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Imaging Appearances, Diagnosis and Treatment of Atypical Brain Abscesses: Review of the Literature

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Authors' contributions

This work was carried out in collaboration between both authors. Author KAM as the primary author put together this work and did the entire write up of this manuscript. Author HA did a thorough review of the facts, presented and edited the work. Both authors read and approved the final manuscript.

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Review Article

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ABSTRACT

Introduction: Atypical brain abscesses mostly occur in immuno-compromised patients especially in various endemic regions of the world. The atypical imaging appearances as well as other diagnostic difficulties cause delays in making diagnoses and hence prognosis is generally very poor. Outcomes can be improved if the clinician has a high index of suspicion in a patient with positive risk factors and suggestive radiological appearances. This will enable early institution of appropriate therapy to improve outcomes.
Methods: A review of existing English literature was done by performing a PubMed search. The various imaging appearances of atypical brain abscesses are described and recommendations made to aid early diagnosis and treatment of atypical brain abscesses.
Results and Discussion: The clinical features of atypical brain abscesses are mostly insidious

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and non- specific and occur frequently with a medical background of obvious or latent immunodeficiency. The imaging appearances of atypical brain abscesses including Brain CT and MRI scans can be very atypical and non-specific but with the application of modalities like Diffusion Weighted Imaging (DWI) and MR Spectroscopy, atypical brain abscesses can be differentiated from pyogenic bacterial brain abscesses, granulomas and brain tumours.
Microbiological identification has also progressed with advances in molecular microbiology, nuclear medicine and immunology, making differentiation of the various causative organisms of atypical brain abscesses possible and more readily.
Clinical management relies upon early surgical drainage or excision and early use of intravenous antimicrobial agents adapted to the strains identified. Most fungal species are susceptible to Amphotericin B, Voriconazole, Caspofungin, Itraconazole and to a lesser extent Fluconazole. Nocardia species are treated with Cotrimoxazole, Amikacin and Linezolid whilst Toxoplasmosis can be successfully treated with Pyrimethamine and Sulphadiazine or Clindamycin. Actinomyces abscess can be treated with Penicillins and Mycobacterium abscesses are treated with antituberculous agents- Isoniazid, Pyrizinamide, Rifampicin and Ethambutol. Adjuncts to therapy include CSF diversion, corticosteroid and antiseizure medications.
Conclusion: A high index of suspicion, careful reviews of radiological images, early pus/abscess wall samples obtained by drainage, biopsy or surgical resection are needed to establish a definitive microbiological diagnosis and prompt administration of appropriate antimicrobial agents will improve outcomes of atypical brain abscesses.

Keywords: Atypical brain abscesses; immunosuppressed; Immunocompromised; immunodeficient.

ABBREVIATIONS

HIV : Human Immune Deficiency virus
AIDS : Acquired Immunodeficiency Syndrome
CT : Computed Tomography
MRI : Magnetic Resonance Imaging
DWI : Diffusion Weighted Imaging
ADC : Apparent Diffusion Coefficient
MRS : Magneti Resonance Spectroscopy
MTB : Mycobacterium Tuberculosis
MAI : Mycobacterium avian complex
FDG-PET : Fluoro-deoxy-glucose Positron Emission Tomography
PCR : Polymerase Chain Reaction
IFA : Immunofluorescence Assay
CD4 : Cluster of Differentiation 4
CNS : Central Nervous system
NAA : N-acetyl aspartate
MT-MRI : Magnetic Transfer Magnetic Resonance Imaging

1. INTRODUCTION

Atypical brain abscesses are basically brain abscesses caused by microbial organisms other than pyogenic bacteria [1]. These include Tuberculous abscesses, fungal abscesses like Aspergillosis and Blastomycosis, Actinomyces abscesses, Nocardia and parasitic abscesses like Toxoplasmosis [1].

The road to making definitive diagnoses from patients' medical histories, physical examination findings, imaging and microbiology investigations, have in most cases not been easy. A better insight into the different clinical presentations of atypical brain abscesses, imaging characteristics, microbiological growth patterns and antimicrobial sensitivity patterns will facilitate early diagnoses and prompt treatment to reduce morbidity and mortality.

There has been an insurgence of tuberculosis in the advent of HIV/AIDS. Approximately a quarter of the world's population is infected with tuberculosis and 1.5 million people worldwide are infected with tuberculosis each year [2-4]. Each Tuberculosis infected individual is likely to infect 10-15 new persons each year [2]. In South Africa, there is a significantly high prevalence of tuberculosis in the Western Cape Province including multidrug resistance forms. Global prevalence of Mycobacterium tuberculosis(MTB) in 2010 was estimated by the WHO at 178/100,000 population and Africa with a prevalence of 332/100,000 population accounted for 24% of all reported prevalent cases in the same year [3,4]. The prevalence of MTB in South Africa in 2010 was estimated at 795/100,000 population and Western Cape Province, the most affected region in the country had an incidence rate as high as 909/100,000 [3,4]. In 2015, WHO estimated 10.4 million new cases of MTB worldwide and South Africa is one of the six countries that accounted for 60% of all the new cases worldwide [5]. Primary infection is mostly via the respiratory tract by an acid fast bacillus,

Mycobacterium tuberculosis. Reactivation infection is also not uncommon. Central nervous system (CNS) tuberculosis infection, like other extra-pulmonary infections and therefore Tuberculous abscess is by hematogenous spread with dissemination usually from a primary pulmonary disease [1]. Not coincidentally, there are more than 5 million people living with HIV in South Africa.

Nocardia infection is primarily caused by Nocardia asteroides, a soil-borne gram positive and partially acid fast staining aerobic actinomycete that is usually inoculated through the respiratory tract [1,6]. Central Nervous System involvement and therefore abscesses are via hematogenous spread [1]. Nocardia is known to constitute 2% of all brain abscesses and more frequently occurs in immunosuppressed individuals [1].

Actinomyces and Aspergillus species are mostly isolated from soil and plants in most regions of the world [1]. They however can cause infection in humans especially in the setting of immunosuppression primarily through the respiratory tract and cause cerebral abscesses through dissemination and hematogenous spread [1].

Toxoplasmosis infection caused by Toxoplasma gondii is mostly acquired by contact with feline faeces [1]. It usually causes infection in severely immunosuppressed persons like HIV/AIDS individuals with very low CD4 counts. Dissemination and hematogenous spread may eventually result in cerebral abscesses.

