

**Infections diseases of the central nervous system**

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In spite of the great advances in diagnostic imaging as well as in therapeutic availabilities, CNS infections have not decreased their present morbi-mortality.

The incidence and characteristics of infectious processes that can affect CNS are very different when we consider those processes in developed or undeveloped countries, when we analyse them from the geographical point of view or as regard to the different periods of life.

Many factors are responsible for this different distribution and persistence of CNS infections.

1. - In the last two decades the increasing incidence of AIDS was under the major scope of CNS infections and hopefully nowadays is much better under control.
2. - The present aggressive and different treatments that induce an immunodepressed state are responsible of many CNS infections.
3. - Many viral infections with a not very effective treatment are involved in CNS infections
4. - The expansion of infections is made easier by the large movement of populations.

CNS has a limited mechanism of defence represented by skull, meninges and BBB their involvement and failure is the first step in CNS involvement.

Present imaging studies, mainly CT and MR, allow a close and prompt diagnosis.

**Learning objectives**

To offer a large overview about the present different infectious processes involving CNS.

To learn the different neuradiological patterns and differential diagnosis of this infectious processes

To emphasise the progressive replacement of advanced MRI over TC as the method of choice in the approach of CNS infections.

**CNS INFECTIONS**

Unfortunately CNS infections still represents a significative group of processes with a quite severe dysfunction's in the follow-up of affected patients.

Several ways to present and describe CNS infections from the neuroradiological point of view:

Clinical point of view, like neurologist, talking about fever, headache, neck stiffness, and loss of neurological functions or CSF findings.

Physio-Pathological aspects of CNS infections, explaining meningeal changes, the abscess process formation, encephalitis or mechanisms of demyelinated processes in AIDS.

The morphological point of view showing different meningeal thickenings and contrast uptakes, describing round masses, granulomatous processes or focal and diffuse white matter diseases.

And other way to explain this topic would be Causal:

Traumatic infections

Surgical infections

Pediatric infections

AIDS related infections

Facial and petrous infections

In my opinion all the aspects are important and helpful in the management of CNS infections. For all of that I insist on how important is the clinical and phisio-pathological knowledge of CNS infections and diseases.

For academic and didactic purposes we classify CNS infections into:

- Brains Abscess
- Meningitis and Ventriculitis
- Encephalitis
- Parasitosis

## **MENINGITIS AND VENTRICULITIS. IMAGING**

Inflammatory process of the dura matter, leptomeninges (pia and arachnoides) and CSF within the subarachnoid space.

Meningoencephalitis represents an extension to the brain parenchyma.

Ventriculitis represents an extension to ventricular ependyma.

Meningitis needs a prompt diagnosis and specific treatment. Is an emergency because untreated patients have a fatal outcome.

### 1. - Normal meninges and extra-axial spaces

Duramatter (pachymeninx): two layers:

Outer or periosteal. Highly vascularized, of not true meningeal origin ending at the foramen magnum.

Inner layer, embryologically derived from the meninx and continuous with the spinal duramatter. Some reflections forms the falx cerebri, falx cerebelli and tentorium cerebelli.

Leptomeninges (arachnoid and piamatter)

The arachnoid is applied to the inner dura and the piamatter covers the brain.

### 2. - Clinical and pathophysiological features

Signs and symptoms are fever, nuchal rigidity as well as neurological signs and symptoms related to stage of the illness, organism, age, state of previous health.

There are four routes of entry infectious agents into the CNS

Hematogeneous spread (arterial or venous) the most frequent

Direct implantation: traumatic, lumbar puncture or surgery

Local extension (air sinuses)

Along the peripheral nervous system. Viruses: rabies and herpes simplex.

The most important pathogens:

#### a) Acute Bacterial Meningitis

Streptococcus pneumoniae	47%	
Neisseria meningitides	25%	59% in patients 19 years and older
Haemophilus influenzae B	7%	(part of human microflora)
Listeria monocytogenes	8%	
Streptococcus group B	12%	45% in infants below 2 years

Meningococcal meningitides (13 different serogroups)

Tbc

#### b) Viral meningitis

Aseptic meningitis syndrome. LCR with pleocytosis with lymphocitic predominance.

Nonpolio enteroviruses

Mumps (the most common cause of aseptic meningitis)

Arboviruses (Encephalitis)

Herpes viruses (Encephalitis)



mainly at the level of the arachnoid villi

B- Extra-axial fluid and pus collections.

Subdural effusion and hygroma

They are sterile collections secondary to irritation of the dura or veins inflammation with an increase of proteins and fluid in the subdural space.

Easily detected by imaging. No treatment. Spontaneously resolved.

Subdural Empyema

13-20% of intracranial infections. Bacterial and fungal infections of the calvaria and paranasal sinuses can produce and Empyema. The mechanism is a thrombophlebitis via the calvarial emissary veins.

