

CAS GRANULOMA

Dr. M. YASSER METWALLY

INDEX Master degree thesis presented by Dr Sherif Aly (2007)



- [INTRODUCTION](#)
- [TUBERCULOSIS](#)
- [FUNGAL GRANULOMA](#)
- [PARASITIC GRANULOMA](#)
- [NON-INFECTIOUS GRANULOMA](#)
- [DISCUSSION](#)
- [RECOMMENDATIONS](#)
- [SUMMARY](#)

INTRODUCTION

Granulomatous inflammation is a distinctive pattern of chronic inflammation characterized by aggregates of activated macrophages that assume a squamous cell like appearance (Mitchell and Cotran, 2003). It is also defined as a special type of chronic inflammation characterized by focal collections of macrophages, epithelioid cells and multinucleated giant cells (Geraint and Jones, 1983).

Granulomatous inflammation is best defined as a special variety of chronic inflammation in which cells of the mononuclear phagocyte system are predominant and take the form of macrophages, epithelioid cells and multinucleated giant cells. In most instances these cells are aggregated into

well demarcated focal lesions called granulomas, although a looser, more diffuse arrangement may be found. In addition there is usually an admixture of other cells, especially lymphocytes, plasma cells and fibroblasts (Geraint and Jones, 1983).

Granuloma is the characteristic lesion of granulomatous diseases which can be defined as a space occupying lesions of non neoplastic origin. It is a mass or nodule of chronically inflamed tissue formed by the response of the mononuclear phagocytic system to a slowly soluble antigen or irritant, that could be infective or non infective. (Metwally, 2006-2).

Granuloma formation is usually regarded as a mean of defending the host from persistent irritants of either exogenous or endogenous origin. The causative agent is walled off and sequestered by cells of macrophage lineage allowing it to be contained, if not destroyed altogether (Geraint and Jones, 1983).

Experimental models of granulomatous inflammation have provided much of our present knowledge of the pathogenesis of granulomas (Boros, 1978) Such studies have shown that both the nature of the irritant and host factors are important in governing the type of reaction that is produced. All injected substances cause an initial influx of mononuclear cells by the phenomenon of chemotaxis. However, what happens next depends on the resistance of the irritant to degradation by macrophages. If it is a soluble substance that is easily digested, then the macrophages move away once degradation is complete (Spector, 1974). However if it is poorly soluble, persistent and undegradable, a granuloma is formed. The exception to this rule is that soluble materials can produce granulomas if they combine with endogenous macromolecules to form insoluble and undegradable compounds, a mechanism considered important in granuloma formation by certain soluble metal salts such as beryllium (Boros, 1978). Experimental granulomas can also be produced by soluble irritants complexed either with insoluble inert materials (Boros and Warren, 1973) or with antibodies to form insoluble immune complexes (Spector and Hessom, 1969).

In the past few decades the cell mediated immune etiology and T lymphocyte-macrophage interaction have been established as the basis of the immune granulomatous inflammatory response, and the essentially protective function of the lesions has been acknowledged (Dov, 2003). the process of granuloma formation is thought to be a critical step in the physiological delayed immune response that stops the spread of noxious and infectious microorganisms (Zulma and James, 1996).

However, it is assumed that the granulomas seen in multi-systemic disorders, like Sarcoidosis, Crohn's disease and Wegener granulomatosis, do not have a protective function, since they may contribute to the tissue pathology favoring focal injuries and inducing appreciable fibrosis at sites of granuloma formation (Agostini and Semenzato, 1999).

The granulomata are classified according to the underlying cause into infective and non infective granuloma, as shown in (table 1).

Also, granulomas can be classified on basis of their microscopic appearance into necrotizing and non necrotizing. Non-necrotizing granulomas are characteristic of sarcoidosis, beryllium disease, hypersensitivity pneumonitis, drug reactions, tuberculoid leprosy, Crohn's disease and others. The presence of non-necrotizing granulomas is generally indicative of a non-infectious etiology. However, non-necrotizing granulomas may occur along with necrotizing granulomas in infectious diseases such as tuberculosis (TB) and may be the only finding in small biopsy specimen. The finding of non-necrotizing granulomas does not exclude infectious etiology. Necrotizing granulomas are characteristic of infectious diseases such as TB and fungal infections as well as rheumatoid nodules, Wegener granulomatosis, necrobiotic post-surgical granulomas and others.

Necrosis usually minimal and focal, may also be seen in the granulomas of sarcoidosis (Metwally, 2006-2).

Table 1. Classification of Granuloma, (Metwally, 2006-2)

INFECTIVE	NONINFECTIVE
<ul style="list-style-type: none"> • Tuberculosis • Fungus infection <ul style="list-style-type: none"> ○ Aspergillosis, candidiasis, coccidioidosis, and cryptococcosis • Parasitic infection <ul style="list-style-type: none"> ○ Toxoplasmosis ○ Cysticercosis ○ Hydatid disease (echinococcosis) ○ Schistosomiasis (Bilharzioma), and paragonimiasis 	<ul style="list-style-type: none"> • Sarcoidosis • Wegener granulomatosis • Histiocytosis (eosinophilic granuloma) • Cholesteatoma • Cholesterol granuloma • Granulomatous angiitis

• **CNS granuloma**

Granulomatous diseases may affect the nervous system, and the majority of cases of Central Nervous System (CNS) granulomatous diseases are infectious in etiology, especially TB, and some cases are non infectious as sarcoidosis (Roongroj et al., 2005).

CNS granulomatous infections usually result from hematogenous spread. An extra-cranial source of infection is found in most cases (usually the lung). Yet, isolated CNS involvement may occur in younger patients with sarcoidosis. In debilitated (e.g. diabetic) and immunocompromised patients, direct spread of fungal disease may occur from the Paranasal sinuses (aspergillosis) or temporal bones (mucormycosis) with an often fatal outcome (Robert, 2004).

The imaging features of granulomatous disease reflect the complex and variable histopathology of this group of diseases. Granulomas are most commonly seen as small, single or multiple, solid or discrete ring-enhancing lesions with surrounding edema at the cortical-subcortical junction, which could have variable intensities on T1W, T2W and DWI in MRI. Due to lack of specificity, and absence of characteristic findings, they may mimic the appearance of each other, or the appearance of metastatic lesions (Robert, 2004).

Most granulomatous inflammations are associated with meningitis which is represented on CT and MRI as cisternal enhancement, usually following the vessel routes. Contrast enhanced images are critical in establishing the diagnosis of granulomatous meningitis (Vincent, 2005).

TUBERCULOSIS

Tuberculosis is one of the most important infective granulomatous disorders along history, and remains a major global problem and a public health issue of considerable magnitude, and was

declared as a global emergency in 1993 by the World Health Organization (WHO) (Dolin et al., 1994). In the late 1980s and the 1990s, TB has reemerged in industrialized countries, largely because of increases in travel from endemic areas to developed nations (Hirsch et al., 1999). This emergence is due in part to infection with the human immunodeficiency virus (HIV) (Glynn, 1998), the development of multiple drug-resistant *M. tuberculosis* (Eltringham and Drobniewski, 1998), and reduced resources for treatment and surveillance of patients (Barry et al., 1999).

- **Epidemiology**

According to the estimates of WHO, TB accounts for 7–8 million new cases every year and is responsible for 2.9 million deaths worldwide annually (Raviglione et al., 1995). The incidence of TB is 8 cases per 100,000 person per year. However, in a recent study in New York City, the incidence in patients receiving welfare was 744 cases per 100,000 person per year. The prevalence is especially high in people infected with HIV, those who abuse drugs and alcohol, immigrants, and homeless persons (Peter, 2004). The rates of TB and tuberculous meningitis (TBM) have increased globally, especially in developing countries of Africa and Asia that are affected by the HIV pandemic. The incidence is 544 and 757 new patients per 100,000 population in Africa and India, respectively (Peter, 2004). Other estimate it to be 110–165 cases per 100,000 population in the developing countries of Asia and Africa. (Harries, 1990; Snider and Roper, 1992).

Mortality in developed American nations for all TB patients was 2000 in 1998. The major causes of morbidity and mortality of CNS TB are the resulting complications of TBM, especially in pediatric patients. Primary complications include communicating hydrocephalus, vasculitis with resulting infarction, and ventriculitis (Peter, 2004).

- **CNS tuberculosis**

Tuberculous involvement of the central nervous system (CNS) is an important and serious type of extra-pulmonary involvement. It has been estimated that approximately 10% of all patients with TB have CNS involvement (Wood and Anderson, 1998). The incidence of CNS tuberculosis is directly proportional to the prevalence of tuberculous infection in general. In developing countries CNS tuberculosis is a disease of younger age group, usually childhood (Molavi and LeFrock, 1985).

Extrapulmonary TB including involvement of the CNS is common in HIV Patients and is considered as AIDS-defining condition (Villora et al., 1995). However, cerebral TB can occur in both immunocompromised AIDS patients and in immunocompetent hosts without AIDS disease (Lesprit et al., 1997), but TB of the CNS is more likely to occur and is rapidly progressive in HIV-infected patients than in HIV-negative individuals (Snider and Roper, 1992). Involvement of the CNS in TB is five times more frequent in HIV-positive than HIV-negative patients (Berenguer et al., 1992).

The clinical spectrum of CNS tuberculosis with HIV infection includes meningitis, cerebral abscesses and tuberculomas. CNS involvement occurs in 10–20% patients with AIDS-related TB, and in these patients mortality is high. HIV-infected intravenous drug abusers are, in particular, at high risk of developing focal CNS tuberculosis. Clinical features, including imaging characteristics, are similar to those seen in patients without HIV infection. In patients with *M. avium* intracellulare infection, single or multiple mass lesions appear to be more than twice as common as meningitis. Every effort should be made to establish the correct diagnosis as most types of CNS tuberculosis in HIV-infected patients are responsive to treatment (Berenguer et al., 1992; Dube et al., 1992; Farrar et al., 1997).

- **Pathology**

Most tuberculous infections of the CNS are caused by *Mycobacterium tuberculosis*. Less frequently, other mycobacteria may be involved. *Mycobacterium tuberculosis* is a non-motile, non-spore forming, and an obligate aerobic acid-fast bacillus (AFB), whose only natural reservoir is man. *M.tuberculosis* grows slowly both in vitro and in vivo, with a doubling time of about 15–22 h, and it requires incubation of at least two weeks to grow on Lowenstein-Jensen(LJ) solid medium (Wyne, 1985).

It is believed that the bacilli reach the CNS by the haematogenous route secondary to disease elsewhere in the body. Rich and Mc Cordock (1933) suggested that CNS tuberculosis develops in two stages, initially small tuberculous lesions (Rich's foci) develop in the CNS, either during the stage of bacteremia of the primary tuberculous infection or shortly afterwards. These initial tuberculous lesions may be in the meninges, the subpial or subependymal surface of the brain or the spinal cord, and may remain dormant for years after initial infection. Later, rupture or growth of one or more of these small tuberculous lesions produces development of various types of CNS tuberculosis (Rich and Mc Cordock, 1933; Berger, 1994, Dastur et al.,1995).

The specific stimulus for rupture or growth of Rich's foci is not known, although immunological mechanisms are believed to play an important role. Rupture of the small tubercles into the subarachnoid space or into the ventricular system results in meningitis. The type and extent of lesions that result from the discharge of tuberculous bacilli into the cerebrospinal fluid (CSF), depend upon the number and virulence of the bacilli, and the immune response of the host. Infrequently, infection spreads to the CNS from a site of tuberculous otitis or calvarial osteitis. A study of immunological parameters showed a correlation between the development of tuberculous meningitis in children and significantly lower numbers of CD4 T-lymphocyte counts when compared with children who had primary pulmonary complex only (Rajajee and Narayanan,1992). The pathogenesis of localized brain lesions is also thought to involve haematogenous spread from a primary focus in the lung (which is visible on the chest radiograph in only 30% of cases). It has been suggested that with a sizeable inoculation or in the absence of an adequate cell-mediated immunity, the parenchymal cerebral tuberculous foci may develop into tuberculoma or tuberculous brain abscess (Sheller and Des Prez, 1986).

- **Clinical Presentations of CNS TB**
 - **Tuberculous meningitis**

TBM is characterized as a meningoencephalitis as it affects both the meninges and the brain's parenchyma and its vasculature. In tuberculous meningitis there is a thick, gelatinous exudate around the sylvian fissures, basal cisterns, brainstem, and cerebellum. Microscopically diffuse exudates consist of polymorph nuclear leukocytes, macrophages, lymphocytes, and erythrocytes with a variable number of bacilli within a loose fibrin network, and as the disease progress, lymphocytes and connective tissue elements predominate (Dastur et al.,1995).

Hydrocephalus may occur as a consequence of obstruction of the basal cisterns, outflow of the fourth ventricle, or occlusion of the cerebral aqueduct. Hydrocephalus frequently develops in children and is associated with a poor prognosis. The brain tissue immediately underlying the tuberculous exudate shows various degrees of oedema, perivascular infiltration, and a microglial reaction, a process known as 'border zone reaction'. The basal exudates of TB are usually more severe in the vicinity of the circle of Willis, and produce a vasculitis-like syndrome. Inflammatory changes in the vessel wall may be seen, and the lumen of these vessels may be narrowed or occluded by thrombus formation. The vessels at the base of the brain are most severely affected, including the internal carotid artery, proximal middle cerebral artery, and perforating vessels of the basal ganglion. Cerebral infarctions are most common around the sylvian fissure and in the basal ganglion. In the majority of patients the location of infarction is in the distribution of medial

striate and thalamoperforating arteries. Haemorrhagic transformation of infarcted tissue is not unusual (Molavi and LeFrock, 1985; Leonard and Des Prez, 1990, Newton, 1994; Dastur et al., 1995)

In most patients with tuberculous meningitis there is a history of vague ill health lasting 2–8 weeks prior to the development of meningeal irritation. These nonspecific symptoms include malaise, anorexia, fatigue, fever, myalgias, and headache. The prodromal symptoms in infants include irritability, drowsiness, poor feeding, and abdominal pain. Eventually, the headache worsens and becomes continuous. Neck stiffness is reported by about 25% of patients, but meningismus is detected in a higher number of patients at the time of examination. Bulging fontanelles develop in infants, who become increasingly irritable. Nausea, vomiting and altered sensorium may develop. Continuous low-grade pyrexia is typically present in about 80% of patients. A prior history of TB is present in approximately 50% of children with tuberculous meningitis and 10% of adult patients (Molavi and LeFrock, 1985; Ahuja,et al., 1994; Newton, 1994).

Cranial nerve palsies occur in 20–30% of patients and may be the presenting manifestation of tuberculous meningitis. The sixth cranial nerve is most commonly affected, and less frequently the third, fourth, seventh and eighth cranial nerves (Garcia-Monco, 1999). Vision loss due to optic nerve involvement may occasionally be a dominant and presenting illness. Optochiasmatic arachnoiditis, third ventricular compression of optic chiasma (if hydrocephalus develops), optic nerve granuloma, and ethambutol toxicity are possible factors for vision loss in these patients. Ophthalmoscopic examination may reveal papilledema. Fundoscopy may reveal choroid tubercles, yellow lesions with indistinct borders present either singly or in clusters. These choroid tubercles are more frequent with tuberculous meningitis associated with miliary TB and are virtually pathognomonic of tuberculous aetiology, although they are present in only 10% of patients in whom the meningitis is not associated with miliary involvement (Leonard and Des Prez, 1990; Berger, 1994).

Hemiplegia may occur at the onset of the disease or at a later stage. Quadriplegia secondary to bilateral infarction or severe cerebral oedema is less common and occurs only at an advanced stage in a few patients. At times, abnormal movements may dominate the clinical picture, more commonly in children than in adults. Seizures, either focal or generalized, may occur during acute illness or months after treatment (Berger, 1994). As the disease progresses, increasing evidence of cerebral dysfunction sets in. Behavioral changes consisting of apathy, confusion, or bizarre behavior, tend to progress to increasing lethargy, stupor, and coma.

In order to assess the severity of illness to a certain degree, the Medical Research Council (MRC) introduced a staging system (Table 2). This staging system has been found to be valuable in structuring and interpreting anti-tubercular treatment (ATT) as well as in the prognosis of TBM. (Medical Research Council, 1948; Holdiness, 1990)

Table 2. MRC staging of tuberculous meningitis (Medical Research Council, 1948)

- Stage I prodromal phase with no definite neurological symptoms
- Stage II signs of meningeal irritation with slight or no clouding of sensorium and minor (cranial nerve palsies), or no neurological deficit
- Stage III severe clouding of sensorium, convulsions, focal neurological deficit and involuntary movements

- Spinal cord tuberculosis

A predominantly spinal form of tuberculous meningitis may result from rupture of Rich's focus into the spinal arachnoid space rather than the basal meninges. The acute form presents with fever, headache, and radiating root pains, accompanied by myelopathy. The chronic form, usually localized to a few segments, presents with progressive spinal cord compression and may suggest a spinal cord tumour (Wadia, 1973; Dastur et al., 1995).

Non-osseous spinal cord TB can occur in the form of tuberculomas. Dastur (1983) reviewed 74 cases of tuberculous paraplegia without evidence of Pott's disease and observed that extradural tuberculomas occurred in 64% while arachnoid lesions without dural involvement, and subdural/extramedullary lesions occurred in 8% of patients each (Dastur, 1983). Intramedullary tuberculomas are extremely rarely reported, reports from developing countries have also been sporadic. The clinical features are indistinguishable from those of any extramedullary or intramedullary tumour, although acute worsening may occur. Intramedullary lesions are frequently located in the thoracic region. More than one site in the spinal cord may also be affected. One case with conus medullaris syndrome has been described. Non-osseous spinal cord tuberculomas may increase in size while the patient is on ATT. MRI is the investigation of choice for these lesions (Dastur, 1983; Mantzoros et al., 1993; Garg et al., 1998).

- **Intracranial tuberculoma**

The pathogenesis of intracranial tuberculomas is identical to that of TBM. Tuberculomas are firm, avascular, spherical granulomatous masses, measuring about 2–8 cm in diameter. They are well limited from surrounding brain tissue which is compressed around the lesion and shows oedema and gliosis. The inside of these masses may contain necrotic areas composed of caseous material, occasionally thick and purulent, in which tubercle bacilli can be demonstrated. Intracranial tuberculomas can occur at any age. In developing countries young adults and children are predominantly affected while in developed countries they are more common in older patients. The symptoms produced by tuberculoma are related to their location. Low-grade fever, headache vomiting, seizures, focal neurological deficit, and papilledema are characteristic clinical features of supratentorial tuberculomas. Infratentorial tuberculomas are more common in children and may present with brainstem syndromes, cerebellar manifestations, and multiple cranial nerve palsies. Symptoms are frequently chronic and slowly progressive, with a mean duration of weeks to months (Vengsarkar et al., 1986; Talamas et al., 1989; Rajshekhar and Chandy, 1997;)

- **Intracranial tuberculous abscess**

Tuberculous brain abscess is a condition distinct from CNS tuberculoma. In developing countries tuberculous abscesses have been reported in 4% to 7.5% of patients with CNS tuberculosis. The histopathological diagnosis of tuberculous brain abscess depends on the following criteria microscopic evidence of pus in the abscess cavity, microscopic changes in the abscess wall, which is devoid of the granulomatous reaction that surrounds tuberculoma, and isolation of M tuberculosis (Dastur et al., 1995). Abscesses are usually solitary, multiloculated, larger and progress much more rapidly than tuberculomas. Clinical features include acute onset, with fever, headache, partial seizures, focal neurological deficit, and raised intracranial tension, and occur mostly in supratentorial region (Whitener, 1978; Farrar et al., 1997).

- **Tuberculous encephalopathy**

Tuberculous encephalopathy, a syndrome exclusively present in infants and children, has been described by Udani and Dastur in Indian children with pulmonary TB (Udani and Dastur, 1970). The characteristic features of this entity are the development of a diffuse cerebral disorder in the form of convulsions, stupor and coma without signs of meningeal irritation or focal neurological

deficit. CSF is largely normal or may show a slight increase in proteins and cells. Pathologically, there is diffuse oedema of cerebral white matter with loss of neurons in grey matter. A picture resembling haemorrhagic leukoencephalopathy or a post-infectious demyelinating encephalomyelitis may be observed (Udani and Dastur, 1970; Dastur et al., 1995).

- **Pott's spine and Pott's paraplegia**

It is estimated that involvement of the spine occurs in less than 1% of patients with TB. It is a leading cause of paraplegia in developing nations. Infection in the vertebral bodies usually starts in cancellous bone adjacent to an intervertebral disc or anteriorly under the periosteum of the vertebral body; the neural arch is rarely affected. Vertebral destruction leads to collapse of the body of the vertebra along with anterior wedging. Spinal cord compression in Pott's spine is mainly caused by pressure from a paraspinal abscess which is retropharyngeal in the cervical region, and spindle shaped in thoracic and thoracolumbar regions. Neurological deficits may also result from dural invasion by granulation tissue and compression from the debris of sequestered bone, a destroyed intervertebral disc, or a dislocated vertebra. Rarely, vascular insufficiency in the territory of the anterior spinal artery has also been suggested. Neurological involvement can occur at any stage of Pott's spine and even years later, when there has been apparent healing, because of stretching of the cord in the deformed spinal canal. The thoracic spine is involved in about 65% of cases, and the lumbar, cervical and thoracolumbar spine in about 20%, 10% and 5%, respectively. The atlanto-axial region may also be involved in less than 1% of cases. Males are affected more often than females in most series, and the disease generally affects young persons (Vidyasagar and Murthy, 1994; Nussbaum et al., 1995; Razai et al., 1995;).

Typically, there is a history of local pain, tenderness over the affected spine or even overlying bony deformity. Paravertebral abscess may be palpated on the back of a number of patients. These patients usually have acute or subacute, progressive, spastic type of sensorimotor paraparesis. The incidence of paraparesis in patients with Pott's spine varies from 27% to 47%.

Differential Diagnosis of CNS tuberculosis

- Partially treated pyogenic meningitis
- Neurocysticercosis
- Cryptococcal meningitis
- Viral meningoencephalitis
- Intracranial malignancy
- Neurosarcooidosis
- Neurosyphilis

- **Investigations**

Because of the non-specific clinical presentation of patients with cerebral TB, the initial differential diagnosis is wide and its early clinical course is compatible with most other bacterial, fungal, viral, or parasitic infections of the CNS as well as non-infectious inflammatory diseases of the CNS. The rapid diagnosis of tuberculous etiology is fundamental to clinical outcome. The diagnosis of cerebral TB cannot be made or excluded on clinical grounds. Diagnosis of different forms of cerebral TB is made based on neurological symptoms and signs, CSF findings, and

neuroimaging characteristics. Evidence of extra-neural TB with appropriate microbiological, radiological or histopathological findings will add to the confirmation of the diagnosis. A history of recent TB contact is also an important supporting feature of tuberculous etiology.

Routine laboratory studies, such as erythrocyte sedimentation rate (ESR) or differential count of peripheral white blood cells, follow no characteristic pattern. However, a definitive diagnosis of TB etiology depends upon lumbar puncture and CSF examination, and detection of TB bacilli in CSF either by microscopy or in culture (Muralidhar, 2004).

The CSF examination abnormalities found in CSF of untreated patients with tuberculous meningitis are well described. Usually, a “cobweb” like appearance of the pellicle on the surface of CSF when allowed to stand for a short time at room temperature is a characteristic feature but not pathognomonic (Zuger and Lowry, 1997). Opening pressure at initial lumbar puncture is significantly elevated in about 50% of patients. There is a predominant lymphocytic reaction (60–400 white cells per ml) with raised protein levels (0.8–4 g/l). In the early stages of infection, a significant number of polymorphonuclear cells may be observed, but over the course of several days to weeks they are typically replaced by lymphocytes. There is a gradual decrease in the sugar concentration of the CSF, which is usually less than 50% of serum glucose concentration, the values may range between 18–45 mg/dl (Molavi and LeFrock.,1985; Leonard and Des Prez, 1990; Ahuja,et al., 1994; Berger, 1994; Newton, 1994). Low chloride levels in CSF, considered earlier as a specific marker for TBM, is actually a reflection of coexistent serum hypochloremia, and is not helpful in distinguishing TB infection from other bacterial and viral infections (Ramkisson and Coovadia, 1998).

Definitive diagnosis of tuberculous meningitis depends upon the detection of the tubercle bacilli in the CSF, either by smear examination or by bacterial culture and both are still considered the golden standard for diagnosis (Muralidhar, 2004). With repeated examinations of sequential CSF examinations Kennedy and Fallon reported tubercle bacilli in 87% of patients (Kennedy and Fallon,1979). In other series especially from developing countries bacteriological confirmation of the diagnosis could be achieved in as few as 10% of the cases (Molavi and LeFrock.,1985). Spinning of large volumes (10–20 ml) of CSF for 30 min and smear examination from the deposit of as many as four serial CSF samples would enhance the detection rate of AFB (Muralidhar, 2004).

Culture of the CSF for tubercle bacilli are not invariably positive. Rates of positivity for clinically diagnosed cases range from 25% to 70% (Kent et al.,1993). The solid media cultures such as Lowenstein-Jensen may take up to 8 weeks to culture *M. tuberculosis*. Semiautomated radiometric culture systems such as Bactec 460 and automated continuously monitored systems have reduced culture time (Gillespie and McHugh.,1997). Although such systems do reduce the time taken for culture the decision to treat the patient should not wait for culture results.

In cases of intracranial tuberculomas and tubercular abscesses, the CSF analyses are unremarkable or show a mild, nonspecific increased protein content and usually negative bacteriology. The “gold standard” remains histological. Approximately 60% of tissue specimens from tuberculomas show AFB in smear and culture (Meyers et al.,1978).

- **Molecular diagnostic approaches (new approach)**

Since the present conventional methods, namely microscopy and culture techniques, are, respectively, less sensitive and time consuming, alternative diagnostic methods have become necessary for the specific diagnosis of TB etiology in the CNS infections. An ideal molecular diagnostic test should be rapid, cost-effective, sensitive, and specific in the diagnosis of TB etiology. The newer diagnostic tests fall into three categories

1. **Biochemical tests detecting some other features of the organism or products released as a result of the host's response.**
2. **Immunological tests that detect mycobacterium antigen or antimycobacterial antibody in the CSF.**
3. **Molecular biological tests that detect DNA fragments of the organism.**

- **Biochemical tests**

Tuberculostearic acid (TSA), a structural cell wall component of *M. tuberculosis*, and 3-(2'-ketoheptyl)-indoline, a mycobacterium metabolite, were identified in CSF as diagnostic praziquantel markers for TBM by electron-capture gas liquid chromatography (Brooks et al.,1977; Mardh et al.,1983). Detection of TSA has not been adopted as a routine test because of the complex instrumentation. Similarly, detection of 3-(2'-ketoheptyl)-indoline has limited use as a routine diagnostic test owing to its low sensitivity of 60% in culture-proven cases (Muralidhar, 2004).

Determination of adenosine deaminase (ADA), an enzyme associated with disorders that induce (T)-cell-mediated immune responses, would be a useful test for differentiating from aseptic meningitis in the diagnosis of cerebral TB, yet this test appears to be a non-specific (Choi et al.,2002).

- **Immunological tests**

Detection of specific mycobacterium antigen or antibody in CSF would certainly be of considerable help to a clinician in arriving at a definitive diagnosis of TB of the brain. Yet the variations in sensitivity and specificity of many immunoassays (table 3) have resulted in a lack of confidence among clinicians in immunodiagnosis of cerebral TB although some of the authors claim specificity of 100% These variations may be because of: (i) The use of different antigenic sources, such as total bacterial sonicate extract, culture filtrate, partially purified antigens, monoclonal antibody-based immunoaffinity purified, or recombinant antigens, (ii) Use of different immunoassays, such as hemagglutination, enzyme linked immuno sorbent assay (ELISA), immunofluorescent assay (IFA), radio immunoassay (RIA), immunoblot assays and T cell-based gamma-interferon release assay(iii) The host's immune response (Muralidhar, 2004).

Table 3. Various immunoassays used for diagnosis of TB.

--

References	Immunoassays used	Sensitivity (%)	Specificity (%)
Antibody based assays			
Prabhakar et al. 1987	ELISA	72	92
Patil et al. 1996	ELISA and Western blotting	93	96
Chandramukhi et al. 1989	ELISA	61	100
Behari et al. 1989	IFA	78	58
Katti 2002	PHA and Western blotting	81	93
Antigen based assays			
Kambovitis et al. 1984	Latex agglutination	94	99
Kadival et al.1987	Radioimmunoassay	79	100
Masteroianni et al.1991	Dot blot assay	92	94
Wagle et al. 1990	ELISA	73	100
Chandramukhi et al. 1985	RPHA	88	95
Katti and Chandramuki, 1990	RPHA and Western blotting	94	99

- **PCR assay**

The advent of detection procedures for the amplification of fragments of mycobacterium DNA, called polymerase chain reaction (PCR), has turned attention away from serological techniques. The PCR test has been assessed against both culture and ELISA for antimycobacterial antibodies in the diagnosis of TBM (Kox et al., 1995). It detected 75% of 20 cases of highly probable TBM, 57% of 7 probable cases, and 43% of 7 possible cases. ELISA detected 55% of highly probable and 29% each of the other two categories (Shankar et al.,1991). The sensitivity of PCR was 48% with a specificity of 100%, whereas culture alone had a sensitivity of 39% and a specificity of 100% (Kox et al.,1995). Furthermore, the PCR test was positive in 90.5% (19 out of 21) of TBM-suspected patients (Liu et al.,1994) and 100% sensitive in HIV-infected patients (Folgueira et al.,1994). In spite of this, PCR is inappropriate for use in many places in the developing world and current studies suggest that PCR does not solve the global diagnostic challenge set by TBM (Thwaites et al., 2000).

- **Neuroimaging**

Radiological diagnostic methods such as computer tomography (CT) and magnetic resonance imaging (MRI) have greatly enhanced the diagnostic accuracy of TB of the CNS, but they are still not pathognomic for the disease (Muralidhar, 2004).

In TB meningitis CT or MRI of the brain may reveal thickening and intense enhancement of

meninges, especially in basilar regions. Ventricular enlargement is present in a majority of patients. The degree of hydrocephalus correlates with the duration of the disease (Muralidhar, 2004).

Infarcts are another characteristic imaging feature of tuberculous meningitis (Ahuja et al., 1994). The reported frequency of infarcts demonstrated by CT varies from 20.5% to 38%, however, in general, the incidence of infarction is significantly higher on MRI than on CT. In addition, a large number of infarcts are seen to be haemorrhagic in nature on MRI, a finding not well documented on CT scan. The majority of infarcts are seen in thalamic, basal ganglion, and internal capsule regions (Berger, 1994).

Thick basilar exudates appear by CT as intensely enhancing areas in the basal cisterns (spider-leg appearance) and in the sylvian fissures (Figure 1)(Ahuja et al., 1994). The thickening of the meninges is better visualized by MRI after enhancing the contrast with gadolinium. MRI shows marked linear enhancement of the ependymal surface of the ventricle following gadolinium injection (Chang et al.,1990).

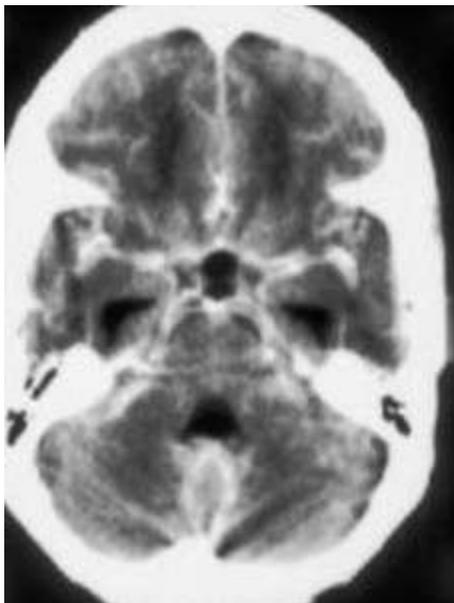


Figure 1. Contrast-enhanced CT scan in a patient with tuberculous meningitis demonstrates marked enhancement in the basal cistern and meninges, with dilatation of the ventricles (Peter, 2004)

CT and MRI show hydrocephalus in 50–80% of cases, cerebral infarctions in 25–30% (Figure 2), and perivascular edema and tuberculomas in 10–20%. In general, all other kinds of lesions associated with TBM are demonstrated better on MRI than on CT scan (Chang et al., 1990).

Tuberculomas are infrequently seen on CT or MRI of patients with tuberculous meningitis. Davis et al (1993) found tuberculomas in 16% of patients with culture-positive or presumptive tuberculous meningitis (Davis et al., 1993). Multiple small intracranial tuberculoma are frequent when tuberculous meningitis is part of miliary TB (Gee et al., 1992; Eide et al., 1993). The carotid or MR angiogram shows changes in vessels of the circle of Willis. These changes include uniform narrowing of large segments, small segmental narrowing, irregular beaded appearance and complete occlusion (Jinkins et al., 1995).

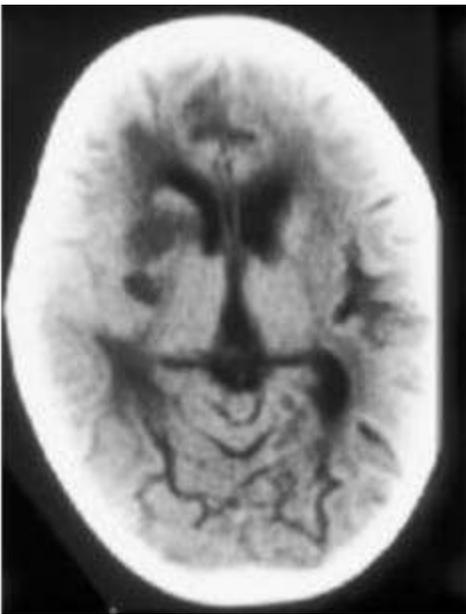


Figure 2. CT scan in a patient with tuberculosis meningitis showing extensive right basal ganglia and internal capsule infarcts after the appearance of vasculitis in the thalamoperforating arteries . (Peter, 2004)

Tuberculomas on CT are characterized as low- or high-density and rounded or lobulated masses and show intense homogenous or ring enhancement after contrast administration (Figure 3). They have an irregular wall of varying thickness. Moderate to marked perilesional oedema is frequently present (Jinkins, 1988). Tuberculomas may be single or multiple and are more common in frontal and parietal, lobes, usually in parasagittal areas. On CT, the ‘target sign’, a central calcification or nidus surrounded by a ring that enhances after contrast administration, is considered pathognomonic of tuberculoma (Van Dyk, 1988). In developing countries like India, tuberculomas are frequently confused with cysticercus granuloma.

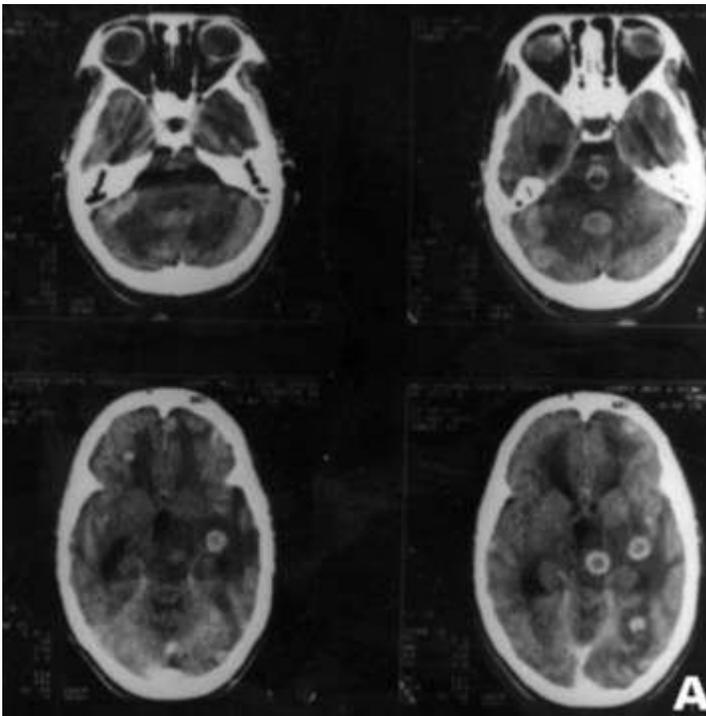


Figure 3. Contrast-enhanced CT of brain showing multiple tuberculomas in a patient with tuberculous meningitis; (Ravindra,1999)

On CT scanning, tuberculoma measure more than 20 mm in diameter, are frequently irregular in outline, and are always associated with marked cerebral oedema (leading to midline shift) and progressive focal neurological deficit (Bhargava and Tandon, 1980).

The MRI features of tuberculoma depend on whether the lesion is non-caseating, caseating with a solid center, or caseating with a liquid center. The non-caseating granulomas are hypointense on T1-weighted images and hyperintense on T2-weighted images; after contrast administration the lesion usually shows homogenous enhancement. The second type of tuberculoma are hypointense or isointense on T1-weighted images and also on T2-weighted image. After contrast administration there is ring enhancement. These types of granuloma have variable degree of perilesional oedema. The tuberculoma with central liquefaction of the caseous material appears centrally hypointense on T1- and hyperintense on T2-weighted images with a peripheral hypointense ring which represents the capsule of tuberculoma. Images after contrast administration show ring enhancement (Jinkins et al., 1995).

Tuberculous abscess pictures in CT and MRI show a granuloma with a liquid center, however, they are much larger and frequently multiloculated and with marked surrounding oedema (Figure 4). The differential diagnosis includes space-occupying lesions such as neoplasm, and granulomas such as sarcoidosis, cysticercosis, toxoplasmosis, and pyogenic and fungal lesions (Farrar et al 1997).

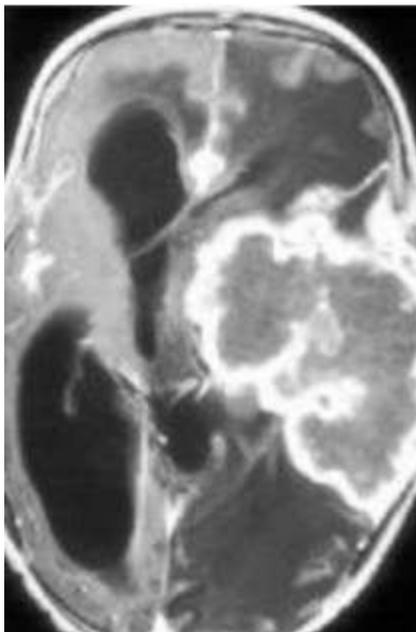


Figure 4. T1-weighted gadolinium-enhanced MRI in a child with a tuberculous abscess in the left parietal region. Note the enhancing thick-walled abscess. (Peter, 2004)

Spinal TB meningitis characteristic MRI features include CSF loculation and obliteration of the spinal subarachnoid space with loss of outline of spinal cord in the cervico-thoracic region and matting of nerve roots in the lumbar region. Spinal forms of tuberculous meningitis may be associated with syrinx formation (Wadia, 1973; Jinkins et al., 1995).

In Pott's disease, Conventional spinal X-rays are usually adequate to demonstrate the destruction of adjacent vertebral bodies and intervening disc spaces. However, superior investigative modalities used for the diagnosis of Pott's paraplegia include myelography, CT scan, MRI and CT-guided needle biopsy (Figure 5). These help to define precisely the level of spinal involvement, amount of bone destroyed, morphology and extent of the paravertebral abscess and cord compression (Miller, 1995; Nussbaum et al., 1995; Razai et al., 1995). Vidyasagar and Murthy (1994), who used only plain radiography, myelography and CT scan, showed that myelography gave the best indication for spinal cord compression even when other superior investigative facilities were available. They found CT-guided needle biopsy to be very useful in establishing the etiological diagnosis in their cases, picking up unexpected tumour metastases in several cases (Vidyasagar and Murthy, 1994).