Blastomyces dermatiditis is a dimorphic fungus which can cause a serious and sometimes fatal disease in humans [7,8]. The route of primary infection is by inhalation. There can be pulmonary or extra pulmonary manifestations or both. Clinical involvement of the Central Nervous System accounts for 5%-10% of extra pulmonary cases [7,8]. Central Nervous System (CNS) Blastomycosis may manifest on Magnetic Resonance Imaging (MRI) and Computed Tomography (CT) Brain scans as an epidural abscess, meningitis or intra-parenchymal mass lesion. This infection mostly occurs in immunosuppressed individuals mostly by way of primary exposure or reactivation [7,8]. Blastomycosis is however not recognized as an AIDS defining illness and unlike other systemic dimorphic mycosis it does not have a more common occurrence among people infected with HIV [7,8]. However, when a severely immunosuppressed individual acquires Blastomycosis, it is usually more severe and multi-systemic including CNS involvement [7,8].

Atypical brain abscesses have frequently been diagnosed and treated by many Departments of Neurosurgery in South Africa and elsewhere. The road to making definitive diagnoses from patients' medical histories, physical examination findings, imaging and microbiology investigation results, have in most cases not been easy. A better insight into the different clinical presentations of atypical abscesses, imaging characteristics, microbiological growth patterns and antimicrobial sensitivity patterns will go a long way to aid the selection of appropriate prompt treatment regimens for patients with suspected atypical brain abscess to reduce morbidity and mortality.

The recommended treatment for CNS fungal infections in most clinical reviews is amphotericin B deoxycolate or its lipid formulation for 4-6 weeks followed by a 6 months course of an azole therapy, preferably Voriconazole. Itraconazole and Fluconazole are also credible alternatives to Voriconazole, despite concerns about the relatively poor concentrations achieved in the CNS. Higher doses of Itraconazole and Fluconazole have been shown to be effective in the treatment of CNS Blastomycosis.

2. METHODS

A review of the English literature via the Pubmed Database was done with the following search terms: *atypical brain abscess, atypical brain abscess imaging, atypical brain abscess treatment, Nocardia brain abscess, Blastomyces brain abscess, TB brain abscess, Toxoplasma brain abscess, fungal brain abscess, aspergillus abscess*. The various presentations and imaging appearances were discussed and recommendations made for making early diagnosis and institution of early appropriate treatment of atypical brain abscesses. All relevant references from the evaluated literature were included.

3. RESULTS AND DISCUSSION

3.1 Epidemiology and Risk Factors

3.1.1 Mycobacteria CNS infections

Mycobacterium avium-intracellulare (MAI) complex is a common opportunistic infection that generally occurs in HIV-AIDS with CD4 cell

counts less than 75 and especially in those who are non-compliant with the recommended once a week prophylaxis regimen of a macrolide [9]. Other immunosuppressed patients like transplant patients are also susceptible to MAI infection [9]. In the advent of HIV-AIDS, there is a resurgence of tuberculosis. Most cases of Central Nervous System tuberculosis are due to hematogenous spread from extracranial locations like the lungs [9,10].

Mycobacterium tuberculosis brain abscess is a rare form of Central Nervous System (CNS) tuberculosis that usually occurs mostly in the supratentorial compartment of the brain. There are however reports of cerebellar tubercular abscesses [9,10]. They are mostly associated with immunodeficiency states. The relatively more common extra pulmonary CNS tuberculosis (TB) manifestations are TB meningitis and tuberculomas (TB granulomas). TB brain abscess can occur at any age even though it frequently occurs in the third and fourth decade of life [9,10]. It constitutes 35% of multiple brain abscesses and the frontal lobe happens to be the most predominant supratentorial location [9,10]. Evidence of extra CNS tuberculosis occurs in 85% of cases [9,10]. TB brain abscess occurs in about 4%- 8% of patients with CNS Tuberculosis who are HIV negative but in 20% of patients who are HIV positive. TB brain abscess constitute 4% of intracranial abscesses [9,10].

3.1.2 Fungal CNS infections

Fungal infections of the CNS occur rarely in the general population and are invariably secondary to a primary focus elsewhere, usually in the lung or intestine. These fungal infections therefore most frequently occur in immunocompromised patients such as AIDS patients, people with longstanding diabetes or after organ transplantation. Intracranial fungal infections are now being diagnosed more frequently due to increased incidence of HIV infection, increased life span of HIV-AIDS patients, more sophisticated radiological investigations, more sensitive microbiological techniques as well as better critical/intensive care services provided to severely ill and moribund patients [11]. The most common CNS fungal infection is Cryptococcus followed by aspergillus and candidiasis [11].

CNS Aspergillosis is a rare condition but has a worldwide distribution pattern [11]. Most cases have been reported in adults, although the disease is also seen in children and neonates. The infection may spread directly to the brain from the nasal sinuses or spread hematogenously from the lungs and gastrointestinal tract. It may on rare occasions contaminate the operative field during neurosurgical procedures [11]. In immunosuppressed patients, CNS Aspergillosis usually occurs as part of a disseminated infection. Aspergillus brain abscess formation is but only one of its several CNS manifestations. Other Aspergillus CNS manifestations include granulomas (aspergillomas), meningitis, infarction and mycotic aneurysms [11]. Most cases are solitary. There have however been reports of cases of multiple Aspergillus brain abscesses. The anterior and middle cranial fossae are more frequently involved and rarely involve the cerebellum. Frequent abuse of antibiotics may be a risk factor [11].

Infection with Cryptococcus neoformans occurs primarily in immunosuppressed patients. However, 30% of this infection has been shown to occur in individuals with no predisposing conditions [11]. Men are noted to be more commonly infected than women [11]. CNS infection is mostly due to hematogenous spread from the lungs. Brain parenchymal involvement may manifest as a granuloma (cryptococcoma), dilated Virchow- Robin spaces (pseudocyst) or post contrast enhancing cortical nodules [11].

Mucormycosis is a life threatening opportunistic fungal infection caused by the mucoraceal family which includes Rhizopus oryzae. It may spread to the brain directly from the nasal sinuses or by way of hematogenous spread. Diabetes accounts for at least 70% of reported cases and less than 5% occur in normal hosts [11]. Acidosis appears to be an important predisposing factor. The infection can also be seen in susceptible individuals like intravenous drug abusers, anaemic patients, leukaemic patients, uraemic patients, severe burns and in those receiving corticosteroids or chemotherapy [11]. The most common form is the rhinocerebral form. A study comparing the frequency of involvement of the basal ganglia in drug abusers and non-drug users showed involvement of the basal ganglia in 82% of drug abusers whilst non drug abusers showed basal ganglia involvement in only 9% of cases [11].

Blastomycosis caused by Blastomyces dermatitidis is endemic in Southwestern and Central United States [11]. CNS involvement is by way of direct extension from the sinus or

orbital infection or from a more distant site via hematogenous spread. CNS involvement occurs in 4% of patients with Blastomycosis [11]. Unlike other fungal infections it is not noted to have a particular predilection for immunocompromised patients and is not an AIDS defining infection [11]. Reports of Blastomycosis in individuals infected with HIV are however increasing [11].

