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Review Article

Favorable Outcomes with Pharmacological Treatment of Patients with Multiple Cerebral Abscesses

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Abstract

Brain abscesses represent a pathology of multifactorial etiology, with a wide range of signs and symptoms, so that it continues to be a diagnostic challenge in the early stages of the disease, given the low specificity it presents in neuroimaging studies in the first stage week of the evolution of the infectious process. It is for these reasons that when there is clinical suspicion, it is essential to start empirical treatment with Ceftriaxone, Vancomycin, and Metronidazole for at least four weeks or until the causal agent is identified, as well as an adequate assessment for those patients who meet criteria for a surgical procedure. This article included characteristics of 5 patients with multiple brain abscesses evaluated at our institution, as well as a brief review of the disease.

Keywords: Brain Abscesses; Etiology; Ceftriaxone

Patient characteristics

Five patients were included, whose characteristics are shown in table 1. Four patients had a favorable evolution with drug treatment. In only one case, antibiotic treatment was administered for only three weeks with subsequent relapse, and modification of the treatment was administered for four weeks with an adequate response. Four patients presented headache and fever as the predominant symptoms; only the post-transplant patient did not present fever, possibly associated with immunosuppressive treatment; All five patients presented altered alertness at the time of admission.

Pathogenesis

The developments of the Brain abscess can be divided into four stadiums: 1) early cerebritis (1-4 days); 2) late cerebritis (4-10 days); 3) early capsule formation (11- 14 days); and 4) late capsule formation (>14 days) [1]. The glial cell activation in brain abscesses is through parenchymal microglia and astrocytes. Activated microglia can influence the antibacterial adaptive immune response's type and extent through up-regulation of MHC class II and costimulatory molecule expression. The release of proinflammatory mediators is continuing, and it could damage the surrounding parenchyma in the brain. Cytokines IL-1 and TNF-alpha individually are related to essential functions to establish an effective antibacterial response in the CNS parenchyma [2].

Predisposing factors

Bacteria enter the brain through a contiguous spread in about half of cases and hematogenous dissemination in about one-third of cases, with no identified mechanisms accounting for the remaining cases. The penetrating trauma in the head and neurosurgery procedures are responsible for a growing proportion of brain abscesses,

Patient	1	2	3	4	5
Age	44	54	33	37	46
Sex	Female	Female	Male	Male	Female
No. Abscesses	3	2	3	10	6
Treatment	*Ceftriaxone Vancomycin Metronidazole → Cefepime Gentamicin [a]Dexamethasone	Ceftriaxone Vancomycin Metronidazole	Meropenem Vancomycin	Ceftriaxone Vancomycin Meropenem Linezolid Trimethoprim	Ceftriaxone Vancomycin Metronidazole **Dexamethasone
Weeks of treatment	*3 weeks → four weeks	Four weeks	Four weeks	Six weeks	Four weeks
Surgical indication	Yes: intracranial hypertension	No	No	Yes: (the diencephalon, adjacent to the III ventricle)	Yes: 2.5cm frontal abscess + intracranial hypertension
Comorbidities	None	None	None	***DM1, SAH, Kidney posttransplantation	None

Table 1

* Initial treatment was only administered for three weeks with relapse, so subsequent treatment was administered for four weeks with an adequate response.

** Dexamethasone treatment was administered for two days as intracranial hypertension data improved.

[a] Dexamethasone treatment was administered for seven days as intracranial hypertension data improved.

***Diabetes mellitus 1, Systemic Arterial Hypertension.

potentially because other predisposing factors have become less prevalent or are more readily recognized and treated (e.g., otitis media). The patients with comorbid conditions, congenital heart disease, diabetes mellitus type 2, alcoholism, corticosteroid use, and more immunocompromised problems may be at higher risk of brain abscess [3].

The supratentorial abscesses are more common than infratentorial abscesses, and single lesions are more common than multifocal. Abscesses are related to infections in a neighboring area are usually unique, while hematogenous dissemination often results in multiple abscesses, commonly localized in the gray-white junction and border zone to the vascular territories. In patients with contiguous dissemination, the abscess is typically a continuum to the infection. The most common frontal abscess lobe site, followed by the temporal lobe, and both are associated with sinusitis. Abscesses associated with otitis media or mastoiditis are frequently located in the temporal lobe and cerebellum [5].