Figure 5. Sagittal T1-weighted MRI of two patients showing vertebral collapse of C6 and 7 vertebra along with posterior wedging and paraspinal abscess compressing the spinal cord. (Ravindra,1999)

- **Treatment of CNS tuberculosis**

In contrast to the rapid advances in the management of pulmonary TB, there have been only a few clinical studies in patients with CNS tuberculosis, including tuberculous meningitis. There is currently no general consensus about the form of chemotherapy or optimal duration of treatment (Garg, 1999). The treatment of cerebral TB, like that of other forms of TB is aimed at killing both intracellular and extracellular organisms and in preventing the development of drug resistance by using several drugs in combination. Early diagnosis, clinical staging of patients at the time of presentation, and the institution of prompt ATT are important factors in determining the outcome of cerebral TB (Muralidhar, 2004).

Based on their efficacy and toxicity, anti-tubercular drugs have been classified into first-line and second-line agents. The first line of antituberculous drugs, namely isoniazid, rifampicin, and pyrazinamide, penetrate well into the CSF. In inflamed meninges, the CSF concentrations of these drugs is at least equal to or higher than those in non-inflamed meninges. Isoniazid, pyrazinamide, ethionamide, and cycloserine penetrate into the CSF well in both inflamed and non-inflamed meninges. Rifampicin penetrates less well. Rifampicin, streptomycin, and ethambutol penetrate in adequate concentrations only when the meninges is inflamed (Donald et al.,1992; Ellard et al.,1993; Joint Tuberculosis Committee of the British, 1998).

- **Regimens of treatment in CNS TB**

The British Thoracic Society (Joint Tuberculosis Committee of the British, 1998) and the Center for Disease Control (CDC) (Snider et al.,1988) recommend quadruple therapy of isoniazid (INH, children 10–20 mg/kg/day, adults 5 mg/kg/day, maximum of 300 mg/kg/day); rifampicin (RMP children 10–20 mg/kg/ day, adults 10 mg/kg/day, maximum of 600 mg/day) for 12 months, supplemented by pyrazinamide (PZA, children and adults 15–30 mg/kg/day, maximum of 2000 mg/day), and a fourth drug at least for the first two months will produce good results. The fourth drug in the initial phase of treatment can be streptomycin (SM, 20–40 mg/kg/day), or ethambutol

(EMB, 15–25 mg/kg/day). Steroids are recommended as adjunctive therapy for severe forms of disease (stage II and III). Recommended duration of therapy is 12 months in uncomplicated cases of cerebral TB, prolonged to 18 months if PZA is omitted or not tolerated. For cerebral tuberculoma without meningitis, the 12-month treatment is still recommended. EMB should be used with caution in unconscious patients (stage III), as visual acuity and other assessment cannot be performed. INH induces peripheral neuropathy in children. Therefore pyridoxine (25–50 mg/kg/day) is included in the treatment regimen, especially for breastfed and malnourished children (Joint Tuberculosis Committee of the British Thoracic Society, 1998).

The occurrence of relapse or the failure of chemotherapy is due to multi drug resistance or poor compliance of patients. Multi-drug resistance (MDR) is defined as resistance to INH or RMP with or without resistance to other anti-tuberculous drugs (Joint Tuberculosis Committee of the British Thoracic Society, 1998). Drug resistance in *M. tuberculosis* isolates may be primary, occurring before chemotherapy, or secondary, developing during the course of ATT. In case of primary resistance to INH, the British Thoracic Society recommends a regimen of RMP, PZA, EMB, and SM for 2 months followed by RMP and EMB for 7 months; in case of secondary resistance, INH must be stopped, EMB (15 mg/kg) and RMP should be administered for 12 months together with PZA for 2 months (Joint Tuberculosis Committee of the British Thoracic Society, 1998). Acquired drug resistance is the main cause of MDRTB. A study by Quy et al., 2003, clearly demonstrates that MDR was the determining factor for failure and relapse cases of TB. Approximately 43% of cases had primary resistance and 65% of cases had acquired drug resistance. TBM caused by MDR *M. tuberculosis* had a very high fatality rate of 85% (Daikos et al., 2003).

The optimal regimens for the treatment of CNS tuberculosis due to atypical mycobacteria in persons with HIV infection have not been finally established, although a four-drug regimen is needed to treat *M. avium* intracellulare infection. Current recommendations include using azithromycin (500–1000 mg/day) and clarithromycin (500 to 1000 mg/day) in combination with ethambutol (15 mg/kg/day) or clofazimine (100 mg/day). Alternative regimens include the use of ciprofloxacin and rifampicin. A significant increase in the frequency of adverse reactions to ATT has been observed in patients with HIV infection (Small et al., 1991; Kemper et al., 1992; Berger, 1994).

○ **Role of corticosteroids**

One of the controversial aspects of treatment of tuberculous meningitis is the use of corticosteroids. The response to steroids may be dramatic with rapid clearing of sensorium, regression of abnormalities of CSF, and relief of headache (Holdiness, 1990; Berger, 1994). It was believed that corticosteroids had no place in the management of tuberculous meningitis because the drug did not alter the clinical outcome, however, more recent studies have shown that corticosteroids improved both survival rate and neurological outcome in patients with tuberculous meningitis (Holdiness, 1990; Kumarvelu et al., 1994). Schoeman et al 1997, confirmed the useful role of corticosteroids in young children. They observed that, in addition to survival, corticosteroids significantly improved intellectual outcome and enhanced resolution of the basal exudates and intracranial tuberculoma shown by serial CT scanning. Corticosteroids is suggested in patients with tuberculous meningitis with one or more of the indications below

- Altered sensorium
- Focal neurological deficit
- Spinal fluid pressure in excess of 300 mmH₂O
- Spinal block (CSF protein > 400 mg/dl)

- Presence of tuberculomas
- Basilar exudates

The usual regimen is prednisolone (60 mg/day in adults and 1–3 mg/kg/day in children) The dosage may reduced by 50% in the second and third week and then be tapered gradually over the next 4 weeks. There is no need for intrathecal corticosteroids (Holdiness, 1990). The main argument against using corticosteroids is that they decrease meningeal inflammation and, in turn, can affect CSF penetration of antituberculous drugs. In a clinical trial in which eight patients were treated with isoniazid, rifampicin, streptomycin and pyrazinamide, in combination with corticosteroids (dexamethasone, 5 mg intravenously hourly during the first week, followed by oral prednisolone, 60 mg daily), the use of corticosteroids did not reduce the CSF concentration of any of the antituberculous drugs (Kaojarern et al.,1991; Schoeman et al.,1997).

Paradoxical worsening has been observed frequently that intracranial tuberculomas appear or paradoxically increase in size while patients are being treated for tuberculous meningitis. These lesions are usually discovered accidentally when follow-up CT scan is performed routinely or when new neurological signs develop during the course of ATT (Teoh et al.,1987) . A recent study noted that about 8% of patients developed asymptomatic tuberculoma during the first month of treatment (Schoeman et al.,1997). Concomitant steroid therapy probably has a preventive role against these focal lesions. Paradoxical enlargement has also been observed in isolated intracranial tuberculoma while the patient was on ATT. However, with continued treatment, eventual resolution of these tuberculoma occurs (Teoh et al.,1987.).

○ Role of Surgery in Treatment of CNS TB

Surgical procedures in patients with tuberculous meningitis are primarily directed to the treatment of hydrocephalus (Holdiness, 1990). Serial lumbar punctures, together with diuretics and osmotic agents are useful as a temporary measure to relieve elevated intracranial pressure, thus probably preventing the progression of hydrocephalus. If these temporary steps fail, ventriculo-peritoneal or ventriculoatrial shunting may relieve the signs and symptoms of hydrocephalus, and may bring considerable improvement in sensorium and neurological deficit. Shunts in these individuals may require revision because the high protein content of CSF causes blockage. As it is generally agreed that shunts can safely be inserted even in the presence of active disease, early shunting with drug therapy may offer the best therapeutic outcome (Leonard and Des Prez, 1990; Berger, 1994).

Intracranial tuberculomas that act as single space-occupying lesions with midline shifts and increased intracranial pressure, and that fail to respond to chemotherapy should be surgically removed. If the tuberculoma is totally removed, about 80% of patients will enjoy long-term recovery, particularly if they were treated in the early stage of the disease (Vengsarkar et al.,1986; Van Dyk, 1988).

In Pott's paraplegia, a combination of surgical decompression and treatment with antituberculous drugs is needed for the majority of patients. A period of 12 months of postoperative ATT is adequate (Miller, 1995; Nussbaum et al.,1995;Razai et al., 1995).

- Prognosis and sequelae

The single most important determinant of outcome, for both survival and sequelae, is the stage of tuberculous meningitis (Table 2) at which treatment has been started. If treatment is started in stage I, mortality and morbidity is very low, while in stage III almost 50% of patients die, and those who recover may have some form of neurological deficit (Holdiness, 1990). About 20% to

30% of survivors manifest a variety of neurological sequelae, the most important of which are mental retardation, psychiatric disorders, seizures, blindness, deafness, ophthalmoplegia and hemiparesis. Endocrinopathies may become evident months or years after recovery. The endocrinopathies are most probably due to progressive damage of either the hypothalamus itself or adjacent basal cisterns. Obesity, hypogonadism, Frolich syndrome, sexual precocity, diabetes insipidus, and growth retardation have been reported. Intracranial calcification develops in 20% to 48% of patients with tuberculous meningitis, usually becoming detectable 2 to 3 years after the onset of the disease (Molavi and LeFrock.,1985; Wallace et al.,1991).

FUNGAL GRANULOMA

Although the first documented case of CNS fungal infection was a case of mucormycosis recorded by Paltauf in 1885, fungal infection of the CNS remained extremely rare. It was not until the advent of immunosuppressive therapy in organ transplant patients and the spread of HIV disease in the general population, that the incidence of CNS fungal infections showed a marked increase. This was evident in a study examining bone marrow transplant patients from 1984 to 1992, 57 of 62 brain abscesses were due to fungi (Alangaden et al., 1994).

Fungal infections of the CNS are almost always a clinical surprise. Their presentation is subtle, often without any diagnostic characteristics, and they are frequently mistaken for tuberculous meningitis, pyogenic abscess, or brain tumor. Only with a high index of suspicion, an aggressive approach to diagnosis, and rapid vigorous therapy may we hope to alter the clinical course in this group of patients (Hall, 1992).

- **Aspergillosis**

Cerebral aspergillosis is a rare condition that affects primarily the immunocompromised host (Walsh et al., 1985; Miaux et al., 1995).

- **Pathology**

Aspergillus is an opportunistic fungus found in soil and plants. It has branching septate hyphae and produces numerous spores. They have worldwide distribution (Saravia-Gomez, 1978). Of more than 200 species of Aspergillus known to exist, only 9 pathogens are known to cause CNS infection, of which the most common is, *A. fumigatus*, but *A. flavus*, *A. niger* and *A. oxyzae* are also frequently seen. Other less common species include *A. amstelodami*, *A. candidus*, *A. glaucus*, *A. versicolor*, and *A. sydowii* (Nov and Cromwell, 1984).

In these patients the common pathway for the fungus to reach the CNS is hematogenous dissemination from extracranial foci, usually the lungs (Cohen, 1991). Infection may also reach the brain directly from the nasal sinuses via vascular channels. Rarely, the infection may also be airborne contaminating the operative field during a neurosurgical procedure (Feely and Sternberg, 1977; Sharma et al., 2000).

Invasive or rhinocerebral aspergillosis results from involvement of the orbit, base of skull, anterior and middle cranial fossae, or parasellar regions with direct extension to the brain. Direct infiltration into the basal bones leads to the more commonly encountered skull base osteomyelitis. Intracranial infection can affect the parenchyma or the meninges. According to the site and nature of infection, the patient may present with features of meningitis, focal neurological signs, or symptoms of raised intracranial pressure (Sharma et al., 1997; Metwally, 2006-3).

The *A. hyphae* can invade directly into the vessel wall, which becomes weakened due to necrosis and polymorphonuclear infiltration, resulting in mycotic aneurysm formation and in one study,

aspergillosis was the most common cause of mycotic aneurysms (Nadkarni and Goel, 2005).

These patients may present with typical subarachnoid hemorrhage syndrome. Intraluminal extension of the hyphae can also initiate thrombus formation. Rarely, major arterial stenosis may occur following leptomenigeal infection. Steroids can inhibit the macrophage response to intracellular fungus and may permit enhanced germination (Nadkarni and Goel, 2005).

Fungal invasion can continue through the arteries and veins (angiotropic) and into the adjacent brain parenchyma (and sometimes in reverse direction). The evolving haemorrhagic infarcts convert into septic infarcts with associated single or multiple abscesses and cerebritis. Purulent lesions may be chronic and have a tendency towards fibrosis and granuloma formation. Microscopically the most striking feature is the intensity of the vascular invasion with thrombosis. In purulent lesions, pus is seen in the center of the abscesses with abundant polymorphs at the periphery. Granulomas consist of lymphocytes, plasma cells, and fungal hyphae (Sharma et al., 2000).

○ Clinical picture

Aspergillosis should be considered in cases manifesting with acute onset of focal neurological deficits resulting from a suspected vascular or space-occupying lesions especially in immunocompromised hosts. In patients with paranasal sinus disease, orbital extension with proptosis, ocular palsies, visual deterioration, and chemosis may occur. The symptoms frequently encountered are headache, vomiting, convulsions, hemiparesis, fever, cranial nerve deficits, paralysis, and sensory impairment of varying degree. Features typical of meningitis and subarachnoid or intracranial hemorrhage may manifest (Saravia, 1978; Hall, 1992; Sharma et al., 2000). Patients are often afebrile or have only a low-grade fever.

In immunocompetent patients, the disease is usually slowly progressive and symptoms may persist for months. However, if brainstem or cerebellar signs were the presenting features rapid neurological deterioration and death usually succumbed (Hall, 1992). Goel et al in 1996, have reported aspergilloma to involve the Gasserian ganglion in two healthy individuals. These paracavernous tumors mimicked a meningioma and a trigeminal neuroma on preoperative imaging and intraoperative consistency and vascularity. The lesions were successfully and completely resected. Both patients developed major cerebral arterial territory infarcts in the postoperative phase, remote from the site of the operation, leading to crippling neurological deficits in one patient, and death in the other. Nadkarni et al in 2003 have reported a similar clinical course in a 32-year-old male with paranasal sinus infection with intracranial extension. This patient succumbed to a basilar artery thrombosis following a left frontal granuloma excision. These cases highlight the unusual location of intracranial aspergilloma and the possibility of ischaemic complications after surgical resection of intracranial aspergilloma (Nadkarni and Goel, 2005).

○ Investigations

Aspergillosis is diagnosed on direct examinations and culture, however, the diagnosis of aspergillosis of the CNS is difficult. The mortality rate of cerebral aspergillosis approaches 100% in these immunocompromised patients (Epstein et al., 1991), but there are occasional case reports noting survival with combined aggressive antifungal therapy and surgical resection (Ashdown et al., 1994). This makes early diagnosis essential. The clinical and laboratory diagnosis of cerebral aspergillosis is difficult, so imaging modalities such as CT and MR are important (Cox et al., 1992; Miaux et al., 1994; Yuh et al., 1994).

■ CSF examination

In general, lumbar puncture is contraindicated in patients with intracranial mass lesions with associated cerebral oedema. So, if possible, spinal fluid analysis frequently shows pleocytosis (600 cells/mm), and moderately elevated CSF proteins are present, but CSF glucose is usually normal (Sharma et al., 1997). There are many exceptions to this picture and virtually any CSF response can occasionally be seen, including a normal spinal fluid. Organisms are rarely found in CSF. The characteristic branching septate hyphae and conidia of *Aspergillus* species are faintly visible with H and E stain and periodic acid-Schiff (PAS) reagent but are most readily seen with Gomori's methenamine silver (GMS) stains. Potassium hydroxide wet preparations can demonstrate *Aspergillus* (Saravia, 1978 ;Hall, 1992).

Aspergillus cultured optimally on Sabourad's agar demonstrates characteristic conidiophores. However, blood and cerebrospinal fluid cultures, even in disseminated disease, are frequently negative (Nadkarni and Goel, 2005).

■ Neuroimaging

To date, there are many reports in the literature about the CT appearance of cerebral aspergillosis in immunocompromised and nonimmunocompromised patients and fewer cases in which MR findings are described. The different neuroimaging patterns reported varied depending on the immune status of the patients and can be divided into infarcts, ring or nodular enhancing lesions consistent with abscesses or granulomas, and localized meningitis. Generally speaking, the more evident is the enhancement, the slower is the course of the illness which in turn implies a better immune status of the patient that is capable of encapsulating the organism and this correlates with a better clinical outcome (Miaux et al., 1995).

On CT scans, septic infarcts present as poorly defined, low-density lesions with little or no mass effect and faint or no contrast enhancement. On T2-weighted MR images, these lesions demonstrate inhomogeneous high signal intensity (Figure 6) (Ashdown et al., 1994), with a low-signal peripheral rim in cases of hemorrhagic infarction and still no apparent contrast enhancement in most of the cases (figure 10)(Yuh et al., 1994).



Figure 6. Aspergillosis, T2-weighted image, Long-repetition-time images shows an infarct in the territory of the left middle cerebral artery due to aspergillosis. (Miaux et al., 1995)

In a study by DeLone et al 1999, examining patients with disseminated CNS aspergillosis, 13 of 18 patients had involvement of the basal ganglia or the thalami (or both), whereas 9 of 10 patients with lesions at the corticomedullary junction also had lesions in the basal ganglia or thalami. Approximately 50% of patients also had associated hemorrhage.

There are few reported cases of patients with ring or nodular enhancing lesions (Wilms et al., 1992; Ashdown et al., 1994). In a case of a bone marrow transplant recipient who survived, there was evolution within several weeks from an infarct to a granuloma, seen as a peripheral rim of low signal intensity on T2-weighted MR images that enhanced after contrast administration (Miaux et al., 1994). However, most of the reported cases of granulomas (Gupta et al., 1990; Coulthard et al., 1991; Wilms et al., 1992) are the result of initial involvement of the paranasal sinuses and/or the orbits and subsequent contiguous spread to the CNS. These lesions present as low- or intermediate- signal lesions on long repetition time MR images (Wilms et al., 1992) with contrast enhancement on CT or MR scans. These cases concern mild to moderate immunocompromised or nonimmunocompromised patients. Most of these patients survived after several weeks or months of evolution. (Gupta et al., 1990; Epstein et al., 1991).

Brain abscess resulting from *Aspergillus* infection is nonspecific on CT scan, typically showing a low-attenuation lesion with an isodense to slightly hyperdense wall, which shows moderate-to-avid enhancement. MR imaging findings may show a low-intensity rim surrounding the abscess with surrounding vasogenic edema on T2-weighted images (figure 7) (Metwally, 2006-3). Pathologic analysis of the wall has shown hemosiderin-laden macrophages and dense population of organisms, which may account for the drop in T2 signal intensity (Cox et al., 1992; Metwally, 2006-3). Ashdown et al in 1994 reported MR findings in four cases of abscesses in mildly to moderately immunocompromised patients. The lesions presented hypointense rings within surrounding edema on T2-weighted images. There was enhancement of the rings on contrast-enhanced T1-weighted images.

- **Biopsy**

Definitive diagnosis requires biopsy or aspiration of a cerebral lesion, but performance of these procedures is often precluded by a patient's clinical status or by coagulation problems. An inferential diagnosis is possible if invasive aspergillosis is documented at other sites (David, 1998).

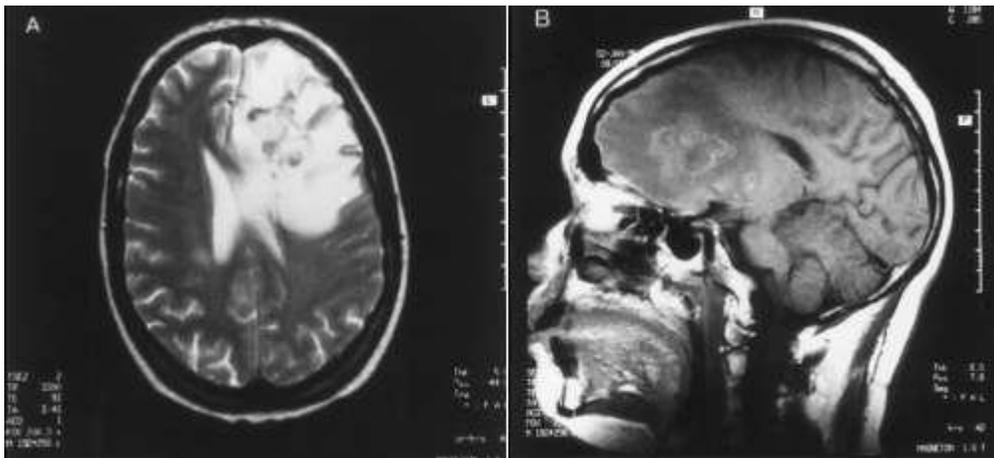


Figure 7. Aspergillosis
Magnetic resonance
images, A (T2-
weighted) shows a
multiloculated abscess
with much surrounding
edema. B, T1-weighted
sagittal image of same
patient showing the
large abscess and
surrounding edema,
although it is less
obvious than on the T2-
weighted image (David,
1998)

- **Treatment**

Aggressive neurosurgical intervention for surgical removal of *Aspergillus* abscesses, granulomas, and focally infarcted brain, correction of underlying risk factors, amphotericin B combined with flucytosine and treatment of the source of infection should form the mainstay of the management (Nadkarni and Goel, 2005).

Surgical debridement enhances abscess penetration by removal of necrotic debris. Radical

surgical debridement can be curative in *Aspergillus* brain abscess if the extent of resection extends into uninvolved tissue. Lobectomy in patients with a single *A. fumigatus* abscess is an acceptable surgical option when noneloquent areas of the brain are involved. In four of seven patients with cerebral aspergillosis, who survived, complete surgical resection of brain abscess was accomplished (Green et al., 1991).

Stereotactic aspiration is the procedure of choice for most brain abscesses, particularly those measuring more than 1.5 cm. Indications for aspiration include aiding in the diagnosis, relieving mass effect, improving the efficacy of drug treatment and it is also used when systemic therapy appears to be ineffective for a presumed organism. Complete aspiration of an abscess is not necessary and can predispose to haemorrhage into the evacuated cavity. Stereotactic drainage or biopsy and systemic, intraventricular or intraocular administration of amphotericin B has been effective in *Aspergillus* abscesses (Hall, 1992).

Amphotericin B has been the mainstay of therapy for the past quarter century. An intravenous test dose of 1 mg or 0.1 mg/kg infused over 30 min to rule out anaphylaxis (occurring in 1% of cases) is recommended. The dose is increased from 0.25 to 1.5 mg/kg as once daily intravenous infusion given over 2-4 h. However, its use is limited by its toxic effects. To reduce the toxicity of amphotericin B, liposomal amphotericin B and its combination with lipids have been introduced. All major advantages of these lipid formulations of amphotericin B are a reduction in two forms of toxicity, which include infusion-related toxicities and nephrotoxicity. In India, Kshirsagar et al upgraded a form of liposomal amphotericin to a patient-worthy, sterile pyrogen free preparation. The same group studied different dosage regimens of liposomal amphotericin in *Aspergillus* model and found that liposomal amphotericin was more effective than equal dose of free amphotericin B. (Kotwani et al., 1996; Kshirsagar et al., 1996; Bohde et al., 2002). This indigenous preparation is significantly cost-effective when compared to similar preparations. Out of the seven patients treated with indigenous liposomal amphotericin B, four had complete response, one had partial response and two had no response (Kshirsagar et al., 2002).

Because of poor penetration into the CSF, when given systemically, direct instillation of amphotericin B into an abscess cavity through an indwelling catheter has also been advocated (Camarata et al., 1992). Combination therapy with 5-fluorocytosine has also been recommended. Rifampicin and 5-fluorocytosine may act synergistically with amphotericin B in CNS fungal disease. The dose of flucytosine is 50-150 mg/kg/day given orally at 6-hourly intervals. Itraconazole (oral 200 mg od), miconazole (infusion of 0.2-1.2 g thrice daily), and sulfamethoxazole have also been effective. These drugs were used to control the spread of the disease and were not curative (Nadkarni Goel, 2005). Another recent study using voriconazole as a monotherapy for 81 patient with definite and suspected CNS aspergellosis showed a complete or partial response occurred in 28 (35%) of 81 patients, which is a promising result (Stefan et al., 2005).

Whenever possible, immunosuppressive therapy should be lowered or discontinued in the compromised host with CNS infection. Unfortunately, rejection is often concomitant with infection, requiring higher doses of immunosuppressive agents. In patients with cancer, systemic disease is frequently stable because of continuing chemotherapy when CNS infection develops.

- **Complications of surgical resection**

The postoperative phase of patients operated for *Aspergillus* infections of the brain is marred by major cerebral arterial territory infarcts remote from the site of infection, leading to crippling neurological deficits and even death. Histological infection has shown fungal hyphae within the wall of the involved arteries. The stress of surgery and the use of steroids to control cerebral edema in the immediate postoperative phase may have been contributory factors in the fungal

growth (Geol et al., 1996; Nadkarni et al., 2003).

- **Prognosis**

The prognosis for CNS aspergillosis is poor, with most reported cases being fatal. Fungal abscesses in patients with cancer are usually fatal (Chernik et al., 1973). An aggressive surgical approach in nonimmunocompromised patients helped to reduce the mortality from 64 to 39% (Young et al., 1985). Intracerebral aspergillosis is frequently fatal in immunocompromised patients, with only 12 reported cases of successful treatment (Camarata et al., 1992).

- **Cryptococcosis**

The HIV pandemic has raised the profile of *Cryptococcus neoformans* from an obscure yeast to the most important fungal cause of morbidity and death worldwide. Previously described as a rare cause of meningitis in the tropics, or in patients with some form of acquired immunodeficiency such as haematological malignancy or organ transplantation, cryptococcal meningitis is now a significant public health burden in developing countries. 20% of all AIDS deaths are due to cryptococcal meningitis, making it the second most common cause of death in HIV infection after TB (French et al. 2002).

- **Pathology**

The organism The genus *Cryptococcus* contains at least 39 species of yeast, but few are able to cause disease in humans (Casadevall and Perfect 1998). Most human infections are due to *C. neoformans*, a dimorphic asexual yeast characterized by oval to spherical cells with a polysaccharide capsule. It reproduces through budding, which is frequently seen in clinical specimens. Yeast form is most commonly found in soil with high concentrations seen predominately in bird droppings, particularly pigeons and chickens (Jeremy, 2004).

The portal of entry into the human body is through inhalation. Once within the pulmonary tree, the organism forms a polysaccharide capsule, which is resistant to phagocytosis. The capsular enlargement may be related to the high carbon dioxide tension present. From the lungs, the cryptococci spread into the intrathoracic lymph nodes and may lie dormant, with reactivation of infection occurring during lapses in the host's immune defenses. On entering the bloodstream, dissemination occurs, predominately within the CNS. In one study, 90% of patients at autopsy had CNS involvement, with the lungs involved in 50% of cases (Karoll and Thomas, 2004). Patients with weakened cell-mediated immunity are at risk, including patients with AIDS, reticuloendothelial malignancies, sarcoidosis, organ transplant, and collagen vascular disease and patients receiving corticosteroid therapy (Perfect and Durack, 1997).

- **Epidemiology**

Incidence Rates of cryptococcosis in non HIV infected individuals approach one case per 100000 population, yet during the AIDS epidemic before highly active antiretroviral therapy in the United States, several cities were reporting rates of 17 to 66 per 1000 patients with AIDS. In Zimbabwe 45% of all meningitis is caused by *Cryptococcus neoformans* (Mwaba et al. 2001).

C. neoformans var A, D are distributed worldwide, while var B, C are present in the tropical and subtropical areas (Jerney, 2004). CNS cryptococcosis is rare in children with AIDS, most cases occur in the 20–50 years old age group (Lewis and Rabinovich, 1972). In contrast to other fungal infections of the CNS, most cases (80%) occur in men. This statistic was evident before the AIDS epidemic and has remained fairly constant and may be related to occupational exposure (Karoll and Thomas, 2004).

○ Clinical picture

The presentation varies. The most frequent symptom in both the immunosuppressed and immunocompetent is headache, occurring in more than 75% of patients. Fever is also common, occurring in more than half of all cases. The duration of symptoms before presentation is likely to be longer in non-AIDS patients, with a history of more than 2 weeks in only 25% of HIV positive patients. Other common symptoms include nausea and vomiting, lethargy, personality change, memory loss, stupor and coma (Casadevall and Perfect, 1998). Neck rigidity seems to be uncommon in HIV patients, occurring in approximately 25%, photophobia (19%), cranial neuropathies (6%) and focal neurological signs appear in 20% (Friedmann et al. 1995). Some African series have reported a higher prevalence of neck stiffness (Moosa and Coovadia 1997).

The commonest complication is raised intracranial pressure (ICP) which occurs in more than 50% of patients. This is probably due to impaired drainage of CSF by polysaccharide capsule (Saag et al., 2000).

Blindness is common in cryptococcal meningitis, particularly in HIV-negative patients. It is thought to be due to raised intracranial pressure, direct invasion of the optic nerve, or adhesive arachnoiditis (Seaton et al., 1997).

○ Investigations

■ CSF examination

Definitive diagnosis of cryptococcal meningitis requires lumbar puncture with demonstration of yeasts with India ink stain, positive cryptococcal antigen testing or culture of the organism. CSF examination generally reveals a mild mononuclear leucocytosis (50–500 cells/ μ L). The CSF protein is rarely greater than 500–1000 mg/dL and it may be normal, especially in HIV patients. In HIV patients, the cell count is usually much lower, and often in single figures. Glucose CSF/blood is usually slightly low (Jerney, 2004). However one study from Africa found that 17% of AIDS patients with cryptococcal meningitis had normal CSF parameters (Moosa and Coovadia 1997).

The CSF India ink test is a simple and relatively sensitive test that enables the rapid diagnosis of cryptococcal meningitis. Its low cost makes it suitable for resource-poor settings. A drop of CSF is placed on a slide and mixed with a drop of India ink. A cover slip is placed on the slide, which is examined under an oil immersion lens. Yeast cells are easily identified through the halo effect that occurs around them because of the glucuronoxylomannan capsule. The sensitivity of the test rises to 75% with centrifugation of the clinical sample. However, a concentration of yeasts less than 10⁴ colony forming units is unlikely to be detected, and therefore all patients should have CSF fungal culture and cryptococcal antigen testing if resources allow (Jerney, 2004).

C. neoformans from CSF or blood grows readily on blood or Sabouraud's agar at 35 °C. But identification can be confirmed through the demonstration of capsule growth on corn meal agar. Culture of CSF is more sensitive in detecting cryptococcal infection than the India ink test, with a sensitivity approaching 90%. Positive culture is more likely with larger volumes of CSF (Jerney, 2004).

Cryptococcal antigen testing is both sensitive and specific in identifying patients with cryptococcal disease. Several commercial kits are available, relying on either latex agglutination or ELISA methodologies. The kits can be used on serum or CSF and the sensitivity in CSF is greater than 90% in cryptococcal meningitis (Aberg et al., 2000).

■ Neuroimaging

The imaging findings related to cryptococcal involvement of the CNS are quite variable, and with regard to cryptococcal meningitis, most cases are negative. The most common finding of cryptococcal infection is a communicating or noncommunicating hydrocephalus (Takasu et al., 1991). Hydrocephalus is more commonly seen in non-AIDS patients in 25% of cases compared with 9% in the immunocompromised population. The lower percentage in the immunocompromised population may be related to an inability to initiate an inflammatory response to the meningoencephalitis or the formation of adhesions within the basal cisterns (Witeman et al., 1996), Leptomeningeal enhancement is an uncommon finding.

Hypoattenuating nonenhancing lesions within the basal ganglia may be present on CT scan and represent dilated Virchow-Robin spaces. These areas are isointense to cerebrospinal fluid without surrounding edema on MR imaging (figure 8). These spaces may become voluminous as the yeasts, which are present in these areas, produce mucoid material that distends these areas. These gelatinous pseudocysts pathologically do not show evidence of an immune response and occasionally may extend into the periventricular region. The presence of gelatinous pseudocysts suggests an immunocompromised state (Zheng et al., 1996). Other patterns of involvement include the miliary form or the presence of granuloma (cryptococcoma), which may be of low or high attenuation on CT scan. On MR imaging, these lesions are typically hypointense on T1-weighted images and hyperintense on T2-weighted images (Figure 9) (Andreula et al., 1993). Immunocompetent patients more often present with cryptococcomas (Ostrow et al., 1994). MR imaging is more sensitive than CT scan in the depiction of these lesions. These lesions may show enhancement after the administration of contrast material. In some instances, the administration of double dose contrast material may show these abnormalities better (Andreula et al., 1993).

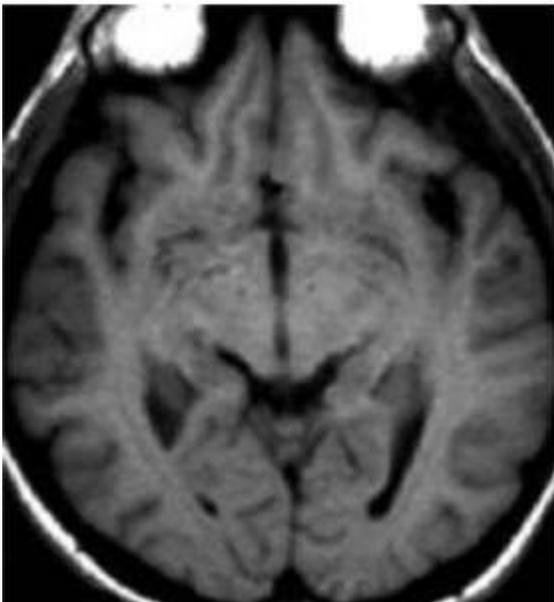
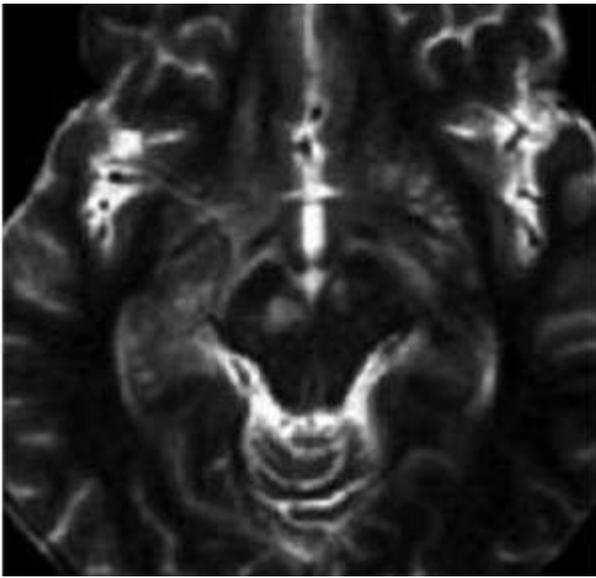


Figure 8. Cryptococcus, T1-weighted MRI demonstrates dilated perivascular spaces in the bilateral basal ganglia (Metwally, 2006-9)

Figure 9. Cryptococcus, T2-weighted axial MRI demonstrates hyperintense cryptococcomas in the



midbrain. (Metwally, 2006-9)

- **Treatment**

Untreated cryptococcal meningitis is uniformly fatal and the anti-fungal drug options are limited.

Amphotericin B is the mainstay of treatment. This broad spectrum drug is fungicidal and in vitro resistance is extremely rare. However, nephrotoxicity is a significant problem, although is usually reversible if the total dose does not exceed 4 g (Khoo et al. 1994).

Flucytosine is a nucleotide analogue. Available in oral and intravenous formulations, it appears to have a synergistic action with amphotericin in vitro (Schwarz et al. 2003). A randomized trial showed a trend towards more rapid CSF sterilization in patients receiving flucytosine in combination with amphotericin compared with amphotericin alone (Van der Horst et al. 1997).

Fluconazole have revolutionized the treatment of fungal infections because of their potency, tolerability, good CSF penetration, and oral and intravenous formulations. Their mechanism of action is inhibition of sterol synthesis by the fungal cell so they may in theory adversely affect the action of amphotericin if used in combination. This has not been born out in animal studies, and there is now good data emerging from the treatment of systemic candidaemia that this is unlikely to be a problem (Rex et al. 2003).

- **Current treatment guidelines**

Treatment guidelines were published for cryptococcal meningitis in 2000 (Saag et al. 2000). There are three phases – induction, consolidation and maintenance (also known as secondary prophylaxis). The guidelines are largely based upon conclusions drawn from a double blind multicenter trial published in 1997 (Van der Horst et al. 1997). This guidelines employs initial induction therapy with amphotericin B at 0.7 mg/kg/day with flucytosine at 100 mg/kg/day for 2 weeks, and then switching to 400 to 800 mg /day of fluconazole for 8 weeks. Patients with AIDS are then given 200 mg/day of fluconazole for indefinite suppressive therapy because of high relapse rate.

- **Rhinocerebral mucormycosis**

Rhinocerebral Mucormycosis is a life-threatening fungal infection that occurs in immunocompromised patients. These infections are becoming increasingly common, yet survival

remains very poor (Brad et al., 2005).

- **Pathology**

Fungi of the order Mucorales are causes of mucormycosis. These fungi are found as ubiquitous bread and fruit molds that thrive in soil, manure, or decaying material (Ribes et al., 2000).

Both mononuclear and polymorphonuclear phagocytes of normal hosts kill Mucorales by the generation of oxidative metabolites and the cationic peptides defensins (Waldorf, 1989). Hyperglycemia and acidosis are known to impair the ability of phagocytes to move toward and kill the organisms by both oxidative and nonoxidative mechanisms. Additionally, corticosteroid treatment affects the ability of bronchoalveolar macrophages to prevent germination of the spores in vitro or after in vivo infection induced by intranasal inoculation (Waldorf et al., 1984)

A recently identified important clinical feature is the increased susceptibility to mucormycosis of patients with elevated available serum iron. It has been known for two decades that patients treated with the iron chelator deferoxamine have a markedly increased incidence of invasive mucormycosis (Boelaert et al., 1994). Multiple lines of evidence support the conclusion that patients in systemic acidosis have elevated levels of available serum iron, likely due to release of iron from binding proteins in the presence of acidosis (Artis et al., 1982).

Transmission occurs through the inhalation of airborne spores, and the typical port of entry is the sinuses. The fungus can grow rapidly, invading the orbit and brain (Metwally, 2006-7).

A hallmark of mucormycosis infections is the virtually uniform presence of extensive angioinvasion with resultant vessel thrombosis and tissue necrosis. This angioinvasion is associated with the ability of the organism to hematogenously disseminate from the original site of infection to other target organs (Bouchara et al., 1996).

Infection spreads along vascular and neuronal structures and infiltrates the walls of blood vessels. Infections cause erosion of bone through walls of the sinus and spread into the orbit and the retro-orbital area and may extend into the brain. Invasion of nerves, blood vessels, cartilage, bone, and meninges is common. Direct invasion by fungal elements results in thrombosis and nerve dysfunction. Advancing infection can result in cavernous sinus thrombosis, carotid artery thrombosis, and jugular vein thrombosis. The term rhinocerebral indicates sinus involvement but does not always mean that CNS invasion has occurred (Metwally, 2006-7).

- **Clinical Presentations**

Rhinocerebral mucormycosis continues to be the most common form of mucormycosis, accounting for between one-third and one-half of all cases. About 70% of rhinocerebral cases are found in diabetic patients in ketoacidosis. More rarely, rhinocerebral mucormycosis has also occurred in patients who received a solid organ transplant or those with prolonged neutropenia (Gleissner et al., 2004). Recently, rhinocerebral disease has been an increasing problem in patients undergoing hematopoietic stem cell transplantation. These cases have largely been associated with steroid use for graft-versus-host disease (Marr et al., 2002).