Coccidioidomycosis is caused by a dimorphic fungus, Coccidioides immitis and is endemic in semiarid regions of the world especially the Southwestern United States and Northern Mexico [11]. There is increased incidence in such endemic areas after severe dust storms. Incidence may also increase during archeological expeditions when the soil is disturbed [11]. It exists in myceal forms within the soil and becomes infective when airborne athrospores are inhaled. Approximately 4%- 5% of patients develop disseminated disease and this is more common in immunocompromised patients [11]. CNS involvement usually occurs by way of hematogenous spread from the lungs. Focal Coccidioides brain abscesses however occur uncommonly in HIV patients [11].

Histoplasmosis caused by a dimorphic fungus Histoplasma capsulatum is endemic in the upper Mississipi River and Ohio River valleys in the United States [11]. This fungal infection is the first manifestation of AIDs in 50%- 75% of patients [11]. CNS involvement is diagnosed clinically in 5%- 10% of cases of progressive disseminated histoplasmosis but autopsy studies report a higher percentage of up to 25% [11].

Disseminated Candidiasis incidence is on the rise due to an increase in the numbers of immunosuppressed patients. Other risk factors for acquiring this infection include lengthened Intensive care unit stay, total parenteral nutrition, the use of multiple antibiotics, infant prematurity, corticosteroid use, chemotherapy and following organ transplant particularly during acute rejections [11]. CNS involvement is reported in 18%- 52% of disseminated Candidiasis [11]. Brain abscess formation occurs as a result of focal necrosis around a microcirculation mainly in the middle cerebral artery territory [11]. Multiple abscesses may however be encountered. It has also been reported that fungi cause more than 90% of brain abscesses in immunocompromised transplant patients with a mortality rate of up to 97% being reported despite aggressive surgery and antifungal therapy [11].

3.1.3 Other atypical CNS infections

Nocardia brain abscess accounts for 2% of brain abscesses [6,12]. It is a rare opportunistic infection which is mainly reported in immunosuppressed patients [12].

Toxoplasmosis is the most common infection in immunsuppressed patients [13]. Acute Toxoplasma infection occurs in AIDS patients and after bone marrow transplantation. Toxoplasma brain abscesses are typically multiple even though atypical large solitary abscess has also been reported [13].

Actinomycosis is a subacute or chronic bacterial infection which most often than not affect immunodeficient subjects. CNS involvement is rare [14].

3.2 Clinical Presentation

The clinical presentation of atypical brain abscesses may be very non-specific. It is therefore imperative that clinicians maintain a high level of suspicion especially in susceptible patients with risk factors for acquiring the infection and from areas highly endemic for the various infections.

Patients may present with symptoms and signs of an intracranial space occupying lesion which includes focal neurological deficits depending on the location of the lesion, seizures of any type, cranial nerve palsies, alterations in level of consciousness, mental status changes, speech problems, cerebellar and brainstem signs [1]. Patients may present with features of increased intracranial pressure from mass effect from the abscess and surrounding oedema or associated hydrocephalus which may include vomiting, headaches and papilloedema on fundoscopy.

Patients with systemic or disseminated infection with Mycobacterium tuberculosis or avium complex may also present with constitutional symptoms and signs of the disease [9]. These symptoms include night sweats, weight loss, cough and other features of pulmonary and gastrointestinal involvement [9].

Fungal abscess may also present non-specifically and may manifest in various ways. Features may be suggestive of nasal sinus involvement, pulmonary and gastrointestinal involvement [11]. Other clinical features may be suggestive of meningitis and subarachnoid

hemorrhage which may be similar to features of mycotic aneurysmal ruptures [11]. Paranasal sinus disease may extend into the orbit resulting in proptosis, ocular palsies, visual deterioration, chemosis and even features suggestive of cavernous sinus thrombosis [11]. Features may also be that of otomastoiditis including ear pain and hearing impairment.

Nocardia and Actinomyces abscesses may also present with features of systemic disease [14,15]. There may be cutaneous and pulmonary manifestations in addition to the features of CNS involvement. The clinical features are mostly insidious in onset, non-specific and mostly occurs with a medical background of obvious or latent immunodeficiency [14,15].

Toxoplasmosis may present with only features suggestive of CNS disease [1].

The non-specific nature of presentations of atypical brain abscesses therefore, makes their diagnoses difficult in most cases. Hence the background medical information, history of obvious or latent immunodeficiency state as well as the endemicity of the area with respect to the suspected infection are very important in making an early diagnoses. A high index of suspicion is thus to be maintained by clinicians as the outcome of any management is highly dependent on the promptness in making the correct diagnosis and institution of the correct treatment.

3.3 Diagnosis: Imaging and Laboratory

Radiological imaging of the brain supported by microbiological, histological and other laboratory investigations constitutes the various arms of the investigative aspect of management. Most of these are directed by the clinical features at presentation as captured in the history and physical examination taking good cognizance of the patient's geographical area, occupation and other risk factors.

The diagnosis of atypical brain abscesses can be very difficult hence the delays encountered in the diagnosis making process in many cases worldwide and therefore the poor outcomes generally reported in literature. The imaging findings can be very non-specific and atypical, laboratory tests can be unrewarding, history and physical examination findings are also unspecific. The history is however more likely to be more insidious and longer compared with pyogenic brain abscesses.

3.4 Imaging Appearances

Typical imaging appearances of pyogenic bacteria brain abscesses as shown in Fig. 1 are as follows: Brain CT- mostly a lesion with a hypodense centre and a post contrast enhancing ring with possible surrounding hypodense area suggestive of oedema [16]. The abscess wall shows enhancement after administration of contrast [16].

MRI as shown in Fig. 2- Central portion of abscess is typically hypointense on T1 weighted images (T1WI) and hyperintense on T2 weighted images (T2WI) with a hyperintense surrounding vasogenic oedema [16]. The abscess wall shows ring enhancement following intravenous gadolinium (Gd) administration. As the abscess matures, the capsule shows decreased T2 signal. On diffusion weighted images (DWI) as depicted in Fig. 3 of this text, pyogenic abscesses are typically hyperintense indicating decreased diffusion of water molecules. This is due to increased viscosity of pus which contains cellular debris, bacteria and large molecules such as fibrinogen which bind water molecules and increase the diffusion restriction [16,17]. Confirmation of this increased diffusion restriction is then made with apparent diffusion coefficient (ADC) map where abscesses have low signal [17].

Magnetic Resonance Spectroscopy (MRS) of pyogenic brain abscess shows cytosolic amino acid peaks, acetate peaks, succinate peaks and absence of choline peaks. FDG- PET shows increased glucose uptake [18].

It is also necessary to further differentiate the appearance of an atypical abscess like a TB brain abscess from a tuberculoma. The usual appearance of a tuberculoma as depicted in Fig. 4 of this text is as follows: Early lesions are usually isointense on T1WI and T2WI and have variable Gd enhancement. Mature lesions have ring enhancement on post Gd T1WI and low signal centrally on T2WI (target sign). Normal DWI signal is common even in mature tuberculoma. DWI may also be hyperintense [17,19].

