güneş AM, Okan M (2015) Acute central nervous system complications in pediatric acute lymphoblastic leukemia. Pediatr Neurol 53(4):312–318
7. Britt RH, Enzmann DR, Yeager AS (1981) Neuropathological and computerized tomographic findings in experimental brain abscess. J Neurosurg 55:590–603
8. Brizuela M, Pérez G, Martiren S, Varela Baino AN, Cedillo C, Ruvinsky S, Epelbaum C, Isasmendi A, Litterio M, Pinheiro JL, Bologna R (2017) Absceso cerebral en niños: experiencia en diez años en un hospital pediátrico de alta complejidad. Arch Argent Pediatr 115(4):e230–e232/e230
9. Brook I (2017) Microbiology and treatment of brain abscess. J Clin Neurosci 38:8–12
10. Brouwer MC, Coutinho JM, van de Beek D (2014) Clinical characteristics and outcome of brain abscess. Systematic review and meta-analysis. Neurology 82:806–813
11. Canpolat M, Ceylan O, Per H, Koc G, Tumturk A, Kumandas S, Patiroglu T, Doganay S, Gumus H, Unal E, Kose M, Gorkem SB, Kurtsoy A, Ozturk MK (2015) Brain abscesses in children: results of 24 children from a reference center in Central Anatolia, Turkey. J Child Neurol 30(4):458–467
12. Capua T, Klivitsky A, Bilavsky E, Ashkenazi-Hoffnung L, Roth J, Constantini S, Grisaru-Soen G (2018) Group a streptococcal brain abscess in the pediatric population - case series and review of the literature. Pediatr Infect Dis J Feb 16:967–970. https://doi.org/10.1097/INF.0000000000001947
13. Carpenter J, Stapleton S, Holliman R (2007) Retrospective analysis of 49 cases of brain abscess and review of the literature. Eur J Clin Microbiol Infect Dis 26:1–11
14. Chowdhry SA, Cohen AR (2012) Citrobacter brain abscesses in neonates: early surgical intervention and review of the literature. Childs Nerv Syst 28(10):1715–1722
15. Cole TS, Clark ME, Jenkins AJ, Clark JE (2012) Pediatric focal intracranial suppuration: a UK single-center experience. Childs Nerv Syst 28:2109–2114
16. Costerus JM, Brouwer MC, van de Beek D (2018) Technological advances and changing indications for lumbar puncture in neurological disorders. Lancet Neurol 17:268–278
17. Dabbah H, Elias N, Bentur L (2009) Foreign-body aspiration as an aetiology for brain abscess. Arch Dis Child 94(8):601
18. Duarte MJ, Kozin ED, Barshak MB, Reinshagen K, Knoll RM, Abdullah KG, Welling DB, Jung DH (2018) Otogenic brain abscesses: a systematic review. https://doi.org/10.1002/lio2.150
19. Felsenstein S, Williams B, Shingadia D, Coxon L, Riordan A, Demetriades AK, Chandler CL, Bassi S, Koutoumanou E, Stapleton S, Sharland M, Bryant PA (2013) Clinical and microbiologic features guiding treatment recommendations for brain abscesses in children. Pediatr Infect Dis J 32(2):129–135
20. Frazier JL, Ahn ES, Jallo GI (2008) Management of brain abscesses in children. Neurosurg Focus 24(6):E8
21. Gadgil N, Patel AJ, Gopinath SP (2013) Open craniotomy for brain abscess: a forgotten experience? Surg Neurol Int 4:3
22. Gaskill SJ, Marlin AE (2008) Brain abscesses and encephalitis. In: Albright AL, Pollack IF, Adelson PD (eds) Principles and practice of pediatric neurosurgery, ed 2. Thieme, New York, pp 1162–1181
23. Gefen A, White A (2017) Asymptomatic pulmonary arteriovenous malformations in children with hereditary hemorragic telangiectasia. Pediatr Pulmonol 52:1194–1197
24. Gelabert-González M, Serramito-García R, García-Allut A, Cutrín-Prieto J (2008) Management of brain abscess in children. J Paediatr Child Health 44(12):731–735
25. George R, Andronikou S, du Plessis J, du Plessis AM, Van Toorn R, Maydell A (2009) Central nervous system manifestations of HIV infection in children. Pediatr Radiol 39(6):575–585
26. Goodkin HP, Harper MB, Pomeroy SL (2004) Intracerebral abscess in children: historical trends at Children's hospital Boston. Pediatrics 113:1765–1770
27. Góralska K, Blaszkowska J, Dzikowiec M (2018) Neuroinfections caused by fungi. Infection. 46:443–459. https://doi.org/10.1007/s15010-018-1152-2
28. Helweg-Larsen J, Astradsson A, Richhall H, Erdal J, Laursen A, Brennum J (2012) Pyogenic brain abscess, a 15 year survey. BMC Infect Dis 12:332
