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BRAIN ABSCESS: PATHOGENESIS, DIAGNOSIS AND MANAGEMENT STRATEGIES

MURTAZA MUSTAFA[1], M. IFTIKHAR[2], M. IKRAM LATIF[3] & RAJESH K. MUNAIDY[4]

[1,2,4]School of Medicine, University Malaysia Sabah, Kota Kinabalu, Sabah, Malaysia

[3]Cyberjaya University College of Medical Sciences, Kuala Lumpur, Malaysia

ABSTRACT

Brain abscess a potentially fatal disease, in the early days diagnosed only before autopsy. Brain abscesses in human are quite uncommon, certain underlying brain pathologies serve as a nidus for abscess. Classification of brain abscess on the basis of the likely entry point of infection. Most patients are presented with: Headache (70%), nausea and vomiting (50%), seizure (25-35%), nuchal rigidity and papilledema (25%), focal neurologic deficit (50%) and fever (45% to 50%). Mortality has ranged from 8% to 25%, poor diagnostic factors included, and underlying disease. Recent advances in the diagnosis and introduction of CT and, MRI scanning have reduced the mortality, Etiologic agents of brain abscess include: Streptococci, S.aureus, Bacteriodes, enteric gram bacilli, Pseudomonas spp., H.influenzae, S.pneumoniae, L.monocytogenes, fungi and protozoa. Diagnosis of brain abscess is a multidisciplinary include: Neuroradiologist, a neurosurgeon, and infectious disease specialist. CT and MRI scanning, image directed stereotactic aspiration and craniotomy are necessary in most cases. Empiric antimicrobial therapy should be initiated on diagnosis include: Vancomycin, third generation cephalosporin, clindamycin, trimethoprim-sulfamerthoxazolemeropenem, metronidazole, fluroquinolone, and fluconazole.

KEYWORDS: Brain Abscess, Fungi, Antibiotic Therapy and Management

INTRODUCTION

Brain abscess is a focal, intracerebral infection that begins as a localized area of cerebritis and develops into a collection of pus surrounded by a well-vascularized capsule [1]. In the early days before the late 1800s, brain abscess was an almost uniformly fatal condition that was diagnosed before autopsy. Remarkable work of William Macewan led to breakthroughs in the treatment of this condition [2]. Before the advent of human immunodeficiency virus (HIV) infection, brain abscess accounted for 1500- to 2500 cases treated in the United States each year; the incidence was estimated at 0.3 to 1.3 per 100,000 people per year [3]. In most pediatric and adult series, a male predominance exists (a ratio of 2:1 to 3:1) with median age of 30 to 40 years, although the age distribution varies depending on the predisposing condition leading to the formation of brain abscess [3]. Brain abscesses are classified on the basis of the likely entry point of infection. The system allows clinicians to predict the most likely micro flora in the abscess and select the optimal antimicrobial therapy. Brain abscesses in human are quite uncommon. In experimental brain abscess models: induction of an abscess usually requires direct inoculation of organisms into the animal's brain, since brain abscess following experimental induced bacteremia is rare [4]. Although certain underlying brain pathologies such as previous stroke, intracereberal hematoma and an underlying neoplasm may serve as a nidus for abscess formation in most cases there is no apparent predisposing brain lesion [5, 6, 7]. Clinical presentation of brain abscess include: headache (70%). Nausea and vomiting (50%), seizures (25% -35 %), nuchal rigidity and papilledema (25%), focal neurologic deficit (50%)

and, fever (45%to 50%). Most patients also have mental status changes [8]. Mortality has ranged from 8% to 25 %; Poor prognostic factors have included poor Glasgow Coma Scale and the presence of underlying disease. In more recent series mortality have decreased with early diagnosis and the introduction of computed tomography (CT) scanning [9, 10]. Common pathogens isolated in the brain abscess include: *Streptococci* (aerobic, anaerobic and microaerophili, *S.milleri* (S.indermedius), *S.aureus*, *Bacteroides*, enteric gram negative bacilli, *Pseudomonas* spp, *H.influenzae*, *S.pneumoniae*, *L.monocytogenes*, fungi and protozoa [8]. Empiric antimicrobial therapy should be initiated dependent on diagnosis, radiologic studies or CT guided diagnosis (aspiration) include Vancomycin, third generation cephalosporins, clindamycin, trimethoprim-sulfamethaoxazole, aztreonam, metronidazol, fluoro-quinolone, and fluconazole for fungi. This paper reviews the current notions on bacterial brain abscess.