Bacteriology

The pathogens and their spectrum responsible for abscess in the brain varies depending on the mechanism of infection, the host's immune status, and local epidemiology. The gram-negative and gram-positive bacteria that colonize the oropharynx and sinuses and anaerobes are common causes, especially when the infection source is suspected to be from a contiguous site. *Streptococcus* species (e.g., *S. anginosus*, *S. intermedius*, *S. viridans*, *S. pneumoniae*) are the most frequently identified organisms in brain abscesses up to half of the cases, followed by anaerobes, which make up another 20% to 25% of cases. *Staphylococcus* species (e.g., *S. aureus*, *S. epidermidis*) are often isolated from postsurgical abscesses, and

Enterobacteriaceae (e.g., *Klebsiella pneumoniae*, *Escherichia coli*, *Proteus species*) are also regularly cultured from brain abscesses. In anaerobic infections, oropharyngeal and gastrointestinal organisms (e.g., *Fusobacterium* species, *Actinomyces* species, *Bacteroides* species) tend to predominate brain abscesses, although genital tract anaerobes (e.g., *Peptostreptococcus* species) could be insulated. At least half of brain abscesses are polymicrobial [6].

Among immunocompromised populations (e.g., related to human immunodeficiency virus infection [HIV], malignancy, prolonged use of corticosteroid or other therapy with immunosuppressive drugs, or transplantation), several pathogens have a predilection for the CNS should be given special attention. For example, *Nocardia* species comprise a small proportion of organisms identified overall in brain abscess but make up a higher percentage of cases in immunocompromised populations; Listeria monocytogenes, which typically causes a meningoencephalitis when the CNS is affected, presents less commonly as a cerebral abscess. The presence of L. monocytogenes as the causal organism in brain abscess is often through blood culture, underlining the prominence of obtaining blood cultures before starting empiric therapy for brain abscess. *Rhodococcus equi* can also cause an abscess in the brain, principally in patients who are HIV disease or otherwise immunocompromised, although cases have been reported in subjects who are immunocompetent [7].

In patients with the proper epidemiologic risk influences, contagions with Mycobacterium tuberculosis (and, uncommonly, Mycobacterium avium complex in individuals with HIV) can also produce pyogenic brain abscess. Pivotal brain lesions in Tuberculosis come in two forms: granulomas and abscesses. Tuberculomas consist of paucibacillary granulomatous inflammatory tissue that does not typically restrict DWI unless the core has begun to necrose and liquefy, in which case they are indistinguishable from abscesses [8].

Mycological pathogens linked with focal space-occupying brain lesions include *Aspergillus* species, *Candida* species, *Mucorales* species, *Cryptococcus* species, *Fusarium* species, and the endemic mycoses (e.g., *Coccidioides immitis*, *Histoplasma capsulatum*), among others. The range to which these pathogens cause true pyogenic (i.e., pus-forming) abscess versus nonsuppurative lesions more similar to tuberculomas without necrosis or associated restricted diffusion is highly variable. In patients who are HIV infected with a depressed CD4 count, Toxoplasma gondii is a common cause of intracerebral ring-enhancing lesions. However, toxoplasmosis does not form real abscesses, and lesions do not characterize associated restricted diffusion on DWI. Similarly, in neurocysticercosis (infection of the nervous system caused by Taenia solium larvae), focal intracranial lesions can enhance when contrast administration as the cysts degenerate, mimicking a pyogenic brain abscess. Nevertheless, in neurocysticercosis, cysts do not characteristically demonstrate the definite, homogeneously restricted diffusion characteristic of pyogenic infections, although some do. Amebic infections, including *Acanthamoeba* species and *Balamuthia mandrillaris*, can cause brain abscess with restricted diffusion on DWI [9].

Clinical manifestations

The principal clinical manifestation of brain abscess is headaches; fever and altered consciousness level are commonly absent. The neurologic signs related to the abscess's site and size can sometimes be very subtle for days and be even by weeks. The behavioral changes may present in patients with abscesses in the frontal and the right temporal lobes. Abscesses in the brainstem and cerebellum can be related to cranial nerve affection, gait disorder (ataxia), besides the headache and alteration in the mental status associated with hydrocephalus, until 25% of patients present with structural epileptic seizures [10].