The initial symptoms of rhinocerebral mucormycosis are consistent with either sinusitis or periorbital cellulitis and include eye or facial pain and facial numbness, followed by the onset of conjunctival suffusion, blurry vision, and soft tissue swelling. Fever is variable and may be absent in up to half of cases; white blood cell counts are typically elevated, as long as the patient has functioning bone marrow (Thajeb et al., 2004). If untreated, infection usually spreads from the ethmoid sinus to the orbit, resulting in loss of extraocular muscle function and proptosis. Marked

chemosis may also be seen. The infection may rapidly extend into the neighboring tissues. Onset of signs and symptoms in the contralateral eye, with resulting bilateral proptosis, chemosis, vision loss, and ophthalmoplegia, is an ominous sign that suggests the development of cavernous sinus thrombosis (Brad et al., 2005).

Upon visual inspection, infected tissue may appear normal during the earliest stages of spread of the fungus. Infected tissue then progresses through an erythematous phase, with or without edema, before onset of a violaceous appearance, and finally the development of a black, necrotic eschar as the blood vessels become thrombosed and tissue infarction occurs. Infection can sometimes extend from the sinuses into the mouth and produce painful, necrotic ulcerations of the hard palate (Petrikkos et al., 2003).

Cranial nerve findings represent extensive infection and signal a grave prognosis. Progressive vision loss and ultimately blindness may result either from involvement of the optic nerve or from arteriolar invasion resulting in infarction or from cavernous sinus thrombosis. Cranial nerves five and seven may also be affected, resulting in ipsilateral loss of facial sensation and ptosis and pupillary dilation. Infection can also spread posteriorly from either the orbit or sinuses to the central nervous system. A bloody nasal discharge may be the first sign that infection has invaded into the brain. When there is extensive central nervous system involvement, the angioinvasive nature of the fungus may result in cavernous sinus thrombosis and internal carotid artery encasement and thrombosis with extensive resulting cerebral infarctions. Occasionally cerebral vascular invasion may lead to hematogenous dissemination of the infection, with or without development of mycotic aneurysms (Thajeb et al., 2004).

- **Investigations**

A high index of suspicion is required to make the diagnosis of rhinocerebral mucormycosis, as evidenced by the fact that autopsy series have found up to half of cases are diagnosed postmortem. Imaging techniques may be suggestive of mucormycosis but are rarely diagnostic. Indeed, the initial imaging study is frequently negative or has only subtle findings (Mori et al., 2003).

Given the limitations of imaging studies, diagnosing mucormycosis almost always requires histopathologic evidence of fungal invasion of the tissues. The organism is rarely isolated from cultures of blood, cerebrospinal fluid, sputum, urine, feces or swabs of infected areas. And even if culture is positive, it is rarely sufficient to establish the diagnosis of mucormycosis, because the causative agent is ubiquitous, may colonize normal persons, and is a relatively frequent laboratory contaminant. Furthermore, waiting for the results of the fungal culture may delay the institution of appropriate therapy (Talmi et al., 2002).

There are no reliable serologic, PCR-based, or skin tests for mucormycosis. Therefore, the diagnosis should be made by biopsy of infected tissues. The biopsy should demonstrate the characteristic wide, ribbon-like, aseptate hyphal elements that branch at right angles. The organisms are often surrounded by extensive necrotic debris. Other fungi, including *Aspergillus*, *Fusarium*, or *Scedosporium* spp, may look similar to the Mucorales on biopsy. However, these molds have septae, are usually thinner, and branch at acute angles (Brad et al., 2005).

- **Imaging**

The most common finding on computerized tomography (CT) scanning of the head or sinuses is subtle sinus mucosal thickening or thickening of the extraocular muscles. It is also common to detect no abnormalities in the bones of the sinuses despite clinical evidence of progressive disease. However, when present, the finding of bony erosion of the sinuses is strongly suggestive of the diagnosis in the appropriate clinical context (e.g., patient in diabetic ketoacidosis with proptosis

(Talmi et al., 2002).

Although evidence of infection of the soft tissues of the orbit may sometimes be seen by CT scan, magnetic resonance imaging is more sensitive. Still, as with CT scans, patients with early rhinocerebral mucormycosis may have a normal magnetic resonance imaging (Fatterpekar et al., 1999).

Because of its propensity for vascular structures, neuroradiologic findings associated with mucormycosis include arteritis, ischemic changes, bland or hemorrhagic infarction, and aneurysm formation. Meningitis is uncommon in the hematogenous form and more common with rhinocerebral or central skull base involvement resulting from direct extension of the infection. Intracranial granuloma formation by mucormycosis is a rare occurrence with few case reports in the literature (Metwally, 2006-3).

In addition to the aforementioned findings, CT scan findings may show hypoattenuating lesions with adjacent edema on precontrast examination. Hemorrhage may also be present. Ring enhancement may be shown after the administration of contrast material. The signal intensity of intracerebral lesions has been described in a number of case reports involving the basal ganglia region with suggestion of hemorrhage as exhibited by high signal intensity on T1-weighted images. The corresponding areas showed hyperintense signal on T2-weighted images secondary to associated edema. The signal intensity seen within the sinuses on MR imaging in the rhinocerebral form of mucormycosis is similar to that described for aspergillosis (Terk et al., 1992).

- **Treatment**

Four factors are critical for eradicating mucormycosis: rapidity of diagnosis, reversal of the underlying predisposing factors (if possible), appropriate surgical debridement of infected tissue, and appropriate antifungal therapy. Early diagnosis is important because small, focal lesions can often be surgically excised before they progress to involve critical structures or disseminate (Nithyanandam et al., 2003).

Because patients with rhinocerebral disease may initially present with normal mental status and appear clinically stable, the urgency for establishing the diagnosis is frequently underappreciated. The key concept is that initial spread of the fungus to the brain may be relatively asymptomatic. Once the fungus has penetrated the cranium or entered the major intracranial vasculature, mortality increases substantially. And it is critically important to emphasize that if mucormycosis is suspected, initial empirical therapy with a polyene antifungal should begin while the diagnosis is being confirmed, rather than waiting while a protracted series of diagnostic tests are completed (Brad et al., 2005).

Only members of the polyene class, including amphotericin B deoxycholate and its lipid derivatives, had been demonstrated to have activity against the agents of mucormycosis. Furthermore, the various species that cause mucormycosis have a broad range of susceptibilities to amphotericin. Therefore, the recommended dose of amphotericin B deoxycholate has been 1 to 1.5 mg/kg/day, which results in a very high toxicity rate (Ibrahim et al., 2003-a). High-dose liposomal amphotericin B (15 mg/kg/day) was considerably more effective than amphotericin B deoxycholate (1 mg/kg/day), nearly doubling the survival rate (Ibrahim et al., 2003-b).

Surgery is necessary due to the massive amount of tissue necrosis occurring during mucormycosis, which may not be prevented by killing the organism. Surgical debridement of infected and necrotic tissue should be performed on an urgent basis (Ibrahim et al., 2005).

- **Coccidioidomycosis**

The organism responsible for coccidioidomycosis, *Coccidioides immitis*, is a dimorphic yeast found in soil and is endemic primarily in Arizona and southern California in the San Joaquin valley as well as parts of Central and South America. These fungi may exist in the mycelial or hyphal forms. The spores are extremely virulent and are resilient to drastic changes in temperature, lying quiescent within the soil. Human inoculation occurs when there is perturbation of the soil, such as from farming or construction, with release of the spores and inhalation. A self-limiting upper respiratory infection may ensue, which may be subclinical in presentation. Dissemination throughout the rest of the body may occur in 0.2 % to 1 % of cases (Ostrow and Kudgins, 1994). Risk factors for disseminated disease include pregnancy, diabetes mellitus, and immunocompromised state (Bouza et al., 1981).

The most common CNS manifestation of coccidioidomycosis was meningitis, which was seen in two thirds of patients. Meningitis usually involves the basilar meninges (Figure 10). A patient may report only a headache; other signs of meningeal irritation are usually absent (Kelly, 1980; Bouza et al., 1981). Meningitis associated with cerebritis and hydrocephalus has also been reported, occurring in 78% and 13% of patients. Other radiological manifestations include abscess formations and granuloma formation (Scanarini et al., 1991). Obstructive hydrocephalus secondary to ependymitis has also been described (Metwally, 2006).

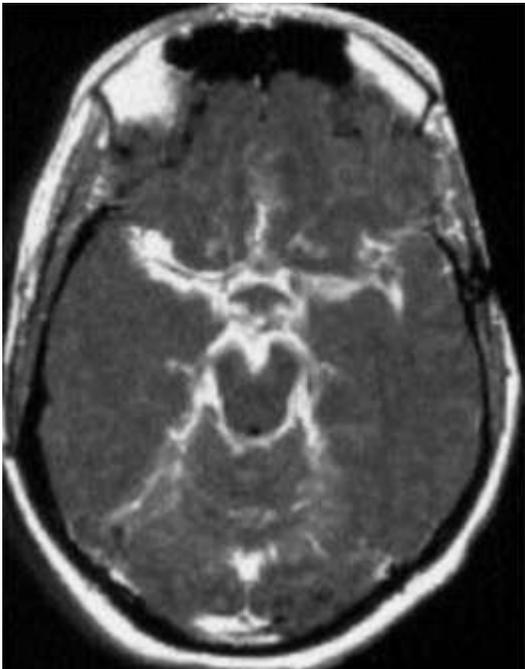


Figure 10. Coccidioidomycosis, Post-contrast axial T1-weighted MRI reveals extensive enhancement throughout the basal cisterns (Anita et al., 2001)

The diagnosis is often late, because the infection is not considered initially. Such cases may occur because of a recent visit to an area where disease is endemic, reactivation of an infection acquired earlier in such an area, or infection by fomites from an area of endemic disease, such as spores on an automobile or on fruit (Pappagianis, 1988).

The diagnosis of *C. immitis* meningitis must be considered in patients who have visited or lived in an area of endemic disease. Examination of the cerebrospinal fluid shows a mononuclear pleocytosis, with a low glucose level and an elevated protein level. Yet, cerebrospinal fluid cultures are usually negative. The demonstration of antibody (IgG) in cerebrospinal fluid is another way to confirm the diagnosis. Since antibody is absent early in the course of the disease, repeated testing may be required (David, 1995). The complement fixing antibodies (CFA) are the hallmark of disseminated coccidiomycosis. If the patient does not have meningitis CFA titers are usually negative in unconcentrated CSF. CFA is positive in at least 70% of patients by time of diagnosis, and almost all patients as the infection progresses, also CFA titre parallels the course of meningeal

disease and can be used as a basis for diagnosis and treatment (Bouza et al., 1981).

The traditional treatment of *C. immitis* meningitis consists of the administration of amphotericin B directly into the cerebrospinal fluid by the lumbar or cisternal route or into the ventricles or other sites through a reservoir (David, 1995). To minimize the possibility of side effects, such as fever, neuropathy, and back pain, it is advisable to begin with a low dose and increase it gradually. Amphotericin B should be given daily at first, then tapered (from every other day to once every six weeks) as clinical improvement occurs, as indicated by signs, symptoms, cerebrospinal fluid leukocyte counts and antibody titers (Drutz, 1983).

Therapy is usually required for at least a year. The cerebrospinal fluid should be examined for one to two years after therapy (at first weekly and eventually every six weeks) if the patient has a complete remission of meningitis, because relapse is common. The drug is delivered by barbotage (gradual instillation and mixing of the drug with cerebrospinal fluid withdrawn into the syringe) or by suspension in hypertonic glucose while the patient is lying on his or her side, with the head of the table tilted down. Complications may include pain, headaches, paresthesias, and nerve palsies. These complications are attributed to arachnoiditis or direct neurotoxic effects and are usually transient, although some neurological deficits may become permanent. The cisternal route of administration places the drug closest to the site of maximal involvement but may entail additional complications, including hypertension, arrhythmias, and impairment of upper motor neurons, as well as the risk of hemorrhage or direct puncture of the brain. Ventricular therapy may be necessary if ventriculitis is present. If the flow of cerebrospinal fluid is obstructed by infection or fibrosis, detected by imaging studies, therapy into several fluid compartments may be necessary. Shunting of the cerebrospinal fluid may be required if hydrocephalus develops (Drutz, 1983).

The oral azoles offer a useful alternative treatment of meningeal disease, at the same doses as those used for nonmeningeal disease, are associated with a high rate of response (67 to 88 percent in various series). Responses with azoles have been seen when used as the primary therapy, after the failure of amphotericin B therapy, or to lessen the amount of intracerebrospinal fluid therapy usually needed to achieve a remission. Unfortunately, preliminary data suggest very high rates of relapse (about 75 percent) after azole therapy is stopped. Even if *C. immitis* infection cannot be cured with azole therapy and lifelong suppression is required, the facts that these medications are well tolerated, do not have the toxic effects of amphotericin B, and do not require administration into the cerebrospinal fluid may represent important advantages in patients with an otherwise fatal illness (Tucker et al., 1990a; Tucker et al., 1990b; Galgiani et al., 1993).

- **Candida**

Candida is present as a part of the normal intestinal flora. It rarely cause CNS disease unless host defenses have been impaired. The factors that encourage spread of *Candida* in the blood include prematurity, broad spectrum antibiotics, hyperalimentation, malignancy, indwelling catheters, corticosteroids, neutropnia, diabetes, and parental drug abuse (Buchs and Pfister, 1983).

Candida are present as yeast forms, with reproduction resulting from budding and the formation of pseudohyphae, which, in general, are smaller than hyphal forms. There are seven clinically important species of *Candida*, including *C. albicans*, *C. tropicalis*, *C. krusei*, *C. stellatoidea*, *C. parapsilosis*, *C. pseudotropicalis*, and *C. guilliermondii*. Of these, *C. albicans* most often causes CNS infection, although there have been reports of meningitis due to *C. tropicalis* and embolic abscess due to *C. guilliermondii* (Salaki et al., 1984; Lyons and Andriole, 1986).

In patients with disseminated *Candida*, the most common organ involved is the kidneys with the brain being the second most common organ involved (Salaki et al., 1984). The frequency of CNS

involvement in the setting of disseminated disease is approximately 50% (Burgert et al., 1995).

In premature infants and neonates, meningitis is the most common form of candida CNS infection (Fernandez et al., 2000). It can also occur in older children (McCullers et al., 2000). In adults, candida infection of the CNS which is common in patients with neutropenic cancer often presents with brain abscesses and granuloma rather than meningitis. Candida meningitis may present with acute symptoms or a chronic neutrophilic meningitis. (Del Pozo et al., 1998)

Candida organisms tend to cause focal necrosis in the area around the microcirculation, producing micro abscesses (Becker, 1992) located mainly at the gray–white matter junction, in the basal ganglia, and in the cerebellum (Pendlebury, 1989). All parts of the CNS are involved with no apparent areas of predilection. Candida organisms also may cause vasculitis, intraparenchymal hemorrhage, mycotic aneurysms, and thrombosis of small vessels with secondary infarction. Granuloma like lesions and large abscess are rare (Lipton et al., 1984).

CNS candidiasis is usually indolent initially, the most consistent features being progressive confusion and lethargy. Because the neurological signs and symptoms of *C. albicans* infection are vague and fleeting, most cases of CNS. Candidiasis are diagnosed just before death or during postmortem pathologic study (Chaabane, 1989).

The radiological presentation of CNS candidiasis includes meningitis, meningoencephalitis, microabscess and granuloma formation, brain abscess, and ependymitis. Vascular complications described include mycotic aneurysm formation as well as vascular invasion with secondary thrombosis and ischemia or infarct. In one series, fungal ball formation was seen in one patient (Lipton et al., 1984; De La Paz and Enzmamm, 1988).

On CT scan, the microabscesses and granulomas typically show enhancement. On MR imaging, a number of authors have suggested that hypointense to isointense signal on T2- weighted images may be helpful in distinguishing fungal granuloma. A target appearance has been previously described in candidal abscess, which on T2-weighted images shows a well-delineated hypointense area surrounded by a hyperintense rim (Zheng et al., 1996).

- **Treatment**

Amphotericin B is the primary therapeutic agent because of experience. The combination of amphotericin B with flucytosine gives a synergistic activity against candida in vitro. Flucytosine reaches high concentration in CSF and appears to be effective. Review of literature suggest that this combination provides a good cure rate. Today the mortality of Candida meningitis has been reduced to approximately 10-20%. Fluconazole is also successful in many cases (Smego et al., 1984).

- **Histoplasmosis**

Histoplasma capsulatum is a yeast form endemic primarily in the Ohio, Mississippi, and St. Lawrence River valleys. Greater than 90% of people living in endemic areas demonstrate previous exposure as shown from skin tests. In nonendemic populations, CNS histoplasmosis is more common in immunocompromised individuals. In immunocompetent individuals, those at risk for infection are primarily infants and the elderly. In a previous study, 24% of patients with disseminated histoplasmosis had CNS involvement. Men outnumber women 5:1, which may be related to occupational exposure. The portal of entry into the human body is through inhalation of airborne spores. As a result, pulmonary manifestations far outweigh CNS involvement (George and Penn, 1993). Intracranial involvement by histoplasmosis results from hematogenous spread and disseminated disease. Meningitis complicates 10% of these cases but occurs occasionally in

immunocompetent patients. Symptoms are usually indolent and chronic, such as fever, headache, and mental status changes. Seizures and focal neurologic deficits can occur. Localized lesions in the brain occur in one third of patients with CNS involvement (Metwally, 2006-3, Metwally, 2006-8).

The laboratory diagnosis of fungal disease is general, and histoplasmosis particularly is challenging because of the nonspecific clinical findings, the difficulty of culturing organisms, and the confusing array of diagnostic tests available (Metwally, 2006-8).

The typical radiologic manifestations of CNS histoplasmosis include meningitis, encephalitis, granuloma formation (histoplasmoma), and brain abscess. In a few case reports, a military form of CNS histoplasmosis as well as vasculitis has been previously reported. The CT scan and MR imaging characteristics of CNS histoplasmosis are nonspecific relative to other fungal infections, and diagnosis is typically made from cerebrospinal fluid analysis or from brain biopsy (Stone et al., 1998; Hadi et al., 1999).

Most acute forms of histoplasmosis in immunocompetent hosts resolve without specific treatment. Systemic antifungal treatment is indicated for severe cases and any manifestation in an immunocompromised patient (George and Penn, 1993).

PARASITIC GRANULOMA

- **Cysticercosis**

Before the introduction of modern neuroimaging diagnostic techniques, knowledge of the natural history of cysticercosis was limited and largely based on cases diagnosed either by the presence of subcutaneous nodules, plain X-rays showing calcifications in the brain or soft tissues, surgery of cases with intracranial hypertension, or from necropsy data (Dixon and Lipscomb, 1961). The image of an aggressive, lethal disease arose from this clearly biased (towards more severe infestations) group of cases. During the last two decades, the introduction of CT and later MRI permitted the identification of mild cases with only a few parenchymal cysts (Estanol et al., 1986). Later, studies in India showed that a vast majority of single enhancing lesions, until then attributed to TB, were in fact degenerating cysticerci (Chandy et al., 1991; Rajshekhar, 1991).

- **Pathology**

Taenia solium is a two-host zoonotic cestode. The adult stage is a 2 to 4mm long tapeworm that lives in the small intestine of humans. No other final hosts are known for *T. solium* tapeworms in nature. As in all cestodes, the gravid proglottids at the terminal end of the worm are full of eggs that are the source of infection with the larval stage, or cysticercoids. The natural intermediate host is the pig, harboring larval cysts anywhere in its body. Humans become infected with cysts by accidental ingestion of *T. solium* infective eggs by fecal-oral contamination (Hector et al., 2002).

After ingestion of *Taenia* eggs containing infective oncospheres, the parasites become established in the tissues as larval cysts and reach their mature size in about 3 months. The parasite may locate almost anywhere in the body. The infection burden varies from a single lesion to several hundreds, and lesions may range in size from a few millimeters to several centimeters (Garcia and Del Brutto, 2000). Laboratory studies and information suggest that viable cysts actively modulate the host's immune system to evade destruction by it (White et al., 1997).

The natural history of cysticercosis has been studied by pathological examination and imaging studies using CT and MRI. Viable cysts are 10 to 20 mm in diameter, thin-walled sacks filled with clear cyst fluid. There is little or no evidence of perilesional inflammation, and they do not

enhance with contrast media on neuroimaging. As the parasite loses the ability to control the host immune response, an inflammatory process begins. Initially, the cysts show slight pericystic contrast enhancement. Later they become markedly inflamed and edematous and appear as ring-like or nodular areas of enhancement after the injection of contrast. This phase has been called "granulomatous cysticercosis," or "enhancing lesions." Finally, the cyst is processed by the cellular response, and its remnants either are not detectable by imaging or become calcified lesions. "Giant" cysts, measuring more than 50 mm in diameter, are occasionally found, located primarily in the Sylvian fissure. Cysticercotic encephalitis is a rare form of the disease in which patients have numerous inflamed cysticerci, leading to diffuse, severe cerebral edema (Escobar, 1983; Kramer et al., 1989; Dumas et al., 1997).

Symptomatic disease results almost exclusively from the invasion of the nervous system (neurocysticercosis) and the eye and is clearly differentiated into parenchymal neurocysticercosis and extraparenchymal neurocysticercosis. The usual presentation of parenchymal neurocysticercosis is with seizures. Occasionally, the cysts may grow and produce a mass effect. Extraparenchymal infection may cause hydrocephalus by mechanical obstruction of the ventricles or the basal cisterns, either by the cysts themselves or by an inflammatory reaction (ependymitis and/or arachnoiditis). The so called racemose variety occurs in the ventricles or basal cisterns and is characterized by abnormal growth of cystic membranes with degeneration of the parasite's head (scolex). These cases follow a progressive course, and even after ventricular shunting, the membranes or inflammatory cells and proteins frequently block the shunt (Rabiela et al., 1989).

○ Clinical picture

In most patients, neurocysticercosis seems to produce symptoms years after the initial invasion of the nervous system (Del Brutto and Sotelo, 1988), by either inflammation around the parasite, mass effect, or residual scarring. There is a clear association between inflammation around one or more cysts and development of symptoms, especially with regard to seizures (White et al., 1997).

The usual presentation of parenchymal neurocysticercosis is with seizures, which is either focal, focal with secondary generalization or generalized. Electroencephalographic (EEG) studies for patients with active disease may reveal focal abnormalities. The seizures are usually easily controlled with antiepileptic drug therapy (Carpio and Hauser, 2002).

Headache is common among patients with Neurocysticercosis. It could be hemicranial or bilateral, and may be seen with parenchymal, ventricular or cisternal involvement (Rajshekhar, 2000). Patients may also present with symptoms and signs of raised ICP. Symptoms may include nausea or vomiting, altered mental status, visual changes, or dizziness. The patients with cysticercal encephalitis may have altered mental status raised ICP, or seizures (Rangel et al., 1987).

○ Diagnosis

The diagnosis of neurocysticercosis is difficult because clinical manifestations are nonspecific, most neuroimaging findings are not pathognomonic, and some serologic tests have low sensitivity and specificity. A set of diagnostic criteria was proposed in 1996 and recently revisited (Del Brutto et al., 2001), based on objective clinical, imaging, immunological, and epidemiological data; these criteria consist of four categories that are stratified according to their diagnostic strength (Table 4). These criteria provide two degrees of diagnostic certainty. Definitive diagnosis, in patients who have one absolute criterion or in those who have two major plus one minor and one epidemiologic criteria; and probable diagnosis, in patients who have one major plus two minor criteria, in those who have one major plus one minor and one epidemiologic criteria, and in those who have three minor plus one epidemiologic criteria. This chart of diagnostic criteria for neurocysticercosis has not yet been tested in hospital-based studies (Del Brutto et al., 2001).

Table 4. Diagnostic criteria for neurocysticercosis (DeI Brutto et al., 2001)

Absolute

- **Histological demonstration of the parasite from biopsy of a brain or spinal cord lesion**
- **Cystic lesions showing the scolex on CT or MRI**
- **Direct visualization of subretinal parasites by fundoscopic examination**

Major

- **Lesions highly suggestive of neurocysticercosis on neuroimaging studies**
- **Positive serum immunoblot for the detection of anticysticercal antibodies**
- **Resolution of intracranial cystic lesions after therapy with albendazole or praziquantel**
- **Spontaneous resolution of small single enhancing lesions**

Minor

- **Lesions compatible with neurocysticercosis on neuroimaging studies**
- **Clinical manifestations suggestive of neurocysticercosis**
- **Positive CSF ELISA for detection of anticysticercal antibodies or cysticercal antigens**
- **Cysticercosis outside the central nervous system**
- **Epidemiologic**
- **Evidence of a household contact with T. solium infection**
- **Individuals coming from or living in an area where cysticercosis is endemic**
- **History of frequent travel to disease-endemic areas**

○ **Investigations**

Demonstration of T. Solium infection in biopsy or autopsy material makes a conclusive diagnosis but is rarely available. Also the parasites may be visualized directly during ophthalmologic examination, when there is ocular involvement(Cardenas et al., 1992). These are considered absolute criteria for diagnosis.

■ **Serology**

Antibody detection assays have proven problematic in cysticercosis because of cross reactions to other common parasites and nonspecific binding of antibody by the parasite. Thus assays that employ crude antigen have proven problematic. The immunoblot assay employing semipurified membrane antigens, termed enzyme-linked immunotranfer blot (EITB) provided better results

and was initially reported to be 98% sensitive and 100% specific for cysticercosis (Tsang et al., 1989). Subsequent studies have confirmed nearly 100% specificity, but the sensitivity is limited in patients with either a single lesion or only calcified lesions. Thus, detection of antibody by the EIBT assay is considered a major diagnostic criterion (Wilson et al., 1991).

- **Neuroimaging**

On imaging studies, Viable cysts appears as 10 to 20 mm cysts, the wall is not visible and the fluid is isodense with the cerebrospinal fluid. There is little or no evidence of perilesional inflammation, and they do not enhance with contrast media (Figure 11,12). As the parasite loses the ability to control the host immune response, an inflammatory process begins. Initially, the cysts show slight pericystic contrast enhancement. Later they become markedly inflamed and edematous and appear as ring-like or nodular areas of enhancement after the injection of contrast. Finally, the cyst is processed by the cellular response, and its remnants either are not detectable by imaging or become calcified lesions. These calcifications appear on CT as solid, dense, supratentorial measuring 2 to 10 mm in diameter, and in the absence of evidence of other illness should be considered as highly suggestive of neurocysticercosis (Del Brutto et al., 2001).

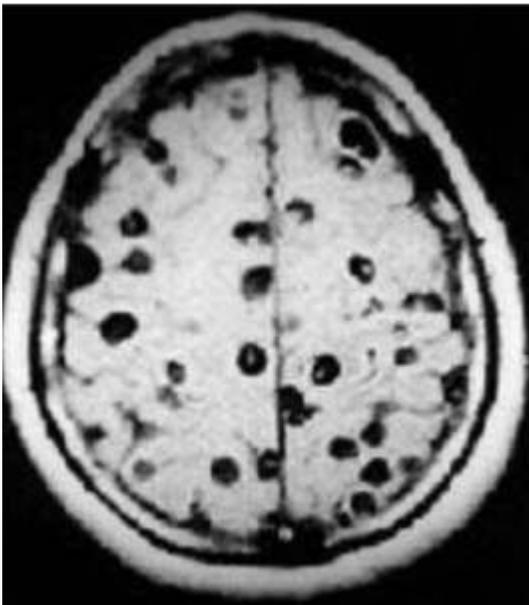
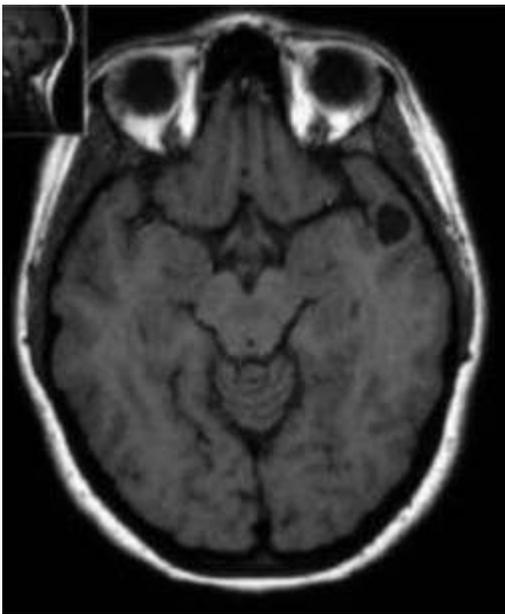


Figure 11. Neurocysticercosis. MRI of multiple cysts (Metwally, 2006-10)

Figure 12. Neurocysticercosis. MRI of a patient with left temporal lobe epilepsy and a single cyst. (Metwally, 2006-10)



Giant cysts, measuring more than 50 mm in diameter, are occasionally found, located primarily in the Sylvian fissure. Extraparenchymal neurocysticercosis includes cysticerci in the ventricles and basal cisterns and since the cyst membrane is thin and the fluid is isodense with the cerebrospinal fluid, uninfamed extraparenchymal cysticerci are usually not visible on CT and may only reveal subtle, indirect findings on MRI. Scans may reveal hydrocephalus without noticeable cysts, ependymitis, distorted basal cisterns, or basal meningitis. Cysticercotic encephalitis is a rare form of the disease in which patients have numerous inflamed cysticerci, leading to diffuse, severe cerebral edema (Kramer et al., 1989; Dumas et al., 1997;). Neuroimaging studies may reveal a cystic lesion with an associated scolex, and this is thought to be pathognomonic for cysticercosis, although it has never been rigorously tested (Zee et al., 2000).

- **Treatment**

Therapeutic measures include antiparasitic drugs, symptomatic medication and surgery.

Antiparasitic drugs as praziquantel and albendazole are effective antiparasitic drugs against *T. solium* cysticerci. Initial studies with praziquantel noted that doses as low as 5 to 10 mg/kg/day had some effect against cysts, and doses as high as 50 to 75 mg/kg/day were well tolerated. A dosage of 50 mg/kg/day for 2 weeks was adopted by most subsequent studies (Bittencourt et al., 1990; Takayanagui and Jardim, 1992), although a single-day regimen of praziquantel has recently been described, with similar rates of cyst disappearance in some groups of patients (Lopez-Gamez et al., 2001; Pretell et al., 2001). No dose ranging studies were performed with albendazole in cysticercosis. Instead, the dose previously used in hydatid disease (15 mg/kg/day) was used for cysticercosis. The initial length of therapy was 1 month, later reduced to 15 days and 1 week (Garcia et al., 1997). There is limited experience with higher doses of both drugs (Gongora et al., 2001). Between 60% and 85% of parenchymal brain cysticerci are killed after standard courses of treatment, with most trials showing a higher parasitocidal effect of albendazole.

Symptomatic and anti-inflammatory medication as Corticosteroids are frequently used in patients with neurocysticercosis. The most frequent regimen is dexamethasone at doses of between 4.5 and 12 mg/day. Prednisone at 1 mg/kg/day may replace dexamethasone when long-term steroid therapy is required. Corticosteroids are frequently used to decrease neurological symptoms due to the death of the parasite and are the primary management for chronic cysticercosis arachnoiditis or encephalitis, where up to 32 mg of dexamethasone per day is needed to reduce the brain edema

(Del Brutto et al., 1993).

Other medications commonly used to treat symptoms in neurocysticercosis patients are antiepileptic drugs and analgesics. Seizures secondary to neurocysticercosis usually respond well to first-line antiepileptic. Withdrawal of antiepileptic drugs can be achieved, although residual calcifications on CT scan mark patients for whom the risk of recurrent seizures is high (Carpio et al., 1998).

Between the second and fifth days of antiparasitic therapy, there is usually an exacerbation of neurological symptoms, attributed to local inflammation due to the death of the larvae. For this reason, both albendazole and praziquantel are generally given simultaneously with steroids in order to control the edema and intracranial hypertension that may occur as a result of therapy (Hector et al., 2002).

After the initial descriptions of successful use of praziquantel and albendazole in neurocysticercosis, several case series noted that some types of parenchymal neurocysticercosis can resolve on imaging studies without being treated with antiparasitic drugs (Mitchell et al., 1988). Since then, an alternative opinion has been voiced that the acute, severe brain inflammation resulting from their use is unnecessary because parenchymal brain cysticercosis follows a benign course and cysts will degenerate and heal by natural evolution of the disease (Carpio et al., 1995).

■ Surgical Treatment

Prior to the advent of antiparasitic drugs, surgery was the primary therapy for neurocysticercosis, mainly open surgery for excision of large cysts or cysts in the ventricles. The role of surgical therapy in the management of neurocysticercosis has significantly decreased over time and is now mainly restricted to placement of ventricular shunts for hydrocephalus secondary to neurocysticercosis. The main problem in these cases is the high prevalence of shunt dysfunction; indeed, it is common for patients with hydrocephalus secondary to neurocysticercosis to have two or three shunt revisions (Madrado and Flisser, 1992). The protracted clinical course of these patients and their high mortality rates (up to 50% in two years) were directly related to the number of surgical interventions to change the shunt (Colli et al., 1986). According to one report, maintenance steroid therapy may decrease the frequency of shunt blockages (Suastegui et al., 1996). Many authors advocate shunting combined with antiparasitic drugs to further reduce the incidence of shunt failure (Bandres et al., 1992; Proano et al., 1997). Recently, less invasive procedures have been described, specifically the use of neuroendoscopic resection for ventricular cysts (Bergsneider, 1999). Overall results have been excellent, with much less morbidity than with open surgery (Bergsneider et al., 2000).

• Toxoplasmosis

Cerebral toxoplasmosis is caused by the protozoan *Toxoplasma gondii*. Disease occurs almost exclusively because of reactivation of latent tissue cysts (Israelski et al., 1993). Primary infection occasionally is associated with acute cerebral or disseminated disease. Seroprevalence varies substantially among different communities (e.g., approximately 15% in the United States and 50%-75% in certain European countries) (Mathews and Fullerton, 1994). In the pre Anti-Retroviral Therapy (ART) era, for patients with AIDS who were seropositive for *T. gondii* and not receiving prophylaxis with drugs active against *T. gondii*, the 12-month incidence of toxoplasma encephalitis was approximately 33%. The incidence and associated mortality in Europe and the United States has decreased substantially with the initiation of Anti Retroviral Therapy ART and the broad use of prophylaxis regimens active against *T. gondii* (Duval and Leport, 2001).

○ Pathology

Toxoplasmosis is caused by an intracellular protozoan. The three forms of the parasite are the trophozoite, cyst and oocyst. The trophozoites are responsible for the acute infection and the cysts are present in multiple organs in the latent form (Bia and Barry, 1986). The human beings acquire the infection by ingestion of the oocyst, the ingestion of poorly cooked infected meat, and by congenital infection in utero. *T. gondii*, like other opportunistic pathogens, has a high prevalence rate in many populated groups and is capable of living in multiple tissues for the entire life of its host (Bollinger et al., 1995).

After oral ingestion, it is carried as latent infection without causing disease. IgG and IgM are produced following an infection with *T. gondii*. Cell mediated immunity may be the critical determinate in controlling toxoplasmosis with assistance of humoral response but it is not fully protective. Interferon gamma is an absolute requirement for resistance against acquired infection with *T. gondii* and development of Toxoplasmic encephalitis during the late stage of the infection.? TE in AIDS patients is most likely from reactivation of latent infection. The most common affected area is the basal ganglia but other lesions may involve cerebellar and brain stem areas. Outside the CNS, the lungs, retina, and myocardium may also be affected (Luis, 2006).

○ Clinical picture

Clinical symptoms depend on the localization of lesions, with acute onset within a few days. The major signs include focal neurological deficits such as paresis, speech problems or sensory loss (Porter and Sande 1992). A febrile psychosyndrome with confusion is also frequently an early sign. It is not unusual to see an epileptic seizure as the initial presentation, in the absence of other symptoms. Headaches with fever or subfebrile temperatures are always suspicious. Meningitic signs, however, are less typical. Atypical manifestations in patients with immune reconstitution under ART have been described (Ghosn et al, 2003).

A fairly rare, but important manifestation is *Toxoplasma* chorioretinitis. It causes impairment of vision and is an important differential diagnosis to CMV retinitis and may occur on its own (Rodgers and Harris, 1996).

The most common clinical presentation of *T. gondii* infection among patients with AIDS is a focal encephalitis with headache, confusion, or motor weakness and fever (Luft et al., 1984). Physical examination might demonstrate focal neurological abnormalities, and in the absence of treatment, disease progression results in seizures, stupor, and coma. Retinochoroiditis, pneumonia, and evidence of other multifocal organ system involvement can be seen after dissemination of infection but are rare manifestations in this patient population (Wong et al., 1984).

○ Investigations

The serological tests are of limited use in clinical diagnosis owing to the high seronegativity (16%-22%) in IgG titers in patients confirmed to have CNS toxoplasmosis. These tests prove to be useful when the non detection of IgG titers along with single lesion in the radiological studies may indicate the need for a histopathological diagnosis before initiating treatment. A negative serological test should not be used to exclude the diagnosis of toxoplasmosis in patients with AIDS (Porter and Sande, 1992).

Detection of *T. gondii* by polymerase chain reaction (PCR) in cerebrospinal fluid has produced disappointing results; although specificity is high (96%-100%), sensitivity is low (50%) and the results usually are negative once specific anti-toxoplasma therapy has been started (Novati et al., 1994 and Cinque et al., 1997).

CT scan shows multiple, bilateral, hypodense lesions which enhance in the periphery with contrast

(Figure 13). Porter et al have found only 10% of lesions to be non enhancing on a CT scan. Among the rest, 82% were peripherally enhancing. The lack of contrast enhancement may be due to the paucity of inflammation or less vigorous peripheral vascular proliferation. The median number of lesions detected in a CT scan was 2 and in about 27% of patients the lesion was solitary (Navia et al., 1986).

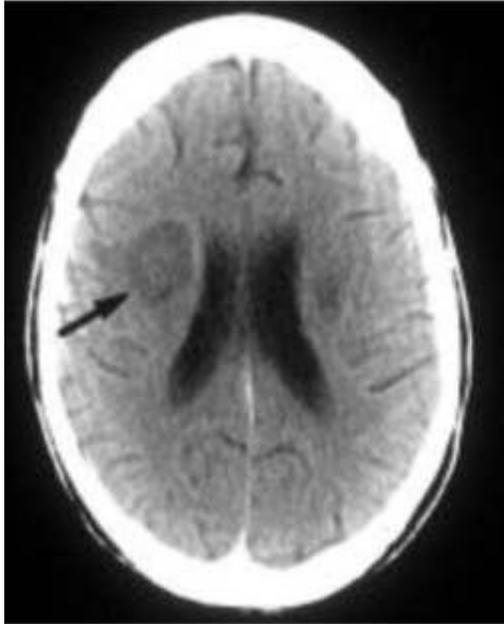
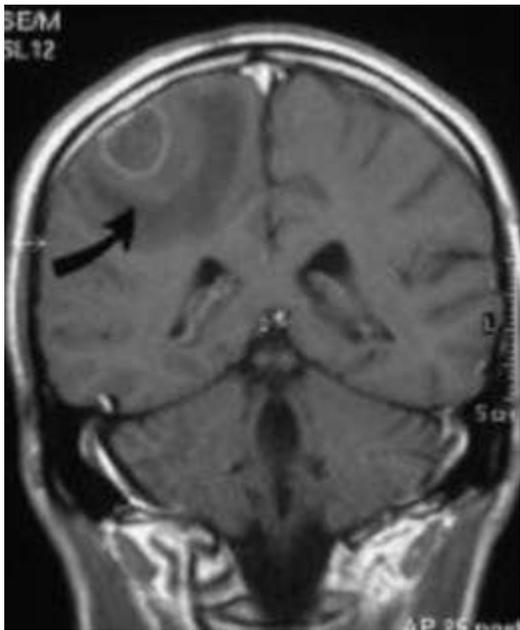


Figure 13. Contrast-enhanced CT scan in a 24-year-old man with HIV infection and CNS toxoplasmosis Image shows a low-attenuating mass with minor ring enhancement (Metwally, 2006-11)

MRI is more sensitive than CT in detecting these lesions. It shows more lesions and it often reveals lesions not detected on a CT scan. MRI detects both the old and the new lesions and without contrast enhancement or perilesional oedema cannot differentiate between the two. On the T1 weighted images the hypodense areas represent the active lesions and these usually enhance with contrast (Figure 14). In the T2 weighted images they are of variable signal intensity and may represent lesions of different age (Mathew and Chandy, 1999). Ciricillo et al in an earlier study had reported that 71% of solitary lesions visualized in an MRI represented primary CNS lymphoma and only about 18% of these were toxoplasmosis. Subsequently, after reviewing more MRI studies of patients with AIDS and by using statistical analysis they have concluded that though the frequency of lymphoma and toxoplasmosis is 30% and 52% respectively, a solitary lesion on MRI is more likely to be lymphoma than toxoplasmosis (56% vs. 34% respectively) (Ciricillo and Rosenblum, 1990).