Mycobacterium brain abscess may appear as follows: smooth, lobulated or crenated walls with no intracavitary projections [19]. Brain CT appearance – hypodense core with variable ring enhancement after contrast administration with or without surrounding hypodense area of

oedema [19]. MRI- TB brain abscesses generally have T1 hypodense and T2 hyperdense core and a capsule which may enhance after Gd administration. DWI shows little or no restriction of water molecules with low ADC signal [18]. MRS- lipid and lactate peaks without the succinate, acetate or amino acid peaks seen in pyogenic abscesses. Magnetization transfer (MT) MR ratio from the wall is lower than for pyogenic abscess walls [18].

Nocardia brain abscess imaging appearance is as follows: Brain CT may show a hypodense core lesion with post contrast ring enhancement with or without loculations or multiplicity [15]. MRI- T1WI hypodense central core with thick ring enhancing walls after Gd administration and T2WI hyperintense central core. FDG- PET shows marked glucose hypermetabolism with maximum uptake values of approximately 11 [15]. DWI may be hyperintense. Typical locations includes the brainstem, basal ganglia, frontal, parietal and occipital lobes. Cerebellar and spinal locations are uncommon.

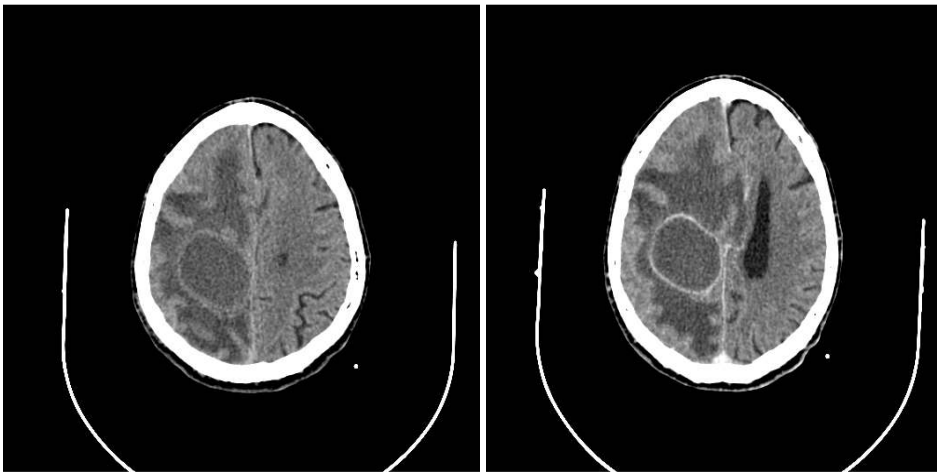

Fig. 1. CT brain appearance of a typical pyogenic bacterial brain abscess- non-contrast enhanced image labeled A and post contrast labeled B showing ring enhancement of a right parietal brain abscess

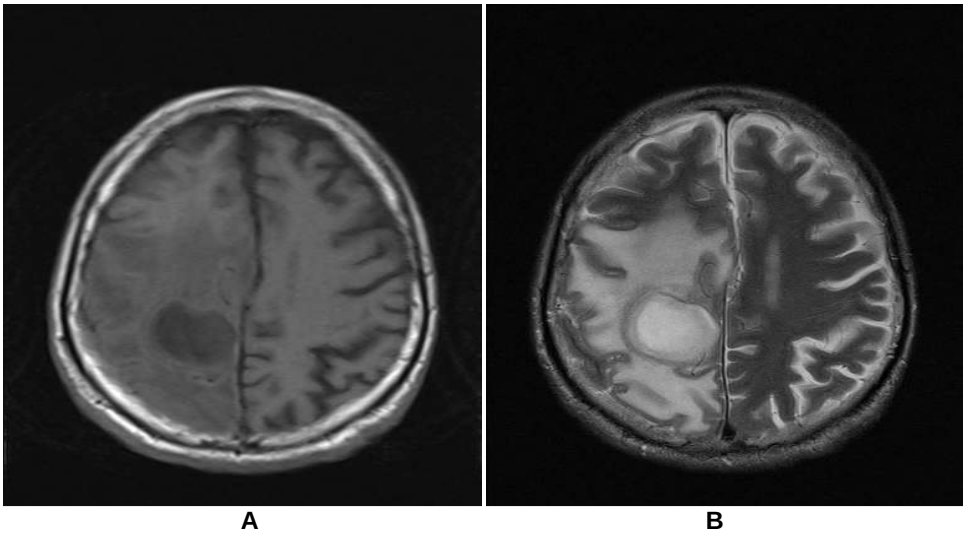

Fig. 2. T1WI (labeled A) and T2WI (labeled B) of the right parietal pyogenic brain abscess- dark centre on T1 and bright center on T2

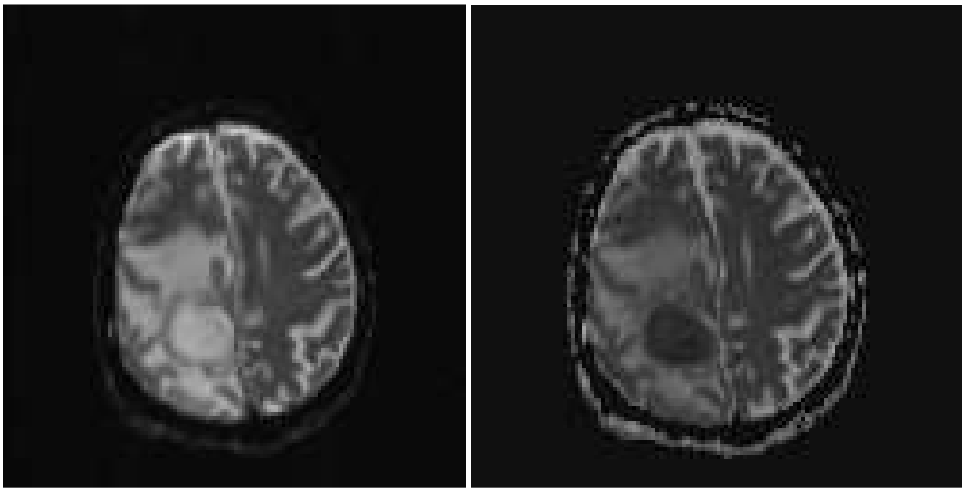

Fig. 3. Trace DWI (labeled A) and ADC (labeled B) showing restriction of water molecules with a hyper intense core on Trace compared with the ADC map. Note the low signal intensity rim around the central core on DWI which is thought to be secondary to susceptibility artifact from local free radicals and indicates a mature abscess