They are extra axial collections slightly hiperdense than CSF with a rim of contrast enhancement (inflammatory membranes). Possibility of thrombophlebitis of bridging veins and cerebral infarctions.

Epidural empyema

c. - Cerebritis and parenchymal abscess formation

Spread from contiguous infections of the meninges by retrograde thrombophlebitis or direct extension into the brain via de pia matter or along the penetrating perivascular spaces: early phase of abscess formation.

d. - Abscess formation

e. - Central nervous system infarction

Secondary to inflammatory arterial spasm, o inflammatory infections of the arterial walls: arteritis. Sometimes is difficult to differential infarction secondary to vascular involvement or focal brain encephalitis. (MRA useful).

6. - VENTRICULITIS

Serious infectious process involving the cerebral ependyma secondary to meningitis, rupture of a parenchymal abscess, surgery, catheter placement.

Imaging:

Some degree of ventriculomegalia

Subtle areas of periventricular low density

Enhancement along ventricular walls

IN chronic stages periventricular calcifications may be seen especially in perinatal ventriculitis especially in the so-called TORCH infection:

Toxoplasma

Other (syphilis, HIV)

Rubella

Cytomegalovirus

Herpesvirus

7. - Acute aseptic (viral) meningitis

Clinical syndrome with lymphocitic pleocytosis in the LCR

8. - Cytomegalovirus (CMV)

Is a ubiquitous DNA virus belonging to the herpesvirus family. Severe neurological dysfunction.

The hallmark in periventricular calcifications detected by CT. CMV has special affinity for the metabolically active neuroblasts of the subependymal matrix and regional vasculature with a result of subependymal degeneration and calcification.

9. - Fungal Meningitis

a) Criptococcus neoformans

The most frequent fungus that enters the body via the respiratory tract, then spread hematogeneously from the lungs to the CNS.

Primary manifested as meningitis, although parenchymal mass lesions can also develop.

Highly prevalent in AIDS.

Imaging:

Meningitis with cystically dilated perivascular spaces filled with mucoid material as a response to the immune system (gelatinous pseudocysts) and parenchymal cryptococcomas formation.

#### 10. Parasitic Meningitis

Cysticercosis (*taenia solium*)

Ingestion of eggs in contaminated water or food.

In the CNS Neurocysticercosis may be parenchymal, leptomeningeal or intraventricular.

When the scolex lodges in the brain develops a cystic covering around it with a first inflammatory parenchymal reaction with a granulation and connective capsule formation.

When the larva dies a secondary inflammation and posterior calcification

#### 11. - Toxoplasmosis (TORCH group).

*Toxoplasma gondii*

Congenital: meningitis, chorioretinitis, hydrocephalus and intracranial calcifications.

#### 12. - Non-infectious meningitis

Neoplastic meningitis

Sarcoidosis

Chemical meningitis

Cranial hypotension

Postsurgical states

ENCEPHALITIS. CEREBRITIS. BRAIN ABSCESS.

Encephalitis

Generalised and diffuse infection of the brain. Often as a result of a viral infection due to prevention and treatment of bacterial diseases, increase of immunosuppressed patients (like AIDS) and in the course of transplant and cancer patients.

Different types according to the site and tempo of infections.

Viruses can lead to:

Meningitis

Acute infective encephalitis

Acute disseminated encephalomyelitis

Subacute or chronic encephalitis

Encephalitis and myelitis

Herpes simplex encephalitis (type 2 predominantly in temporal lobe)

Enteroviruses and arboviruses encephalitis

Mechanism of CNS viral infection

Infections of the CNS by viruses begin with the local growth of virus in nonneural tissue. Spread of viruses to the CNS primarily occurs by the Hematogeneous or neural route.

Most of them gains access through the bloodstream (viremia).

The viruses protect themselves against the reticuloendothelial system (RES) entering and growing in lymphocytes (measles and mumps). HIViruses enter mononuclear cells that carry the CD4 antigen. Poliovirus infects and grows in the lymphoid tissue of the gut. Arboviruses grow in the spleen and lymph nodes.

From there viruses gain the CNS through perivascular spaces traversing the endothelium by pinocytosis or growing into the endothelial cells. Entrance in the CSF is through the epithelial cells of the choroid plexus.