Figure 14. Toxoplasmosis T1-weighted gadolinium-enhanced MRI shows a ring-enhancing lesion in the right parafalcine cortex (arrows) (Metwally, 2006-11)



Despite the lower sensitivity of CT scan, it would be still appropriate and useful as a screening test for patients with suspected CNS toxoplasmosis, as only about 3% of cases will have normal scan at the time of presentation. MRI need only be used when the CT scan is negative for a lesion or when it reveals a solitary lesion (Porter and Sande, 1992).

- **Treatment**

Patients with ring-enhancing brain lesions on CT scan or MRI along with positive IgG antibody to *T gondii*, should receive empiric therapy. A clinical and radiological response to the specific therapy will support the diagnosis of Toxoplasmosis. Patients who fail to show a radiographic or clinical response within 2 weeks of therapy should have a brain biopsy performed. If the biopsy confirms Toxoplasmosis, a switch to an alternative therapy should be considered (Luis, 2006).

Initial Therapy should be continued for at least 6 weeks, and the preferred regimen is Pyrimethamine 200 mg po as a loading dose, followed by 50 mg (< 60 kg body weight) to 75 mg (>60 kg) po qd, plus leucovorin (folinic acid) 10–20 mg per day (can increase = 50 mg) po qd, + sulfadiazine 1000 (< 60 kg) to 1500 mg (= 60 kg) po q 6h.

Alternative regimen includes Pyrimethamine + leucovorin (as above) + clindamycin 600 mg IV or po q6h (preferred alternative), or another regimen of TMP-SMX (5 mg/kg TMP and 25 mg/kg SMX) IV or po bid.

Maintenance (suppressive) therapy should be lifelong in immunocompromised patients unless immune reconstitution occurs and is composed of Pyrimethamine 25 – 50 mg po qd + leucovorin 10–25 mg po qd, + sulfadiazine 500–1000 mg po q6h (preferred). With an alternative regimen (the relapse rate on these regimens is approximately 25%) Clindamycin 300–450 mg po q6–8h + pyrimethamine + leucovorin dosed as above (Luis, 2006)

- **Echinococcus infection**

Human infection with the different echinococcal species is termed hydatid disease (Eckert et al., 2001). The word hydatid Refers to the fluid-filled larval forms found in the intermediate hosts (hydatid is derived from a Latin hydatis, or drop of water). *Echinococcus granulosus* causes cystic hydatid disease, which is characterized by cystic lesions found mainly in the liver or lungs.

Isolated brain lesions or second lesions in the brain occur in 5% of patients. *Echinococcus multilocularis* causes alveolar hydatid disease, characterized by tumor-like collections of vesicular parasites in the liver. Isolated lesions in the brain are very rare, but metastatic lesions from the liver to the brain may occur. *Echinococcus vogeli* and *Echinococcus oligarthrus* cause polycystic hydatid disease, a rare cause of visceral organ infection noted only in Latin America. CNS involvement has not been described (David et al., 2004).

- **Epidemiology**

E. granulosus has a wide geographic distribution. Highly endemic areas include countries surrounding the Mediterranean Sea, the Middle East, East Africa, parts of Russia, and many countries in South America. Locally acquired cases are occasionally noted in Australia, New Zealand, North America, China, and South Asia. *E. multilocularis* is mainly found in alpine and arctic zones (David et al., 2004).

- **Pathology**

E. granulosus has two obligate mammalian hosts (Eckert et al., 2001). The dog and other canines are the main definitive host containing the tapeworm form. The tapeworms are 2 to 5 mm in length and contain only three to four proglottids. The normal intermediate hosts are ruminants, which are infected when eating material contaminated with ova passed in the feces of the canines. In the intermediate host, the eggs hatch and release the invasive larva (termed the oncosphere), which then penetrates the intestine and migrates to the tissues, primarily the liver. The larva develops into a large cystic lesion containing an external laminar membrane, a germinal layer (the brood capsule), and a central fluid layer. Within the cyst fluid are numerous protoscolexes, which form from the brood capsule. When ingested by the definitive host, the protoscolexes develop into tapeworms. If the cyst ruptures, however, the protoscolexes develop into additional cysts. Foxes and wolves are the main definitive hosts for *E. Multilocularis*. However, domestic dogs can also be infected. The normal intermediate hosts are rodents. In contrast to *E. granulosus*, the parasite develops as multiple adjacent vesicles, usually without internal protoscolexes. However, the vesicles may bud and may spread as metastatic lesions (Thompson and McManus, 2002).

Humans are infected by ingesting the ova shed by dogs or other canines. After hatching in the intestine, the invasive larva (or oncosphere) is released, attaches to and penetrates the intestine, and spreads hematogenously. In the case of *E. granulosus*, approximately 70% of the parasites develop in the liver. Another one third develop in the lung. Less common sites include bone, pelvis, spleen, and the CNS. The echinococcal cysts slowly expand and generally remain asymptomatic until symptoms result from their expanding size or their space-occupying effect. Because years may elapse before cysts enlarge sufficiently to cause symptoms, cysts may be discovered incidentally on routine x-ray or ultrasound studies (Taratuto and Venturiello, 1997; Gutierrez, 2000).

E. multilocularis characteristically presents as a slowly growing hepatic tumor, with progressive destruction of the liver and extension into vital structures. Patients commonly complain of right upper quadrant and epigastric pain, and obstructive jaundice may be apparent. The liver lesions metastasize to brain or lung (Kern et al., 2003).

- **Clinical picture**

CNS disease typically presents as a mass lesion. In this case, the slowly enlarging lesion may cause headaches, seizures, or focal neurologic abnormalities (Altinors et al., 2000).

- **Investigations**

Diagnosis is primarily made by imaging studies. In the case of *E. granulosus*, CT or MRI scans of brain typically demonstrate a spherical cystic lesion with smooth borders (Figure 15, 16) (Tuzun et al., 2002). When the internal images from the protoscolexes "hydatid sand" are seen, the image can be diagnostic. Midline shift and distortion of the ventricles are common. Lesions are usually not inflamed and thus do not have surrounding edema or enhancement. The cyst wall usually shows a rim of low signal intensity on both T1- and T2-weighted images. T2-weighted images are better than T1-weighted images in revealing the wall of the hydatid cyst because the low-signal-intensity cystic wall contrasts well with the high-signal-intensity fluid content. Cysts may be found outside the CNS, which suggests that the CNS lesion is also due to hydatid disease (Haliloglu et al., 1997). The CT appearance of *E. multilocularis* is less distinct. It may present as an ill-defined mass lesion and most cases will also have evidence of liver involvement (David et al., 2004).



Figure 15. Hydatid. Axial contrast enhanced T1 weighted image reveals round well-circumscribed hypointense cyst. Note Marked shift of midline structures to left. No contrast enhancement is seen. (Meric and Baki, 1998)

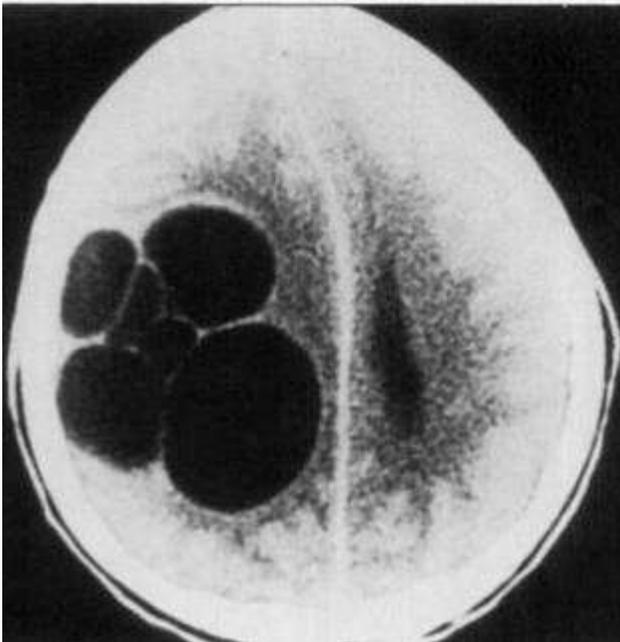


Figure 16. Hydatid. Axial contrast enhanced T1 weighted image reveals multiple cerebral cysts. Note shift of midline structures to left.. (Meric and Baki, 1998)

In doubtful cases, serologic assays can be diagnostic. Enzyme-linked immunosorbent assay (ELISA) or indirect hemagglutination assays are readily available and can be confirmed by immuno blot assays. However, the sensitivity is not optimal for extrahepatic disease. For *E. multilocularis*, the EM2 ELISA with purified antigen is the confirmation test (David et al., 2004).

○ Treatment

The treatment of choice for CNS hydatid disease is surgical removal. In the case of *E. granulosus*, care must be taken not to rupture the cyst with resultant spread of the protoscolices. This is more readily accomplished if the diagnosis is made before surgery. Antiparasitic drugs, particularly albendazole, are routinely recommended before surgery in hepatic cases. However, the role of preoperative antiparasitic drugs in CNS infection has not been clearly defined. Recent data, however, suggest that adjuvant chemotherapy is associated with an improved outcome (Altinors et al., 2000). The practice of aspirating the cyst and injecting scolicidal agents is no longer recommended because of the increased risk of spillage of the protoscolices (David et al., 2004).

In the case of *E. multilocularis*, CNS involvement is often a manifestation of advanced disease. Few cases of alveolar hydatid disease can be cured with surgery alone, so chemotherapy is now routinely recommended postoperatively. In patients in whom the lesion is completely resected, albendazole is recommended for 2 years after surgery. In other patients, albendazole should be continued indefinitely (Schmid et al., 1998).

The dose of albendazole for patients weighing more than 60 kg is 400 mg PO twice daily for 28 days. A dose of 15 mg/kg of body weight daily in 2 divided doses (not to exceed total daily dose of 800 mg) has been suggested for patients weighing less than 60 kg. For CE, the 28-day course may be repeated after 14 days without treatment to a total of 3 treatment cycles (Metwally, 2006-1).

• Schistosomiasis

Schistosomiasis is caused by *Schistosoma hematobium*, *Schistosoma mansoni*, *Schistosoma japonicum* and. Two other species (*Schistosoma mekongi* and *Schistosoma intercalatum*) can also cause human infection in circumscribed foci in Southeast Asia and Africa, respectively. Human contact with water is necessary for infection by schistosomes (David et al., 2004).

○ Epidemiology

Schistosomiasis affects more than 200 million people worldwide. *S. mansoni* is found in Africa, Southwest Asia, the Caribbean, the Middle East, and South America. *S. hematobium* is found in Africa, the Middle East, and Southwest Asia. *S. japonicum* is found in Japan, China, the Philippines, and Southeast Asia. No nonhuman reservoirs have been found for *S. mansoni* and *S. hematobium*, although these species are rarely found in other hosts. Domestic animals are important reservoirs for *S. japonicum* (King, 2001).

○ Pathology

Schistosoma is a trematode, with man as a definitive host. When the parasite eggs are passed into freshwater, they can release ciliated miracidia, which swim and penetrate freshwater snails. Once inside the snail, the miracidium is able to mature into a mother sporocyst which can produce motile daughter sporocysts that target the snail's hepatic and gonadal tissues. The daughter sporocysts develop into cercariae within the snails hepatic and gonadal tissues, migrate to the vascular sinuses, and exit through the mantle. Humans, particularly children and adolescents, become infected when released motile cercariae attach to and penetrate skin. The cercariae shed their forked tail and develop into the schistosomula, which migrates to the heart, lung, and the liver. From the liver, each *Schistosoma* species is able to migrate to its preferred sites and to its residence in venules. Nevertheless, the parasites occasionally migrate to other sites (Sturrock, 2001).

The adult worms of the *Schistosoma* live in the human vasculature. *S. mansoni* lives in the inferior

mesenteric veins draining the large intestine, *S. hematobium* lives in the venous plexus surrounding the bladder and in the rectal venules, and *S. japonicum* lives in the superior mesenteric veins draining the small intestine. After the adult worms mate in the blood vessels, the female worm (7 to 20 mm) travels against the flow of the blood to reach the vessels surrounding the intestine or bladder. There, she releases hundreds to thousands of eggs in the small venules of the portal and periportal systems (David et al., 2004).

Early in the course of infection, adult worms may localize in the spinal cord vasculature or cerebral vessels (Pittella, 1997). More commonly and later in the course of infection, CNS schistosomiasis results from ectopic deposition of the parasite eggs. In heavy infection, the ova are able to reach the CNS by retrograde flow from the iliac veins and inferior vena cava by the valveless venous plexus of Batson. Eggs reach the brain and spinal cord by embolization from this vertebral venous plexus. Egg size may have an effect on deposition (Scrimgeour and Gajdusek, 1985). Cerebral schistosomiasis is thought to be more common with *S. japonicum* because *S. japonicum* releases small eggs, which are able to reach the brain. The eggs of *S. mansoni* are larger, containing a lateral spine, and are found more commonly in the spinal cord. The eggs of *S. hematobium* are of intermediate size and are found more commonly in the brain parenchyma compared to *S. mansoni* but less commonly than *S. japonicum*. (Ferrari, 1999).

Schistosoma eggs have been identified in leptomeninges, parietal, occipital and temporal lobes, basal ganglia, hippocampus, brainstem, cerebellum, choroid plexus, and spinal cord. Eggs that localize to the brain or spinal cord may cause inflammation with perivascular infiltration of lymphocytes, eosinophils, and macrophages, focal and diffuse vasculitis, microinfarction, or granuloma formation (Pittella, 1997).

- **Clinical picture**

Involvement of the CNS occurs in about 1% to 2% of patients, but most patients do not have neurologic symptoms (Pittella and Lana, 1981). Neurologic symptoms include mental confusion, meningitis, encephalitis, headache, vertigo, seizures, coma, visual changes, optic neuritis, papilledema, hemiplegia, opisthotonos and tremors. Schistosomal myelopathy is characterized by lumbar pain (often radicular), followed by muscle weakness, sensory deficits, and loss of sphincter control (Gomes et al., 2002). Other spinal cord involvement includes multiple nodules on the spinal cord, cord compression, and cord necrosis and less likely involvement of the cauda equina and thoracic portion of the spinal cord. Additional CNS syndromes include cerebellar and vestibular syndromes, tumor-like mass lesions, cerebral edema, and intracerebral and subarachnoid hemorrhage (Ferrari, 1999).

- **Diagnosis**

Peripheral blood eosinophilia may occur, but other general laboratory studies are not particularly helpful. The CSF may show pleocytosis typically with a lymphocyte predominance. Eosinophils are present only in a few patients. Protein concentrations are increased, glucose concentrations are normal, and ICP may be increased (Ferrari, 1999). CSF from patients with schistosomal myelopathy may be xanthochromic.

CT and MRI scans of the brain may show cerebral edema or atrophy. Many patients present with large granulomas, which can cause focal latencies, enhancing lesions and tumor-like lesions (Pittella et al., 1996; Sanelli et al., 2001). Some patients display a characteristic central linear enhancement surrounded by multiple enhancing punctate nodules. This tree like pattern is thought to be highly suggestive of schistosomiasis. Myelography with CT may show schistosomiasis involvement with intramedullary cord swelling and partial or complete spinal cord block. MRI images reveal lesions that are isointense to cord in T1-weighted images and patchy

hyperintense in T2-weighted images (Figure 17) (Bennett and Provenzale, 1998; Sahar et al., 2005).

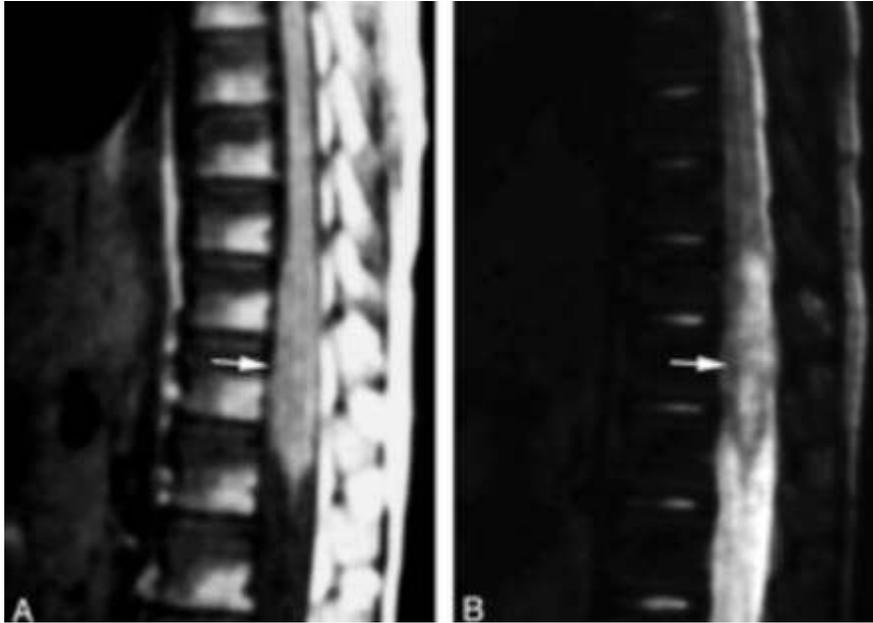


Figure 17. MR imaging of dorso-lumbar spine in a patient with spinal cord schistosomiasis. A, Sagittal T1-weighted image shows moderate expansion of the distal cord and conus medullaris (arrow). The lesion is isointense to the cord. B, Sagittal T2-weighted image. The lesion has heterogeneous hyperintense signal intensity (arrow). (Sahar et al., 2005)

Definitive diagnosis is made by identification of the characteristic ova in stool (*S. mansoni* and *S. japonicum*) or urine (*S. hematobium*) (Strickland and Ramirez, 1999). Because eggs are intermittently passed, repeated examinations increase the yield of detection. Centrifugation and examination of urine sediment can also aid in isolating eggs. Rectal biopsy may be a more sensitive way to detect the ova (Harries et al., 1986). Ova are not found in the CSF. Although demonstration of ova in biopsies is possible, it is preferable to make the diagnosis with less invasive tests. Serologic tests using egg or other parasite derived antigens are available to support the diagnosis of schistosomiasis. An ELISA using adult worm microsomal antigens is available, and is more than 99% specific for *Schistosoma* infection and more than 95% sensitive for *S. mansoni* and *S. haematobium* (Al-Sherbiny et al., 1999). However, the sensitivity is poor for *S. japonicum* infection. Species specific immunoblot assays are also available using adult microsomal antigens (Van Lieshout et al., 2000).

○ Treatment

Medical therapy for cerebral schistosomiasis of all species is with praziquantel (60 mg/kg orally in three divided doses over a single day) (Watt et al., 1986). Patients who have schistosomiasis myelopathy can be treated at a lower dose of praziquantel (40 mg/kg in two divided doses over 1 day) (Gomes et al., 2002). Although no data are available, corticosteroids are often given to reduce the edema associated with myelopathy and cerebral lesions. In patients unable to take praziquantel, oxamniquine (30 mg/kg daily for 2 days) may be given as an alternative treatment for *S. mansoni* (Gomes et al., 2002).

Surgical therapy is an important adjunctive therapy in patients who have tumor-like masses. Laminectomy has been used in some patients with schistosomal myelopathy and still may be required in the case of acute paraplegia (Scrimgeour and Gaidusek, 1985). With recent improvement in prompt diagnosis plus treatment with corticosteroids and praziquantel, surgical therapy is now less frequently required (Ferarri, 1999).

NON-INFECTIOUS GRANULOMA

- **Sarcoidosis**

Sarcoidosis is a granulomatous (mononuclear) inflammatory disease, systemic in scope, of undetermined etiology. In 1877, the cutaneous aspects of the disease was first described, but mistook them for gout. Caesar Boeck subsequently described several patients with similar skin manifestations and called them "sarkoid," because of the resemblance of the histological features to sarcoma. He emphasized the systemic nature of the disease. Heerfordt in 1909, in his description of "uveoparotid fever," first reported neurological manifestations in the form of cranial nerve palsies (Metwally, 2006-4).

- **Pathophysiology**

The causes of sarcoidosis are not clear. The present evidence suggests that active sarcoidosis results from an exaggerated cellular immune response to either foreign or self-antigens. An alternative hypothesis says that sarcoidosis may be a clinical syndrome that includes a collection of different diseases, each with a different etiology. Various infectious, allergic, chemical, drug, and autoimmune causes have been suggested and dismissed for lack of conclusive evidence, and some form of atypical mycobacteria is now suspected (American Thoracic Society, 1999).

T-helper cells proliferate, resulting in an exaggerated response. They undergo differentiation to a Th1-type cell under the influence of interleukin-4 (IL-4) and co-stimulator CD28. The Th1 cell induces IL-2 and interferon gamma (IFN-gamma) on the macrophages, followed by a cascade of chemotactic factors that promote formation of granuloma. IFN-gamma increases the expression of major histocompatibility class (MHC) class II on macrophages, and activated macrophages receptors carry an Fc receptor of immunoglobulin G (IgG) which potentiates their phagocytosis function. This results in tissue destruction and granuloma formation is thought to be a secondary process (Moller, 2003).

The pathologic hallmark of sarcoidosis is the noncaseating epithelioid granuloma composed of nodules of epithelioid histiocytes that are non-caseating (unlike TB). A mixed inflammatory reaction commonly surrounds the granulomas. Langerhans type giant cells are common. Special intracytoplasmic inclusions—stellate shapes called asteroid bodies—and also Schaumann bodies (laminated basophilic calcifications) are found. A similar picture may appear in other diseases so that eventually the diagnosis may become a matter of excluding an infectious agent (Jones et al., 1999). In neurosarcoidosis, the granulomas in the CNS, consists of lymphocytes and mononuclear phagocytes surrounding a noncaseating epithelioid cell granuloma (Metwally, 2006-5).

- **Epidemiology**

Internationally, the incidence of sarcoid varies from 0.04 per 100,000 in Spain to 64 per 100,000 in Sweden. In the US, the prevalence of sarcoid varies widely, but generally it is more common in African Americans. In Asia it is extremely rare, being almost unknown in Chinese and Southeast Asians. Data from Japan showed native Japanese to be affected (Hunninghake et al., 1999). Most symptomatic patients are aged 20-40 years. Sarcoidosis also can be seen in children and elderly persons.

- **Neurosarcoidosis**

Involvement of the CNS is referred to as neurosarcoidosis. Neurosarcoidosis is an uncommon but severe, sometimes life-threatening, manifestation of sarcoidosis. It generally occurs in 5-16% of cases usually if the disease has had substantial systemic involvement and signs of active disease (Lower et al., 1997 and James, 1998). However, strictly neurological forms are seen in fewer than 10% of patients (Bourahoui et al., 2004). Neurosarcoidosis carries a mortality rate of 10%, twice

the overall mortality rate of sarcoidosis (James, 1998).

Virtually any part of the nervous system can be affected by sarcoidosis, but certain presentations are more common. Those with an acute onset present with isolated cranial neuropathies or aseptic meningitis, and those with chronic onset usually present with parenchymal involvement, hydrocephalus, multiple cranial neuropathies, or peripheral nervous system manifestations (Luke et al., 1987). Pathologically, the meninges are most commonly involved, especially at the base of the brain (Greg et al., 1999), explaining the common occurrence of cranial neuropathies and hypothalamic dysfunction. They tend to occur early and respond favorably to treatment (Sharma, 1997). From the meninges, the inflammatory process extends into the brain and spinal cord through Virchow-Robin perivascular spaces (Keith et al., 2004). Irreversible neurological damage can occur once the inflammation becomes chronic and induces fibrosis (Waxman and Cher., 1979). Primary involvement of the blood vessels is not common, but they can be involved in the general inflammatory process (Caplan et al., 1983). The severity of the inflammatory reaction correlates with the clinical picture.

In the peripheral nervous system, the epineurium and perineurium are primarily involved by the granulomatous process, but only the endoneurium shows mononuclear cell accumulation. Axonal damage, rather than demyelination, is the most common consequence of the inflammatory changes. Teased nerve fiber preparations suggest that axonopathy sparing unmyelinated fibers is the most prominent feature rather than a compressive injury from granulomas (Galassi et al., 1984). Muscle involvement is common, but is mostly asymptomatic. About 50% of all sarcoidosis patients show granulomatous changes on muscle biopsy (Soemberg et al., 1981).

- **Clinical picture**

- **Systemic involvement**

The clinical presentation of sarcoidosis varies with the specific organ involved. It may present with symptoms referable to a single organ or to multiple organ systems. The lungs are involved in 90% of patients with sarcoidosis, and the severity ranges from asymptomatic to severe interstitial lung disease. Other organs commonly involved include the lymph nodes (33%), skin (25%), eyes (11%-83%), musculoskeletal system (25%- 39%). It also may have upper respiratory, marrow and spleen, renal, liver, cardiac, and endocrine manifestations (Jennifer and Karin, 2004).

Among the most common symptoms of sarcoidosis are constitutional symptoms as fatigue, anorexia, weight loss, and fever at onset. Also, symptoms of pulmonary affection may occur in one third to one half of all patients and these include dyspnea on exertion, retrosternal chest pain, and cough. Even in patients with primarily extrathoracic sarcoidosis, subclinical pulmonary sarcoidosis is usually present (Andrew, 2006).

- **Neurosarcoidosis**

In patients known to have sarcoid, the appearance of neurological symptoms usually poses no diagnostic problems, but the possibility of unrelated disease must be kept in mind, especially infections. When nervous disease complicates systemic sarcoidosis, it usually does so within 2 years of onset and it has variable clinical presentations (Bucurescu, 2006).

Cranial neuropathy is the most common manifestation of neurosarcoidosis, occurring in up to 75% of patients (Oksanen, 1986). The majority of patients have more than one cranial neuropathy. The cranial nerve involved most commonly is the facial nerve. It is also the single most common neurological manifestation, seen in 25% to 50% of neurosarcoidosis patients. Though unilateral involvement is most common, bilateral facial palsy can occur simultaneously or

sequentially in approximately one third of patients (Oksanen, 1986). In isolated facial nerve palsy secondary to sarcoidosis, the CSF is usually normal; however, when associated with other neurological manifestations, the CSF can be abnormal in up to 80% of cases. The site of facial nerve involvement in neurosarcoidosis is unclear. Facial neuropathy often is associated with dysgeusia, suggesting that the lesion is proximal to the stylomastoid foramen. Other possible sites include the parotid glands secondary to local inflammation, the intracranial course secondary to meningitis, and intra-axial involvement within the brain stem. In one study of 16 patients with facial palsy, none had meningitis, suggesting that basal meningitis is an unlikely etiology. Facial paresis in neurosarcoidosis, when isolated, has a good prognosis in more than 80% of cases, with or without treatments (Lower et al., 1997).

The eighth cranial nerve is involved in 10% to 20% of cases (Waxman and Sher, 1979), but is usually asymptomatic. Brain stem auditory-evoked potential abnormalities, however, are more commonly observed. Bilateral involvement is highly suggestive of neurosarcoidosis. Symptoms may include either vestibular or hearing dysfunction. They may be acute or chronic and can fluctuate.

Optic neuropathy has been reported as an uncommon but serious manifestation of neurosarcoidosis, seen in about 15% of cases (Stern et al., 1985). On the contrary, Zajicek and colleagues (1999), reported it as the most common neurological manifestation of sarcoidosis in his series, which is the largest single series of neurosarcoid to date, in which optic nerve or chiasmal involvement was seen in 38% of the 68 patients with neurosarcoid; of these patients, 69% had unilateral involvement and 31% had bilateral disease. That can be explained by the results of Visual Evoked Potentials (VEP) which may reveal frequent abnormalities even in those with no visual symptoms. Of Oksanen's patients with neurosarcoid, 23 out of 50 patients (48%) had VEP abnormalities, but only 3 patients had visual symptoms (Oksanen, 1986)

Optic neuropathy manifests as acute or chronic visual loss, with or without pain. It may be associated with papilledema or optic atrophy. Optic nerve involvement may be difficult to diagnose and differentiate from optic nerve glioma or meningioma. Papilledema is seen in 14% of patients with ocular involvement. Rarely, visual impairment occurs because of involvement of the optic chiasma (Stern et al., 1985).

Oculomotor dysfunction can be caused by involvement of the third, fourth, or sixth nerves in their courses in the subarachnoid space caused by meningitis and rarely secondary to disease processes within the brain stem or orbit. Extraocular muscles are rarely involved by sarcoidosis directly. Pupillary dysfunction is noted occasionally (Graham et al., 1986).

Olfactory nerve dysfunction can present as anosmia or hyposmia and occurs in 2% to 17% of patients, secondary to subfrontal meningitis or nasal mucosal involvement by sarcoidosis. Nasal biopsy should be considered in patients with olfactory dysfunction. Other cranial nerves are rarely involved in neurosarcoidosis.

Meningeal involvement commonly presents as aseptic meningitis. It is reported to occur in up to 64% or as much as 100% of patients in some pathologic studies (Oksanen, 1986). It can occur occasionally as a meningeal mass lesion. The course of meningitis can vary from an acute monophasic illness to recurrent episodes. It is usually associated with a good outcome. When chronic, it is generally associated with multiple cranial neuropathies. Aseptic meningitis is mostly asymptomatic and only identified in autopsy studies (Delaney, 1977). Occasionally, meningeal sarcoid mass lesions may present on cerebral imaging as intracranial tumors (Sethi et al., 1986).

Hydrocephalus, which can be either communicating or obstructive, occurs in 6% to 30% of neurosarcoidosis patients (Oksanen and Salmi, 1986). Mechanisms of hydrocephalus include

chronic basilar meningitis with obliteration of CSF flow, granulomas in the ventricular system causing obstruction, and compression of the cerebral aqueduct. Associated meningeal enhancement on imaging studies suggests active inflammation and a likely response to corticosteroids. Lack of enhancement may suggest chronicity and fibrosis (Krumholz and Stern, 1998).

Brain parenchymal involvement is common, and there are a variety of manifestations. Supratentorial granulomatous lesions are more common than infratentorial masses. They are often asymptomatic (Brooks et al., 1982), but may present with focal cerebral dysfunction or raised intracranial pressure, with other nonspecific manifestations like headaches, lethargy, seizures, papilledema, and optic atrophy. The most common intracranial sites of involvement are the hypothalamus, the third ventricle region, and the pituitary gland. Hypothalamic and pituitary gland granulomatous infiltration are well recognized. Involvement ranges from a low of 1.3% to 26% in Mayock's review. Delaney found symptoms of diabetes insipidus in 35% of patients. Hyperprolactinemia and inappropriate antidiuretic hormone secretion (SIADH) may occur, but hypothalamic hypothyroidism is rare. In addition, hypothalamic dysfunction can affect vegetative functions like appetite, temperature, sleep, and libido (Chapelon et al., 1990).

Sarcoid mass lesions can be mistaken for meningiomas, intraventricular tumors, cerebellopontine angle tumors, and en plaque subdural lesions indistinguishable from meningiomas, and they may necessitate biopsies for definitive diagnosis. In fact, neurosarcoid masses can mimic any type of intracranial tumor (Clark et al., 1985).

Psychiatric manifestations occur in up to 48% of patients, but are not usually the presenting symptoms. Psychiatric symptoms vary, including apathy, poor judgment, agitation, hallucinations, depression, and memory loss (Chapelon et al., 1990).

Diffuse Encephalopathy and Seizures are manifestations of neurosarcoidosis. It generally presents as delirium, psychiatric disorder, memory disturbance, cognitive impairment, or as a multifocal relapsing encephalopathy. Patients have diffuse contrast enhancement of meninges and increased signal intensity on T-2-weighted MRI. Diffuse encephalopathy can also be caused by the metabolic disturbance or endocrine dysfunction seen in systemic sarcoidosis (Nakao et al., 1970). In addition to meningeal pathology in diffuse encephalopathy, there is usually histological evidence of granulomatous involvement of arteries and veins, commonly a small vessel arteritis (Caplan et al., 1983). Diffuse encephalopathy and vasculopathy occur commonly together; however, vasculitic changes are rarely observed on cerebral angiography (Corse and Stem, 1990). Occasionally, transient ischemic attack (TIA) and ischemic stroke-like events occur because of arteritis, external compression of arteries by inflammatory mass lesions, or emboli secondary to cardiac involvement. Dural venous obstruction or thrombus formation also occur. Vasculitis with granulomata in the leptomeninges suggests neurosarcoidosis, but granulomata confined to blood vessels suggests isolated CNS vasculitis (Brown et al., 1989).

Seizures occur in up to 20% of neurosarcoidosis patients (Krumholz and Stern, 1998). They reflect CNS parenchymal involvement. They can be focal, generalized, psychomotor, or myoclonic. The usual underlying causes for seizures include cerebral mass lesions, hydrocephalus, encephalitis, vasculopathy, and hypercalcemia. Many studies associate a poor prognosis with the occurrence of seizures in neurosarcoidosis. This is mainly because of underlying severe parenchymal disease. As expected, seizures can be better controlled if the parenchymal disease is treated (Krumholz et al., 1991).

Myelopathy was rare in neurosarcoidosis, but several cases have been reported in the last 2 decades. Possible causes include granulomatous disease in intramedullary, extramedullary, intradural, or extradural sites (Zajicek, 2000).

Furthermore, the majority of the patients are males. This is especially interesting because sarcoidosis more frequently affects females. Lesions have been reported to occur throughout the spinal cord but more frequently in the cervical spine (C4, C6). The clinical presentation varies according to the location and extent of disease in the spinal cord (Bose, 2002).

Peripheral neuropathy is a less common manifestation of neurosarcoidosis. It is seen in 15% to 18% of patients (Chapelon et al., 1990). Symmetric axonal sensorimotor neuropathy is the most common type of neuropathy. Other presentations include mononeuritis multiplex, polyradiculopathy and rarely, Guillain-Barre syndrome. Peripheral neuropathy is usually mild and asymptomatic in most patients (Scott, 1993).

Myopathy is common, but is usually asymptomatic. Noncaseating granulomata are found on muscle biopsy specimens in 25% to 75% of cases (Chapelon et al., 1990). Symptomatic muscle involvement is seen in < 1% of systemic sarcoidosis patients. The incidence is higher in those with primary neurological disease. The mode of presentation of muscle involvement varies from acute to chronic myopathy, myositis, palpable intramuscular nodules, and, rarely, pseudohypertrophy. Differentiation from other inflammatory myopathies can be difficult, but any evidence of systemic sarcoidosis strongly supports the diagnosis. Myopathic involvement is more common in women at a ratio of 4:1 to 8:1 (Miller et al., 1988).

Rarer presentations of neurosarcoidosis include cerebellar involvement, pseudotumor cerebri, and generalized myotonia (Beardsley et al., 1984).

Differential diagnosis of neurosarcoidosis

- **Chronic Inflammatory Demyelinating Polyradiculoneuropathy**
- **Craniopharyngioma**
- **Diabetic Neuropathy**
- **HIV-1 Associated Distal Painful Sensorimotor Polyneuropathy**
- **Inclusion Body Myositis**
- **Infectious Myositis**
- **Leptomeningeal Carcinomatosis**
- **Metabolic Neuropathy**
- **Multiple Sclerosis**
- **Neurosyphilis**
- **Pituitary Tumors**
- **Polyarteritis Nodosa**
- **Primary CNS Lymphoma**
- **Systemic Lupus Erythematosus**

- Tuberculous Meningitis
- Tuberos Sclerosis
- Wegener Granulomatosis
- (Bucurescu, 2006)

- **Investigations**

Sarcoidosis is a diagnosis of exclusion, and establishing evidence for systemic sarcoidosis often requires an extensive search for the disease in commonly involved organs like the lungs, lymph nodes, skin, and eyes. The common abnormalities on chest radiograph include bilateral hilar lymphadenopathy and interstitial infiltrates. If pulmonary involvement is evident, diagnostic confirmation can be often obtained by transbronchial or mediastinoscopic biopsy or bronchoalveolar lavage. Also, the clinical evaluation may help in the selection of other sites for biopsy, including the skin, parotid gland, lymph nodes, liver, or conjunctiva (Rodan and Putman, 1983).

The diagnostic approach for neurosarcoidosis differs depending on the clinical presentation. Diagnosis is often difficult because of the unknown etiology, diverse clinical manifestations, and lack of confirmatory diagnostic tests. The diagnosis is particularly difficult if neurological symptoms are the only presenting features because of the difficulty in obtaining tissue for histological confirmation. Evidence of systemic disease in this setting is very helpful. The criteria for diagnosis of neurosarcoidosis include a compatible clinical picture, typical radiological findings, and histological evidence of noncaseating granulomata in any tissue. A different diagnostic approach is warranted if patients with known systemic sarcoidosis develop neurological symptoms. In this group, the diagnosis is relatively easy if the neurological manifestations are typical of neurosarcoidosis and supported by imaging studies or other laboratory tests. Tissue diagnosis is not mandatory in these patients; however, not every neurological symptom in someone with systemic sarcoidosis should be considered caused by neurosarcoidosis (Metwally, 2006-4).

- **Investigations in systemic sarcoidosis**

The Kveim test involves intracutaneous inoculation of a suspension derived from the spleen of patients with sarcoidosis, when positive, will produce a cutaneous nodule containing noncaseating granulomata. The Kveim test is reported to be positive in 67% to 92% of patients with sarcoidosis (Chapelon et al., 1990). Although it is a very specific and sensitive test, the agent for the test is not widely available. This, with the fact that it takes 4 to 6 weeks to report positive, makes it an impractical test.

Serum Angiotensin Converting Enzyme (ACE) levels are elevated in 56% to 86% of patients (Israel et al., 1986). Levels may correlate with the disease activity post-treatment, but they have little prognostic value in the initial evaluation. Serum ACE levels are also elevated in patients with liver disease, diabetes mellitus, hyperthyroidism, systemic infection, malignancy, Gaucher's disease and in normal young individuals, but they are much higher in sarcoidosis (Consensus Conference, 1994).

Nonspecific laboratory abnormalities in sarcoidosis include anemia, leukopenia, thrombocytopenia, hypergammaglobulinemia, hypercalcemia, hypercalciuria, elevated liver enzymes, and elevated blood urea nitrogen (BUN) and creatinine levels (Metwally, 2006-4).

■ Imaging Studies

Chest x-rays have been used to stage disease activity. A good quality chest x-ray is sufficient when typical changes are observed. The international X-ray staging classification for pulmonary disease is :

Type 0: Clear chest films

Type I: Bilateral hilar adenopathy with no parenchymal abnormalities

Type II: Bilateral hilar adenopathy with diffuse parenchymal changes

Type III: No hilar adenopathy with diffuse parenchymal changes

Type IV: Pulmonary fibrosis (Kwekkeboom, 1998).