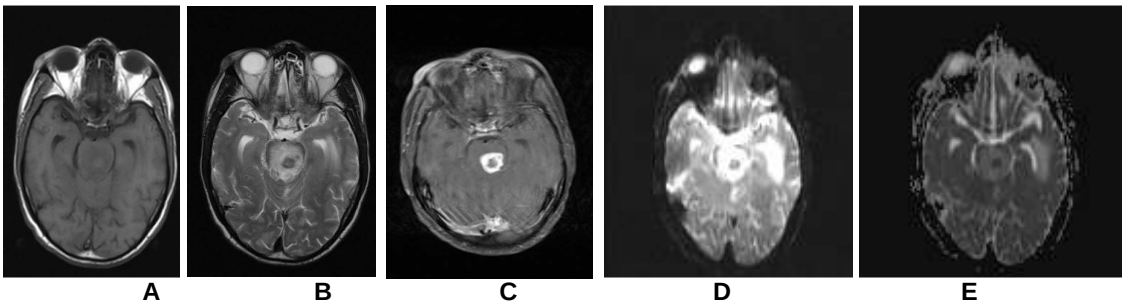

Fig. 4. Images show a tuberculoma in the pons- T1 isointense(A), T2 hypointense core (B), post Gd ring enhancement (C), Trace DWI hypointense with no restriction of water molecules (D)and ADC map (E)

Toxoplasmosis may appear in most cases as multiple ring enhancing or solid lesions on Brain CT and Brain MRI scans [13]. Calcified lesions may also be found [13]. In severe immunosuppression, MRI appearance can be completely atypical, an appearance which can mislead radiologists and clinicians [13]. In fulminant encephalitic variants of the disease, lesions are notably widespread on T2WI and are completely devoid of enhancement [13]. In these cases, appropriate therapy may have to be started until the diagnosis have been clarified further. Also in cases of atypical large solitary toxoplasma lesions showing marked enhancement resembling lymphoma, the clinician must look for additional diagnostic modalities other than conventional imaging while treating the patient for Toxoplasmosis. DWI appearance may be variable [13]. DWI with ADC map is useful in differentiating toxoplasmosis from lymphoma in AIDS patients. DWI mostly shows no restriction of water diffusion in the core tissue. However Toxoplasma brain lesions may be hypointense, isointense or hyperintense on DWI. Perfusion studies demonstrate an extremely hypovascular lesion. MRS shows a predominant lipid peak [13]. Thalium-201 brain SPECT helps in differentiating Toxoplasma lesions from a lymphoma. There is marked uptake in the case of lymphoma in contrast to Toxoplasma abscess which does not show this pattern of uptake [13]. TB abscess may also show increased uptake.

In an article by Miguel et al. [13] which looked at CT and MR images of Cerebral Toxoplasmosis

compared to other differentials in AIDS patients, 94.9% of Toxoplasma lesions were round shaped, 94.5% had ring or nodular enhancement, 81.3% were multiple lesions, 60.2% of the lesions were localized at the cerebral cortical or corticomedullary junction (all the cases showed at least one lesion in this location), 34.6% were less than 1 cm in diameter. On non-enhanced CT, 91.3% of the lesions were hypodense. On T2WI MRI, 53.4% of the lesions had at least one hypodense zone on T2WI. The existence of target shaped lesions with hypo-intense centre on T2WI (29.3% of observed lesions) is also suggestive of Cerebral Toxoplasmosis. The visualization of iso/hyperintense lesions on non- enhanced CT or irregular shaped lesions is uncommon in Toxoplasmosis. The finding of a solitary lesion of CT or MR is not by itself a good criterion for making a differential diagnosis [13].

Actinomyces brain abscess imaging appearance may show multiloculated ring enhancing abscesses on post contrast CT and MR images [14].

The imaging appearances of fungal brain abscesses are often non-specific and frequently mistaken for TB, pyogenic bacteria abscesses or brain tumour mostly due to lack of appropriate inflammatory response.

Several patterns of Aspergillus infection have been reported using CT and MRI: oedematous lesions, hemorrhagic lesions, solid enhancing lesions and ring enhancing lesions. MRI may show a typical T1 hypodense and T2 hyperdense central core with ring enhancement after Gd administration [11,20]. DWI may show water diffusion restriction with hyperdensity and corresponding ADC map hypodensity [16,17,20]. MRS may show elevation of glutamine-glutamate, lactate and amino acids at the central non enhancing part of the Aspergillus brain abscess [18,21]. MRS in solid lesions of Aspergilloma is non- specific with high choline, low creatine and lactate and no N-acetyl aspartate (NAA) peak.

Associated CT appearance of Aspergillosis sinusitis has been described as a hyperdense mass lesion from the wall of the sinuses with calcification. Adjacent bony structures may show areas of erosion or sclerosis [21]. Aspergillosis of the sinus is also hypointense on T1 and T2 (can be mistaken for air) MRI.

Aspergillus brain abscess generally appear as hypointense on CT with accompanied hemorrhagic change, hypointense on T1WI (but in some cases high signal intensity) and on T2, the lesions are of low signal intensity at the periphery corresponding to hemorrhage and can be seen on gradient echo T2WI [11,17,20]. Zeinreich et al. demonstrated that areas of low signal intensity on T2WI are traced to the presence of iron, manganese and magnesium in the fungal structures. Aspergillus abscess have a dense population of hyphal elements on the periphery with few centrally. On DWI, the abscess appears hyperintense centrally and the rim may appear hypointense caused by hemorrhagic or iron products.

Cryptococcal pseudocysts (soap bubble lesions) may be seen or circumscribed , round to oval low density lesions may be seen on CT with cerebrospinal fluid (CSF) intensity on both T1WI and T2WI which does not enhance after Gd [11]. The appearance of clusters of these cysts in the basal ganglia and thalamus is strongly suggestive of cryptococcal infection [11]. Cryptococcomas may present as masses of variable density on CT and are hypointense on T1WI but hyperintense on T2WI and may show post contrast enhancement [11]. Immunocompetent individuals with good immunologic reaction are more likely to present with cryptococcomas. Cryptococcal infection is also notably associated with meningeal enhancement [11]. On DWI cryptococcoma appear with hypointense central cavity and mimics a necrotic brain tumour rather than a pyogenic abscess [11,17]. MRS may show increased lactate and decreased NAA, choline and creatine [11].

The imaging findings of mucormycosis include dense opacification of the paranasal sinuses with variable mucosal thickening and a usual absence of fluid levels. MRI imaging characteristics are variable [11,21]. Associated abscesses may show contrast ring enhancement on CT and MRI. As reported by Siegal et al there is elevated lactate levels, depleted NAA and the presence of succinate and acetate in Mucormycosis without the commonly seen elevations of valine, leucine and isoleucine observed in bacterial abscess on MRS [21]. Diffusion restriction with ADC values have been noted to be similar to that for pyogenic abscesses. Infarction may also be associated with this infection [21].