MICROBIAL ETIOLOGY OF BRAIN ABSCESS

Bacterial Brain Abscess

Streptococci are the bacteria most commonly (70%) cultured from patients with bacterial brain abscess, and they are frequently isolated from the mixed infections (30% to 60% of cases) [3]. These bacteria, especially the *Streptococcus anginosus* (*milleri*) and *S.indermedius* normally reside in the oral cavity, appendix, and female genital tract, and they have the proclivity for abscess formation. Although streptococcal brain abscess are seen most often in patients with oropharyngeal infections or infective endocarditis, they are also isolated after neurological or other medical procedures [11].

Staphylococcus Aureus Accounts for 10% to 20% of isolates. Usually in patients with cranial trauma or infective endocarditis, and is often isolated in pure culture, cases caused by community- associated methicillin-resistant *S.aureus* have been reported [12]. Attention to proper culture techniques has increased the isolation of anaerobes from brain abscesses, with *Bacteriodes*, and *Prevotella spp, i*solated in 20% to 40% of patients, often in mixed cultures [3]. Enteric gram –negative bacilli (e.g., *Proteus* spp, *Escherichia coli*, *Klebsiella* spp, and *Pseudomonas* spp) are isolated in 23 % to 33 % of patients, often in patients with otitic foci of infection with septicemia, who have had neurological procedures, or who are immune compromised.

At one center, *Klebsiella* was most prevalent pathogen (usually associated with hematogenous dissemination or post neurological states), followed by *Proteu*s and *Enterobacte*r spp. [13, 14]. In one review of 41 patients with autogenic brain abscess, *Proteus* was isolated in 41% of cases [15]. Multiple organisms are cultured in 14% to 28% of cases in patients with positive culture results [3]. The incidence of negative cultures has ranged from 0% to 43% in selected series [3].

Wide range of bacterial pathogens may be isolated in brain abscesses in selected patients or from immune compromised patients. Although *Haemophilus influenza*, *Streptococcuspnerumoniae* and *Listeria monocytogenes* are common etiologica agents of bacterial meningitis they are rarely isolated from patients with pyogenic brain abscesses (< 1 % of cases) [16]. Brain abscess accounts for about 10% of central nervous system (CNS) infections caused by *L.monocytogenes* [17]. In a review of 39 cases of Listeria brain abscess, 85% of patients had significant underlying condition (including leukemia, lymphoma, HIV infection, and various conditions requiring corticosteroids or other immunosuppression), and disease was often associated with concomitant meningitis (39% of cases) and bacteremia (86% of cases) [18].

***Salmonella* spp**. have rarely been reported to cause brain abscess, usually after bacteremia in the presence of some compromise of the reticuloendothelial system [19]. Cereberal abscess may also be a complication of neurologic infection with *Burkholderiapseudomallei* [20]. Actinomycosis of CNS may manifest brain abscess, usually secondary to hematogenous spread from a primary infection in the lung, abdomen, or pelvis, although contiguous spread from foci of infection in the ears, paranasalsinuses, orcervicofacial regions may occur [21].

Nocardial brain abscess is caused by *Nocardia asteroids* may occur as an isolated CNS lesion or as a disseminated infection in association with pulmonary or cutaneous disease [21]. In a series of organ transplant recipients with *Nocardia* brain abscess, use of trimethoprim-sulfametoxazole prophylaxis for *Pneumocysticjirovecii* (formerly *P.carinii*) was not shown to be protective against *No cardia* infection [22].