29. Jain A, Arora N, Meher R, Passey JC, Bansal R (2017) Intracranial complications of CSOM in pediatric patients: a persisting problem in developing countries. Int J Pediatr Otorhinolaryngol 100:128–131
30. Kao KL, Wu KG, Chen CJ, Wu JJ, Tang RB, Chang KP, Wong TT (2008) Brain abscesses in children: analysis of 20 cases presenting at a medical center. J Microbiol Immunol Infect 41:403–407

31. Kim JY, Park SY, Lee JM, Kim YK, Kim SY (2016) Intracranial abscess as a complication of X-linked Agammaglobulinemia. Childs Nerv Syst 32:2049–2051
32. Kocherry XG, Hegde T, Sastry KVR, Mohanty A (2008) Efficacy of stereotactic aspiration in deep-seated and eloquent-region intracranial pyogenic abscesses. Neurosurg Focus 24(6):E13
33. Krzysztofiak A, Bozzola E, Lancella L, Quondamcarlo A, Gesualdo F, Ugazio AG (2010) Linezolid therapy of brain abscess. Pediatr Infect Dis J 29(11):1063–1064
34. Krzysztofiak A, Zangari P, De Luca M, Villani A (2017) Brain abscesses: an overview in children. J Pediatr Infect Dis 14:002–005. https://doi.org/10.1055/s-0037-1615786
35. Kum RO, Özcan M, Ulusal T, Dündar G, Yılmaz YF, Ünal A (2017) A rare complication of chronic otitis media: cerebellar abscess. Turk Arch Otorhinolaryngol 55(3):140–143
36. Lackner H, Sovinz P, Benesch M, Smolle-Jüttner F, Mokry M, Schwinger W, Moser A, Urban C (2009) Management of brain abscesses in children treated for acute lymphoblastic leukemia. Pediatr Blood Cancer 52(3):408–411
37. Laulajainen-Hongisto A, Lempinen L, Färkkilä E, Saat R, Markkola A, Leskinen K, Blomstedt G, Aarnisalo AA, Jero J (2016) Intracranial abscesses over the last four decades; changes in aetiology, diagnostics, treatment and outcome. Infect Dis (Lond) 48(4):310–316
38. Lechowicz M, Dąbek K, Majewska U, Bekesińska-Figatowska M, Borszewska-Kornacka MK, Bokiniec R (2017) Multiple brain abscesses caused by Citrobacter Koseri in a preterm neonate - case report. Pol J Radiol 82:837–841
39. Lee CG, Kang SH, Kim YJ, Shin HJ, Choi HS, Lee JH, Lee MH (2010) Brain abscess in Korean children: a 15-year single center study. Korean J Pediatr 53(5):648–652
40. Liu J, Bai R, Li Y, Staedtke V, Zhang S, van Zijl PCM, Liu G (2018) MRI detection of bacterial brain abscesses and monitoring of antibiotic treatment using bacCEST. Magn Reson Med 80:662–671
41. Louie JP, Osterhoudt KC, Christian CW (2000) Brain abscess following delayed endoscopic removal of an initially asymptomatic esophageal coin. Pediatr Emerg Care 16(2):102–105
42. Maraki S, Papadakis IS, Chronakis E, Panagopoulos D, Vakis A (2016) Aggregatibacter aphrophilus brain abscess secondary to primary tooth extraction: case report and literature review. J Microbiol Immunol Infect 49(1):119–122
43. Menon S, Bharadwaj R, Chowdhary A, Kaundinya DV, Palande DA (2008) Current epidemiology of intracranial abscesses: a prospective 5 year study. J Med Microbiol 57(Pt 10:1259–1268
44. Mishra P, Prasad KN, Singh K, Sahu RN, Ojha BK (2016) Association of ICAM-1 (K469E) and MCP-1 −2518 a>G gene polymorphism with brain abscess. J Neuroimmunol 292:102–107
45. Muccio CF, Caranci F, D'Arco F, Cerase A, De Lipsis L, Esposito G, Tedeschi E, Andreula C (2014) Magnetic resonance features of pyogenic brain abscesses and differential diagnosis using morphological and functional imaging studies: a pictorial essay. J Neuroradiol 41(3):153–167
46. Muzumdar D, Jhawar S, Goel A (2011) Brain abscess: an overview. Int J Surg 9(2):136–144
47. Naderi S, Nejat F, Shahjouei S, El Khashab M (2012) Cranial dermal sinus: presentation, complications and management. Pediatr Neurosurg 48(2):86–92
48. Nathoo N, Nadvi SS, Narotam PK, van Dellen JR (2011) Brain abscess: management and outcome analysis of a computed tomography era experience with 973 patients. World Neurosurg 75(5–6): 716–726
49. Nau R, Seele J, Djukic M, Eiffert H (2018) Pharmacokinetics and pharmacodynamics of antibiotics in central nervous system infections. Curr Opin Infect Dis 31(1):57–68
50. Nicolosi A, Hauser WA, Musicco M, Kurland LT (1991) Incidence and prognosis of brain abscess in a defined population: Olmsted County, Minnesota, 1935–1981. Neuroepidemiology 10:122–131