Blastomycosis findings on Brain CT and MRI are non- specific. CT shows the presence of an isodense or hyperdense lesion with surrounding oedema and shows variable enhancement after contrast [11]. On MRI, most granulomatous lesions are hyperintense on T2WI. However, dural lesions can be isointense or hypointense on both T1WI and T2WI with marked enhancement after contrast [11]. MRI appearance of Blastomyces abscess is generally indistinguishable from other causes of brain abscess making isolation of the organism a requirement for its diagnosis. Serologic tests are typically negative and therefore not useful [11].

Coccidioidomycosis lesions are mostly granulomatous lesions. The imaging appearance pattern is thus similar to other granulomatous lesions on CT and MRI as described above [11].

The imaging features of CNS Histoplasmosis are non- specific. CT is abnormal in about 90% of cases. They usually appear as enhancing mass lesions with associated cerebral atrophy or hydrocephalus [11]. On MR, the lesions are hyperintense on T2WI and hypointense on T1WI with perilesional oedema and ring enhancement. The abscess rim may be hypointense on T2WI due to the presence of paramagnetic free radicals in its walls. Diffuse leptomeningeal enhancement may also be an imaging feature [11].

Candida species mostly cause focal necrosis around the microcirculation most especially in the territory of the middle cerebral artery with resultant formation of microabscesses [11]. The paranasal sinuses may be involved and can extend into the brain with formation of multiple abscesses. Brain CT usually underestimates the extent of the disease. The microabscesses may appear iso to hypodense on non- enhanced CT and show multiple punctate enhancing nodules after contrast administration [11]. A Candida granuloma may appear as a hyperdense nodule on CT with nodular or ring enhancement. On MRI, granuloma and abscess may have hypointense signals on T2WI due to the magnetic susceptibility effect of hemorrhage. Lesions show ring enhancement on contrast administration [11]. Features of associated meningitis, vasculitis and infarction may also be shown on MRI [11].

Common MRI features of fungal brain abscesses include: hypointensity on T1WI, hyperintensity on T2WI with well-defined rim enhancement on post contrast images in immunocompetent patients [11]. However in immunocompromised patients, abscesses appear as patchy or punctate T2 hyperintense lesions with absent enhancement in most cases [11]. Contrast enhanced imaging still decreases the number of false negatives [11]. Fungal lesions are known to show MRS peaks in lipids (1.2- 1.3 ppm), alanine (1.5 ppm), lactate (1.3 ppm), acetate (1.9 ppm), succinate (2.4 ppm), choline (3.2 ppm) and an unidentified resonance at 3.8 ppm [11,21]. A ring enhancing T2 heterointense lesion with irregular walls and non-enhancing intracavitary projections having low ADC makes high the probability of a brain lesion being a fungal abscess. These projections, directed centrally from the wall are isointense to hypointense on T1WI and hypointense on T2WI [11,17]. The identification of multiple signals seen between 3.6 ppm and 3.8 ppm assigned to trehalose sugars on (*ex vivo*) proton MRS may further add to the diagnostic confidence [11,21].

A simplified guide to making a quick diagnosis using the various radiological imaging modalities in the form of an algorithm is proposed as shown in Fig. 5 of this text.

3.5 Microbiological and Other Laboratory Tests

Early biopsy (partial or complete excision) and microbiologic confirmation of diagnosis of an atypical brain abscess and early administration of appropriate sensitive antimicrobial agents immensely impact on the outcome of the disease. Specimen (pus or abscess wall) taken at surgery is subjected to various staining procedures and also cultured to identify the causative organism [9,19].

Mycobacterium will stain positive with Zeihl Nielsen (ZN) staining which is biological proof of the presence of an Acid Fast Bacilli (AFBs) [9]. Histology will reveal an inflammatory reaction in the abscess wall, composed predominantly of vascular granulation tissue containing acute and chronic inflammatory cells particularly polymorphonuclear leukocytes. Microbial cultures will grow positive for Mycobacterium [9]. Newer techniques like Polymerase Chain Reaction (PCR) may provide a useful tool for the diagnosis of TB from paucibacillary specimens like pus in which conventional methods may show low sensitivity [22].

Aerobic, anaerobic and fungal cultures in addition to TB cultures are advised in all suspected cases of atypical brain abscesses. TB culture specimens are inoculated on Lowenstein Jensen's medium and incubated at 37℃ for 6-8 weeks [9]. Colonies obtained are then confirmed with ZN stain for AFBs and then identified by conventional methods such as growth, pigment production, niacin accumulation, nitrate reduction test and sensitivity to paranitrobenzoic acid [8]. Immunological tests like Mantoux and Quantiferon gold test may be negative because Mycobacteriae are mostly secluded within the thick abscess wall [9,10].

In his excellent review of the subject of TB brain abscess, Whitener et al gives the following diagnostic criteria: (1) true abscess formation within the brain substance characterized by cavity formation and central pus. (2) vascular granulation tissue containing acute and chronic inflammatory cells, particularly polymorphs histologically. (3) proof of tuberculous origin by either positive pus culture for Mycobacterium tuberculosis or by demonstration of AFBs in the pus or abscess wall [10]. Tuberculomas on the contrary show typical granulomatous reaction, comprising epitheloid cells and giant cells around a central area of necrosis [9,10].