Mycobacterium tuberculosis and nontuberculous my cobacteria have been increasingly observed to cause focal CNS lesions, with several cases reported in patients with HIV infection [3, 23].

Fungal Brain Abscess

The incidence of fungal brain abscess has increased as a result of the prevalent administration of immunosuppressive agents, broad- spectrum antimicrobial therapy and corticosteroids [24].

***Candida* spp**

The diagnosis of fungal brain abscess id often unexpected and many cases are not discovered until autopsy. In autopsy studies, *Candida* spp. have emerged as the most prevalent etiologic agents; neuropathological lesions include micro abscesses, noncaseating granulomas, and diffuse glial nodules. Risk factors for invasive *Candida* infection include the use of corticosteroids, broad –spectrum antimicrobial therapy, and hyperalimentation.

Disease also seen in premature infants; in patients with malignancy, neutropenia, chronic granulomatous disease, diabetesmellitus, or thermal injuries, and in patients with catheter in place [25].

***Aspergillus* spp**

Intracranial seeding of *Aspergillus* species occurs during dissemination of the organism from the lungs or by direct extension from a site anatomically adjacent to the brain [26]. Cases of intracranial infection caused by *Aspergillus* spp. have been reported worldwide, with most cases occurring in adults. Cerebralaspergillosis is reported in 10% to 20% of all cases of invasive aspergillosis, and rarely is the brain the only site of infection [27].

Mucromycosis

Mucromycosis is one of the most fulminant fungal infections known [26]. Many predisposing conditions to mucromycosis have been described, including diabetes mellitus,(70% of cases)usually in association with acidosis, acidemia from profound systemic illnesses (e.g. sepsis, severe dehydration, severe diarrhea, chronic renal failure [25].

Pseudallescheriaboydii

CNS disease may occur in both normal and immune compromised hosts. This organism is being increasingly referred to as *Scedos poriumapiospermum*, the sexual form of P.boydii. The organism may enter the CNS by direct trauma, by hematogenous dissemination from primary site of infection, via an intravenous catheter, or direct extension from

infected sinuses [26]. Many etiologic agents of fungal meningitis may also cause brain abscess, e.g. Cryptococcus neoformans, Coccidioidesspp, *Histoplasmacapsulatum*, and *Blastmycesdermatiditis* [25].

Parasitic Brain Abscess

Various protozoa and heliminths have been reported to produce brain abscess, including *Trypanosomacruzi*, *Entamoebahistolyitica*, *Schistosoma* spp, and *Paragonimus* spp., *Neurocysticcercosis*, caused by the larval form of *Taneiasolium*, is a major cause of brain lesions in the developing world [28, 29].

PATHOGENESIS

Microorganisms can reach the brain by several different mechanisms [3]. The most common pathogenic mechanism of brain abscess formation spread from a contiguous focus of infection, most often in the middle ear, mastoid cells, or paranasal sinuses. Brain abscess occurring secondary to otitis media is usually localized to temporal lobe or cerebellum; in one review of 41 cases of brain abscess from anoctogenic source, 54% were in temporal lobe, 44% were in cerebellum, and 2% were in both location [15]. If antimicrobial therapy of otitis media is neglected, however there is an increased risk of intracranial complications [15]. Paranasal sinusitis continues to be an important condition predisposing to brain abscess. The frontal lobe is predominant abscess site, although when brain abscess complicates sphenoid sinusitis, the temporal lobe or sellaturcica is usually involved. Dental infections are a less common cause of brain abscess; infections of molar teeth seem most often to be the inciting factor. The frontal lobe is the usual site of the abscess after dental infection, but temporal lobe extension has also been reported [30].

Other mechanism of brain abscess formation is hematogenous dissemination from distant focus of infection. These abscesses are usually multiple and multilocated, and they have a higher mortality rate than abscesses that arise secondary to contiguous foci of infection [3]. The most common source of initial infection in adults are chronic lung pyogenic lung disease, especially lung abscess, bronchiectasis. Empyema, and cystic fibrosis. Brain abscess may also occur hematogenously from wound skin infections, osteomyelitis, pelvic infection, choleocystitis, and other intra –abdominal infections. Another predisposing factor leading to hematogenous acquired brain abscess is cyanotic congenital heart disease, which account for about 5% to 15% of all brain abscess cases, with higher percentage in some pediatric series [30].