51. Ong CT, Tsai CF, Wong YS, Chen SCC (2017) Epidemiology of brain abscess in Taiwan: a 14-year population-based cohort study. PLoS One 12(5):e0176705
52. Özsürekci Y, Kara A, Cengiz AB, Çelik M, Özkaya-Parlakay A, Karadağ-Öncel E, Ceyhan M (2012) Brain abscess in childhood: a 28-year experience. Turk J Pediatr 54(2):144–149
53. Pal D, Bhattacharyya A, Husain M, Prasad KN, Pandey CM, Gupta RK (2010) In vivo proton MR spectroscopy evaluation of pyogenic brain abscesses: a report of 194 cases. Am J Neuroradiol 31:360–366
54. Pandey P, Umesh S, Bhat D, Srinivas D, Abraham R, Pillai S, Balasubramaniam A, Devi I, Sampath S, Chandramouli BA (2008) Cerebellar abscesses in children: excision or aspiration? J Neurosurg Pediatrics 1:31–34
55. Patel AP, Masterson L, Deutsch CJ, Scoffings DJ, Fish BM (2015) Management and outcomes in children with sinogenic intracranial abscesses. Int J Pediatr Otorhinolaryngol 79(6):868–873
56. Raffaldi I, Garazzino S, Castelli GG, Lipreri R, Lancella L, Esposito S, Giannini AM, Montagnani C, Marseglia GL, Pignata C, Bernardi F, Tovo PA (2017) SITIP BRAIN ABSCESSES REGISTRY. BRAIN abscesses in children: an Italian multicentre study. Epidemiol Infect 145(13): 2848–2855
57. Ratnaike TE, Das S, Gregson BA, Mendelow AD (2011) Review of brain abscess surgical treatment—78 years: aspiration versus excision. World Neurosurg 76(5):431–436
58. Reiche W, Schuchardt V, Hagen T, Il'yasov KA, Billmann P, Weber J (2010) Differential diagnosis of intracranial ring enhancing cystic mass lesions—role of diffusion-weighted imaging (DWI) and diffusion-tensor imaging (DTI). Clin Neurol Neurosurg 112(3): 218–225
59. Renier D, Flandin C, Hirsch E, Hirsch JF (1988) Brain abscesses in neonates. A study of 30 cases. J Neurosurg 69(6):877–882
60. Roche M, Humphreys H, Smyth E, Phillips J, Cunney R, McNamara E, O'Brien D, McArdle O (2003) A twelve-year review of central nervous system bacterial abscesses; presentation and aetiology. Clin Microbiol Infect 9(8):803–809
61. Rossi A, Martinetti C, Morana G, Severino M, Tortora D (2016) Neuroimaging of infectious and inflammatory diseases of the pediatric cerebellum and brainstem. Neuroimaging Clin N Am 26(3): 471–487
62. Sahbudak Bal Z, Eraslan C, Bolat E, Avcu G, Kultursay N, Ozkinay F, Kurugol Z, Vardar F (2018) Brain abscess in children: a rare but serious infection. Clin Pediatr (Phila) 57(5):574–579
63. Sedaghat AR, Wilke CO, Cunningham MJ, Ishman SL (2014) Socioeconomic disparities in the presentation of acute bacterial sinusitis complications in children. Laryngoscope 124(7):1700–1706
64. Shachor-Meyouhas Y, Bar-Joseph G, Guilburd JN, Lorber A, Hadash A, Kassis I (2010) Brain abscess in children – epidemiology, predisposing factors and management in the modern medicine era. Acta Paediatr 99(8):1163–1167
65. Sheehan JP, Jane JA, Ray DK, Goodkin HP (2008) Brain abscess in children. Neurosurg Focus 24:E6. https://doi.org/10.3171/FOC/2008/24/6/E6
66. Shovlin CL, Condliffe R, Donaldson JW, Kiely DG, Wort SJ, on behalf of the British Thoracic Society (2017) British Thoracic Society clinical statement on pulmonary arteriovenous malformations. Thorax 72:1154–1163

67. Sonneville R, Magalhaes E, Meyfroidt G (2017) Central nervous system infections in immunocompromised patients. Curr Opin Crit Care 23(2):128–133
68. Udayakumaran S, Onyia CU, Kumar RK (2017) Forgotten? Not yet. Cardiogenic brain abscess in children: a case series based review. World Neurosurg 107:124–129
69. Van de Beek D, Cabellos C, Dzupova O, Esposito S, Klein M, Kloek AT, Leib SL, Mourvillier B, Ostergaard C, Pagliano P, Pfister HW, Read RC, Resat Sipahi O, Brouwer MC, for the ESCMID Study Group for Infections of the Brain (ESGIB) (2016) ESCMID guideline: diagnosis and treatment of acute bacterial meningitis. Clin Microbiol Infect 22:S37–S62
70. Zhang Z, Cai X, Li J, Kang X, Wang H, Zhang L, Yan R, Gao N, Liu S, Yue S, Zhang J, Yang S, Yang X (2016) Retrospective analysis of 620 cases of brain abscess in Chinese patients in a single center over a 62-year period. Acta Neurochir 158:733–739