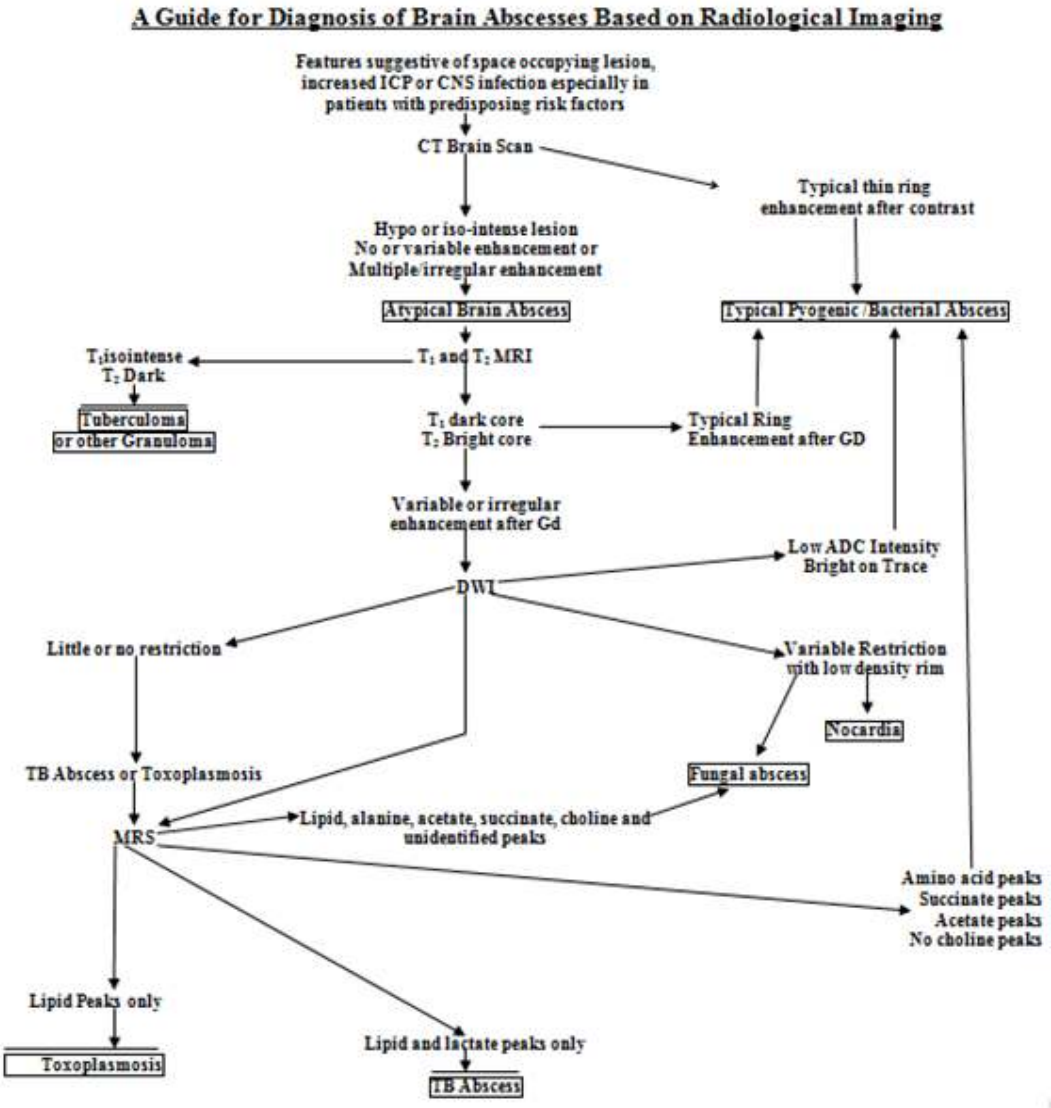

Fig. 5. Algorithm guiding the use of Brain CT, T_1 MRI, T_2 MRI, DWI and MRS imaging modalities to differentiate between the various types of brain abscesses

Table 1. Summary of imaging appearances, microbiological test results and treatment options for brain abscesses

Type of brain abscess	CT brain	T1&T2 MRI	DWI	MRS	Microbiology & other confirmatory tests	Treatment
Pyogenic bacterial brain abscess	Well circumscribed, hypointense centre, post contrast ring enhancement, hypointense surrounding oedema	T1 hypointense and T2 hyperintense centre and surrounding oedema, post Gd ring enhancement	Low signal on ADC and bright signal on Trace= restricted diffusion of water	Acetate, succinate and amino acid peaks, No choline peak	Gram stain and cultures (aerobic and anaerobic) of pus or abscess wall positive for a pyogenic bacteria	According to suspected organism(s) but initial broad spectrum antibiotic then narrowed according to sensitivities
TB brain abscess	Hypointense centre, variable post contrast ring enhancement, hypointense surrounding oedema	T1 hypointense and T2 hyperintense centre and surrounding oedema, capsule enhance after Gd. T1 isointense and T2 hypointense core with variable post Gd enhancement= Tuberculoma	Low ADC signal, little or no restriction on Trace	Lipid and lactate peak. No succinate, no amino acid and no acetate peaks	Positive acid fast stain with ZN, positive TB culture positive for Mycobacterium	Anti-tuberculous agents-isoniazid, ethambutol, pyrizinamide, rifampicin
Toxoplas-mosis brain abscess	Typically multiple post contrast ring enhancing lesions +/- calcification. Target lesions	Multiple post Gd ring enhancing lesions. Typically T2 hypointense core lesions	Variable but mostly no water molecules restriction	Lipid peaks	Direct microscopic observation of parasitic cysts or trophozoites in stained tissue sections	Pyrimethamine and Sulphadiazine or Clindamycin in patients with sulphur allergy
Nocardia brain abscess	Hypointense centre, post contrast ring enhacement, loculations or multiplicity	T1 hypointense and T2 hyperintense centre. Thick post Gd ring enhancement.	Variable water molecule restriction	Variable	Gram positive filamentous branching rods, Positive acid fast stain with ZN and positive aerobic growth (Actinomyces are anaerobic orgnisms)	Cotrimoxazole or Amikacin, Linezolid

Type of brain abscess	CT brain	T1&T2 MRI	DWI	MRS	Microbiology & other confirmatory tests	Treatment
Fungal brain abscesses	Variable appearances and enhancement patterns.Eg: Aspergillus may appear as solid or post contrast ring enhancing lesions with hemorrhagic or oedematous periphery. Cryptococcal pseudocyst has low intensity and no enhancement	May be like bacterial abscess above or patchy/ punctuate T2 hyperintensity, no Gd enhancement or T2 heterointense irregular walls, non-enhancing intra-cavitary projections but contrast ring enhancing rim.	Variable but may have low ADC signal of core and hyperintense on Trace. Aspergillus abscess may have hypointense rim on Trace.	General: Lipid peak, alanine peak, acetate peak, succinate peak, choline peak and an unidentified peak. Aspergillus-glutamine/glutamate peak, amino acid and lactate peaks. Mucormycosis: Lactate peak, succinate and acetate peaks, decreased NAA, No amino acid peak. Cryptococcal: Lactate peak, Decreased choline, NAA and creatine	Fungal cultures and identifica-tion of specific fungus with H&E staining of hyphae.	Antifungal agents: Amphotericin B, Voriconazole, Itraconazole, Caspofungin, fluconazole

A specimen from a fungal brain abscess will show histologically wide non-septated hyphal fragments with granulomatous inflammation [11]. Microbiologically, the specific causative fungus will be identified from fungal cultures and hyphae will stain in hematoxylin- eosin. For example, hyphae with 45 degrees branches is a typical and specific finding for Aspergillus. Rhizopus hyphae are broad, non- septated and right angle branching [11]. Candida will show as Gram positive yeast cells. Cryptococcus will show yeast cells and the immunologic test for cryptococcal antigen in CSF and blood may be positive. This is highly sensitive and specific [11].