Trauma is a pathogenic mechanismin the development of brain abscess. Brain abscess occurs secondary to an open cranial fracture with dural breach, or as a result of neurosurgery or a foreign body injury [31]. The incidence of brain abscess formation after head trauma ranges from 3% to 17% in military populations, where it is secondary to retained bone fragments or contamination of initially “sterile” missile sites with bacteria from skin, clothes, and the environments [32]. In a study of 160 war missile penetrating craniocereberal injuries in Croatia in which 21 skull base injuries were treated surgically. Three cases of brain abscess were seen for which repeat surgery was required [33]. Traumatic predisposing conditions to brain abscess in the civilian population (incidence of 2.5% to10.9% after trauma) include depressed skull fracture, dog bites, rooster pecking, tongue piercing, and, especially in children lawn darting and pencil tips [34].

CLINICAL PRESENTATION

A common misconception among physicians concerns the frequency with which fever is found during the initial clinical presentation of brain abscess. In some cases fever occurs in <50% of cases, and its absence should not be used to

exclude the diagnosis [35]. The course of brain abscess ranges from indolent to fulminant [3]. Most clinical manifestations are not due to systemic signs of infection, but rather to the size and location of a space occupying lesions within the brain, and the virulence of the infecting organism. Headache is the most common presenting symptom, and is observed in an average of 70% to 75% of patients. Headache may be moderate to severe and hemicranial or generalized in location, but it lacks particularly distinguishing features for frequent delays in diagnosis. Sudden worsening of the headache, accompanied by a new onset of meningimus, may signify rupture of the abscess into ventricular space, this complication is often associated with high mortality rate (85% in some cases), [36]

Location of the brain abscess defines the clinical presentation [3]. Patients with frontal lobe abscess often present with headache, drowsiness, inattention, deterioration of mental status, hemiparesis with unilateral motor signs, and a motor speech disorder.

Hemiparesis with unilateral motor signs, and a motor speech disorder [37]. Patents with *Aspergillus* brain abscess most commonly manifest signs of a stroke (secondary to ischemia of intracereberal hemorrhage or both) referable to the involved area of brain [25]. Rhinocereberalmucromycosis initially manifests with complaints referable to the eyes or sinuses, including headache (often unilateral) facial pain, diplopia, lacrimation, and nasal stuffiness or epistaxis. Fever is usual [25].

The clinical manifestations of CNS disease caused by *Cryptococcus*, *Histoplasma*, *Coccidioides*, *Candida*, and other fungal pathogens depend on the intracranial location of abscess. In one view, nearly one third of bone marrow transplant recipients with brain abscess caused by Candida spp., no sign of or symptoms; these infections were commonly diagnosed postmortem [38]. Patients with acquired immunodeficiency syndrome (AIDS) and toxoplasmic encephalitis often presents sub acutely with nonspecific symptoms, such as neuropsychiatric complaints, headache, disorientation, confusion, and lethargy progressing over 2 to 8 weeks; associated fever weight loss are common [39].

DIAGNOSIS AND MANAGEMENT

The initial approach to the patient with a suspected brain abscess is a multidisciplinary one and should include neuroradiologist, a neurosurgeon, and infectious disease specialist [40]. The diagnosis of brain abscess was revolutionized by the availability of CT, which is excellent for examining the brain parenchyma and the paranasal sinuses mastoid, and middle ear [8, 41]. Typical CT reveals a hypodense lesion with a peripheral uniform ring of contrast enhancement. There may be surrounding hypodense area of brain edema. MRI is now the first imaging procedure of choice for patients suspected of having this disorder. RI offers significant advantages over CT including the early detection of cerebritis, detection of cerebral edema with greater contrast between edema and brain, more conspicuous spread of inflammation into the ventricles and subarachnoid space, and earlier detection of satellite lesions. Administration of the paramagnetic agent gadolinium diethylenetriaminepenta-acetic acid permits clear differentiation of the central abscess, surrounding enhancing rim, and cerebral edema. [42].