■ Biopsy

As a rule, the most accessible biopsy site with lowest morbidity should be considered. A biopsy should be performed on palpable lymph nodes or elevated superficial skin lesions, if present. Bronchoscopy, particularly fiberoptic bronchoscopy, yields positive biopsy results in 60% of stage I disease and greater than 80% of stage II or III pulmonary sarcoidosis. Transbronchial or airway mucosal sampling is useful in the initial histological confirmation of sarcoidosis (Andrew, 2006).

The typical histological findings from transbronchial or open lung biopsies include diffuse noncaseating epithelioid granulomas (Andrew, 2006).

■ Investigations in neurosarcoidosis

■ CSF examination

If mass lesions and hydrocephalus are ruled out, LP is imperative, especially in presence of cranial neuropathy and meningeal signs, due to high probability of meningeal involvement (Metwally, 2006-4).

CSF commonly shows a mononuclear pleocytosis, usually less than 50 white blood cell (WBC)/mm, reflecting the common underlying meningeal process. Up to 80% of neurosarcoidosis patients show some CSF abnormalities. Other abnormalities include elevated CSF pressure, increased protein (< 100 mg%), and hypoglycorrhachia. These abnormalities are nonspecific, and other CSF tests should be conducted to exclude infectious diseases or other inflammatory or neoplastic processes, including cytology, and culture (bacteria, acid-fast bacillus [AFB], fungal) (Statement on sarcoidosis, 1999; Zajicek, 2000).

There has been some interest in the use of CSF ACE assay. This enzyme is elevated in the CSF of about 50% of neurosarcoidosis patients. Levels tend to fall with treatment and correlate with the activity of the disease. Serum ACE elevation may be less prominent in those with only neurological involvement. Recent evidence indicates there is a lack of specificity and that levels of this enzyme are elevated in CNS infections and malignant processes, and, in fact, they may be raised in any condition that would increase the CSF protein. Moreover, normative values have not been standardized. In some cases there can even be evidence of oligoclonal bands and elevated IgG index (Otake et al., 1990). However, these findings are more consistently abnormal in multiple sclerosis than in neurosarcoidosis. CSF lysozyme and P-2 microglubulin are increased in some

patients. The validity of these findings is not determined; they could be markers of disease activity (Scott, 1993)

■ Hormonal studies

It should be performed whenever involvement of the pituitary-hypothalamic axis is suspected. This includes thyroid function tests, prolactin, testosterone, growth hormone, luteinizing hormone, follicle-stimulating hormone, corticotropin-releasing hormone, estradiol, urine osmolality determination, and insulin like growth factor (Bucurescu, 2006).

■ Neuroimaging

Both CT scan and MRI of the brain are indispensable in assessing nervous system involvement in sarcoidosis. Yet, MRI has become the modality of choice because of the superior images obtained (Bucurescu, 2006). MR imaging with and without contrast is a very sensitive test. Abnormalities are seen in up to 82% of patients with neurosarcoidosis. There are abnormalities that suggest neurosarcoidosis, but none of the findings are very specific. Contrast MR imaging increases the sensitivity by showing areas of enhancement of the meninges and parenchymal lesions which occurs in 40% of cases. This is consistent with the frequent demonstration of inflammation of the meninges on pathologic examination (Sherman and Stern, 1990).

Most common lesions on MRI include: multiple white matter lesions (43% of patients), meningeal enhancement (38% of patients), optic nerve enhancement (28% of patients) and mass lesions in brain parenchyma (Zajicek et al., 1999)

Leptomeningeal involvement is best shown on spin-echo contrast-enhanced T1-weighted images (Consensus Conference, 1994). The gadolinium enhancement shows leptomeningeal involvement in cases that unenhanced images might have missed (Figure 18). The enhancement can follow the contour of the brain, extending into the cortical sulci. Leptomeningeal infiltration typically involves the suprasellar and frontal basal meninges but may occur anywhere and is more concentrated in the depths of the sulci.

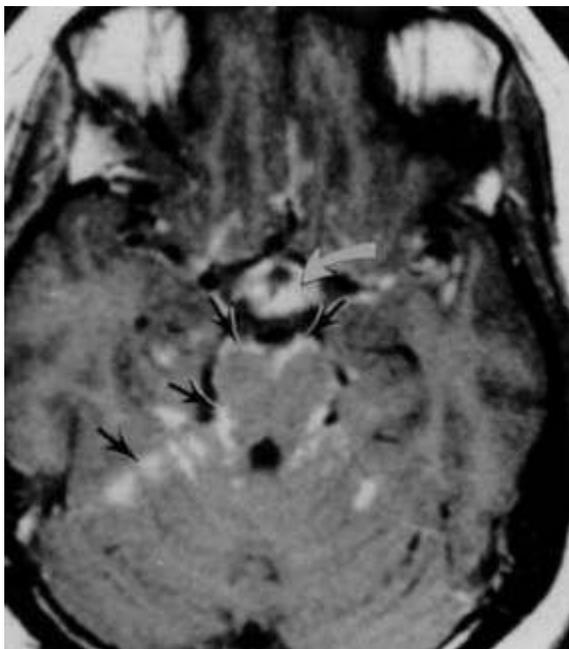


Figure 18. Sarcoidosis. Enhanced T1-weighted axial image. Enhancement around midbrain and cerebellar hemisphere (straight arrows) indicates breakdown of blood-CSF barrier. Optic chiasm involvement (curved arrow). (John and Barney, 1990)

Granulomatous lesions are accompanied by varying degrees of fibrosis and hyalinization.

Occasionally, granulomas coalesce to form mass like lesions, particularly in the region of the chiasma, floor of the third ventricle, and pituitary stalk. Clinical symptoms correlate with the location of the lesion on MR images. Furthermore, it was found that these lesions recur frequently (Ando et al., 1985). Disease entities that can involve the basal leptomeninges and mimic leptomeningeal sarcoidosis on imaging include granulomatous disease (such as TB), Wegener granulomatosis and fungal meningitis, pyogenic meningitis, leptomeningeal lymphoma, demyelination, meningoangiomatosis, acute lymphocytic leukemia, and leptomeningeal carcinomatosis (Brooks et al., 1982).

Dural/epidural mass lesions have an imaging appearance similar to that of meningioma/epidural lymphoma and are not associated with intraparenchymal extension. Dural/epidural sarcoidosis probably represents blood borne deposits of the disease in the epidural spaces. The annual incidence of these lesions exceeds the annual incidence of meningiomas (2.3 per 100,000) by 130 times. These lesions tend to be isointense with gray matter on T1-weighted MR images and hypointense on T2-

weighted images, and they enhance uniformly (Figure 19). This hypointensity on T2-weighted images has been reported previously (Chafrenor et al., 1984) and is thought to be related to fibrocollagenous buildup. Unfortunately, this is not a unique finding. Eighteen percent of meningiomas (typically fibroblastic or transitional types) demonstrate low signal on T2-weighted images.



Figure 19. Sarcoidosis. Contrast-enhanced T1-weighted coronal image. Nodular enhancing sarcoid granulomatous mass is on right (arrowheads). There is erosion of inner table of calvaria (straight arrow). Falx is involved also (curved arrow). (John and Barney, 1990)

In addition to meningioma, differential considerations for sarcoidosis involvement of the dura should include other causes of chronic meningitis, such as lymphoma, adenocarcinoma, Wegener, idiopathic hypertrophic cranial pachymeningitis (IHCP), granulomatous infection, and leukemia (Chan et al., 1985).

Enhancing Brain Parenchymal Lesions show in T2 weighted and gadolinium-enhanced T1 weighted MR imaging as high-signal intensity lesions, especially in periventricular regions (Figure 20), Enhancing brain parenchymal lesions commonly start in the subependymal or the pial (leptomeningeal) microvascular systems then invade the brain in a centrifugal or centripetal ways forming multiple enhancing masses in the periventricular or corticomedullary regions.

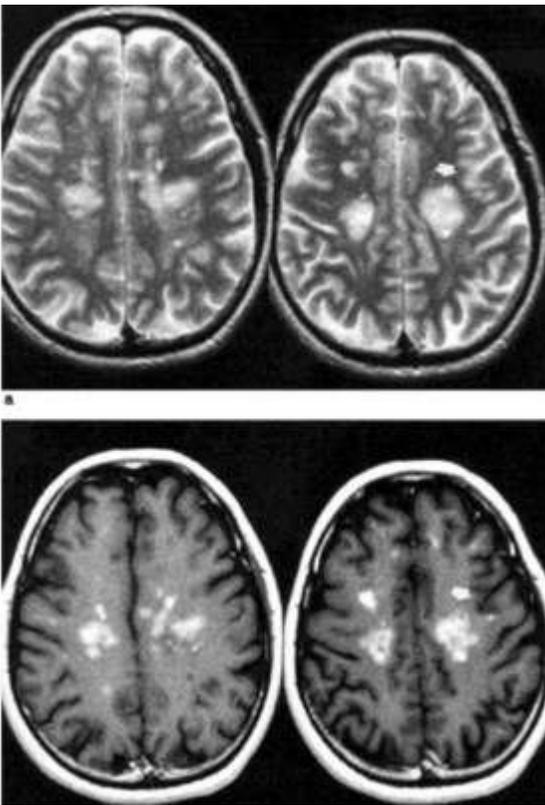


Figure 20. Sarcoidosis axial T2W and gadolinium-enhanced T1W brain images with multiple, extensive white-matter periventricular and subcortical enhancing lesions, some of which are large (arrowed). (Zajicek et al., 1999)

White matter lesions can mimic lesions seen in multiple sclerosis (Smith et al., 1989). In contrast to multiple sclerosis, linear enhancement along blood vessels in the region of white matter changes is seen in neurosarcoidosis. These signal changes along the Virchow-Robin spaces suggest that lesions infiltrate the brain through perivascular Virchow-Robin spaces, and are believed to be the result of infarctions caused by granulomatous vasculitis (Corse and Stem, 1990).

Non enhancing brain parenchymal lesions is best seen on the MRI T2 and FLAIR studies and is seen as confluent or nonconfluent hyperintense patches, that do not show contrast enhancement and have no mass effect. These lesions tend to occur in the periventricular white matter but may also occur in the brain stem and basal ganglia and the corticomedullary junction. Periventricular lesions are nonspecific and can occur in association with multiple sclerosis, hypertension, and vasculitis. Theoretically, they can result from periventricular granulomas or from small areas of infarction caused by granulomatous angiopathy. The exact nature of these lesions has not been identified in the literature. Symptomatic improvement usually did not correspond to improvement on MR imaging studies. This behavior differed from that of enhancing brain lesions for which symptoms often correlated with imaging findings and symptomatic improvement correlated with regression on MR images. These facts also imply that the nonenhancing brain parenchymal lesions and the enhancing lesions have different pathophysiologic mechanisms (Greg et al., 1999).

Involvement of cranial nerves have been described in association with sarcoidosis. Most frequently, the facial nerve is involved clinically. Imaging, however, revealed that the optic nerve and/or chiasma are the most frequently affected cranial nerves (Zajicek et al., 1999).

Spinal Cord and Nerve Root Involvement manifest as cord swelling, with increased signal intensity on T2-weighted images and a pattern of enhancement on T1-weighted contrast-enhanced images (Figure 21), that predominates in the periphery of the cord but includes patchy multifocal enhancement of the cord. Imaging findings are thus nonspecific and can mimic multiple sclerosis, cord tumor, vacuolar myelopathy, TB, or fungal infection (Gideon and Mannino, 1996).

Patients with spinal cord sarcoidosis progress in four phases, which begin with a linear leptomeningeal pattern of enhancement and progress to a phase in which there is cord enlargement with faint enhancement or no enhancement. Enhancement then progresses but the cord begins to reduce in size until it reaches a final stage of atrophy without any enhancement. Although it is fairly evident that patients who present with cord atrophy will most likely not respond to steroid treatment, it is unclear whether the degree of enhancement plays a role in treatment response (Greg et al., 1999).



Figure 21. Sarcoidosis. T1W gadolinium-enhanced sagittal MRI of the thoracic spinal cord showing focal contrast enhancement and expansion of the cord at T6–T7 level (arrowed). (Zajicek et al., 1999)

In general, resolution of lesions on MR imaging lags behind resolution of clinical symptoms. The role of MR imaging in neurosarcoidosis is to confirm clinical suspicion, establish subclinical disease, and document the response of pathologic lesions to treatment (Zylberberg et al., 2001).

■ Neurophysiological Studies

Evoked potential (EP) studies may be of value in supporting the diagnosis and monitoring the course of the disease. VEPs and brainstem auditory evoked potentials (BAEPs) tend to be abnormal in about one third of the patients with neurosarcoidosis. Somatosensory evoked potentials tend to show abnormalities less frequently. All 3 modalities of EPs can show abnormalities in patients before the appearance of clinical signs (Oksanen, 1986).

EMG/nerve conduction studies can be used to confirm neuropathy or myopathy. The most characteristic electrodiagnostic finding is mononeuropathy multiplex, showing axonal degeneration and segmental demyelination. With treatment and clinical improvement, motor, sensory and mixed nerve conduction tend to improve. In cases of myopathy, the EMG shows myopathic potentials (Ando et al., 1985).

■ Nuclear studies

Gallium 67 citrate scans often are supportive when typical findings are lacking. This is especially true in neurosarcoidosis or uveitis when biopsy may not be feasible. Gallium 67 scanning may help demonstrate sites of inflammation. Positive scans secondary to increased uptake can identify asymptomatic lesions. Though the test can be positive in any inflammatory or neoplastic lesions,

the appearance of pulmonary lesions is relatively specific for sarcoidosis. Sites of inflammation can be accessed for directed biopsy. The combination of gallium 67 scanning and Serum ACE levels yields a specificity of 83% to 99%, thus making the combination an excellent, minimally invasive evaluation for sarcoidosis (Corse and stem, 1990).

Ultimately, in cases where the diagnosis of neurosarcoidosis is in doubt despite the above evaluation, tissue biopsy from neural lesions should be considered. The common sites for biopsy are the meninges and mass lesions. The sensitivity of meningeal biopsy improves if there is enhancement on contrast imaging. In the case of focal meningeal enhancement, the imaging studies should be used to choose the site for biopsy. In case the biopsy from a cerebral mass lesion shows evidence of noncaseating granulomata, cultures should be obtained to rule out infection as a cause. A generous sample of tissue should be obtained, because granulomatous changes can be seen around primary cerebral tumors (Peeples et al., 1991).

○ Treatment

Unlike pulmonary sarcoidosis, where a period of observation is recommended for mild and asymptomatic cases (Hunninghake et al., 1994), neurosarcoidosis patients almost always should be treated on diagnosis. Much of the information regarding specific treatment of neurosarcoidosis comes from multiple case reports and small case series. Otherwise, most treatment choices are made based on studies of systemic sarcoidosis (Agboughu et al., 1995).

Immunosuppression is the principal method of controlling the disease, and corticosteroids are the cornerstone of therapy. Spontaneous remission has been observed. Relapses may respond poorly, however, requiring chronic steroid therapy. Before initiating immunosuppressive therapy, an infectious etiology for the symptoms must be excluded (Bucurescu, 2006).

■ Role of Immunotherapies

Treatment with corticosteroids has shown impressive responses in many cases. Postulated mechanisms of action include inhibition of lymphocyte and mononuclear phagocytic activity, inhibition of transcription of proinflammatory cytokines, down regulation of important cellular receptors, and interference with collagen synthesis. Although steroids have a biological use in sarcoidosis, there is no evidence that they change the natural history and outcome of the illness. The main goal of treatment is to salvage tissue function and prevent progression of the disease, especially fibrosis and ischemia. Corticosteroids should be started in high doses and, after a clinical response occurs, gradually tapered, similar to their use in other inflammatory conditions (Chapelon et al., 1990). Complete withdrawal can be attempted if the clinical course permits. In case of relapse, a repeat course of high-dose steroid treatment should be attempted. Patients should be monitored for complications and treated appropriately. It is very important to reduce the morbidity related to the treatment to avoid discontinuation of the medication because of side effects. In one study, only 29% of patients with neurosarcoidosis continued long-term steroids; the remainder discontinued treatment because of intolerable side effects or failure to respond. (Lower et al., 1997)

Johns Hopkins prednisone treatment schedule (for management of symptomatic pulmonary sarcoidosis)

- Initial treatment 40 mg daily or 20 mg twice daily if fever is prominent, then 30 mg daily in single morning dose, then 25 mg daily. Then 20 mg daily, each dose level lasting 2 weeks.
- Daily maintenance (after 8 wk) 15 mg daily (10 mg may be adequate later)

- Monthly tapering after 8 months over 4 months

- **Corticosteroid-sparing agents (second-line drugs) (Johns and Michele, 1999).**

There is much less information known about alternative medications. Indications for their use include the presence of contraindications to corticosteroids, serious steroid side effects, or lack of response to treatment. The available alternative therapeutic agents include cyclosporine, azathioprine, methotrexate, cyclophosphamide, chlorambucil, hydroxychloroquine, and radiation therapy (Agbogu et al., 1995). There are no rigorous clinical trials of the different treatment modalities.

Among the alternative therapies, cyclosporine is the best studied. Though there is evidence suggesting that it is ineffective in pulmonary sarcoidosis because of poor penetration into lung tissue (Wyser et al., 1997), it is effective in neurosarcoidosis. It is even beneficial in some patients refractory to corticosteroids (Stern et al., 1992). It specifically inhibits CD4 cell immune responses. It is ineffective as a single agent, but is a good adjunct to steroids. It can be started at 4 mg/kg /day in two divided doses, given 12 hours apart. Trough levels should be monitored monthly to maintain a therapeutic drug level. This will help to avoid side effects, which include hypertension, renal dysfunction, hypomagnesemia, and toxic encephalopathy. There is no strict correlation between blood levels and clinical response. Approximately 75% of patients may respond to cyclosporine sufficiently to allow reduction of the steroid dose to one third to one sixth of the stabilizing dose. The majority of patients will relapse on discontinuation of treatment (Agbogu et al., 1995).

Chloroquine has been used for treatment of neurosarcoid, and is an antimalarial drug with Anti-inflammatory effects used as well in rheumatologic disorders, but the precise mechanism of action is unknown. Chloroquine was shown to be beneficial, but its major limiting factor was retinal toxicity (Sharma, 1998).

Methotrexate has shown benefit in systemic sarcoidosis and in 61 % of a small series of neurosarcoidosis patients. Its use has been recommended in neurosarcoidosis along with corticosteroids and hydroxychloroquine. It is well tolerated, and there is less risk of carcinogenicity when it is given at a dose of 5-15 mg/week. The effects may not be seen until 6 months after treatment. The risk of liver toxicity requires that liver enzymes be monitored every 6 to 9 weeks, and a liver biopsy should be done after a cumulative dose of 1 gram has been given. Hypersensitivity pneumonitis develops in a small number of patients. Drug toxicity can be minimized by the use of folic acid (Sharma, 1998).

Azathioprine is an effective alternative. Its major advantage is moderate cost and tolerability. Treatment is initiated with small doses that are gradually escalated to a target dose of 2-3 mg/kg/day. Blood counts and liver function tests should be monitored. Treatment should be stopped if the white cell count drops below 3000 /MM3 or if liver enzymes rise to greater than five times the upper limit of normal. Approximately 10% of patients develop an idiosyncratic reaction to the drug, which manifests as a "flu-like" illness.

The major advantage of alternative medications is that they provide a "steroid sparing" effect and make it possible to reduce the dose of the steroids to 15% to 30% of a stabilizing dose. These immunosuppressants are best used as an adjunct to corticosteroids rather than as primary agents, because complete withdrawal or tapering of steroids below 10 mg/day usually results in relapse. No factors are known to predict response to a particular agent. Side effect profiles of most of the alternative medications are few and reversible on withdrawal of the medication (Stern et al., 1992; Agbogu et al., 1995).

Newer immunomodulatory agents and other modalities of treatment under research include tacrolimus, sirolimus, anticytokine therapy, anticellular adhesion molecules, T-helper-2 cytokines, and gene therapy targeting proinflammatory cytokines. No data are available to judge efficacy (Vital et al., 1982).

- **Radiation**

A small number of patients, specifically those with diffuse encephalopathy and vasculopathy, have undergone radiation treatment. These patients were treated with total nodal and craniospinal irradiation with some benefit (Chapelon et al., 1990). The usual recommended total dose is 19.5 Gy. This option is generally considered a last resort for refractory cases. The concomitant use of steroids or other immunosuppressive agents is generally required.

- **Surgical treatment of neurosarcoid**

Surgery is indicated for hydrocephalus, expanding mass lesions, or lesions that cause increased intracranial pressure (Andrew, 2006).

If presumed sarcoid lesions do not respond to medical treatment, a biopsy should be considered. Other surgical indications are mass lesions unresponsive to corticosteroids and hydrocephalus (Krumholz and Stern, 1998).

For severe hydrocephalus with evidence of raised intracranial pressure, a ventriculoperitoneal shunt or ventricular drain should be placed promptly. Some clinicians recommend high-dose IV methylprednisone (20 mg/kg/day for 3 days) to stabilize severe hydrocephalus before surgical intervention is obtained. Shunt procedures are associated with a significant risk of secondary infection and obstruction of the shunt from the inflammatory changes (Krumholz and Stern, 1998).

- **Prognosis**

Prognosis of sarcoidosis is highly variable. Spontaneous remissions occur in nearly two thirds of systemic disease. The course may be chronic or progressive in 10-30% (Andrew, 2006).

The overall prognosis for patients with neurosarcoidosis is poorer than for patients with disease outside the nervous system; however, certain neurological manifestations have favorable outcomes. In some patients, the disease is a monophasic illness with a good prognosis, but others show either a remitting-relapsing disease or a chronic progressive course. Approximately 35% to 50% of neurosarcoid patients improve spontaneously before diagnosis and treatment (Chapelon et al., 1990). Similarly, treated patients show good improvement in some reports. In contrast, in some series, the majority worsened despite treatment (Junger et al., 1993). In a recent series of 60 patients, 75% of those treated with steroids deteriorated. There is evidence to suggest that patients with an acute to subacute course tend to have better outcomes than those with chronic disease. Approximately one third of patients relapse, mimicking multiple sclerosis, but the relapses tend to occur in sites of earlier involvement (Junger et al., 1993). Clinical manifestations are the best predictors of course and prognosis (Agbogou et al., 1995).

Cranial neuropathy and aseptic meningitis carry the best prognosis. More than 90% of patients experience improvement or recovery. Approximately 32% of patients with neurosarcoidosis, especially those with cranial neuropathies, relapse after the initial neurological episode. Patients with the other neurological manifestations, especially those with parenchymal disease, generally have a prolonged chronic course with significant morbidity (Luke et al., 1987). Only 40% of individuals with optic nerve involvement make appreciable recovery, and approximately 78% of

patients with spinal cord involvement deteriorate with corticosteroids. Among the peripheral nervous system manifestations, polyradiculitis and acute myopathy tend to respond well to steroids compared with slowly progressive peripheral neuropathy and myopathy (Olek et al., 1995).

Patients who relapse and those with high risk of disease should be considered for low-dose maintenance steroid therapy rather than complete withdrawal. The mortality rate from neurosarcoidosis is approximately 5% to 15%. The true natural history of neurosarcoidosis is difficult to know because most patients are treated with immunosuppressants. Despite this drawback, corticosteroids seem to help contain the inflammatory process and improve functional outcome (Luke et al., 1987).

- **Wegener granulomatosis**

Wegener granulomatosis (WG) is a unique clinicopathological disease entity characterized by necrotizing granulomatous vasculitis of the upper and lower respiratory tract, pauci-immune segmental necrotizing glomerulonephritis, and small vessel vasculitis. (Carol, 2003).

- **Pathology**

The etiology of WG remains uncertain; however, a number of observations implicate ANCA, in conjunction with intercurrent infection, in the pathogenesis. The proposed mechanism implies that infection leads to the production of cytokines such as interleukins 1 and 8 and tumor necrosis factor alpha, which cause neutrophils to express adhesion molecules (leading them to stick to vascular endothelium), and to express proteins that provide the targets for ANCA (proteinase 3 and myeloperoxidase). Circulating ANCA then binds to these proteins and induces neutrophil degranulation, generation of oxygen-free radicals, and endothelial cell injury. By this mechanism, infection might potentiate disease activity in WG, and there is compelling empirical evidence that this occurs (Leavitt et al., 1990).

Wegener granulomatosis (WG) is distinguished from other vasculitides by the pattern of organ involvement and by the histological features of granulomatosis and necrotizing inflammation. Primary involvement occurs in upper and lower respiratory tracts and the kidneys (glomerulonephritis). Neurological involvement, seen primarily as cranial neuropathies and peripheral neuropathies, occurs in about 34% of cases. Other commonly affected organs include skin and salivary glands (Nishino et al., 1993).

Vasculitis may involve medium and small sized vessels, both venous and arterial; pathological specimens generally show both acute and chronic inflammation. Vascular scarring may be permanent (Leavitt et al., 1990).

The lungs may be affected acutely with alveolitis. Necrotizing granulomatosis develops and may initially appear histologically as microabscesses or necrosis, surrounded by palisading histiocytes. Granulomas may be either intravascular or extravascular. The renal lesion of WG is usually a necrotizing glomerulonephritis; however, many types of nephritis may be seen (Metwally, 2006-6).

The reported frequency of neurologic involvement in WG ranges from 22% to 54% and three pathophysiologically relevant processes has been recognized to explain the CNS affection. Contiguous spread of granulomatous disease from the ear, nose, and throat tract into the brain and cranial nerves; formation of granuloma primarily in the nervous system; and vasculitis affecting the peripheral nervous system or the CNS causing intracerebral hemorrhage, subarachnoid hemorrhage, and cerebral arterial or venous thrombosis (Kirsten et al., 2001). Most patients were affected by peripheral neuropathy or cranial neuropathies. A pattern of

symmetrical polyneuropathy was seen in some patients, but peripheral neuropathy most often manifests as acute mononeuritis multiplex. Cranial nerves II, VI, and VII are affected most commonly (Nishino et al., 1993).

- **Clinical picture**

The diagnosis of WG is suspected when patients present with constitutional symptoms such as fever, weight loss, and anorexia with symptoms of upper respiratory tract affection chronic sinusitis, nasal ulceration, other upper respiratory tract symptoms, or lower respiratory symptoms of hemoptysis, dyspnea, or cough (Hoffman et al., 1992).

It is much less common for the patient to present with symptoms of renal involvement, although renal involvement is often clinically evident at presentation. Manifestations include proteinuria, hematuria, and renal insufficiency. Ocular disease is commonly manifested by conjunctivitis, uveitis, dacryocystitis, retinitis, and/or proptosis due to orbital pseudotumor, which may cause loss of vision in approximately 50% of patients with this complication (Paul, 2005).

Neurologic involvement manifestations are extremely varied, the most common neurological presentation was peripheral neuropathy with mononeuritis multiplex or cranial neuropathy involving the second, sixth, and seventh cranial nerves. Some patients has manifestations in the CNS such as seizures, altered cognition (cerebritis), focal motor and sensory complaints, stroke syndromes, or diabetes insipidus due to pituitary involvement. Presentations may involve chronic, acute, or stepwise deterioration referable to parenchymal or meningeal inflammation and scarring. A history of headaches and other symptoms related to inflammation of meningeal or parenchymal structures should be sought initially and on follow up visits (Metwally, 2006-6).

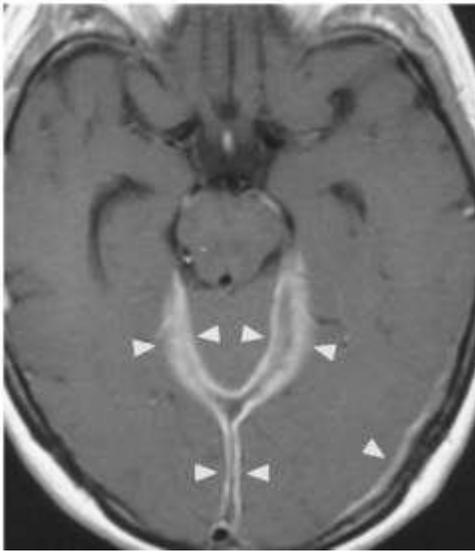
- **Investigation**

Abnormal findings on routine laboratory tests are nonspecific in WG. Abnormalities include leukocytosis, thrombocytosis (>400,000/mm³), marked elevation of erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), and normocytic and normochromic anemia.

Laboratory diagnosis of WG has been greatly aided by emergence of testing for c-antineutrophil cytoplasmic antibodies (c-ANCA), which if present, is 97% specific for WG. Testing for c-ANCA is 90% sensitive for the diagnosis when the presentation is classic involving both upper and lower respiratory system and kidneys; sensitivity drops to 40% in limited WG (limited to only kidneys or respiratory system) (Hagen et al., 1998).

- **Neuroimaging**

In Wegener granulomatosis, MRI is superior to CT, and it shows variable findings. The meninges are considered to be abnormal (involved by the disease) if they showed either diffuse or focal thickening on contrast-enhanced MR images. Involvement of both the tentorium cerebelli and the dura overlying the convexity of the cerebrum might occur in combination; however the tentorium cerebelli might be the sole site of involvement (Figure 22, 23).



weighted contrast-enhanced spin-echo MR images demonstrate diffuse symmetric linear dural thickening and enhancement (arrowheads). (Metwally, 2006-6)

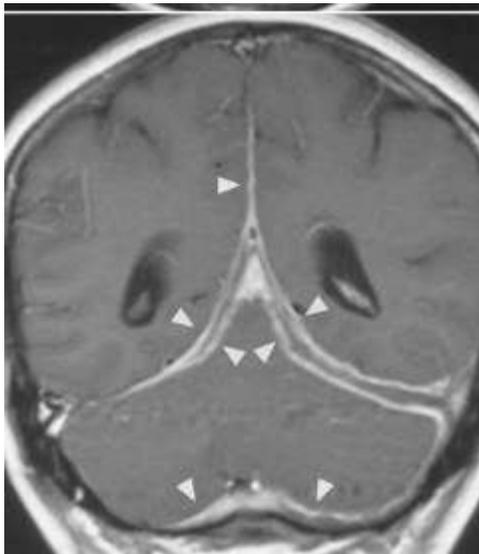


Figure 23. Wegener. Granulomatosis. Coronal T1-weighted contrast-enhanced spin-echo MR images demonstrate diffuse symmetric linear dural thickening and enhancement (arrowheads)., (Metwally, 2006-6)

Two distinct MRI patterns of distribution of meningeal involvement are noted Focal dural thickening and enhancement adjacent and /or contiguous with orbital, nasal, or paranasal disease. This represent direct invasion of paranasal and para-aural tissues by the granulomatous process. Diffusely abnormal meninges unrelated to sinus or orbital disease reflects "metastatic disease" that is not contiguous with disease of the upper airways. This pachymeningitis (primarily dural involvement) can extend well up over the cerebral convexity or along the flax or tentorium (Joseph et al., 1999).

Non hemorrhagic infarcts that affect the cortex, white matter, or both, in a typical vascular distribution might be seen in Wegener granulomatosis (Figure 24). Multiple infarctions can also occur. Nonspecific white matter lesions with high signal intensity on intermediate-weighted and T2-weighted images are occasionally seen in Wegener granulomatosis. These lesions can be multiple and are commonly seen in the per ventricular, subcortical regions and the basal ganglia. they show high signal intensity on intermediate-weighted and T2-weighted images, low signal intensity on T1-weighted images, and some peripheral enhancement on gadolinium-enhanced images are occasionally demonstrated. Enhancement and/or enlargement of the pituitary gland are occasionally demonstrated in Wegener granulomatosis. The enhancement is commonly homogeneous with thickening and / or enhancement of the infundibulum (Joseph et al., 1999).

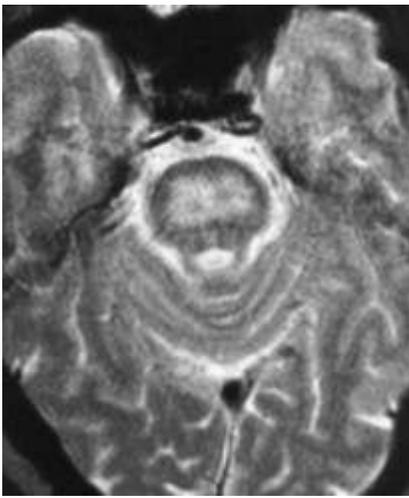


Figure 24. Wegener. Granulomatosis. T2-weighted axial MRI shows hyperintense signal throughout much of the pons, (Metwally, 2006-6)

○ Treatment

The therapeutic goals in WG have expanded dramatically over the past 30 years. Prolongation of patient survival was the primary objective prior to the 1970s as 82% of patients with active WG died within 1 year. Long-term survival became possible with the introduction of prednisone and cyclophosphamide, although morbidity and mortality continued to occur as a result of treatment-induced toxicity and disease relapse (De Groot et al., 2001).

Glucocorticoids combined with cyclophosphamide or methotrexate are the only two regimens that have thus far been shown to induce remission of active WG affecting a major organ. Patients with alveolar hemorrhage, rapidly progressive glomerulonephritis, CNS disease, or other manifestations that are immediately life threatening should initially be treated with cyclophosphamide and glucocorticoids. Optimal treatment consists of daily intravenous or oral cyclophosphamide (2 mg/kg/day). Monthly pulse intravenous cyclophosphamide is preferred because of its better side effect profile, yet is insufficient to reliably induce remission, however it may be employed to sustain remission. Cyclophosphamide treatment is generally maintained through 1 year of stable remission. Daily prednisone, 1 mg/kg/day is routinely employed during the first 6- 12 months. With this approach, marked improvement or partial remission was achieved in 91% of patients and complete remission in 75%. The high morbidity rate associated with this treatment (infections, hemorrhagic cystitis, secondary neoplasia) has led to an avid search for alternative approaches. Methotrexate is successfully employed to induce remission in patients who present with relatively more indolent disease and may be effective in sustaining remission. (Hoffman et al., 1992) Azathioprine can maintain remission after induction with CYC (Jayne, 2001).

The experience with other cytotoxic and immunosuppressive agents in the treatment of WG comes solely from case reports and small series, and there remain insufficient data to assess efficacy. These agents include cyclosporine, deoxyspergualin, intravenous immunoglobulin, trimethoprim/sulfamethoxazole. Also new selective immunomodulatory agents are under trial now, including alemtuzumab, etanercept, infliximab and rituximab (Carol, 2003).

● Granulomatous angiitis

Many forms of vasculitis may involve the CNS, including Behcet's disease, polyarteritis nodosa, vasculitis associated with connective tissue diseases such as lupus (systemic lupus erythematosus; SLE), and others. Most of these diseases can produce vasculitis or other problems outside of the brain, however in the description of intracranial granulomatous angiitis, it is a more specific type of vasculitis in which the disease process is confined to the CNS and no known infection can be

identified within the CNS (Calabrese and Duna, 1995).

Granulomatous angiitis of the nervous system, is a name that draws attention to a pathological feature of the disease seen in some, but not all, cases. More recently, the preferred name for this form of vasculitis has been primary angiitis of the central nervous system (PACNS). Finally, recognition that a subgroup of patients appear to have milder disease courses has led to the designation of benign angiopathy (as opposed to angiitis) of the CNS, or “BACNS” (Calabrese et al., 1993).

- **Pathology**

The cause of granulomatous angiitis is not known. It is very possible that viral infections (which remain difficult to diagnose) initiate the inflammatory process that somehow becomes self-sustaining. Although anecdotal experience and case series associate BACNS with heavy nicotine or caffeine use as well as with oral contraceptive and cold remedy use, the true associations between these exposures and the development of BACNS remain uncertain (Calabrese, 1995).

Pathologically there are monocytes, lymphocytes and plasma cells infiltrating the walls of small arteries, particularly in the leptomeninges, although occasional involvement of the internal carotid and vertebral arteries is seen. Numerous small foci of infarction are common, but there maybe large areas of ischemia, sometimes with superimposed hemorrhage (George et al., 1995).

- **Epidemiology**

The distribution of PACNS is nearly equal between the sexes, with perhaps a slight male predominance (4 3). The mean age of people affected by the disease is approximately 42 years, but the range is wide. In contrast, patients with BACNS tend to be young women, often those with previous histories of headaches (such as migraines). These patients often have histories of heavy nicotine or caffeine use, over-the-counter cold remedy use (e.g., ephedrine), and oral contraceptive or estrogen replacement therapy (Hankkey, 1991).

- **Clinical picture**

The clinical manifestations of PACNS and BACNS may be identical, and include many neurologic symptoms and signs such as headache, focal weakness (like that with a stroke), seizures, bleeding within the CNS, confusion, disorders of memory, and altered consciousness. All of these symptoms and signs are non-specific, and can be mimicked by a variety of other conditions (Arora and white, 1994).

There are two main differences in the clinical presentations of PACNS and BACNS. First, whereas PACNS patients are more likely to develop symptoms subacutely and remain undiagnosed for months, those with BACNS are more likely to have relatively acute presentations and be diagnosed within weeks of onset (in either case, however, making the diagnosis is challenging). Second, without treatment, patients with PACNS tend to have progressively downhill courses that often lead to death. In contrast, BACNS patients may require less aggressive treatment than PACNS (Bettoni et al., 1984).

- **Investigations**

Because many diseases may mimic granulomatous angiitis and because its treatment is potentially dangerous, it is essential to confirm the diagnosis before starting treatment. Nearly all patients therefore require either an angiogram or biopsy of the brain. Tests such as MRI studies and lumbar punctures (spinal taps) are also helpful in the work-up of a patient with possible

granulomatous angiitis (Duna and Calabrese, 1995).

The ESR is elevated in 66% of patients, and CSF should be examined if PACNS is suspected. CNS examinations show nonspecific abnormalities, in 81% of patients, in the form of pleocytosis, and elevated protein levels. CT scan may show infarcts, low density lesions and giriform enhancement, while MRI may show focal areas of infarctions in multiple vascular territories (Duna and Calabrese, 1995).

As angiography is less invasive than brain biopsy, this test is often performed before biopsy. The classic angiographic findings in granulomatous angiitis include “beading” (alternating dilatations and narrowings of blood vessels), aneurysms, and other irregularities within blood vessels (Figure 25). It must be recognized, however, that many conditions not caused by vasculitis (e.g., spasm of the blood vessels) can cause an angiographic appearance that is impossible to distinguish from true vasculitis (Heiserman et al., 1994).

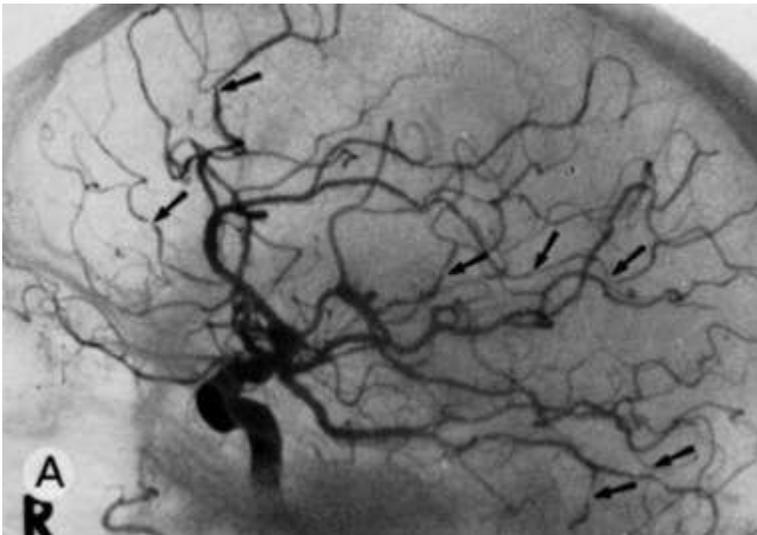


Figure 25. Intracranial Granulomatous Angiitis. Cerebral angiograms showing diffuse irregular segmental arterial narrowing (arrows) involving peripheral distribution of anterior, middle, and posterior cerebral arteries. Note asymmetric depression of right posterior cerebral artery (Micheal et al., 1977)

Because the diagnosis cannot be proven with 100% certainty by angiography, consideration is often given to performing a brain biopsy before initiating treatment with the combination of cyclophosphamide and steroids. If non-invasive imaging studies such as an MRI indicate a site of probable pathology within the brain, the neurosurgeon may opt to perform the biopsy at that site if it is surgically accessible. If no obvious site for biopsy is identified by non-invasive studies or by angiography, the brain biopsy is usually performed on the non-dominant side of the patient's brain. Biopsy of the meninges is usually performed at the same time (this increases the chance that the procedure will yield a piece of tissue containing pathology). Although brain biopsy remains the “gold standard” in the diagnosis of CNSV, 25% of the time a brain biopsy will be negative even in the setting of true vasculitis; i.e., the likelihood of a “false-negative” biopsy is unfortunately rather high (Lie, 1992).