Nocardia is identified from culture of specimen obtained at surgery. Nocardia bacteriological identification has improved markedly with advances in molecular microbiology. For instance, 16SrRNA sequencing employed has allowed more routine identification of Nocardia strains from clinical samples [15]. Gallium 67 and Technetium-99 HMPAO leukocytes have also been employed in the identification of Nocardia [23]. Nocardia stains as Gram positive with delicate filamentous branching rods like Actinomyces species. Nocardia is usually differentiated from Actinomyces by ZN acid fast staining as Nocardia typically exhibit varying degrees of acid fastness due to the mycolic acid content of the cell wall [15]. Another useful clue is that Nocardia grow under aerobic conditions whilst Actinomyces grow under anaerobic conditions [15]. The culture environment is normally aerobic on blood agar and Lowenstein Jensen media with no antibiotics [15]. Cultured Nocardia has a very distinct, strong mildew odour that allows experienced microbiologists to suspect their presence readily [15].

Toxoplasmosis diagnosis may be aided by measuring antibody titres for Toxoplasma which will be raised in the case of positive infection. The test measures IgG and also IgM in pregnant women [13]. Toxoplasma can be stained by immunofluorescence- IFA [13]. The diagnosis can be made by direct observation of the parasite (cyst or trophozoite) in stained tissue sections, CSF or other biopsy material. Parasites can also be isolated from blood [13]. Molecular techniques like PCR that can detect Toxoplasma DNA in the amniotic fluid can be useful in cases of possible mother to child (congenital) transmission [13]. Occular disease is diagnosed based on the appearance of lesions in the eyes, symptoms, course of the disease and often serologic testing [13].

The diagnosis of atypical brain abscesses can therefore be very challenging. However, with careful thorough history taking and physical examination, very careful scrutiny of radiological imaging features, microbiological and other laboratory tests coupled with utmost consideration of environmental and patient risk factors, the much needed early diagnosis of atypical brain abscesses can be ascertained and prompt appropriate treatment instituted to help improve the existing poor outcomes of atypical brain abscesses. It is therefore very important to have a very good communication with the Microbiologist right from the beginning in guiding the various arrays of culture media, conditions and identification techniques needed to be employed as well as facilitating effective treatment based on antimicrobial sensitivity patterns.

3.6 Treatment

The treatment of atypical brain abscesses basically consists of surgical and/or non-surgical treatment modalities.

Surgical treatment:

- Open burr hole with needle aspiration or stereotactic aspiration/biopsy of abscess wall especially in cases of deep seated lesions.
- craniotomy and excision of the abscess
- repeated aspiration +/- direct administration of antimicrobials from a previously inserted Ommaya reservoir has been described.

Non-surgical treatment basically involves the use of preferably intravenous and to a lesser extent oral sensitive antimicrobial agent in the treatment of atypical abscesses.

Combination of surgical and non-surgical treatment: In most situations both modalities need to be combined i.e. surgery followed by administration of antimicrobial agents to achieve the best possible outcomes.

Adjunctive therapy may also be required in certain situations. For example, endoscopic third ventriculostomy, ventriculoperitoneal shunt and external ventricular drain placement in cases complicated by hydrocephalus. Other adjuncts include corticosteroid and antiseizure treatments [1].

Mycobacterium brain abscesses have proven to be responsive to the recommended antituberculous combination therapy which comprises isoniazid, pyrazinamide, rifampicin and ethambutol [9,10]. Resistance forms may require the use of quinolones. A once weekly dose of a macrolide has proven to be a very effective prophylaxis for HIV/AIDS patients with CD4 counts less than 75 against MAI [9].

The recommended effective therapy for most fungal brain abscesses is intravenous amphotericin B as the initial treatment of choice [11]. Voriconazole with its relatively high CNS penetration has also proven to be very effective. A large randomized study has demonstrated that voriconazole offered greater benefit over amphotericin B as the mainstay of therapy for Aspergillosis [11].

A study by Herbrecht et al. which compared voriconazole and amphotericin B in invasive Aspergillus infection reported a high success rate of treatment for voriconazole. Amphtericin B is also associated with serious side effects like renal and hepatic toxicity, anaemia, fever and electrolyte derangements [11,20,24].

Aspergillus infection refractory to first line treatment with liposomal Amphotericin B was found to be responsive to a combination treatment with Voriconazole and Caspofungin [24].

A combination of Amphotericin B and Flucytocine after surgical excision has also been used with some success in some studies to treat Aspergillus infections [20].

Itraconazole has been used with favourable results in some cases of CNS Blastomycosis [25]. Fluconazole and other antifungal agents have also been used but their relative poor CNS penetration have not generally resulted in the expected good outcomes [11]. Other agents in use are posakonazole and caspofungin. All treatments are preferably administered over a 3-6 month period [26].

The recommended effective treatment for proven or highly suspected Toxoplasmosis is Pyrimethamine and Sulphadiazine [13]. In cases of sulphur allergy, patients can alternatively be treated with Clindamycin (600 mg qid in adults) plus dexamethazone 4 mg qid in the first 7 days [13]. In cases of typical imaging appearances highly suggestive of Toxoplasmosis, treatment can be started promptly until the diagnosis is clarified. In about 80% of patients, radiological and clinical improvement can be seen in about one week, thus supporting the diagnosis. Should the lesions be unchanged or progressive the diagnosis of Toxoplasmosis has to be reconsidered and the therapy reevaluated. Osmodiuretics may also be employed in case of progressive oedema [13].

The recommended effective medical treatment for Nocardia brain abscess is Cotrimoxazole mostly combined with surgical drainage or excision [15]. Amikacin and Linezolid have also been used with success [15]. Early diagnosis and early use of intravenous antibiotics coupled with surgical treatment remain the mainstay of therapy [15].

The imaging appearances, diagnostic microbiological test results and recommended treatments of pyogenic and the various types of atypical brain abscesses are concisely summarized in Table 1 of this text.

3.7 Monitoring Treatment

Treatment of patients diagnosed with atypical brain abscesses can be monitored by way of serial clinical evaluation, serial brain CTs and especially serial DWI-MR imaging to refute or confirm initial diagnosis made as well as the appropriateness of the treatment instituted.

4. CONCLUSION

The diagnosis and treatment of atypical brain abscesses may be quite challenging. Their imaging appearances may simulate pyogenic bacterial brain abscesses and other pathologies including non-infective causes like infarcts and tumours. However, with the use of MRI modalities like DWI, MRS and Magnetic Transfer- MRI coupled with advanced microbiological, molecular and serologic techniques as well as utmost consideration of patient and environmental risk factors, early specific diagnosis of an atypical brain abscess can often be made and reliably differentiated from other differentials. The mainstay of treatment remains early surgical drainage or excision and/or early administration of appropriate sensitive intravenous antimicrobial agents. Appropriate adjuvant therapies like CSF diversion procedures in case of existing hydrocephalus may need to be instituted promptly to reduce morbidity and mortality.

Clinicians therefore need to maintain a high index of suspicion for atypical brain abscesses as existing poor outcomes can be improved by making early diagnosis and instituting appropriate treatment strategies. Early biopsy for histological and microbiological confirmation of the diagnosis of atypical brain abscess will facilitate prompt commencement of appropriate treatment.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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