The clinical manifestations become more evident as the abscess increases in size and the surrounding edema increases. These symptoms and signs may be difficult to recognize due to the location, the inflammatory and infectious nature of the underlying neurological, and often systemic disease. The subjects with hematogenous spread of bacteria can present the underlying infection symptoms and localization problem. The differential diagnosis includes a range of infectious diseases and other neurological diseases, such as other brain tumors, stroke with luxe circulation, bacterial meningitis, epidural abscess, and inclusive subdural empyema. The primary central nervous system lymphoma is part of the differential diagnosis, especially in patients infected with HIV [11].

Diagnosis

CT facilitates early detection, exact localization, accurate characterization, determination of the number of abscesses, the size, and stadium of the abscess, the presence of hydrocephalus, a raised ICP, edema, and associated infections like subdural empyema, ventriculitis, and treatment planning. It is invaluable in the assessment of

the adequacy of treatment and sequentially follows up. The Hematogenous abscesses can be seen in endocarditis, cardiac shunts, or pulmonary vascular malformations, usually multiple, identified at the grey-white matter junction and located in the middle cerebral artery territory. In the earlier phases, a non-contrast CT; may use to show hypodense areas with mass effect. Posteriorly, a complete peripheral ring may be seen. In contrast, CT, uniform ring enhancement is virtually always present in later phases. In the early stadium, the capsule will be challenging to visualize via conventional techniques, and double-contrast CT often helps define encapsulation of abscess. Positive labeling in radionuclide imaging with III-Indium labeled leukocytes, C-reactive protein, 99mTc-hexamethyl propylene amine oxime leukocyte scintigraphy, diffusion-weighted MR imaging, Thallium-201 single-photon emission computed tomography, and proton magnetic resonance spectroscopy help in differentiating abscess from the tumor [12].

MRI features recognize pyogenic abscesses reasonably soon. A central area (liquefaction) gives high signals with a surrounding edematous brain tissue that gives low signals on T1 weighted images. In the T2 weighted images, the necrosis shows higher signals similar to the grey matter. The abscess's maturity is related to the rim's presence, which is presented probably formed by the collagen and the surrounding inflammation are due to free radicals and microhemorrhages in the abscess wall. The inflammation zone is significantly thicker in tubercular than another pyogenic abscess in the histologic sections' morphometric analysis. The MRI findings also depend on the stadium of the infection.

The MRI can have a low T1-weighted image signal and a high T2-weighted image signal with patchy enhancement in the early phase.

The low T1WI signal becomes better demarcated in later phases, with a high T2WI signal both in the cavity and the surrounding parenchyma.

The abscess cavity shows a hyperintense rim with non-contrast T1- weighted images and a hypointense rim on T2WI [13].

As on a CT, the MRI usually demonstrates a ring of enhancement surrounding the abscess. Abscesses tend to increase the white matter's size, away from the better-vascularized grey matter, thinning the medial wall. Elsewhere, the enhancing-ring sign is a nonspecific finding and must be evaluated with the clinical history. The thickness, the irregularity, and the enhancing ring's modularity suggest tumors (in most cases) or, possibly, a fungal infection. The vascularity of the wall was not significantly different in abscesses of different etiology. The differential diagnosis of the abscesses on MRI is necessary to consider hematomas, metastases, and granulomas because they have a similar low signal rim obtained on the T2 images in such cases. Brain abscesses are life-threatening, and their identification of the etiology pathogens is essential to diagnose and choose the best antibiotic regimen. It is well known that in 20% of the patients, the cultures of microbiological material from the abscess can remain sterile. The polymerase chain reaction (PCR) gives an alternative to have a specific diagnosis. However, data from reports of the specific use of wide-spectrum PCR assays for detecting pathogens in brain abscesses are uncommon in reviews of the medical literature. The PCR is an excellent tool to detect enduring and obligate organisms that require stringent growth conditions like *Fusobacterium* species and Aspergillus. PCR is fast, sensitive, and does not depend on tubercle bacilli's viability in the samples [14].

Treatment

It is well known that the successful treatment of brain abscesses requires a high index of suspicion of the infectious process since patients can present subtle and variable symptoms and often require a combination of drainage and antimicrobial therapy. Pharmacological treatment is based on the use of Metronidazole, which provides adequate penetration of abscesses and is effective due to its bactericidal action against anaerobes; Ceftriaxone is useful as it covers most anaerobes; Vancomycin, a drug that must be started until a culture and susceptibility result is obtained; Ceftazidime, Cefepime, and Meropenem are especially helpful when abscess formation is associated with neurosurgical procedures or Pseudomonas infection [15,16].