Noninvasive studies e.g, CSF examination, CT, MRI for the diagnosis of fungal brain abscess usually are nonspecific, although some exceptions do exist. For example the finding of a cerebral infarct in a patient with factors for invasive aspergillosis suggests that diagnosis; such an infraction typically develops into either single or multiple abscesses.

In rhino- cerebral mucromycoses, CT and MRI typically show sinus opacification, erosion of bone, and

obliteration of deep fascial planes; cavernous sinus involvement may also be seen on MRI, In injection drug users with cerebral mucromycosis, the most frequent site of CNS disease is the basal ganglia [26].

Definitive diagnosis of fungal brain abscess requires biopsy with appropriate fungal stains. The mucicaramine stain will specifically identify *C.neoformans. Aspergillus* species appear as septate hyphae with-angle dichotomous branching, whereas typical nonseptate hyphae with right angle branching are seen in mucromycosis. *P.boydii* appears as septate hyphae in clinical specimens, although the hyphae are narrower and do not show the dichotomous branching seen in aspergillosis. Fluorescent antibody staining is also a sensitive method for identifying *P.boydii* [26].

Laboratory Workout

When a brain abscess is suggested by radiologic studies, a microbiologic diagnosis ideally should be made to guide antimicrobial therapy. CT has made it possible to perform stereotactically guided abscess aspiration. Specimens should be sent for Gram- stain, aerobic and anaerobic cultures. Ziehl –Nelsen stain for *Mycobacteria*, modified stain for *Nocardia*, and silver stain for fungi. Cultures for *Mycobacteria*, *Nocardia*, and fungi to be performed [8].

ANTIMICROBIAL THERAPY

Empiric Antibiotic Therapy

In patients with bacterial brain abscess, once a diagnosis is made either presumptively by radiologic studies or by CT-guided aspiration of the lesion, antimicrobial therapy should be initiated. If an aspiration cannot be performed or if Gram staining in unrevealing, epiric therapy should be initiated based on the presumed pathogenic mechanism of abscess formation e.g. Otitis media or mastoid, Sinusitis frontoethmoidal or spheroidal, dental abscess, penetrating trauma or postneurosugery, Congenital heart disease, lung abscess, empyema, bronchiectasis, and bacterial endocarditis.

Antimicrobial regimen include: Metronidazole plus third generation cephalosporin, Vancomycin plus metronidazole plus third generation cephalosporin, Penicillin plus metronidazole, Vancomycin plus third generation cephalosporin, and Vancomycin plus gentamicin or nafcillin plus ampicillin plus gentamicin [8, 41, 43].

Antibiotic Therapy

With confirmed pathogen. If positive cultures are obtained, antimicrobial therapy can be modified for optimal treatment. High- dose intravenous antimicrobial therapy should be continued for 6 to 8 weeks; this often is followed by oral antimicrobial therapy if appropriate agents are available. A shorter course of therapy (i.e. 3 to 4 weeks) may be appropriate for patients who have undergone complete surgical excision of the abscess [8, 41, 43].

Surgical Therapy

Most bacterial brain abscesses require surgical incision for optimal therapy. Abscess aspiration by stereotactic CT guidance affords the surgeon rapid, accurate, and safe access to virtually any intracranially location and allows for swift relief of increased intracranial pressure. However, aspiration has the major disadvantage of incomplete drainage of multiloculated lesions [8, 41, 44]

CONCLUSIONS

Brain abscess a fatal disease. Recent advances in the diagnosis, management, CT and MRI scanning, antimicrobial therapy and stereotactic brain aspiration techniques have reduced the mortality. High clinical suspicion is required and appropriate empiric antibiotic therapy should be instituted.

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