○ Treatment

Until recently, PACNS was a fatal condition in a high percentage of cases, with death following diagnosis in a mean of 45 days after diagnosis. The availability of powerful immunosuppressive therapy, however, has significantly improved the prognosis for people with this condition. Some patients with PACNS respond well to treatment with high doses of steroids alone. Others require the addition of cyclophosphamide to the steroid regimen. In many cases, a reasonable approach is to attempt to control the disease with high doses of steroids first (e.g., for one month), adding cyclophosphamide only if steroids fail or if patients begin to develop unacceptable side-effects of steroid treatment (Scolding et al., 1997).

Balancing control of the disease with the possibility of serious side-effects of treatment is often challenging. For PACNS, treatment must often be continued for a year or more.

Patients who fit the typical patient profile of BACNS and who have clinical presentations compatible with that diagnosis may be candidates for less intensive treatment regimens than those used in clear-cut cases of PACNS. Patients believed to have BACNS may be treated with calcium-channel blockers (a class of drug used to treat high blood pressure and spasm of blood vessels that occurs in a variety of conditions) for a few weeks, along with a comparatively short course of steroids (prednisone). However, no firm guidelines exist regarding the length of therapy, however, and decisions about the length of treatment must be made on a case-by-case basis (Scolding et al., 1997).

- **Langerhans cell histiocytosis**

Histiocytosis is a rare blood disease that is caused by an excess of white blood cells called histiocytes. The histiocytes cluster together and can attack the skin, bones, lung, liver, spleen, gums, ears, eyes, or the CNS. The disease can range from limited involvement that spontaneously regresses to progressive multiorgan involvement that can be chronic and debilitating. In some cases, the disease can be life-threatening. In some ways, histiocytosis is similar to cancer and has historically been treated by oncologists with chemotherapy and radiation. Unlike cancer, histiocytosis sometimes goes into remission without treatment.

It is estimated that 1 in 200,000 children are affected each year. 76 percent of the cases occur before 10 years of age, but the disease is also seen in adults of all ages. Langerhans cell histiocytosis has also been known as Histiocytosis-X, Eosinophilic Granuloma, Letterer-Siwe disease, and Hand-Schuller-Christian Syndrome. The cause of LCH is unknown. It may be triggered by an unusual reaction of the immune system from something commonly found in the environment (Vassallo et al., 2000).

- **Clinical picture**

The LCH can affect many organs causing varied clinical picture. Skin Involvement manifest as scaly, waxy rash that does not respond to treatment. Bone involvement is in the form of Single or multiple lesions, causing bone pain, headaches (skull lesions), and limping (leg lesions). The eye may be involvement with vision problems or eye bulging. The gastrointestinal tract manifest as abdominal pain and jaundice, vomiting, diarrhea, bleeding from the esophagus, and weight loss. The affection of the lungs causes feeding problems (infants), vomiting, diarrhea, chest pain, labored breathing, failure to thrive, cough, haemoptesis, and weight loss. The ear Involvement manifests as inflamed condition of ear canal, rash behind ear or on scalp, formation of cysts in the ear, and oozing from ear (foul-smelling discharge) (Sheehan and Chu, 1991).

Diabetes insipidus is the hallmark of involvement of the hypothalamic-pituitary region and is the most common and best recognized feature of CNS disease in LCH. Hypothalamic pituitary involvement is seen in about 10 percent of LCH patients. The incidence ranges from 5 to 50 percent in the different reports, according to the various stratification systems or treatment approaches. Polyuria and polydipsia as symptoms of posterior pituitary dysfunction are the most frequent finding in about 90 percent of patients with morphological changes in this region. However, other endocrine deficiencies like growth failure, precocious or delayed puberty, amenorrhea, hypothyroidism, or hypocortisolism resulting from anterior pituitary failure, are seen in about 50 percent of the DI patients. In rare cases of hypothalamic tumors, disturbances of appetite and social behavior with binge or rage attacks and dysregulation of sleep or temperature may be seen (Vassallo et al., 2000).

Extraparenchymal space-occupying lesions are derived from the meninges or choroid plexus. They mostly occur in patients with concomitant lesions in the hypothalamic-pituitary axis and may also be associated with neurodegenerative lesions. Symptoms depend on the site and size of the lesions and include headaches, seizures, vomiting, papilledema, optic nerve compression, or other focal symptoms (Martin et al., 2006)

Affection of cerebellum, pons, basal ganglia or the cerebral grey and white matter is observed in 1% of the overall LCH population and is associated with a neurodegenerative syndrome of highly variable severity and course. The symptoms range from subtle tremor or coordination problems to severe ataxia, dysarthria, and dysphagia, sometimes combined with intellectual impairment or behavioral changes. Eventually progressive neurological degeneration renders the patients wheelchair bound and severely disabled and may lead to a fatal deterioration in the worst cases. Neuropsychological sequelae are frequently seen in LCH patients with CNS changes on MRI. Global cognitive deficits, as well as more specific changes in memory, concentration and attention have been observed. (Daniela et al., 2004)

○ Investigations

During the last few years MRI has become readily available. More LCH patients with lesions in the skull or with DI are investigated with this modern imaging technique. Unexpectedly, an increasing number of patients are diagnosed with lesions in other parts of the brain, apart from the hypothalamic-pituitary region, some even before any clinical symptoms develop. MRI findings comprise a thickening of the pituitary stalk (figure 26), a loss of the normal hyperintense signal of the posterior pituitary on T1-weighted images (bright spot), partial or completely empty sella, or mass lesions (Schmitt et al., 1993).



Figure 26. Langerhans Cell Histiocytosis. Coronal section, T1-weighted, contrast enhanced MRI showing thickened enhancing pituitary stalk (type IV a) with impingement of the optic chiasm (arrow). (Metwally, 2006-12)

Recent MRI studies showed variable radiological findings in LHC. Dura-based masses was present in 29% of patients (figure 27). These masses were isointense to hypointense to brain on T1WI with contrast enhancement; they appeared hypointense on T2WI . Choroid-plexus lesions had intermediate signal intensity on T1WI and marked hypointensity on T2WI. The pineal gland had cystic changes in 28% of patients and increased size (>10 mm) in 14%, with a maximum size of 24 mm. Thickening of the infundibulum (>3.00 mm) was seen on about 50% of patients (Schmitt et al., 1993).

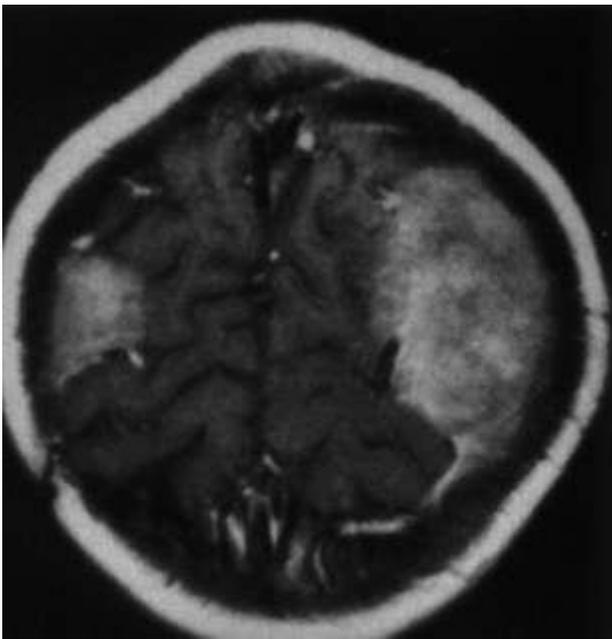


Figure 27. Langerhans Cell Histiocytosis. Axial section, T1-weighted, contrast enhanced: MRI showing bilateral dural-based enhancing mass lesions (Metwally, 2006-12)

Two major patterns of white matter lesions were distinguished. The most frequent signal-intensity changes were dilated Virchow-Robin spaces, which was noted in 61% of patients with LCH; other patients had supratentorial white matter lesions with a leukoencephalopathy like but no vascular pattern. Deep infratentorial gray matter affection was found in 40% of patients (Daniela et al., 2004).

Endocrine evaluation should be done in all patients with diabetes insipidus, growth failure, or other evidence of hormonal dysfunction. Brain biopsy may be necessary in mass lesions, often combined with a curative surgical approach. In neurodegenerative lesions, biopsies are rarely indicated in the context of a history of LCH outside the CNS (Daniela et al., 2004).

- **Treatment**

No general recommendations concerning treatment are established till now. The individual strategy is dependent on the type and site of the lesions and the state of LCH outside the CNS. Chemotherapeutic agents like vinblastine, etoposide or mercaptopurine, together with steroids are being assessed. (Daniela et al., 2004)

The management of patients with DI is dependent on the disease state of LCH outside the brain and on the cerebral MRI. In patients with known LCH and longstanding DI who do not show a thickened infundibulum on MRI, no specific therapy is needed, but regular evaluations should be performed. In the case of new-onset DI with an infundibular thickening, active LCH must be assumed, and systemic therapy with corticosteroids and chemotherapeutic agents should be considered, even in the absence of LCH activity outside the brain (Daniela et al., 2004).

Space-occupying tumors may need to be completely or partially resected if they exert a mass effect. Chemotherapy with agents of established efficacy in systemic LCH that are known to cross the blood brain barrier might be beneficial in cases of a diagnosis of active LCH in such masses. Local irradiation might be another option when a radical surgery is not possible. Apart from these mass lesions, radiation therapy rarely seems indicated in CNS LCH. Irradiation of the hypothalamic-pituitary region does not seem to be the method of choice, considering the potential endocrine sequelae and the small chance of reversal of established DI (Sessa et al., 1994)

- **Cholesteatoma**

Cholesteatoma has been recognized for decades as a destructive lesion of the skull base that can erode and destroy important structures within the temporal bone. Its capacity for CNS complications (e.g. brain abscess, meningitis) makes it a potentially fatal lesion. The term cholesteatoma is actually a misnomer since the lesion is not a neoplasm and does not contain cholesterol (Ferlito, 1993).

A cholesteatoma consists of squamous epithelium that is trapped in the skull base. Squamous epithelium trapped within the temporal bone, middle ear, or mastoid can expand only at the expense of the bone that surrounds and contains it. Consequently, the complications associated with a growing cholesteatoma include the possible injury to any of the structures normally found within the temporal bone. Occasionally, cholesteatoma will escape the confines of the temporal bone and skull base. Extratemporal complications may occur in the neck and/or the CNS. Cholesteatoma sometimes will reach sufficient size within the cranium, so as to distort normal brain and produce mass effects. (Ferlito, 1993).

Microscopically, squamous epithelium (called matrix by the otologist) forms a cyst of desquamating squames. The epithelium of a cholesteatoma and its cyst appears identical to that of epithelial inclusion cysts. The epithelium may rest on granulation tissue or fibrous tissue. (Topalogue et al., 1997).

Three separate types of cholesteatoma generally are identified on the basis of differing etiologies; congenitally-acquired, primary-acquired, and secondary-acquired. Congenital cholesteatomas arise as a consequence of squamous epithelium trapped within the temporal bone during embryogenesis. Primary acquired cholesteatomas arise as the result of tympanic membrane retraction. Secondary-acquired cholesteatomas occur as a direct consequence of some type of injury to the tympanic membrane. This injury can be a perforation, which arises as a result of acute otitis media or trauma, or may be due to surgical manipulation of the drum. (Topalogue et al., 1997).

Bony erosion occurs by 2 principle mechanisms. Pressure effects produce bone remodeling, just as what occurs regularly throughout the normal skeleton. Moreover, Enzymatic activity at the margin of the cholesteatoma enhances osteoclastic activity, which greatly increases the speed of bone erosion. These osteolytic enzymes appear to increase when a cholesteatoma becomes infected (Topalogue et al., 1997).

- **Clinical picture**

The hallmark symptom of cholesteatoma is painless otorrhea, either unremitting or frequently recurrent. Hearing loss is common while dizziness is less common. Occasionally, cholesteatoma will first present with the signs and symptoms of central nervous complications, like sigmoid sinus thrombosis, epidural abscess, or meningitis. (Matra et al., 2003))

- **Investigations**

CT scan is the imaging modality of choice. CT scan can detect subtle bony defects, and some surgeons feel any patient with a cholesteatoma scheduled for surgical intervention should have a preoperative CT scan. However, it cannot always distinguish between granulation tissue and cholesteatoma. CT scan shows a non-specific, non-enhancing soft tissue mass that has a smooth margin and variable bone erosion (Figure 28) (Lustig et al., 1998).



Figure 28. CT scan showing Cholesteatoma on the left with bone erosion and tegmen tympani dehiscence. (Mauricio et al., 2005)

By MRI, cholesteatomas are hypointense or isointense on T1-weighted images and hyperintense on T2 images. Yet, MRI is used when very specific problems involving surrounding soft tissues are expected, like dural involvement or invasion, subdural or epidural abscess, herniated brain into the mastoid cavity, inflammation of the membranous labyrinth or facial nerve, or sigmoid sinus thrombosis (Chang et al., 1998).

- **Treatment**

Medical therapy is not a viable treatment for cholesteatoma. Patients who refuse surgery or whose medical condition makes a general anesthetic too hazardous should have the ear cleaned on a regular and routine basis. Regular cleaning can help control infection and may slow growth, but it will not stop further expansion and will not eliminate risk. Main treatment of cholesteatoma, regardless of size, is complete surgical removal, with a recurrence rate of up to 50%, and often result in hearing loss (Chang et al., 1998).

- **Cholesterol granuloma**

Cholesterol granuloma is not a neoplasm but a descriptive term used for a granulomatous reaction to blood breakdown products, primarily cholesterol. They are thought to arise secondarily following disease states where normally ventilated air-containing bony spaces are obstructed, such as in chronic or acute otitis media, cholesteatoma, or mastoiditis (House and Brackmann, 1982). Cholesterol granulomas occur most commonly in the pneumatized petrous apex of the temporal bone but also may be seen in other pneumatized portions of the temporal bone, including mastoid air cells and middle ear space (Lustig et al., 1998). They generally grow silently, with clinical presentation after the lesion has caused bony destruction and compression of cranial nerves V-VIII, structures within the inner ear, or the brainstem (Chang et al., 1998). Symptoms can include headache, diplopia, vertigo, dizziness, hearing loss, and facial paralysis (Lusting et al., 1998).

Cholesterol granulomas are usually cystic lesions with a thin brown-yellow fibrous capsule and luminal contents consisting of watery chocolate-colored fluid (Chang et al., 1998). Histologically, they consist of an extensive granulomatous response with cholesterol crystals that are thought to be the byproducts of blood degradation components (Rosenberg et al., 1986). The crystals are lost with routine histologic processing leaving classic cholesterol clefts that are surrounded by multinucleated giant cells, hemosiderin-laden and foamy macrophages, lymphocytes, plasma cells, and abnormal blood vessels. In extensive lesions, there may be evidence of bone destruction (Ferlito et al., 1997).

The primary lesion in the differential diagnosis with cholesterol granuloma is cholesteatoma

(Table 5). Cholesteatomas arise in similar regions as cholesterol granulomas and are usually contained within the tympanomastoid region but aggressive lesions do occur with erosion of bone (Topalogue et al 1997).

CT scan, in both cholesteatomas and cholesterol granulomas, shows a non-specific, non-enhancing soft tissue mass that has a smooth margin and variable bone erosion (Chang et al., 1998). By MRI, cholesteatomas are hypointense or isointense on T1-weighted images and hyperintense on T2 images. Cholesterol granulomas typically are homogenous and show bright signal intensity on both T1- and T2-weighted images without significant enhancement with gadolinium contrast (Iustig et al., 1998). When large, however, cholesterol granulomas can exhibit a more heterogeneous MRI pattern (Martin et al., 1989).

Table 5. Points of difference between Cholesterol Granulomas and Cholesteatoma (Topalogue et al 1997)

	Cholesterol Granuloma	Cholesteatoma
CT	Soft tissue density with possible bone erosion	Soft tissue density with possible bone erosion
MRI	Hypo- or isointense on T1; hyperintense on T2	Hyperintense on T1 and T2
Gross	Partially cystic with a thin fibrous capsule and chocolate-colored fluid	Cyst with pearly-white contents
Histology	Granulomatous reaction with abundant cholesterol clefts, multinucleated giant cells, hemosiderin-laden macrophages, lymphocytes, and plasma cells	Keratinized stratified squamous-lined cyst filled with anucleate squamous debris
Treatment and Outcome	Drainage with restoration of normal pneumatization; if extensive, surgical excision	Complete surgical excision with 50% recurrence rate and hearing loss

It is important to make the distinction between cholesterol granuloma and cholesteatoma because of treatment differences. Cholesterol granulomas will resolve after internal drainage into the mastoid cavity or middle ear, relieving the obstruction and restoration of the normal pneumatization of the bone. However, there have been reports of large destructive cholesterol granulomas that require complete surgical excision (Lustig et al., 1998).

DISCUSSION

The granulomatous disorders involving the CNS are a diverse confusing medical problem. They are assumed to be multifactor difficulties regarding clinical picture, poor investigational yield, some have controversial treatment and many of them are difficult to be cured if not fatal. The hallmark for these difficulties is the diverse non specific systemic and neurological clinical presentations for such patients to the extent that many medical specialties face these patients separately on the first time, and unless the physicians have a high index of clinical suspicion to such non specific clinical presentations, there will be subsequent delay in diagnosis with deterioration of clinical picture making the management of poor outcome.

Furthermore, each of these diseases has its own diagnostic workup on one hand and most of the

non invasive investigations are not specific, doesn't lead to a solid management decisions and are time consuming on the other hand. Thus, the gold standard for definite diagnosis for most of these disorders is tissue biopsies and cultures, which is hindered by technical obstacle.

Even if a definite diagnosis is reached, treatment studies on neurological manifestations of granulomatous diseases are lacking. Treatment decisions are either following the guidelines of management of the systemic side of these disorders, or are lacking clear guidelines due to absence of controlled studies or controversy on lines of management.

It is worth mentioning that the role of epidemiological distribution is of ultimate importance in the diagnosis of such overlapping conditions. This can be applied clinically when atypical cases are met to prioritize the differential diagnosis and the subsequent investigational panel and treatment plan. For example TB is endemic in developing countries especially in India, this is due to lack of eradication programs, increased prevalence of HIV, and poor sanitation. Yet recently it started spreading again in developed countries with migration. Cysticercosis is also prevalent in India and many developing countries due to poor sanitation. Hydatid disease is prevalent in middle east, east Africa, parts of Russia and South America. Bilharziasis is endemic in parts of Asia, South America and Africa including Egypt, while absent in Europe and North America. Although some types of fungal infections are present world wide, such as candida and Cryptococcus, yet others have a limited geographical distribution like Aspergillosis which is prevalent in the tropical zones and Mediterranean, and coccidioidomycosis is present only in Arizona in the United States of America.

Even the non infectious granulomas have a rather clinically significant pattern of distribution. For example, sarcoidosis is prevalent in northern Europe while almost absent in China and southern Asia.

In the last few decades, both the incidence and the prevalence of some of these disorders have increased. This is directly related to the increased prevalence of immunosuppressive states, due to the pandemic of HIV infection, use of immunosuppressive drugs, and organ transplantation.

The most common granulomatous disorders encountered in relation to the immune system condition are TB, Toxoplasmosis, Cryptococcus, candidacies, coccidioidosis, aspergillosis and mucormycosis. These conditions were thoroughly studied in HIV infected population compared to other immunosuppressed states, to the extent that the guidelines of HIV treatment is now recommending prophylactic treatment for many of these disorders according to the immunostatus of the patient (CD cell count).

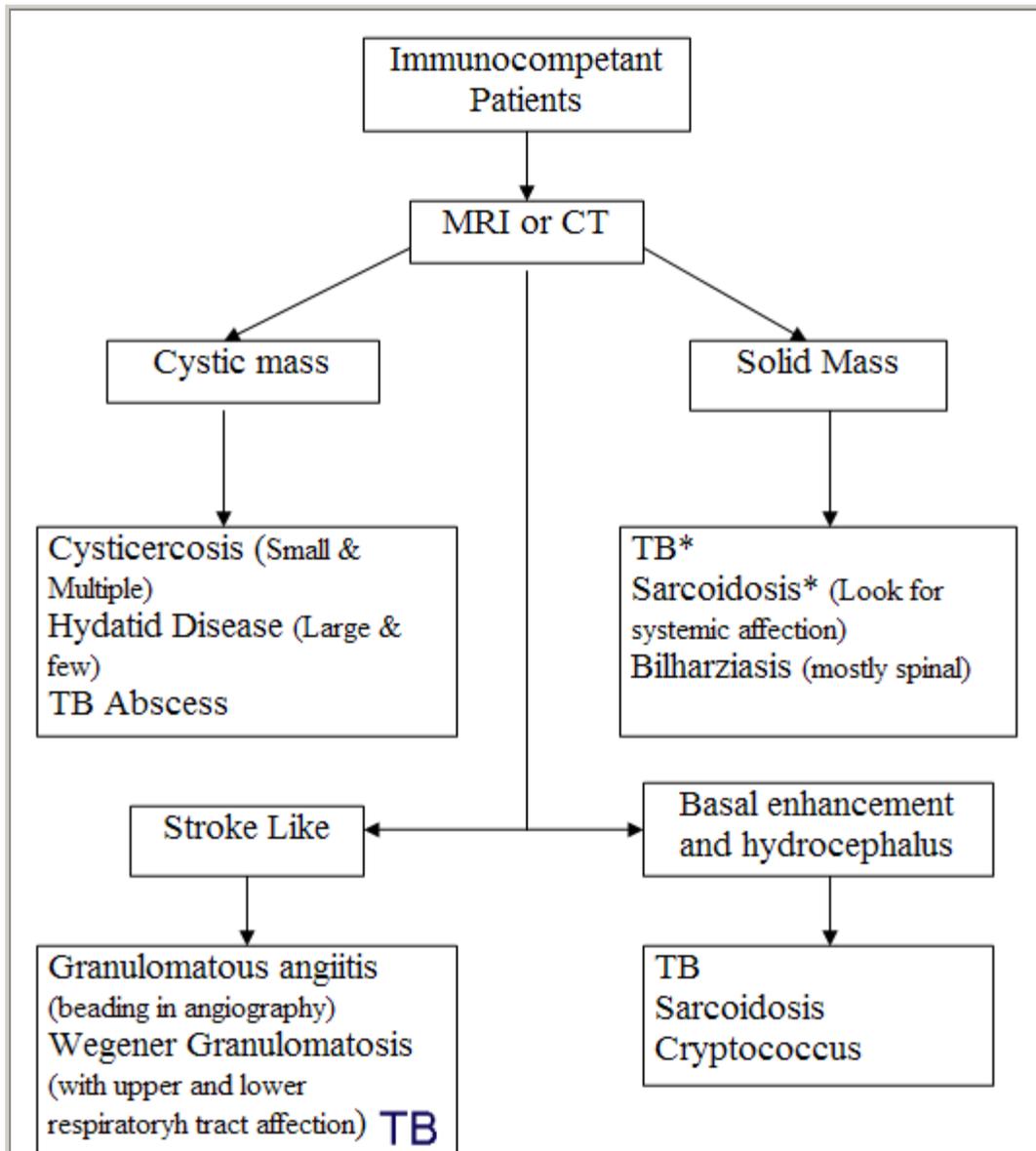
Clinically, the above mentioned granulomatous disorders have an overlapping widely varied clinical presentation. Moreover these symptoms overlap with other CNS neoplastic lesions (e.g. lymphoma) or other opportunistic infections. Rarely the clinical picture may have some specific features according to the cause, for example, blindness is common in cryptococcal meningitis, while acute onset of focal neurologic deficits is more suggestive of aspergillosis, and CNS candidiasis usually present in the context of systemic affection.

Because of the formentioned confusing clinical presentations we rely on investigations to reach a reliable diagnosis. The definitive diagnosis of CNS tuberculosis needs to be rapid as the prognosis differs radically depending on the time of start of treatment. Yet the gold standard (smear, culture) are time consuming and not sensitive. Lately PCR is showing promising results, with relatively higher sensitivity compared to culture, rapid, but expensive, technically demanding, and unavailable in endemic area. In CNS toxoplasmosis radiological studies show multiple brain enhancing lesions which when combined with positive serology empirical treatment should be started and if there is no response in 2 weeks, a tissue biopsy should be obtained. As regard fungal

CNS granulomas, MRI may show multiple infarctions, with hemorrhage in 50%. The CSF exam and culture carries the main brunt for diagnosing the fungal etiology affecting CNS if positive. Moreover, CNS affection due to fungi may affect immunocompetent patients, mainly *Cryptococcus*. And the therapeutic yield is variable according to the type of organism and the immune status of the patient.

The emergence and rapid development in the neuroradiology has offered many clues yet insufficient to diagnose and differentiate the causative disorder. As a result, it is worth mentioning a postulated guideline to differentiate CNS granulomas based on the relatively specific radiological findings (Figure 29).

Figure 29. Postulated guidelines to differentiate common CNS granulomas in immunocompetent patients



Common CNS granulomatous disorders in immunocompetent patients include TB, sarcoidosis, cysticercosis, Wegener granulomatosis, Langerhans cell histiocytosis, primary CNS angiitis, bilharziasis, and echinococcus granulosus. Clinically, these disorders have varying systemic manifestations that are helpful in guiding the diagnosis. Neurologically, there are some

overlapping features however in sarcoidosis the most common features is cranial nerve affection, in cysticercosis the patients usually present by fits, in bilharziasis most cases involve the spinal cord, and hydatid disease behave as a space occupying lesion.

Regarding the investigations, Sarcoidosis is best diagnosed by tissue biopsy yet recently the combination of gallium scan and serum ACE level is not invasive and has shown specificity of 83-99%. There are common MRI findings which are suggestive of certain diagnosis. large cystic lesions, not surrounded by edema, is suggestive of hydatid disease, while Cysticercosis shows multiple cysts, surrounded by variable degrees of edema, and may show scolices or enhancement. Multiple small vessel infarcts are suggestive of Wegener granulomatosis, which present also with meningeal enhancement, while evidence of beading of cerebral arteries on angiography is suggestive of primary CNS angiitis.

Despite of this accumulation of data regarding the individual disorders causing granulomatous CNS affection, it is still far beyond doubt that reaching the definite diagnosis for these disorders is still lacking. This is attributed to heterogeneity of clinical presentation of the disorders on one hand, with lack of awareness among the medical staff through their various specialities on the other hand. Adding to this hinders, the yield of investigational work up is still many steps behind reaching a rapid conclusive final diagnosis.

Owing to the difficulty in diagnosis and the high morbidity and fatality of these conditions, a comprehensive approach for management of suspected cases should be formulated. This approach includes an integrated multidisciplinary team from different medical specialities, to achieve the following objectives: to avoid missing cases with mainly systemic presentations and to formulate an integrated management plan tackling all the systems involved. Even in cases presenting only with neurological symptomatology proper management is sometimes hindered by the immunocompromised status of the patient, and therefore involvement of other relevant medical specialities would maximize the therapeutic yield. On the other hand cases without overt neurological affection should still warrant a neurological consultation. The neurologist can help elicit subtle neurological deficits and guide the diagnostic investigations concerning CNS involvement to help reach a rapid early diagnosis, leading to early start of treatment and better prognosis.

RECOMMENDATIONS

Clinical

- Forming integrated multidisciplinary team from different medical specialities to detect and manage patients of CNS granulomas.
- Formulating defined investigational channels to guide clinicians to a definitive diagnosis.
- Establishing treatment protocols specific for CNS granulomas to replace those based on systemic granulomatous disorders.
- Preparing training course to clinicians and neurologists illustrating clinical picture and clues for diagnosis of CNS granulomas to increase awareness with these disorders, and provide a higher index of suspicion to diagnoses patients early.

Research

- Searching and testing new diagnostic tools and investigations that would provide

better sensitivity and specificity and less time consuming.

- **Looking for new treatments that is more effective and less toxic.**
- **More studies about the current and possible treatment regiments for CNS granulomatous disorders instead of focusing studies on the systemic aspects of these disorders.**

SUMMARY

Granulomatous inflammation is a distinctive pattern of chronic inflammation due to infectious or non infectious agents. Its formation is due to the cell mediated immune response to such agents (Mitchell and Cotran, 2003; Dov, 2003).

Granulomatous inflammatory disorders involving the CNS have a wide variety of etiologies, clinical presentations, overlapping with each other and with other CNS disorders. And up till now, they have non conclusive investigations results making rapid accurate diagnosis sometimes difficult or impossible without tissue biopsy. Also many medical specialties are involved in the management of such cases, which leads to a lack in comprehensive integrated approach (Metwally, 2006).

Tuberculosis remains a major global problem and a public health issue of considerable magnitude, and was declared as a global emergency in 1993 by the World Health Organization (WHO). This was due to spread of HIV and multiple antituberculous drug resistance (Dolin et al., 1994). Common presentations of CNS tuberculosis include basal meningitis, focal cerebral lesions, myelopathy, Pott's disease, rarely myelitis. In young age it may present with rapid onset encephalopathy (Dastur et al., 1995)

Rapid diagnosis of CNS TB is difficult, and usually Treatment is started on clinical assumption. Diagnostic studies, mainly smear examination and culture have low sensitivity and are time consuming (Muralidhar, 2004), while the PCR has higher sensitivity, yet it is not technically and financially available in many endemic areas. Most common imaging studies findings are hydrocephalus and basal meningitis, which is not specific (Chang et al.,1990).

Treatment should start with quadruple therapy, and in cases of INH resistance, it should be replaced by Ethambutol. Steroids should be used in cases of clinically or radiological evident of meningoencephalitis or increased CSF pressure to more than 300 cc H₂O. Prognosis is related to the severity of meningoencephalitic symptoms at the start of treatment. It should be noted that the most common causes of treatment failure is multiple drug resistance and poor compliance (Daikos et al.,2003).

Fungal infections or the CNS has increased recently due to increase prevalence of HIV and immunosuppressive states specially that is related to organ transplantation. Diagnosis is mostly a clinical surprise, and it requires a high index of suspicion. The most common CNS fungal infection is Cryptococcosis. It is specially prevalent in the HIV seropositive population with 20% of HIV mortality cases due to Cryptococcal meningitis.

Cryptococcus usually spreads from a pulmonary focus with high tendency to affect the CNS, and is protected from the immune system by a polysaccharide capsule. The most common clinical presentations are headache, fever, increased intracranial tension and blindness. The definitive diagnostic test is CSF examination with India ink stain showing the cryptococci. It is treated with amphotericin B and Flucytosine (Jermeý, 2004).

Aspergillosis is another form of fungal infection that can spread to the CNS either hematogenously from the lung or by direct invasion from the nasal sinuses. Unlike cryptococcosis, it is specially prevalent in cases of organ transplantations clinical features vary from diffuse presentation of meningitis and increased ICT to focal lesions. It characteristically invade cerebral vessels and adjacent brain parenchyma, causing thrombosis and secondary haemorrhagic infarcts. It generally has poor prognosis which varies according to patient immunity, in cases of markedly suppressed immunity it is fatal within few weeks, otherwise it may develop to granulomas, abscesses evident as ring enhancing lesions in radiological studies (enhancement = immunity). Definitive diagnosis require brain biopsy. Treatment should be started as early as possible, and it includes surgical debridement with adequate safety margin (to avoid postoperative cerebrovascular complications) and administration of amphotericin B and flucytosine, in addition to correcting the general condition (immune reconstitution). Recently voriconazole has shown promising results when combined with surgery (Sepkowitz et al., 1997).

Rhinocerebral Mucormycosis is a life-threatening fungal infection that occurs in immunocompromised patients, mainly diabetics. These infections are becoming increasingly common, yet survival remains very poor, as many cases are diagnosed late and treatment strategies based on available antifungal and surgical debridement with control of risk factors are not effective (Brad et al., 2005).

Invasive candidal CNS infection is more common in premature infants and neonates, and present usually by meningitis with insidious vague clinical picture (lethargy, confusion), and it is also treated with amphotericin B and flucytosine (Burgert et al., 1995).

There has been an increased awareness of the parasitic CNS infection in the last few decades. Cysticercosis, one of the common parasitic infections, was frequently under diagnosed due to the lack of adequate diagnostic tools, and even after the advent of modern neuroimaging techniques, it was frequently misdiagnosed as TB. Viable CNS cysticerci don't induce an immune reaction and are frequently asymptomatic, while the immune system is stimulated by the dying organism, leading to the development of the clinical manifestations of the illness (fits, hydrocephalus). This has provoked an unsettled debate about the necessity of use of parasiticidal drugs in asymptomatic patients. Solid diagnosis is difficult except by tissue biopsy, MRI showing cysts with scolices, or subretinal scolices on funduscopy. Recently EITB has proved to be 100 % specific (Carpio et al., 1998).

Toxoplasmosis is another form of parasitic CNS infection. It commonly presents with afebrile focal cerebral lesions, commonly ganglionic, cerebellar and brain stem. When manifest in an HIV Patient, it presents with encephalitis, fever and disseminated multi organ affection. Diagnosis is difficult, serology and PCR are not sensitive. Radiological studies show multiple brain enhancing lesions which when combined with positive serology empirical treatment (pyrimethamine + leucovorin) should be started and if there is no response in 2 weeks, a tissue biopsy should be obtained (Luis, 2006).

In hydatid disease, 5% of cases have CNS affection, in the form of space occupying lesions presenting clinically as increased ICT, fits of focal cerebral lesions. Imaging studies show a cystic brain lesion with no enhancement. Diagnosis rests on the evidence of systemic affection, and ELISA is done in doubtful cases. Treatment is surgical excision under albendazole cover (Eckert et al., 2001).

Bilharziasis affect the CNS in 1% of cases, through granulomatous inflammation around ova deposited in brain and spinal cord. It present by myelopathy, meningoencephalitis, optic neuritis and rarely space occupying lesion. It is diagnosed by demonstrating ova in urine, stool or rectal biopsy, also ELISA is 99% specific. Brain imaging reveals central linear enhancement surrounded

by central punctuate nodules. It is treated by praziquantel or oxamniquine (David et al., 2004).

Sarcoidosis is a granulomatous inflammation of unknown etiology. And neurological manifestations occur in 5 – 16% of patients, usually with correlation to disease activity. Isolated neurosarcoidosis is reported in less than 10 % of cases (James, 1998). Although neurosarcoidosis can affect any part of the central or peripheral nervous system, the most common presentations are, aseptic basal meningitis, multiple cranial neuropathies usually facial and optic nerves, focal supratentorial parenchyma involvement, axonal polyneuropathy and polyneuritis multiplex (Waxman and Sher, 1979).

Neurosarcoidosis is a diagnosis of exclusion. It relies on the systemic features if present. The most diagnostic investigation is tissue biopsy (Transbronchial mediastinal biopsy, skin, superficial lymph nodes, parotid). The combination of positive gallium scan and elevated serum ACE is a highly diagnostic non invasive tool (83 to 99% specificity). In cases of isolated neurosarcoidosis, routine CSF studies and Neuroimaging are not conclusive. ACE level in CSF is elevated in 50 % of cases, otherwise we should rely on tissue biopsies for solid diagnosis (Bourahoui et al., 2004).

Treatment of neurosarcoidosis should start immediately with corticosteroids. Other steroid sparing agents (cyclosporine, azathioprine, methotrexate, cyclophosphamide) can be used to decrease maintenance doses of steroids, and in refractory cases. Newer agents as tacrolimus, sirolimus, anticytokine therapy are under trial (Vital et al., 1982).

Wegener granulomatosis (WG) is a unique clinicopathological disease entity characterized by necrotizing granulomatous vasculitis of the upper and lower respiratory tract, segmental necrotizing glomerulonephritis, and small vessel vasculitis (Carol, 2003).

The reported frequency of neurologic involvement in WG ranges from 22% to 54%., and its manifestations are extremely varied. the most common neurological presentations are mononeuritis multiplex, cranial neuropathies, seizures, altered cognition (cerebritis), focal motor and sensory complaints, stroke syndromes, or diabetes insipidus (Metwally, 2006).

Routine laboratory investigations are not specific, yet testing for c-antineutrophil cytoplasmic antibodies (ANCA) is 97% specific for WG, and 90% sensitive for classical systemic disease. MRI findings include diffuse or focal thickening of the meninges with contrast enhancement, Nonhemorrhagic infarcts and occasionally Nonspecific white matter lesions (Joseph et al., 1999).. Glucocorticoids combined with cyclophosphamide or methotrexate are the only two regimens that have been shown to induce remission of active WG affecting a major organ (Hoffman et al., 1992).

Primary angiitis of the CNS is a rare disease characterized by vasculitis of small and medium arteries in the brain and spinal cord. Presentations are highly variable, but the triad of headache, organic brain syndrome, and multifocal neurologic deficits is most suggestive. Most affected patients do not have systemic symptoms, signs, or abnormal routine blood tests, including ESR (Bettoni et al., 1984).

Noninvasive tests have limited sensitivity and specificity. MRI is most sensitive, being abnormal in more than 80% of patients. The diagnosis is very rare when both the lumbar puncture (with regards to cells and protein level) and the MRI are normal. Angiography showing beading produced by alternating stenosis and dilation suggests the diagnosis but is not specific. Analysis of biopsy specimens of brain cortex and leptomeninges can help establish the diagnosis. In the absence of positive results on biopsy specimen analysis, the diagnosis of primary angiitis of the CNS should be doubted (Lie, 1992).

The best therapy has not been established many patients are treated with prednisone and

cyclophosphamide (Scolding et al., 1997).

Histiocytosis is a rare blood disease that is caused by an excess of white blood cells called histiocytes. It mainly affects children with 76 % of the cases occurring before 10 years of age (Vassallo et al., 2000).

Clinically it affects the skin, bone, eyes, gastrointestinal tract, with diabetes insipidus being the hallmark of CNS affection. Other symptoms due to CNS affection include other endocrinal deficiencies and rarely behavioral changes or manifestations of increased ICT (Martin-Duverneuil et al., 2006).

MRI findings in histiocytosis include thickening of the pituitary stalk, dura based masses, white matter lesions and cystic changes in pineal gland (Daniela et al., 2004). No general recommendations concerning treatment are established till now. The individual strategy is dependent on the type and site of the lesions and the state of LCH outside the CNS. And chemotherapeutic agents like vinblastine, etoposide or mercaptopurine, together with steroids are being assessed. (Daniela et al., 2004)

Cholesteatoma and cholesterol granuloma are 2 destructive lesions affecting the temporal bone, with possible CNS complication secondary to local invasion. They can be diagnosed by CT scan, differentiated by MRI, and treated by different surgical approaches (Ferlito et al., 1997; Topalogue et al 1997; Chang et al., 1998).