In all patients with brain abscesses of undetermined origin, it is essential to start treatment with Vancomycin, Metronidazole, and Ceftriaxone with an average treatment duration of 4 to 8 weeks clinical and imaging evolution of the patient [16]. Therefore, in patients with multiple abscesses of hematological origin, the previous scheme is ideal. In patients with abscesses of odontogenic, otogenic, and paranasal sinus origin, the use of Metronidazole plus Ceftriaxone or Cefotaxime is recommended; in patients with neu-

rosurgical procedures, Vancomycin plus Ceftazidime, Cefepime, or Meropenem are the most appropriate drugs; In patients with a history of penetrating trauma, the use of Vancomycin plus Ceftriaxone or Cefepime is recommended if Pseudomonas is suspected [17].

The steroids should be considered in intracranial hypertension or deviation of the midline. Initially, dexamethasone 10 mg IV is suggested, followed by 4 mg every six hours. However, it will stop in the patient as soon as the condition improves. Although the use or not of steroids has not been associated with an increase in mortality, it should be considered that their use slows down the encapsulation of the abscess and increases the risk of ventricular rupture [18].

Treatment with aspiration is recommended if the lesion is in the language areas and cortical sensory and motor regions. This procedure should be considered when there is no decrease or increase in the size of the abscesses. It should be regarded as impossible to perform this type of operation when the abscesses are in the early cerebritis phase or are located in inaccessible areas [19].

Surgical treatment is suggested in the following situations: post-trauma abscess, encapsulated fungal abscess, multiloculated abscesses, if there is no evidence of clinical improvement in the first week, if a neurological deterioration its present, data of intracranial hypertension, increase in the diameter of the abscesses, abscesses >2.5 centimeters or located in the cerebellum [20,21].

Outcomes

Different studies carried out since the 1970s have shown a decrease in mortality from 40 to only 10% and a more favorable recovery from 30 to 70%. Despite this, it is not uncommon for patients to present neurological sequelae, mainly epileptic seizures, mostly when the abscesses are located in the frontal and temporal lobes. Before every patient with brain abscesses, those factors and poor prognosis that will complicate their evolution and increase mortality should be determined: rapid progression of the disease before hospitalization, severe neurological deterioration, stupor or coma (60 - 100% mortality), rupture towards the ventricular system (80-100% mortality) [22,23].

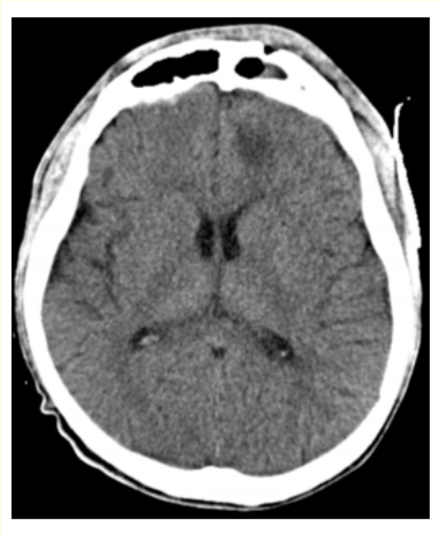

Figure 1: This image corresponds to patient three and shows a hypodense left frontal lesion between the gray and white matter in the phase of cerebritis.

Figure 2: This image corresponds to patient 4, on admission and three weeks after starting the pharmacological management, with a late cerebritis lesion and capsule formation, in the diencephalon, adjacent to the III ventricle. In the photograph on the right, the control three weeks after antimicrobial management.

Figure 3: The image of patient one at admission and some weeks after pharmacological management was concluded.

Conclusions

Brain abscesses are a problematic pathology to diagnose practically due to the significant variability of symptoms and signs they present and the differential diagnoses that have to be ruled out in neuroimaging studies. Although surgical indications for its drainage, pharmacological treatment is essential for adequate patient recovery, considering various associated factors such as its origin or the causative agent. The use of steroids should not be indicated in all patients, and despite low mortality and high recovery rates, it is essential to take into account the low prognostic factors that can complicate the patient's evolution.

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