References

1. Aberg JA, Watson J, Segal M & Chang LW (2000). Clinical utility of monitoring serum cryptococcal antigen (sCRAG) titers in patients with AIDS-related cryptococcal disease. *HIV Clinical Trials*, 1, 1–6.
2. Agbogu BN, Stem Bj, Sewell C, et al (1995). Therapeutic considerations in patients with refractory neurosarcoidosis; *Arch Neurol*; 52:875-879.
3. Agostini C. and Semenzato G. (1999); *Biology and immunology of the granuloma*; In : the *Granulomatous Disorders*; Geraint James D. and Zumla A.; Cambridge University Press;3-4.
4. Ahuja GK, Mohan KK, Prasad K, Behari M (1994); Diagnostic criteria for tuberculous meningitis and their validation; *Tubercle Lung Dis*; 75:149–52.
5. Al- Sherbiny MM, Osman AM, Hancock K, et al. (1999) Applications of immunodiagnostic assays: detection of antibodies and circulating antigens in human schistosomiasis and correlation with clinical findings. *Am J Trop Med Hyg*: 60:960-966.
6. Alangaden G, Chandrasekar PH, Bailey, E, Khaliq Y, Bone Marrow Transplantation Team (1994); Antifungal prophylaxis with low-dose fluconazole during bone marrow transplantation; *Bone Marrow Transplant*; 14:919-24.
7. Altinors N, Bavbek M, Caner HH, et al (2000). Central nervous system hydatidosis in Turkey: a cooperative study and literature survey analysis of 458 cases. *J Neurosurg*; 93:1-8.

8. **American Thoracic Society (1999). Statement on sarcoidosis. Am J Respir Crit Care Med; 160:736–55.**
9. **Ando DG, JP Lynch, Fantone JC (1985). Sarcoid myopathy with elevated creatine phosphokinase. Am Rev Respir Dis 131:298-300.**
10. **Andreula CF, Burdi N, Carella A (1993). CNS cryptococcosis in AIDS: Spectrum of MR findings. J Comput Assist Tomogr 17:438-441.**
11. **Andrew A. Dahl; Sarcoidosis, at <http://www.emedicine.com/OPH/topic451.htm> , last updated Oct. 2006.**
12. **Anita Hawkins, Joseph M. Aulino, and Gregg H. Zoarsk; Cerebral coccidioidomycosis complicated by basal ganglia lacunar infarction; Applied Radiology Online; 30 Number: 7 July 2001.**
13. **Anonymous: Statement on sarcoidosis. Joint Statement of the American Thoracic Society (ATS), the European Respiratory Society (ERS) and the World Association of Sarcoidosis and Other Granulomatous Disorders (WASOG) adapted by the ATS Board of Directors and by the ERS Executive Committee (1999). Am J Respir Crit Care Med 160:736-755.**
14. **Arora R and VWhite HH (1994). Clinical recognition of granulomatous angiitis of the brain; j Neuroimag; 4:45.**
15. **Artis, W. M., J. A. Fountain, H. K. Delcher, and H. E. Jones (1982); A mechanism of susceptibility to mucormycosis in diabetic ketoacidosis: transferrin and iron availability; Diabetes; 31:1109-1114.**
16. **Ashdown BC, Tien RD, Felsberg GJ. (1994). Aspergillosis of the brain and paranasal sinuses in immunocompromised patients: CT and MR imaging findings. AJR Am J Roentgenol ;162:155–159**
17. **Bandres, J. C., A. C. White, Jr., T. Samo, E. C. Murphy, and R. L. Harris. (1992). Extraparenchymal neurocysticercosis: report of five cases and review of management. Clin. Infect. Dis. 15:799-811.**
18. **Banuelos AF, Williams PL, Johnson RH, et al (1996). Central nervous system abscesses due to Coccidioides species. Clin Infect Dis 22:240-250.**
19. **Barney J. S., Allan K.; Carol J. J. (1986) Neurosarcoidosis: Presentation and Management; Annals of the New York Academy of Science; 465 (1):722–730.**
20. **Barry SM, Lipman MC, Johnson MA et al (1995); Respiratory infections in immunocompromised patients; Curr Opin Pulm Med; 5: 168–73**
21. **Beal MF, O'Carroll CP, Kleinman GM, Grossman RI. (1982). Aspergillosis of the nervous system. Neurology;32:473–479**
22. **Beardsley TL, Brown SVL, Syndor CR, et al (1984): Eleven cases of sarcoidosis of the optic nerve. Am J Ophthalmol 97:62-77.**
23. **Becker LE. (1992). Infections of the developing brain. AJNR Am J Neuroradiol;13:537–549**

24. Behri M, Raj M, Ahuja GK et al (1989); Soluble antigen fluorescent antibody test in the serodiagnosis of tuberculous meningitis; J Assoc Physicians India;370: 499–501
25. Bennett G and Provenzale JM. (1998). Schistosomal myelitis: findings at MR imaging. Eur J Radiol ;27:268-270.
26. Berenguer J, Moreno S, Laguna F et al (1992) Tuberculous meningitis in patients infected with human immunodeficiency virus; N Engl J Med; 326: 668–72
27. Berger JR. (1994). Tuberculous meningitis; Curr Opin Neurol ;7:191–200.
28. Bergsneider, M. (1999). Endoscopic removal of cysticercal cysts within the fourth ventricle. J. Neurosurg. 91:340-345.
29. Bergsneider, M., L. T. Holly, J. H. Lee, W. A. King, and J. G. Frazee (2000). Endoscopic management of cysticercal cysts within the lateral and third ventricles. J. Neurosurg. 92:14-23.
30. Bettoni L, Borquvatta G, Lecki A (1984).Isolated benign cerebral vasculitis; Arch Neurol; 84:161.
31. Bhargava S and Tandon PN (1980) Intra cranial tuberculomas; A CT study; Br J Radiol; 53: 935
32. Bia PJ, Barry M (1986). Parasitic infections of the central nervous system. Neurol Clin; 4 : 171-206.
33. Bittencourt, P. R., C. M. Gracia, A. M. Gorz, S. Mazer, and T. V. Oliveira. (1990). High-dose praziquantel for neurocysticercosis: efficacy and tolerability. Eur. Neurol. 30:229-234.
34. Bodhe PV, Kotwani RN, Kirodian BG, Kshirsagar NA, Pandya SK.(2002).Open label, randomized, comparative Phase III safety and efficacy study with conventional amphotericin B and liposomal amphotericin B in patients with systemic fungal infection. J Assoc Physicians India; 50:662-70.
35. Boelaert, J. R., J. Van Cutsem, M. de Locht, Y. J. Schneider, and R. R. Crichton (1994);. Deferoxamine augments growth and pathogenicity of Rhizopus, while hydroxypyridinone chelators have no effect; Kidney Int; 45:667-671.
36. Bollinger RC, Tripathy SP, Quinn TC (1995). The Human immunodeficiency virus epidemic in India : Current magnitude and future projections. Medicine; 74 : 97-106
37. Boros DL (1978) Granulomatous inflammation; Prog Allergy;24: 183-267.
38. Boros DL and Warren KS (1973). The bentonite granuloma. Immunology;24:511-29.Quoted from G T Williams and W J Williams (1983); Granulomatous inflammation-a review; J Clin Pathol; 36(7): 723–733.
39. Bose B. (2002); Extramedullary sarcoid lesion mimicking intraspinal tumor,. The Spine Journal; 2(5):381-385.
40. Bouchara, J. P., N. A. Oumeziane, J. C. Lissitzky, G. Larcher, G. Tronchin, and D. Chabass

- (1996); Attachment of spores of the human pathogenic fungus *Rhizopus oryzae* to extracellular matrix components; *Eur. J. Cell Biol*; 70:76-83.
41. Bourahoui A., J. de Seze, R. Gutierrez, B. Onraed, B. Hennache, D. Ferriby, T. Stojkovic, P. Vermersch (2004); CSF isoelectrofocusing in a large cohort of MS and other neurological diseases; *European Journal of Neurology* 11(8):525–529.
 42. Bouza E, Dreyer JS, Hewitt WL, Meyer RD.(1981).Coccidioidal meningitis: an analysis of thirty-one cases and review of the literature. *Medicine (Baltimore).*;60:139-172.
 43. Brad Spellberg, John Edwards Jr., and Ashraf Ibrahim (2005); Novel Perspectives on Mucormycosis: Pathophysiology, Presentation, and Management; *Clinical Microbiology Reviews*; 18(3):556-569.
 44. Brooks BS, El Gammal T, Hungerford GD (1982): Radiologic evaluation of neurosarcoidosis: Role of computed tomography. *Am j Neuroradiol* 3:513-521.
 45. Brooks JB, Chaudhary G, CravenRB et al (1977) Electron capture gas liquid chromatography and mass spectrum identification of 3-(2'- ketohexyl) indoline in spinal fluids of patients with tuberculous meningitis; *J Clin Microbiol*; 5: 625–28
 46. Brown NW, Thomson Aj, Wedzicha JA, et al (1989). Sarcoidosis presenting with stroke. *Stroke* 20:400-405.
 47. Buch S and Pfister P. (1983). *Candida meningitis: course, prognosis, and mortality before and after introduction of the new antimycotics*; *Mykosen*; 26;73-81
 48. Bucurescu, G. . Neurosarcoidosis at <http://www.emedicine.com/NEURO/topic649.htm> , last updated Nov. 7, 2006.
 49. Burgert Sj, Classen DC, Burke JP, et al (1995). Candidal brain abscess associated with vascular invasion: A devastating complication of vascular catheter-related candidemia. *Clin Infect Dis* 21:202-205.
 50. Calabrese LH (1995). Vasculitis of the central nervous system; *Rheum Clin North Am*; 21: 1059.
 51. Calabrese LH and Duna G (1995). Evaluation and treatment of central nervous system vasculitis; *Curr Opin Rheumatol*; 7:37.
 52. Calabrese LH, Graff LA, Furlan AJ (1993). Benign angiopathy: A distinct subset of angiographically defined primary angiitis of the central nervous system;. *J Rheum*; 20:2046.
 53. Camarata PJ, Dunn DL, Farney AC, Parker RG, Seljeskog EL (1992). Continual intracavitary administration of amphotericin B as an adjunct in the treatment of aspergillus brain abscess: case report and review of the literature. *Neurosurgery*;31:575-9
 54. Caplan L, Corbett J, Goodwin J, et al (1983). Neuro-ophthalmologic signs in the angiitic form of neurosarcoidosis. *Neurology* 33:1130-1135.
 55. Cardenas F, Quiroz H, Plancarte A, et al (1992). *Taenia solium* ocular cysticercosis: findings in 30 cases. *Ann Ophthalmol*; 24:25-28.

56. Carol A Langford (2003), Wegener's granulomatosis: current and upcoming therapies; *Arthritis Res Ther*; 5(4): 180–191.
57. Carpio A, Hauser WA (2002); Prognosis for seizure recurrence in patients with newly diagnosed neurocysticercosis; *Neurology*; 59:1730-34.
58. Carpio, A., A. Escobar, and W. A. Hauser. (1998). Cysticercosis and epilepsy: a critical review. *Epilepsia* 39:1025-1040.
59. Carpio, A., F. Santillan, P. Leon, C. Flores, and W. A. Hauser. (1995). Is the course of neurocysticercosis modified by treatment with antihelminthic agents? *Arch. Intern. Med* 155:1982-1988.
60. Casadevall A and Perfect JR (1998). *Cryptococcus neoformans*. American Society for Microbiology Press, Washington.
61. Chaabane M, Krifa H, Ladeb MF (1989). Cerebral candidiasis: CT appearance. *Pediatr Radiol*;19:436
62. Chafenor YB, Felton CP, Brust JCM (1984) Peripheral nerve involvement in sarcoidosis: An electrodiagnostic study. *J Neurol Neurosurg Psychiatry*; 47:1219-1222.
63. Chan Seem CP, Norfolk G, Spokes EG (1985). CSF angiotensin-converting enzyme in neurosarcoidosis: An electrodiagnostic stud;. *J Neurol Neurosurg Psychiatry*; 47:1219- 1229.
64. Chandramukhi A, Allen PRJ, Keen M et al (1985) detection of mycobacterial antigen and antibodies in the cerebrospinal fluid of patients with tuberculous meningitis; *J Med Microbiol*; 20: 239–47
65. Chandramukhi A, Bothamley GH, Brennan PJ et al (1989) Levels of antibody to defined antigens of *Mycobacterium tuberculosis* in tuberculous meningitis; *J Clin Microbiol*; 27: 821–25
66. Chandy, M. J., V. Rajshekhar, S. Ghosh, S. Prakash, T. Joseph, J. Abraham, and S. M. Chandi. (1991). Single small enhancing CT lesions in Indian patients with epilepsy: clinical, radiological and pathological considerations. *J. Neurol. Neurosurg. Psychiatry* 54:702-705.
67. Chang KH, Han MH, Roh JK et al (1990) Gd-DTPA-enhanced MR imaging of the brain in patients with meningitis; comparison with CT; *Am J Neuroradiol*; 11: 69
68. Chang P, Fagan PA, Atlas MD, Roche J (1998) Imaging destructive lesions of the petrous apex. *Laryngoscope* 108: 599-604.
69. Chapelon C, Ziza JM, Piette JC, et al (1990). Neurosarcoidosis: Signs, course and treatment in 35 confirmed cases; *Medicine (Baltimore)*: 69:261-276.
70. Chernik NL, Armstrong D, Posner JB (1973). Central nervous system infections in patients with cancer. *Medicine* ; 52:563-81.
71. Choi SH, Kim YS, Bae IG et al(2002) The possible role of cerebrospinal fluid adenosine deaminase activity in diagnosis of tuberculous meningitis adults; *Clin Neurol Neurosurg*; 104: 10–15

72. **Cinque P, Scarpellini P, Vago L, Linde A, Lazzarin A. (1997) Diagnosis of central nervous system complications in HIV-infected patients: cerebrospinal fluid analysis by the polymerase chain reaction. AIDS;11:10-17.**
73. **Ciricillo SF, Rosenblum ML (1990): Use of CT and MRI imaging to distinguish intracranial lesions and to define the need for biopsy in AIDS patients. J Neurosurg ; 73 : 720-724**
74. **Clark WC, Acker JD, Dohan C, et al (1985). Presentation of central nervous system sarcoidosis as intracranial tumors; J Neurosurg; 63:851-856.**
75. **Cohen J. (1991); Clinical manifestations and management of aspergillosis in the compromised patient. In: Warnock DW, Richardson MD,eds. Fungal Infection in the Compromised Patient. Pub: John Wiley and Sons :117–151**
76. **Colli, B. O., N. Martelli, J. A. Assirati, Jr., H. R. Machado, and S. de Vergueiro Forjaz. (1986). Results of surgical treatment of neurocysticercosis in 69 cases. J. Neurosurg. 65:309-315.**
77. **Consensus Conference (1994). Activity of sarcoidosis. Eur Respir J; 7:624-627.**
78. **Corse AM and Stem Bj (1990). Neurosarcoidosis and stroke (letter);. Stroke; 21:152-153.**
79. **Coulthard A, Gholkar A, Sengupta RP.(1991). Case report: frontal aspergilloma: a complication of paranasal aspergillosis. Clin Radiol; 44:425–427**
80. **Cox J, Murtagh FR, Wflfong A, et al (1992). Cerebral aspergillus abscess: MR imaging and histopathologic correlation. AJNR Am j Neuroradiol 13:1489-1492,**
81. **Crystal RG (2000). Sarcoidosis. In: Harrison's Principles of Internal Medicine. 15th ed. NY: McGraw-Hill; 1969-74.**
82. **Daikos GL, Cleary T, Rodriguez A, Fischl MA (2003) Multi drug resistant tuberculous meningitis in patients with AIDS; Int J Tuberc Lung Dis; 7(4); 394–98**
83. **Daniela Prayer, Nicole Grois, Helmut Prosch, Helmut Gadner and Anthony J. Barkovich (2004). MR Imaging Presentation of Intracranial Disease Associated with Langerhans Cell Histiocytosis; American Journal of Neuroradiology; 25:880-891.**
84. **Dastur DK, Manghani DK, Udani PM (1995)Pathology and pathogenetic mechanisms in neuro tuberculosis; Radiol Clin North Am;33: 733–52.**
85. **Dastur HM (1983) Diagnosis and neurosurgical treatment of tuberculous diseases of the CNS Neurosurg Rev;6:111–9.**
86. **David A. Stevens (1995); Coccidioidomycosis; The NEW ENGLAND JOURNAL of MEDICINE; 332:1077-1082**
87. **David B. Huang, Peter M Schantz and A Clinton White (2004); Helminthic infections; in: infections of the Central Nervous System (Third Edition); W Michael Scheld, Richard J Whitley, Christina M Marra; Lippincott Williams & Wilkins ; 797-821.**
88. **David W..Denning (1998); State of the art clinical article: Invasive Aspergillosis; Clinical**

89. **Davis LE, Rastogi KR, Lambert LC, Skipper BJ(1993) Tuberculous meningitis in the southwest United States; a community based study; Neurology;43:1775–8.**
90. **De Groot K, Adu D, Savage CO (2001). The value of pulse cyclophosphamide in ANCA-associated vasculitis: meta-analysis and critical review; Nephrol Dial Transplant;16:2018–2027.**
91. **De La Paz RL, Enzmamm D (1988).: Neuroradiology of acquired immunodeficiency syndrome. In Rosenblum ML, et al (eds). AIDS and the Nervous System. New York, Raven Press; pp 121, 153**
92. **Del Brutto O H, Rajshekhar V, White A C Jr et al (2001), Proposed diagnostic criteria for neurocysticercosis; Neurology; 57:177-183.**
93. **Del Brutto O. H., and J. Sotelo. (1988). Neurocysticercosis: an update. Rev Infect. Dis. 10:1075-1087.**
94. **Del Brutto O. H., J. Sotelo, and G. C. Roman. (1993). Therapy for neurocysticercosis: a reappraisal. Clin. Infect. Dis. 17:730-735.**
95. **Del Brutto, O. H., V. Rajshekhar, A. C. White, Jr., V. C. Tsang, T. E. Nash, O. M. Takayanagui, P. M. Schantz, C. A. Evans, A. Flisser, D. Correa, D. Botero, J. C. Allan, E. Sarti, A. E. Gonzalez, R. H. Gilman, and H. H. Garcia. (2001). Proposed diagnostic criteria for neurocysticercosis. Neurology 57:177-183**
96. **Del Pozo MM, Bermejo F, Molina JA (1998). Chronic neutrophilic meningitis caused by Candida albicans; Neutrologia; 13:362-366**
97. **Delaney P (1977). Neurologic manifestations in sarcoidosis: Review of literature, with report of 23 cases; Ann Intern Med; 87:336-345.**
98. **DeLone DR, Goldstein RA, Petermann G, et al (1999). Disseminated aspergillosis involving the brain: Distribution and imaging characteristics. AJNR Am j Neuroradiol 20:1597-1604.**
99. **Dixon, H. B., Lipscomb, F. M. (1961); Cysticercosis: an analysis and follow-up of 450 cases, vol. 299. Medical Research Council, London, UK.. Quoted from Hector H. García, Carlton A. W. Evans, Theodore E. Nash, Osvaldo M. Takayanagui, A. Clinton White Jr., David Botero, Vedantam Rajshekhar, Victor C. W. Tsang, Peter M. Schantz, James C. Allan, Ana Flisser, Dolores Correa, Elsa Sarti, Jon S. Friedland, S. Manuel Martinez, Armando E. Gonzalez, Robert H. Gilman, and Oscar H. Del Brutton (2002); Current Consensus Guidelines for Treatment of Neurocysticercosis; Clinical Microbiology Reviews; 15(4): 747-756.**
100. **Dolin PJ, Raviglione MC, Kochi A (1994) Global tuberculosis incidence and mortality during 1990–2000; Bull WHO; 72: 213–20**
101. **Donald PR, Gent WL, Seifart HI, Lamprecht JH, Parkin DP (1992) Cerebrospinal fluid isoniazid concentrations in children with tuberculous meningitis; the influence of dosage and acetylation status; Pediatrics ;89:247–50.**

102. **Dov L. Boros (2003). The Cellular Immunological Aspects of the Granulomatous Response; In: Granulomatous Infections and Inflammations; Susan L Leddy, Dov L Boros; P 2**
103. **Drutz DJ. (1983). Amphotericin B in the treatment of coccidioidomycosis. *Drugs* ; 26:337-346.**
104. **Dube MP, Holtom PD, Larsen RA (1992); Tuberculous meningitis in patients with and without human immunodeficiency virus infection; *Am J Med*; 93:520–4.**
105. **Dumas, J. L., J. M. Vusy, and C. Belin. (1997). Parenchymal neurocysticercosis: follow up and staging by MRI. *Neuroradiology* 39:12-16.**
106. **Duna G, Calabrese LH (1995). Limitations in the diagnostic modalities in the diagnosis of primary angiitis of the central nervous system (PACNS); *J Rheumatol*; 22:662.**
107. **Duval X, Leport C (2001). Toxoplasmosis in AIDS. *Current Treatment Options in Infectious Diseases*;3:113-28.**
108. **Eckert J, Gemmell MA, Meslin FX, et al. (2001). WHO/OIE manual on Echinococcus in humans and animals: a Public Health Problem of Global Concern. Paris: World Organization for Animal Health.**
109. **Eddy A. Bresnitz and Brain L. Storm (1983). Epidemiology of sarcoidosis; *Epidemiol Rev*; 5: 124-156**
110. **Eide FF, Gean AD, So IT (1993) Clinical and radiographic findings in disseminated tuberculosis of the brain; *Neurology* ;43:1427–9.**
111. **Einstein HE, Holeman CW Jr, Sandidge LL, Holden DH. (1961).Coccidioidal meningitis: the use of amphotericin B in treatment. *Calif Med* ; 94:339-343**
112. **Ellard GA, Humphries MJ, Allen BW (1993) Cerebrospinal fluid drug concentrations and the treatment of tuberculous meningitis; *Am Rev Resp Dis*;148:650–5.**
113. **Eltringham IJ, Drobniewski F (1998) Multiple drug resistant tuberculosis: etiology, diagnosis and outcome; *Br Med Bull*; 54: 569–78**
114. **Epstein NE, Hollingsworth R, Black K, Farmer P (1991). Fungal brain abscesses (aspergillosis/mucormycosis).in two immunosuppressed patients. *Surg Neurol*; 35:286–289**
115. **Escobar, A. (1983). The pathology of neurocysticercosis, p. 27-54. In E. Palacios, J. Rodriguez-Carbajal, and J. M. Taveras (ed.), *Cysticercosis of the central nervous system*. Charles C. Thomas, Springfield, Ill.**
116. **Estanol, B., T. Corona, and P. Abad. (1986). A prognostic classification of cerebral cysticercosis: therapeutic implications. *J. Neurol. Neurosurg. Psychiatry* 49:1131-1134**
117. **Farrar DJ, Flanigan TP, Gordon NM, Gold RL, Rich JD (1997) Tuberculous brain abscess in patient with HIV infection: case report and review; *Am J Med* ;102:297–30**
118. **Fatterpekar, G., S. Mukherji, A. Arbealez, S. Maheshwari, and M. Castillo (1999); Fungal diseases of the paranasal sinuses; *Semin. Ultrasound CT MR*; 20:391-401.**

119. Feely M, Sternberg M (1977). Aspergillus infection complicating transsphenoidal yttrium-90 pituitary implant. *J Neurosurg*; 46:530-2.
120. Ferlito A (1993) A review of the definition, terminology and pathology of aural cholesteatoma; *J Laryngol Otol*; 107: 483-8.
121. Ferlito A, Devaney KO, Rinaldo A, Milroy CM, Wenig BM, Iurato S, McCabe BF (1997). Clinicopathological consultation. Ear cholesteatoma versus cholesterol granuloma; *Ann Otol Rhinol Laryngol*;106: 79-85.
122. Fernandez M, Moylett EH, Noyola DE (2000). Candida meningitis in neonates, a 10 year review; *Clin Infect Dis*; 31:458-463.
123. Ferrari TC (1999). Spinal cord schistosomiasis: a report of 2 cases and review emphasizing clinical aspects. *Medicine (Baltimore)*;78:176-190.
124. Folgueira L, Delgado R, Palenque E et al (1994) Polymerase chain reaction for rapid diagnosis of tuberculous meningitis in AIDS patients; *Neurology*, 44: 1336–38
125. French N, Gray K, Watera C, et al (2002) Cryptococcal infection in a cohort of HIV-1-infected Ugandan adults; *AIDS*;16:1031-1038.
126. Friedmann PD, Samore MH, Kraemer KL & Calkins DR (1995).Clinical correlates of secondary meningitis in HIV-infected adults. *Archives of International Medicine*, 155, 2231–7.
127. Gabriel Bucurescu; Neurosarcoidosis, emedicine; last updated November 7, 2006; <http://www.emedicine.com/neuro/topic649.htm>
128. Galassi G, Gibertoni M, Mancini A (1984). Sarcoidosis of the peripheral nerve: Clinical, electrophysiological and histological study of two cases; *Eur Neurol*; 23:459-465.
129. Galgiani JN, Catanzaro A, Cloud GA, et al. (1993); Fluconazole therapy for coccidioidal meningitis. *Ann Intern Med*; 119:28-35.
130. Garcia, H. H., and O. H. Del Brutto. (2000). Taenia solium cysticercosis. *Infect. Dis. Clin. North Am.* 14:97-119.
131. Garcia, H. H., R. H. Gilman, J. Horton, M. Martinez, G. Herrera, J. Altamirano, J. M. Cuba, N. Rios-Saavedra, M. Verastegui, J. Boero, and A. E. Gonzalez. (1997). Albendazole therapy for neurocysticercosis: a prospective double-blind trial comparing 7 versus 14 days of treatment. Cysticercosis Working Group in Peru. *Neurology* 48:1421-1427.
132. Garcia-Monco JC (1999) Central nervous system tuberculosis; In: Marra CM, editors; *Neurologic clinics – central nervous system Philadelphia: WB Saunders Company*; 17(4): 737–58
133. Garg K.R. (1999)Classic diseases revisited:Tuberculosis of the central nervous System; *Postgrad Med J* ;75:133–140
134. Garg RK, Karak B, Misra S (1998) Acute paraparesis with tuberculous meningitis; *Postgrad Med J* ;74:269–71.

135. **Gee GT, Bazan III C, Jinkins JR (1992) Miliary tuberculosis involving the brain: MR findings; AJR ;159:1075–6.**
136. **George R, Duna GF, Rybicki L (1995). A reappraisal of primary angiitis of the central nervous system: pathologically versus angiographically defined cases, abstracted; Arthritis Rheum; 38(9):340.**
137. **George R, Penn R (1993); Histoplasmosis. In: Fungal Diseases of the Lung; Sarosi GA, Davies SF,; 39-50.**
138. **Geriant Williams T. and Jones Williams W (1983). Granulomatous inflammation- a review; J Clin Pathol ;36:723-733**
139. **Ghosn J, Paris L, Ajzenberg D, et al. (2003) Atypical toxoplasmic manifestation after discontinuation of maintenance therapy in a HIV type 1-infected patient with immune recovery. Clin Infect Dis, 37:112-114.**
140. **Gideon NM and Mannino DM (1996). Sarcoidosis mortality in the United States 1979-1991: An analysis of multiple-cause mortality data. Am j Med; 100:423-427.**
141. **Gleissner, B., A. Schilling, I. Anagnostopolous, I. Siehl, and E. Thiel (2004); Improved outcome of zygomycosis in patients with hematological diseases?; Leukemia Lymphoma; 45:1351-1360.**
142. **Glynn JR (1998) Resurgence of tuberculosis and impact of HIV infection; Br Med Bull; 54: 579–93**
143. **Goel A, Nadkarni T, Desai AP. (1996); Aspergilloma in the paracavernous region. Two case reports. Neurologia medico-chirurgica; 36:733-6.**
144. **Gomes CM, Trigo-Rocha F, Arap MA, et al. (2002) Schistosomal myelopa-thy: urologic manifestations and urodynamic findings. Urology; 59:195-200.**
145. **Gongora, F., J. Santos, R. Hernandez, H. Jung, D. Gonzalez, J. L. Soto, and C. Marquez. (2001). Albendazole therapy for subarachnoidal and intraventricular cysticercosis: a prospective double-blind trial comparing 15 versus 30 mg/kg/day. Neurology 56**
146. **Graham EM, Ellis CJK, Sanders MD (1986). Optic neuropathy in sarcoidosis. j Neurol Neurosurg Psychiatry; 49:756-763.**
147. **Green M, Wald ER, Tzakis A, Todo S, Starzl TE. (1991); Aspergillosis of the CNS in a pediatric liver transplant recipient: Case report and review. Rev Infect Dis; 13:653-7.**
148. **Greg A. Christoforidis, Eric M. Spickle, Maria V. Recio and Bharat M. Mehta (1999). MR of CNS Sarcoidosis: Correlation of Imaging Features to Clinical Symptoms and Response to Treatment; American Journal of Neuroradiology; 20:655-669.**
149. **Gupta R, Singh AK, Bishnu P, et al (1990). Intracranial aspergillus granuloma simulating meningioma on MR imaging. J Comput Assist Tomogr 14:467-469.**
150. **Gutierrez Y. (2000); Echinococcus—hydatid disease. In: Gutierrez Y, ed. Diagnostic pathology of parasitic infection with clinical correlation. Oxford: Oxford University**

151. Hadi M, Boncoeur-Martel MP, Bouteille B, et al (1999); Cerebral miliary granulomatosis with Histoplasma capsulatum in an HIV seronegative patient; Rev Neurol (Paris); 155:231-233.
152. Hagansee ME, Bauwens JE, Kjos B, et al (1994). Brain abscess following bone marrow transplantation: Experience at the Fred Hutchinson Cancer Research Center, 1984-1992. Clin Infect Dis 19:402-408.
153. Hagen EC, Daha MR, Hermans J (1998). For the EC/BCR Project for ANCA Assay Standardization. Diagnostic value of standardized assays for anti-neutrophil cytoplasmic antibodies in idiopathic systemic vasculitis; Kidney Int; 53:743-753.
154. Haliloglu M, Saatci I, Akhan O, Ozmen MN, Besim A. (1997); Spectrum of imaging findings in pediatric hydatid disease. AJR; 169:1627-1631.
155. Hall WA.(1992).Neurosurgical Infections in the Compromised Host in Haines SJ, Hall WA, editors, Neurosurgery Clinics of North America, Infections in Neurologic Surgery, Vol 3, Philadelphia: WB Saunders Co; 435-42.
156. Hankkey GJ (1991). Isolated angiitis/angiopathy of the central nervous system;. Cerebrovasc Dis; 1:2.
157. Harries A and Maher D (1997) TB: a clinical manual for South East Asia. Geneva: World Health Organization.
158. Harries AD (1990) Tuberculosis and human immunodeficiency virus infection in developing countries; Lancet;335:387-90.
159. Harries AD, Fryatt R, Walker J, et al. (1986) Schistosomiasis in expatriate returning to Britain from the tropics: a controlled study; Lancet; 1:86-88.
160. Hector H. García, Carlton A. W. Evans, Theodore E. Nash, Osvaldo M. Takayanagui, A. Clinton White Jr., David Botero, Vedantam Rajshekhar, Victor C. W. Tsang, Peter M. Schantz, James C. Allan, Ana Flisser, Dolores Correa, Elsa Sarti, Jon S. Friedland, S. Manuel Martinez, Armando E. Gonzalez, Robert H. Gilman, and Oscar H. Del Brutton (2002); Current Consensus Guidelines for Treatment of Neurocysticercosis; Clinical Microbiology Reviews; 15(4): 747-756.
161. Heiserman J, Dean B, Hodak J, (1994). Neurologic complications of cerebral angiography; AJNR; 15:1401.
162. Hirsch CS, Johnson JL, Ellner JJ (1999) Pulmonary tuberculosis; Curr Opin Pulm Med; 5: 143-50
163. Hoffman GS, Kerr GS, Leavitt RY (1992). Wegener granulomatosis: an analysis of 158 patients; Ann Intern Med; 116:488-498.
164. Holdiness MR (1990) Management of tuberculous meningitis, Drugs ;39:224-33.
165. House JL, Brackmann DE (1982) Cholesterol granuloma of the cerebellopontine angle;

166. Hunninghake GW, Costabel U, Ando M, et al. (1999). Statement on sarcoidosis. American Thoracic Society/European Respiratory Society/World Association of Sarcoidosis and other Granulomatous Disorders. *Sarcoidosis Vasc Diffuse Lung Dis*; 16:149-173.
167. Hunninghake GW, Gilbert S, Pueringer R, et al (1994). Outcome of the treatment of sarcoidosis. *Am J Respir Care Med*; 149:893-898.
168. Ibrahim, A. S., B. Spellberg, V. Avanesian, Y. Fu, and J. E. Edwards. (2005); *Rhizopus oryzae* adheres to, is phagocytosed by, and damages endothelial cells in vitro; *Infect. Immun*; 73:778-783.
169. Ibrahim, A. S., J. E. J. Edwards, and S. G. Filler (2003-a); Zygomycosis. In: W. E. Dismukes, P. G. Pappas, and J. D. Sobel (ed.), *Clinical mycology*. Oxford University Press, New York, N.Y.; 241-251.
170. Ibrahim, A. S., V. Avanesian, B. Spellberg, and J. E. Edwards, Jr (2003-b); Liposomal amphotericin B, and not amphotericin B deoxycholate, improves survival of diabetic mice infected with *Rhizopus oryzae*; *Antimicrob. Agents Chemother*; 47:3343-3344.
171. Israel HL, Gushue G, Park CH (1986). Assessment of gallium-67 scanning in pulmonary and extrapulmonary sarcoidosis. *Ann NY Acad Sci*: 465:45-62.
172. Israelski DM, Chmiel JS, Poggensee L, Phair JP, Remington JS (1993). Prevalence of *Toxoplasma* infection in a cohort of homosexual men at risk of AIDS and toxoplasmic encephalitis. *J Acquir Immune Defic Syndr.*;6:414-8.
173. James DG (1998). Life-threatening situations in sarcoidosis; Source: *Sarcoidosis Vasculitis & Diffuse Lung Diseases*; 15(2):134-9.
174. Jayne D (2001). Update on the European Vasculitis Study Group trials; *Curr Opin Rheumatol*; 13:48-55.
175. Jennifer J. WU and Karin Rashcovisky Schieff (2004). Sarcoidosis; *American Family Physician*; 70:2.
176. Jeremy N Day (2004); Cryptococcal Meningitis; *Practical Neurology*; 4;274-285.
177. Jinkins JR (1988) Focal tuberculous cerebritis; *Am J Neuroradiol*; 9: 121
178. Jinkins JR, Gupta R, Chang KH, Rodriguez- Carbajal J(1995) MR imaging of central nervous system tuberculosis; *Radiol Clin North Am* ; 33:771-86.
179. Johns Carol Johnson; Michele Theresa Marie (1999). The Clinical Management of Sarcoidosis: A 50-Year Experience at the Johns Hopkins Hospital, *Medicine*; 78(2):65-111.
180. John L. Sherman, Barney J. Stern (1990); Sarcoidosis of the CNS: Comparison of Unenhanced and Enhanced MR Images; *AJNR* 11:915-923.
181. Joint Tuberculosis Committee of the British Thoracic Society (1998): Chemotherapy and management of tuberculosis in the United Kingdom: recommendations. *Thorax*; 53: 536-48

182. **Jones Richard E. ; Chatham W. Winn (1999), Update on sarcoidosis; Current Opinion in Rheumatology; 11(1):83.**
183. **Joseph M. Murphy, Beatriz Gomez-Anson, Jonathan H. Gillard, Nagui M. Antoun, Justin Cross, Jane D. Elliott, BSc, RGN and Martin Lockwood, (1999). Wegener Granulomatosis: MR Imaging Findings in Brain and MeningesRadiology; 213:794-799**
184. **junger SS, Stern Bj, Levine SR (1993). Intramedullary spinal sarcoidosis: Clinical and magnetic resonance imaging characteristics; Neurology; 43:333-337.**
185. **Kadival GV, Samuel AM, Mazarelo TBMS et al (1987) Radioimmunoassay for detecting Mycobacterium tuberculosis antigen in cerebrospinal fluid samples of patients with TBM; J Infect Dis; 155: 608–11**
186. **Kambovitis E, McIlmurray MB, Lock PE et al (1984) Rapid diagnosis of tuberculous meningitis by latex particle agglutination; Lancet; 2: 1229–31**
187. **Kaojarern S, Supmonchai K, Phuapradit P, Mokkhavesa C, Krittiyanunt S (1991) Effects of steroids on cerebrospinal fluid penetration of antituberculous drugs in tuberculous meningitis; Clin Pharmacol Ther ;49:6–12.**
188. **Karoll J. Cortez and Thomas J. Walsh (2004). Space-occupying fungal infections. In Scheld WM, Whitley Rj, Durack DT (eds). Infections of the Central Nervous System, ed 2. Philadelphia, Lippincott-Raven Publishers**
189. **Katti MK (2002) Assessment of antibody responses to antigens of Mycobacterium tuberculosis and Cysticercus cellulosae in cerebrospinal fluid of chronic meningitis patients for definitive diagnosis of TBM/NCC by passive haemagglutination and immunoblot assays; FEMS Immunol Med Microbiol; 33: 57–61**
190. **Katti MK, Chandramuki A (1990) detection and characterization of circulating cysticercal antigens in human cerebrospinal fluid; Serodiagn Immunother Infect Dis; 4: 441–50**
191. **Keith Smith, Maria Gisele Matheus and Mauricio Castillo (2004). Imaging Manifestations of Neurosarcoidosis; AJR; 182:289-295.**
192. **Kelly PC (1980). Coccidioidal meningitis. In: Stevens DA, ed. Coccidioidomycosis: a text. Current topics in infectious disease; Pub: New York: Plenum Medical Book:163-93.**
193. **Kemper CA, Meng TC, Nussbaum J, et al (1992) Treatment of mycobacterium avium complex bacteremia in AIDS with a four drug regimen: rifampin, ethambutol, clofazimine and ciprofloxacin; Ann Intern Med ;116:466–72.**
194. **Kennedy DH, Fallon RJ (1979)Tuberculous meningitis; JAMA ;241:264–8.**
195. **Kent SJ, Crow SM, Yung A et al (1993) Tuberculous meningitis: a 30 year review; Clin Infect Dis; 17: 987–94**
196. **Kern P, Bardonnnet K, Renner E, et al (2003). European echinococcosis registry: human alveolar echinococcosis, Europe, 1982—2000. Emerg Infect Dis ;9:343-349.**
197. **Keye JD and Magee WE (1956). Fungal diseases in a general hospital. J Clin Pathol 9:1235-**

198. **Khoo SH, Bond J, Denning DW (1994).Administering amphotericin B--a practical approach. Journal of Antimicrob Chemother, 33, 203–13.**
199. **King CH. (2001) Epidemiology of schistosomiasis: determinants of transmission of infection. In: Mahmoud AAF, ed. Schistosomiasis. London: Imperial College Press:115-132.**
200. **Kirsten de Groot, Diego K. Schmidt, Andreas C. Arlt, Wolfgang L. Gross, Eva Reinhold-Keller (2001). Standardized Neurologic Evaluations of 128 Patients With Wegener Granulomatosis; Arch Neurol; 58:1215-1221.**
201. **Kotwani RN, Gokhale PC, Kshirsagar NA, Pandya SK. (1996); Optimizing dosage regimens of liposomal amphotericin B using aspergillus murine model. Ind J Pharm; 28:88-92.**
202. **Kox LFF, Kuijper S, Kolk AHJ (1995) Early diagnosis of tuberculous meningitis by polymerase chain reaction; Neurology; 45: 2228–32**
203. **Kramer, L. D., G. E. Locke, S. E. Byrd, and J. Daryabagi. (1989). Cerebral cysticercosis: documentation of natural history with CT. Radiology 171:459-462.**
204. **Krumholz A, Stern Bj (1998). Neurological manifestations of sarcoidosis. In: Handbook of Clinical Neurology, Aminoff Mj, Goetz (eds); Elsevier Science, Amsterdam: 27(71):463-499.**
205. **Kruniholz A, Stem Bj, Stem EG (1991). Clinical implications of seizures in neurosarcoidosis; Arch Neurol; 48:842-844.**
206. **Kshirsagar NA, Gokhale PC, Pandya SK. (1996); Drug treatment of systemic fungal infection: Our experience with liposomal amphotericin B. Ind J Hematol Blood Transf ;11:72-9.**
207. **Kshirsagar NA, Kirodian BG.(2002); Liposomal Drug Delivery System from Laboratory to Patients: Our Experience. Proc Indian Natn Sci Acad; B68:333-48.**
208. **Kumarvelu S, Prasad K, Khosla A, Behari M, Ahuja GK (1994) Randomized controlled trial of dexamethasone in tuberculous meningitis; Tubercle Lung Dis ;75:203–7.**
209. **Kurita H, Shiokawa Y, Furuya K, et al (1995). Parasellar aspergillus granuloma extending from the sphenoid sinus: Report of two cases. Surg Neurol 44:489-494.**
210. **Kwekkeboom Dik J, Eric P. Krenning, G. Siang Kho, Wout A. P. Breeman, P. Martin Van Hagen, (1998). Somatostatin receptor imaging in patients with sarcoidosis; European Journal of Nuclear Medicine and Molecular Imaging; 25:9.**
211. **Leavitt RY, Fauci AS, Bloch DA (1990). The American College of Rheumatology criteria for the classification of Wegener's granulomatosis; Arthritis Rheum; 33:1101-7.**
212. **Leonard JM and Des Prez RM (1990) Tuberculous meningitis; Infect Dis Clin North Am;4: 769–87.**
213. **Lesprit P, Zagolanski AM, de la Blanchardiere A et al (1997) Cerebral tuberculosis in patients with acquired immunodeficiency syndrome (AIDS); Report of 6 cases and review;**

214. Levy RM, Bredesen DE, Rosenblum ML (1985): Neurological manifestations of acquired immunodeficiency syndrome (AIDS): Experience at UCSF and review of the literature. *J Neurosurg* ; 62 : 475-495
215. Lewis JL and Rabinovich S (1972). The wide spectrum of cryptococcal infections. *American Journal of Medicine*, 53, 315–22.
216. Lie JT (1992). Primary (granulomatous) angitis of the central nervous system: A clinicopathologic analysis of 15 new cases and a review of the literature; *Hum Pathol*; 23:164.
217. Lipton SA, Hickey WF, Morris JH, et al (1984). Candidal infection in the central nervous system. *Am j Med* 76:101-108.
218. Liu P, Shi ZY, Lau YJ et al (1994) Rapid diagnosis of tuberculous meningitis by simplified nested amplification protocol; *Neurology*; 44: 1161–64
219. Lopez-Gomez, M., N. Castro, H. Jung, J. Sotelo, and T. Corona. (2001). Optimization of the single-day praziquantel therapy for neurocysticercosis. *Neurology* 57:1929-1930
220. Lower EE, Broderick JP, Brott TG, et al (1997). Diagnosis and management of neurological sarcoidosis; *Arch Intern Med*; 157:1864-1868.
221. Luft BJ, Brooks RG, Conley FK, McCabe RE, Remington JS. (1984) Toxoplasmic encephalitis in patients with acquired immune deficiency syndrome. *JAMA* ;252:913-7.
222. Luis A. Espinoza (2006); *Toxoplasmosis; HIV/AIDS Primary Care Guide (Paperback)* (Eds): Jeffrey Beal, Joanne Orrick, Kimberly Alfonso, Mobeen Rathore; Publisher: Crown House Publishing :360-3
223. Luke RA, Stem Bj, Krumholz A (1987). Neurosarcoidosis: The long-term clinical course; *Neurology*; 37:461-463.
224. Lustig LR, Cheung SW, Jackler RK (1998). Subcochlear petrous cholesterol granuloma involving the infratemporal fossa; *Otolaryngol Head Neck Surg*; 119: 685-9
225. Lyons RW, Andriole VT. (1986). Fungal infections of the CNS. *Neurol Clin*; 4:159–170
226. Madrazo, I. and A. Flisser. (1992). Cysticercosis, p. 1419-1430. In M. L. J. Apuzzo (ed.), *Brain surgery: complication avoidance and management*. Churchill Livingstone, New York, N.Y.
227. Mantzoros CS, Brown PD, Dembry L (1993) Extraosseous epidural tuberculoma; Case report and review; *Clin Infect Dis*;17:1032–6.
228. Mardh PA, Larsson L, Holby N et al (1983) Tuberculostearic acid as a diagnostic marker in tuberculous meningitis; *Lancet*; 1: 367
229. Marr, K. A., R. A. Carter, F. Crippa, A. Wald, and L. Corey (2002); Epidemiology and outcome of mould infections in hematopoietic stem cell transplant recipients; *Clin. Infect.*

Dis; 34:909-917.

230. **Marta E. Heilbrun, Karen L. Salzman, Christine M. Glastonbury, H. Ric Harnsberger, Richard J. Kennedy and Clough Shelton (2003). External Auditory Canal Cholesteatoma: Clinical and Imaging Spectrum; American Journal of Neuroradiology; 24:751-756.**
231. **Martin N, Sterkers O, Mompont D, Julien N, Nahum H (1989) Cholesterol granulomas of the middle ear cavities: MR imaging. Radiology 172: 521-5.**
232. **Martin-Duverneuil N., A. Idbah, K. Hoang-Xuan, J. Donadieu, T. Genereau, R. Guillevin, J. Chiras and French Langerhans Cell Histiocytosis Study Group (2006). MRI features of neurodegenerative Langerhans cell histiocytosis; European Radiology; 16(9): 2074-2082.**
233. **Masteroianni CM, Vullo V, Paoletti F et al(1991) Detection of mycobacterial antigen by dot blot assay in the cerebrospinal fluid of patients with TBM; J Infect; 22: 106–7**
234. **Mathew MJ, Chandy MJ (1999); Central nervous system toxoplasmosis in acquired immunodeficiency syndrome : An emerging disease in India; Neurology India; 47 (3):182-7**
235. **Mathews WC, Fullerton SC. (1994). Use of a clinical laboratory database to estimate Toxoplasma seroprevalence among human immunodeficiency virus-infected patients. Overcoming bias in secondary analysis of clinical records. Arch Pathol Lab Med;118:807-10.**
236. **Maurício S. Miura, Rita C. Krumennauer, José F. Lubianca Neto (2005); Intracranial complications of chronic suppurative otitis media in children; Rev. Bras. Otorrinolaringol; 71 No 5.**
237. **Mayers MM, Kaufman DM, Miller MH (1978) Recent cases of intra cranial tuberculomas; Neurol; 28: 256**
238. **McCormick WF, Schochet SS, Weaver PR. (1975). Disseminated aspergillosis. Arch Pathol; 100:353-9.**
239. **McCullers JA, Vargas SL, Flynn PM, (2000). Candidal meningitis in children with cancer; Clin Infect Dis; 31:451-457.**
240. **Medical Research Council (1948) Streptomycin in tuberculosis trials committee; Streptomycin treatment of tuberculous meningitis; Lancet ;i:582–96.**
241. **Meric Tuzun and Baki Hekimoglu (1998); Hydatid Disease of the CNS: Imaging Features; AJR; 171:1497-1500.**
242. **Metwally Y (2006-1).; Hydatid disease; Text book of Neuroimaging (web based e-book); Ver 7.2.**
243. **Metwally Y(2006-2). CNS granuloma; Text book of Neuroimaging (web based e-book); Ver 7.2.**
244. **Metwally Y(2006-3). Fungal infections of the CNS; Text book of Neuroimaging (web based e-book); Ver 7.2.**

245. **Metwally Y.(2006-4); Neurological manifestation of sarcoidosis; Text book of Neuroimaging (web based book); Ver 7.2..**
246. **Metwally Y.(2006-5); Neuro-ocular Sarcoidosis ; Text book of Neuroimaging (web based book); Ver 7.2.**
247. **Metwally Y.(2006-6); Wegener Granulomatosis; Text book of Neuroimaging (web based book); Ver 7.2**
248. **Metwally Y.(2006-7); Rhinocerebral Mycormycosis; Text book of Neuroimaging (web based book); Ver 7.2**
249. **Metwally Y.(2006-8); Histoplasmosis: an overview; Text book of Neuroimaging (web based book); Ver 7.2**
250. **Metwally Y.(2006-9); Neuroimaging in CNS Cryptococcosis; Text book of Neuroimaging (web based book); Ver 7.2**
251. **Metwally Y.(2006-10); Neuroimaging of Neurocysticercosis: An Update; Text book of Neuroimaging (web based book); Ver 7.2**
252. **Metwally Y.(2006-11); Neuroimaging of CNS Toxoplasmosis; Text book of Neuroimaging (web based book); Ver 7.2**
253. **Metwally Y.(2006-12); Langerhans Cell Histiocytosis; Text book of Neuroimaging (web based book); Ver 7.2**
254. **Miaux Y, Singer B, Leder S, Guermazi A, Bourrier P. (1994); MR imaging of cerebral aspergillosis: different patterns in the same patient. AJNR Am J Neuroradiol;15:1193–1195**
255. **Miaux Y., P. Ribaud, M. Williams, A. Guermazi, E. Gluckman, C. Brocheriou, and M. Laval-Jeantet (1995); MR of Cerebral Aspergillosis in Patients Who Have Had Bone Marrow Transplantation; AJNR Am J Neuroradiol 16:555–562.**
256. **Michael J Faer, Jay H. Mead, AND Richard D. Lynch (1977); Cerebral Granulomatous Angiitis: Case Report and Literature Review; Am J Ro.ntg.nol; 129:463-467.**
257. **Miller DH, Kendall BE, Barter S (1988). Magnetic resonance imaging in central nervous system: sarcoidosis; Neurology; 38:378-383.**
258. **Miller JD (1995) Pott’s paraplegia to day; Lancet; 340:264.**
259. **Mitchell RN and Cotran RS (2003). Acute and chronic inflammation; In: Robbins Basic Pathology; Kumar V., Cotran R.S. and Robbins S. L. (eds). W.B. Saunders; P 56-57.**
260. **Mitchell, W. G., and T. O. Crawford. (1988). Intraparenchymal cerebral cysticercosis in children: diagnosis and treatment. Pediatrics 82:76-82.**
261. **Molavi A, LeFrock JL (1985) Tuberculous meningitis; Med Clin North Am ;69:315–31.**
262. **Moller D. R. (2003). Treatment of sarcoidosis – from a basic science point of view; Journal of Internal Medicine; 253(1):31 – 40.**

263. Moosa MY & Coovadia YM (1997). Cryptococcal meningitis in Durban, South Africa: a comparison of clinical features, laboratory findings, and outcome for human immunodeficiency virus (HIV)-positive and HIV negative patients. *Clinical Infection and Disease*, 24, 131–4.
264. Mori, T., M. Egashira, N. Kawamata, K. Oshimi, K. Nakamura, T. Oguri, H. Aida, A. Hiruma, and M. Ichinohe (2003); Zygomycosis: two case reports and review of reported cases in the literature in Japan; *Nippon Ishinkin Gakkai Zasshi*; 44:163-179.
265. Muralidhar K. Katti (2004) Pathogenesis, diagnosis, treatment, and outcome aspects of cerebral tuberculosis; *Med Sci Monit*; 10(9): RA215-229
266. Mwaba P, Mwansa J, Chintu C et al. (2001). Clinical presentation, natural history, and cumulative death rates of 230 adults with primary cryptococcal meningitis in Zambian AIDS patients treated under local conditions. *Postgraduate Medicine*, 77, 769–73.
267. Nadkarni T, Goel A (2005); Aspergilloma of the brain: an overview; *Journal of Postgraduate Medicine*; 51 (5)L:37-41
268. Nadkarni TD, Desai KI, Muzumdar D, Goel A, Shenoy A.(2003); Ischaemic complications after surgical resection of intracranial aspergilloma. *J Clin Neurosci*;10:500-2.
269. Nakao K, Noma K, Sato B (1970). Serum prolactin levels in 80 patients with sarcoidosis; *Eur J Clin Invest*; 8:37-40.
270. Navia BA, Jordan BD, Price RW (1986): Cerebral toxoplasmosis complicating the acquired immune deficiency syndrome. Clinical and Neuropathological changes in 27 patients. *Ann Neurol*; 9 : 224-238.
271. Newton RW (1994) Tuberculous meningitis; *Arch Dis Child* ;70:364–6.
272. Nishino H, Rubino FA, DeRemee RA (1993). Neurological involvement in Wegener's granulomatosis: an analysis of 324 consecutive patients at the Mayo Clinic; *Ann Neurol*; 33 (1): 4-9.
273. Nithyanandam, S., M. S. Jacob, R. R. Battu, R. K. Thomas, M. A. Correa, and O. D'Souza (2003); Rhino-orbito-cerebral mucormycosis. A retrospective analysis of clinical features and treatment outcomes; *Indian J. Ophthalmol*; 51:231-236.
274. Nov AA, Cromwell LD (1984). Computed tomography of neuraxis aspergillosis. *J Comput Assist Tomogr* 8: 413-415.
275. Novati R, Castagna A, Morsica G, et al. (1994) Polymerase chain reaction for *Toxoplasma gondii* DNA in the cerebrospinal fluid of AIDS patients with focal brain lesions. *AIDS* ;8:1691-4.
276. Nussbaum ES, Rockswold GL, Bergman TA, Erickson DL, Seljeskog(1995) Spinal tuberculosis: a diagnostic and management challenge; *J Neurosurg* ;83:243–7.
277. Oksanen V (1986): Neurosarcoidosis: Clinical presentations and course in 50 patients. *Acta Neurol Scand* 73:283-290.

278. **Oksanen V, Salmi (1986). Visual and auditory evoked potentials in the early diagnosis and follow-up of neurosarcoidosis; Acta Neurol Scand; 74:38-42.**
279. **Olek M, Jaitly R, Kuta A (1995). Sarcoidosis and spinal cord atrophy; Neurologist; 1:240-243.**
280. **Ostrow TD, Kudgins PA (1994). Magnetic resonance imaging of intracranial fungal infections. Top Magn Reson Imaging 6:22-31.**
281. **Otake S, Banno T, Ohaba S (1990). Muscular sarcoidosis: Findings at MR imaging. Radiology 176:145-148,1990**
282. **Paltauf A (1885). Mycosis mucorina. Virchows Arch Pathol Anat 102:543-564.**
283. **Pappagianis D. (1988); Epidemiology of coccidioidomycosis. Curr Top Med Mycol; 2:199-238.**
284. **Patil SA, Gouri-Devi M, Ray Chuadhury J et al (1996) Identification of antibody responses to Mycobacterium tuberculosis antigens in the cerebrospinal fluid of tuberculous meningitis patients by western blotting; Clin Immunol Immunopathol; 81: 35–40**
285. **Paul A. Bacon (2005). The Spectrum of Wegener's Granulomatosis and Disease Relapse; The New England Journal of Medicine; 352:330-332.**
286. **Pauranik A, Behari M, Maheshwari MC (1987) Appearance of tuberculoma during treatment of tuberculous meningitis; Jpn J Med;26:332.**
287. **Peeples DM, Stem Bj, Jiji V, (1991). Germ cell tumors masquerading as central nervous system Sarcoidosis; Arch Neurol; 48:554.**
288. **Pendlebury WW, Perl DP, Munoz DG.(1989); Multiple microabscesses in the central nervous system: a clinicopathologic study. J Neuropathol Exp Neurol; 48:290–300**
289. **Perfect JR, Durack DT (1997); Fungal meningitis. In: Scheld WM, Whitley Rj, Durack DT (eds). Infections of the Central Nervous System, ed 2. Philadelphia, Lippincott-Raven; 691-712.**
290. **Peter D Corr; Tuberculosis, CNS; last updated November 2004 <http://www.emedicine.com/radio/topic720.htm>**
291. **Petrikkos, G., A. Skiada, H. Sambatakou, A. Toskas, G. Vaiopoulos, M. Giannopoulou, and N. Katsilambros (2003); Mucormycosis: ten-year experience at a tertiary-care center in Greece; Eur. J. Clin. Microbiol. Infect. Dis; 22:753-756.**
292. **Pittella JE (1997). Neuroschistosomiasis. Brain Pathol ;7:649-662.**
293. **Pittella JE, Gusmao SN, Carvalho GT, et al. (1996) Tumoral form of cerebral schistosomiasis mansoni: a report of four cases and a review of the literature. Clin Neurol Neurosurg ;98:15-20.**
294. **Pittella JE, Lana-Peixoto MA. (1981) Brain involvement in hepatosplenic Schistosomiasis mansoni. Brain; 104:621—632.**

295. Porter SB, Sande MA (1992). Toxoplasmosis of the central nervous system in the AIDS. *N Engl J Med*, 327:1643-8.
296. Prabhakar S, Oomen A (1987) Enzyme-linked immunosorbent assay using mycobacterial antigen as a diagnostic aid for tuberculous meningitis; *J Neurol Sci*; 78: 203–11
297. Pretell, E. J., H. H. Garcia, R. H. Gilman, H. Saavedra, M. Martinez, and the Cysticercosis Working Group in Peru. (2001). Failure of one-day praziquantel treatment in patients with multiple neurocysticercosis lesions. *Clin. Neurol. Neurosurg.* 103:175-177
298. Proano, J. V., I. Madrazo, L. Garcia, E. Garcia-Torres, and D. Correa. (1997). Albendazole and praziquantel treatment in neurocysticercosis of the fourth ventricle. *J. Neurosurg.* 87:29-33.
299. Quy HT, Lan NT, Borgdorff MW et al (2003) Drug resistance among failure relapse cases of tuberculosis: is the standard treatment regimen adequate? *Int J Tuberc Lung Dis*; 7(7): 631–36
300. Rabiela, M. T., A. Rivas, and A. Flisser. (1989). Morphological types of *Taenia solium* cysticerci. *Parasitol. Today* 5:357-359.
301. Rajajee S and Narayanan PR (1992) Immunological spectrum of childhood tuberculosis; *J Trop Pediatr* ;21:490–6.
302. Rajshekhar V, Chandy MJ (1997) Tuberculomas presenting as isolated intrinsic brain stem masses; *Br J Neurosurg* ;11:127–33.
303. Rajshekhar V. (2000); Severe episodic headache as the sole presenting ictal event in patients with a solitary cysticercus granuloma; *Acta Neurol Scand*; 102:44-46.
304. Rajshekhar, V. (1991). Etiology and management of single small CT lesions in patients with seizures: understanding a controversy. *Acta Neurol. Scand.* 84:465-470.
305. Ramkisson A and Coovadia HM (1998) Chloride levels in meningitis; *S Afr Med J*; 73: 522–23
306. Rangel R, Torres B, Del Brutto O, et al. (1987); Cysticercotic encephalitis: a severe form in young females. *Am J Trop Med Hyg*; 36:387-392.
307. Raviglione MC, Snider DE, Kochi A (1995) Global epidemiology of tuberculosis; Morbidity and mortality of a world wide epidemic; *JAMA* ;273:220–6.
308. Ravindra Kumar Garg (1999); Tuberculosis of the central nervous system; *Postgrad Med J* ;75:133-140.
309. Razai AR, Lee M, Cooper PR, Errico TJ, Koslow M (1995) Modern management of spinal tuberculosis; *Neurosurgery*;36:87–98.
310. Rex JH, Pappas PG, Karchmer AW et al. (2003). A randomized and blinded multicenter trial of high-dose fluconazole plus placebo versus fluconazole plus amphotericin B as therapy for candidemia and its consequences in nonneutropenic subjects. *Clinical Infection and Disease*, 36, 1221–8.

311. Ribes, J. A., C. L. Vanover-Sams, and D. J. Baker. (2000). Zygomyces in human disease; *Clin. Microbiol. Rev*; 13:236-301.
312. Rich AR, McCordock HA (1933) Pathogenesis of tubercular meningitis; *Bull John Hopkins Hosp* ;52:5–13.
313. Robert D. Zimmerman (2004). Physiological imaging in infection, inflammation and demyelination; In: *Clinical MR Neuroimaging*; Jonathan H. Gillard, Adam D. Waldman, Peter B. Barker (eds); Cambridge University Press; P 359-361
314. Rodan BA, Putman CE (1983). Radiological alterations in sarcoidosis. In: Fanburg BL (ed); *Sarcoidosis and Other Granulomatous Diseases of the Lung*. New York, Marcel Dekker; 37-75
315. Rodgers CA, Harris JR. (1996) Ocular toxoplasmosis in HIV infection. *Int J STD AIDS* , 7:307-9.
316. Roongroj Bhidayasiri, Michael F Waters, Christopher C Giza (2005). Neuroanatomy and Neuropathology; In: *Neurological Differential Diagnosis*; Blackwell Publishing; P 37-38
317. Rosenberg RA, Hammerschlag PE, Cohen NL, Bergeron RT, Reede DL (1986). Cholesteatoma vs. cholesterol granuloma of the petrous apex; *Otolaryngol Head Neck Surg*; 94: 322-7.
318. Sessa S, D Sommelet, P Lascombes and J Prevot (1994). Treatment of Langerhans-cell histiocytosis in children. Experience at the Children's Hospital of Nancy; *The Journal of Bone and Joint Surgery*; 76(10):1513-1525.
319. Saag MS, Graybill RJ, Larsen RA et al. (2000). Practice guidelines for the management of cryptococcal disease. Infectious Diseases Society of America. *Clinical Infection and Disease*, 30, 710–8.
320. Sahar Saleem, Adel I. Belal and Nasser M. El-Ghandour (2005); Spinal Cord Schistosomiasis: MR Imaging Appearance with Surgical and Pathologic Correlation, *American Journal of Neuroradiology*; 26:1646-1654
321. Salaki JS, Louria DB, Chmel H. (1984); Fungal and yeast infections of the central nervous system: a clinical review. *Medicine*; 63:108– 132
322. Sanelli PC, Lev MH, Gonzalez RG, et al. (2001) Unique linear and nodular MR enhancement pattern in schistosomiasis of the central nervous system: report of three patients. *AJR Am J Roentgenol*; 177: 1471-1474.
323. Saravia-Gomez J. (1978); Aspergillosis of the Central Nervous System, in Vinken PJ, Bruyn GW, editors, *Handbook of Clinical Neurology Vol 35*, Holland: North-Holland Publishing Company; p.395-400
324. Scanarini M, Rotiho A, Rigobello L, et al (1991). Primary intrasellar coccidioidomycosis simulating a pituitary adenoma. *Neurosurgery* 28:748-751.
325. Schmid M, Pendl G, Samonigg H, et al. (1998) Gamma knife radiosurgery and albendazole for cerebral alveolar hydatid disease. *Clin Infect Dis* ;26:1379-1382.

326. Schmitt S., W. Wichmann, E. Martin, M. Zachmann and E. J. Schoenle (1993) Pituitary stalk thickening with diabetes insipidus preceding typical manifestations of Langerhans cell histiocytosis in children; *European Journal of Pediatrics* ; 152(5): 399-401.
327. Schoeman JF, Vanzyl LF, Laubscher JA, Donald PR (1997) Effect of cortico- steroids on intracranial pressure, computed tomographic findings, and clinical outcome in young children with tuberculous meningitis; *Pediatrics*;99:226–31.
328. Schwarz P, Dromer F, Lortholary O & Dannaoui E (2003).In vitro interaction of fl ucytosine with conventional and new antifungals against *Cryptococcus neoformans* clinical isolates. *Antimicrob Agents Chemother*, 47, 3361–4.
329. Scolding NJ, Jayne DRW, Zajicek JP (1997). Cerebral vasculitis-recognition, diagnosis, and management; *Q J Med*; 90:61.
330. Scott TF (1993): Neurosarcoidosis: Progress and clinical aspects. *Neurology* 43:8-12.
331. Scrimgeour EM, Gajdusek DC (1985). Involvement of the central nervous system in *Schistosoma mansoni* and *S. haematobium* infection: a review. *Brain*; 108:1023-1038.
332. Seaton RA, Verma N, Naraqi S, Wembri JP & Warrell DA (1997).Visual loss in immunocompetent patients with *Cryptococcus neoformans* var. *gattii* meningitis. *Transactions of the Royal Society of Tropical Medicine Hygiene*,
333. Sethi KD, El Gammal T, Patel BR (1986). Dural sarcoidosis presenting with transient neurologic symptoms; *Arch Neurol*; 43:595-597.
334. Shankar P, Manjunath N, Mohan KK et al (1991) Rapid diagnosis of tuberculous meningitis by polymerase chain reaction; *Lancet*; 337: 5–7
335. Sharma BS, Khosla VK, Kak VK, et al (1997). Intracranial fungal granuloma. *Surg Neurol* 47:489-497.
336. Sharma OP (1997): Neurosarcoidosis: A personal perspective based on the study of 37 patients. *Chest* 11 2:220-228.
337. Sharma OP (1998). Effectiveness of chloroquine and hydroxychloroquine in treating selected patients with sarcoidosis with neurological involvement; *Arch Neurol*; 55:1248-1254.
338. Sharma RR, Lad SD, Desai AP, Lynch PG. (2000); *Surgical Management of Fungal Infections of the Nervous System*, in Schmidek HH, editor, *Schmidek and Sweet Operative Neurosurgical Techniques: Indications, Methods and Results*, 4 th edn. Philadelphia: WB Saunders Company; p.1726
339. Sheehan MP, Chu AC (1991). Oral, skin and bone multisystem Langerhans cell histiocytosis and its response to etoposide-a case report ; *Clinical and Experimental Dermatology* 16 (6), 463–466.
340. Sheller JR, Des Prez RM (1986) CNS tuberculosis; *Neurol Clin*;4:143–58.
341. Sherman JL, Stern Bj (1990). Sarcoidosis of the CNS: Comparison of unenhanced and

enhanced MR images; *AJNR*; 11:915-923.

342. Small PM, Schechter GF, Goodman PC, Sande MA, Chaisson RE, Hopewell PC (1991) Treatment of tuberculosis in patients with advanced human immunodeficiency virus infection; *N Engl J Med* ;324:289–94.
343. Smego RA, Perfect JR, Durack DT (1984); Combined Therapy with Amphotericin B and 5-fluorocytosin for *Candida meningitis*; *Rev Infect Dis*; 6:791-801.
344. Smith AS, Meisler DM, Weinstein MA (1989). High-signal periventricular lesions in patients with sarcoidosis: Neurosarcoidosis or multiple sclerosis?; *Am J Roentgenol*; 153:147-152.
345. Snider DE and, Roper WL (1992) The new tuberculosis; *N Engl J Med* ;226:703–5.
346. Snider DE, Rieder HL, Combs D, Bloch AD, Hayden CH (1988) Tuberculosis in children; *Pediatr Infect Dis J* ;7:271–8.
347. Soemberg N, Cajander S, Truedsson H (1981). Muscle involvement in sarcoidosis; *Acta Med Scand*; 209:213-216.
348. Spector WG (1974). The macrophage: its origin and role in pathology; *Pathobiol Ann* 4:33-64. Quoted from G T Williams and W J Williams (1983); *Granulomatous inflammation-a review*; *J Clin Pathol*; 36(7): 723–733.
349. Spector WG, Heesom N (1969). The production of granulomata by antigen-antibody complexes; *J Pathol* 1969;98:31-9. quoted from G T Williams and W J Williams; *Granulomatous inflammation-a review*; *J Clin Pathol*;1983; 36(7): 723–733.
350. Stefan Schwartz, Markus Ruhnke, Patricia Ribaud, Lawrence Corey, Timothy Driscoll, Oliver A. Cornely, Ulrich Schuler, Irja Lutsar, Peter Troke, and Eckhard Thiel (2005); Improved outcome in central nervous system aspergillosis, using voriconazole treatment; *Blood*; 106 (8): 2641-2645.
351. Stern Bj, Krumholz A, Johns C (1985). Sarcoidosis and its neurological manifestations; *Arch Neurol*; 42:909-917.
352. Stern Bj, Schonfeld SA, Sewell C (1992). The treatment of neurosarcoidosis with cyclosporine; *Arch Neurol*; 49:1065-1072.
353. Stone JH, Pomper MG, Hellman DB (1998); Histoplasmosis mimicking vasculitis of the central nervous system. *J Rheumatol*; 25: 1644-1648.
354. Strickland GT, Ramirez BL (1999). Schistosomiasis. In: Strickland GT, ed. *Hunter's tropical medicine*, 8th ed. Philadelphia: WB Saunders: 804-832.
355. Sturrock RE (2001). The schistosomes and their intermediate hosts. In: Mahmoud AAF, ed. *Schistosomiasis*. London: Imperial College Press,:7-83.
356. Suastegui Roman, R. A., J. L. Soto-Hernandez, and J. Sotelo. (1996). Effects of prednisone on ventriculoperitoneal shunt function in hydrocephalus secondary to cysticercosis: a preliminary study. *J. Neurosurg*. 84:629-633.

357. Takasu A, Taneda M, Otuki H, et al (1991). Gd-DPTA-enhanced MR imaging of cryptococcal meningoencephalitis. *Neuroradiology* 33:443-446.
358. Takayanagui, O. M., and E. Jardim. (1992). Therapy for neurocysticercosis. Comparison between albendazole and praziquantel. *Arch. Neurol.* 49:290-294.
359. Takeshita M, Izawa M, Kubo O, et al (1992). Aspergillotic aneurysms formation of cerebral artery: Following neurosurgical operation. *Surg Neurol* 38:146-151.
360. Talamas O, Del Brutto OH, Garcia-Ramos G (1989) Brainstem tuberculoma; *Arch Neurol* ;46: 529–35.
361. Talmi, Y. P., A. Goldschmied-Reouven, M. Bakon, I. Barshack, M. Wolf, Z. Horowitz, M. Berkowicz, N. Keller, and J. Kronenberg (2002); Rhino-orbital and rhino-orbito-cerebral mucormycosis; *Otolaryngol Head Neck Surg*; 127:22-31.
362. Taratuto AL, Venturiello SM. (1997); Echinococcosis; *Brain Pathol*; 7: 673-679.
363. Tenth International Conference on Sarcoidosis and Other Granulomatous Disorders (1986); 465:722.
364. Teoh R, Humhrie MJ, O' Mahoney G (1987) Symptomatic intracranial tuberculomas developing during treatment of tuberculosis; a report of 10 patients and review of literature; *Q J Med* ; 63:449–53.
365. Terk MR, Underwood DJ, Zee C, et al (1992); MR imaging in rhinocerebral and intracranial mucormycosis with CT and pathologic correlation; *Magn Reson Imaging*; 10:81-87.
366. Thajeb, P., T. Thajeb, and D. Dai (2004); Fatal strokes in patients with rhino-orbito-cerebral mucormycosis and associated vasculopathy; *Scand. J. Infect. Dis*; 36:643-648.
367. Thompson RC, McManus DP (2002). Towards a taxonomic revision of the genus *Echinococcus*. *Trends Parasitol* ; 18:452-457.
368. Thwaites G, T T H Chau, N T H Mai, F Drobniowski, K McAdam and J Farrar (2000) Neurological aspects of tropical disease: Tuberculous meningitis; *J. Neurol; Neurosurg. Psychiatry* ;68;289-299
369. Topaloglu I, Uguz MZ, Ardic FN (1997) Giant cholesteatoma presenting as a postauricular mass; *Otolaryngol Head Neck Surg*; 116: 678-9.
370. Tsang V C W, Brand J A, Boyer A E (1989); An enzyme linked immunoelectrotransfer blot assay and glycoprotein antigens for diagnosing human cysticercosis (*Taenia solium*); *J Infect Dis*; 159:50-59.
371. Tucker RM, Denning DW, Dupont B, Stevens DA.(1990b); Itraconazole therapy for chronic coccidioidal meningitis. *Ann Intern Med*; 112:108-112.
372. Tucker RM, Galgiani JN, Denning DW, et al. (1990a).Treatment of coccidioidal meningitis with fluconazole. *Rev Infect Dis*; 12(3).380-389.

373. **Tuzun M, Altinors N, Arda IS, et al (2002). Cerebral hydatid disease CT and MR findings. Clin Imaging ;26:353-357.**
374. **Udani PM, Dastur DK (1970) Tuberculous encephalopathy with and without meningitis: clinical features and pathological correlations; J Neurol Sci ;10:541–61.**
375. **Van Der Horst CM, Saag MS, Cloud GA et al. (1997) Treatment of cryptococcal meningitis associated with the acquired immunodeficiency syndrome. National Institute of Allergy and Infectious Diseases Mycoses Study Group and AIDS Clinical Trials Group. New England Journal of Medicine, 337, 15–21.**
376. **Van der Knaap MS, Valk J, Jansen GH, Kappelle LJ, Van Nieuwenhuizen O. (1993); Mycotic encephalitis: predilection for grey matter. Neuroradiology; 35:567–572**
377. **Van Dyk A (1988) CT of intracranial tuberculomas with special reference to the “target sign”; Neuroradiology ;30:329**
378. **Van Lieshout L, Polderman AM, Deelder AM.(2000); Immunodiagnosis of schistosomiasis by determination of the circulating antigens CAA and CCA, in particular in individuals with recent or light infections; Acta Trop; 77:64-80.**
379. **Vasconcelos, D. (1990). Del quiste al granuloma cisticercoso mediante tomografia craneal computarizada. Gac. Med. Mex. 126:401-404.**
380. **Vassallo R., J. H. Ryu, T. V. Colby, T. Hartman, and A. H. Limper (2000). Pulmonary Langerhans'-Cell Histiocytosis; N. Engl. J. Med.; 342(26): 1969 - 1978.**
381. **Vengsarkar US, Pisipati RP, Parekh B, Panchal VG, Shetty MN (1986) Intracranial tuberculoma and CT scan; J Neurosurg ;64:568–74**
382. **Vidyasagar C, Murthy HKRS (1994) Management of tuberculosis of the spine with neurological complications; Ann J Coll Surg Engl;76:80–4.**
383. **Villora MF, Fortea F, Moreno S et al (1995) MR Imaging and CT of central nervous system tuberculosis in the patient with AIDS; Radiol Clin North Am; 33: 805–20**
384. **Vincent Dousset (2005). Viral and Non-viral infections in immunocompetent and immunocompromised patients; In: Mr Imaging In White Matter Diseases Of The Brain And Spinal Cord; M Filippi; Springer Publication; P 408.**
385. **Vital C, Aubertin J, Ragnault JM (1982).: Sarcoidosis of the peripheral nerve: A histologic and ultrastructural study of two cases; Acta Neuropathol (Berl); 58:111-114.**
386. **Wadia NH (1973) Radiculomyelopathy associated with spinal meningitis (arachnoiditis) with special reference to spinal tuberculous variety; In: Spillane JD, ed, Tropical neurology; London: Oxford University Press; pp 63–72.**
387. **Wagle N, Vaidya A, Joshi S et al (1990) Detection of tubercle antigen in cerebrospinal fluids of ELISA for diagnosis of tuberculous meningitis; Indian J Pediatr; 57: 679–83**
388. **Waldorf, A. R. (1989);. Pulmonary defense mechanisms against opportunistic fungal pathogens; Immunol. Ser.; 47:243-271.**

389. Waldorf, A. R., N. Ruderman, and R. D. Diamond (1984); Specific susceptibility to mucormycosis in murine diabetes and bronchoalveolar macrophage defense against *Rhizopus*; *J. Clin. Investig*; 74:150-160.
390. Wallace RC, Burton EM, Barrett FF, Leggiadro RJ, Gerald BE, Lasater OE (1991) Intracranial tuberculosis in children: CT appearance and clinical outcome; *Pediatr Radiol* ;21:241–6.
391. Walsh TJ, Hier DB, Caplan LR. (1985); Aspergillosis of the central nervous system: clinicopathological analysis of 17 patients. *Ann Neurol*; 18:574–582
392. Watt C, Adapon B, Long GW, et al.(1986) Praziquantel in treatment of cerebral schistosomiasis. *Lancet*:529-532.
393. Waxman JS, Sher JH (1979). The spectrum of central nervous system sarcoidosis: A clinical and pathologic study; *Mt Sinai j Med*; 46:309-317.
394. White, A. C., Jr., P. Robinson, and R. Kuhn. (1997). *Taenia solium* cysticercosis: host-parasite interactions and the immune response. *Chem. Immunol.* 66:209-230.
395. Whitener DR (1978) Tuberculous brain abscess; Report of a case and review of the literature; *Arch Neurol*; 35: 148
396. Wilms G, Lammens M, Dom R, et al. (1992); MR imaging of intracranial aspergilloma extending from the sphenoid sinus in an immunocompromised patient with multiple myeloma. *J Belge Radiol*;75:29–32
397. Wilson M, Bryan R T, Fried J A, Et al (1991); Clinical evaluation of the cysticercosis enzyme-linked immunoelectrotransfer blot in patients with neurocysticercosis; *J Infect Dis*; 164:1007-1009.
398. Witeman MLH, Bowen BC, Post JD, et al (1996). Intracranial infection. In Atlas SW (ed). *Magnetic Resonance Imaging of the Brain and Spine*, ed 2. Philadelphia, Lippincott-Raven; 707-772
399. Wong B, Gold JW, Brown AE, et al (1984). Central-nervous-system toxoplasmosis in homosexual men and parenteral drug abusers. *Ann Intern Med* ;100:36-42.
400. Wood M and Anderson M (1998) Chronic meningitis; In: *Neurological infections; major problems in Neurology*, vol 16. Philadelphia: WB Saunders; pp 169–248.
401. Wyne LG (1985) The atypical mycobacteria: recognition and disease association; *Crit Rev Microbiol*; 12: 185–92
402. Wyser CP, van Schalkwyk EM, Alheit B (1997). Treatment of progressive pulmonary sarcoidosis with cyclosporine A: A randomized controlled trial; *Am J Respir Crit Care Med*; 1556:1371-1376.
403. Young RF, Gade G, Grinnell V.(1985); Surgical treatment for fungal infections in the central nervous system. *J Neurosurg* 63:371-81.
404. Yuh WTC, Nguyen HD, Gao F, et al.(1994); Brain parenchymal infection in bone marrow

transplantation patients: CT and MR findings. AJR Am J Roentgenol;162:425–430

405. **Zajicek JP (2000). Neurosarcoidosis; Curr Opin Neurol; 13:323-325**
406. **Zajicek J. P., N.J. Scolding, O. Foster, M. Rovaris, J. Evanson, I.F. Moseley, J.W. Scadding, E.J. Thompson, V. Chamoun, D.H. Miller, W.I. McDonald and D. Mitchell (1999); Central nervous system sarcoidosis—diagnosis and management; Q J Med; 92: 103-117**
407. **Zee C S, Go J L, Kim P E, et al (2000); Imaging of neurocysticercosis; Neuroimaging Clin N Am; 10:391-407.**
408. **Zheng L, Okabe S, Hino K, et al (1996). Intracranial fungal granuloma with CSF space dissemination: A case report. No Shinkei Geka 24:389-392.**
409. **Zuger A, Lowry RD (1997) Tuberculosis; In: Scheld WM, Whitley RJ, Durack DT, editors; Infections of the central nervous system, 2nd edition; Philadelphia: Lippincott-Raven Press; 417–43**
410. **Zulma A and James DG (1996). Granulomatous infections: etiology and classification. Clin Infect Dis; 23: 146–158.**
411. **Zylberberg F, Méary E, Cérez D, Meder JF, Frédy D (2001). Aspects en irm de la sarcoïdose du système nerveux central; Journal de radiologie; 82: 623-631.**

This thesis was supervised by professor Yasser Metwally

Visit my web site at:<http://yassermetwally.com>

Master degree thesis prepared by Dr Sherif Aly, resident in the neuropsychiatry department, Ain shams university school of medicine, supervised by Professor Yasser metwally, Dr. Azza abdel nasser, assistant professor of neurology Ain shams university school of medicine and Dr lobna Elnabil, lecturer in neurology Ain shams university school of medicine