Once in the CNS two major factors affect the general pathologic features:

The cell type infected (different susceptibility): specific viral receptors.  
The host's immune response  
The tempo leads to a varied appearance of CNS viral infections

#### a) Cells susceptibility

Coxsackie, echovirus and mumps rarely infect neurons but frequently meninges.  
Poliovirus infects neurons (motoneurons) leaving sensory pathways untouched.  
Rabies infects neurons and much less oligodendrocytes  
Herpesvirus infects neuron and glial cells: predilection for cell population in limbic system.  
JC virus attacks only oligodendrocytes leading to demyelination

#### Host immune response

Humoral response against the virus

Acquired antibody after previous infections or vaccination. Local infections is quelled (sofocada) by IgA in the respiratory tract, tears, saliva or gut. IgA or IgM restricts blood-borne dissemination. Antibodies in tissue spaces prevent spread of infection between cells.  
Cell-mediated response directed against the infected cell

#### Pathological features

Macroscopic: meningeal opacity, vascular congestion and brain swelling.  
Microscopically: infiltration of brain by inflammatory cells.

Early on by polymorphonuclear cells

Later on by lymphocytes, plasma cells and large mononuclear cells. Perivascular cuffing of mononuclear cells in the Virchow-Robin spaces in small venules and thicker cuffs of lymphocytes around larger vessels are characteristic.

Microscopic response of host cells: hypertrophy and proliferation of microglial cells (mainly in the cortex and deep grey matter), astrocytosis present when necrosis has occurred), neuronal changes (the result of terminal hypoxia or brain swelling. Cytoplasm vacuolation specific of the spongiform encephalopathy) and presence of inclusion bodies (specific of viral infection)

## ACUTE INFECTIVE ENCEPHALITIS

Brain damage is the result of viral intracellular growth and the host's inflammatory response.

Most common: herpes, rabies, arthropos-borne viruses and enteroviruses (polio).

Brain necrosis is frequent either selective or complete brain infarction.

Herpes viruses: simplex type 1 and 2 (HSV-1, HSV-2), CMV, Epstein-Barr V., varicella-zoster v., B virus, herpesvirus 6 and 7.

Perivascular cuffing and inflammatory infiltrates are key features. Necrosis present in the more aggressive.

HSV-1 is the cause of 95% of all herpetic encephalitis

Necrosis of temporal and Occ-frontal lobes. Less frequent in insula, occipital and cingulate gyrus. Putamen frequently spared. Trigeminal ganglion is the site of viral reactivation o a latent infection with spread along his branches. Biopsy is not needed because imaging is quite specific and the non-toxic treatment with acyclovir.

Imaging HSV-1. Uptake of technetium pertechnetate in various regions mainly in temporal lobe positive in 85% of cases.

CT: hypodensity in 75% of cases present in the first 2-3 days. Hemorrhage frequent and highly suggestive but sometimes difficult to be seen by CT.

MR study of choice. Temporal and inferior frontal lobes involvement. Basal ganglia spared. Often bilateral involvement. Gyriiform enhancement.

## **ACUTE DISSEMINATED ENCEPHALOMYELITIS (ADEM)**

5 days-2 weeks after viral illness or a vaccination. Headache, fever and drowsiness and focal neurological deficits.

Pervious demyelination is the hallmark of ADEM with a probably immunologic mechanism.

MR study of choice. Scattered plaques throughout the white matter of cerebellar and cerebral

hemispheres. No mass effect. Contrast enhancement very variable. Differential diagnosis with ME.

High-dose of steroids is the treatment.

## **SUBACUTE ENCEPHALITIS**

Includes:

Subacute Sclerosing panencephalitis (measles virus)

Progressive Multifocal Leukoencephalopathy (PML). JC-virus

HIC encephalitis

Tropical Spastic paraparesis (HTLV-1)

CMV encephalitis

Creutzfeldt-Jakob disease (proteinaceous particle: the prone)

All of them have and a relatively insidious onset.

Creutzfeldt-Jakob disease (proteinaceous particle: the prion)

Human spongiform encephalopathy as a result of infection by a slow unconventional virus. The infective prion is a proteinaceous infectious particle that resists activation by procedures that modify nucleic acids. They contain little or no nucleic acid and do not evoke an immune response.

1/1m. Dementia. Poor prognosis.

Brain atrophy non-specific. Pathologic changes: neuronal loss, reactive astrocytosis, neuronal vacuolation with spongiform changes.

MR: to exclude treatable lesions. Hypersignal T2 in the corpus striatum (frequent). Cortical hyperintensities have been described. Atrophy with rapid progression. MRE, decreased NAA/Cr. PET: decreased perfusion and hypometabolism.

## **CEREBRITIS AND ABSCESS**

Decline in the incidence and mortality (14%) thanks to the efficient use of antibiotics.

Source of infection: local or blood-borne. The first related to trauma or petrous and sinus infections.

The second related to infections in the respiratory tract and in immunocompromised patients. 25% of brain abscess have an unknown origin.

Abscess formation follows different stages described by Enzmann: 1) Early cerebritis 2) late cerebritis 3) early capsule formation 4) late capsule formation. The abscess is preceded by focal cerebritis with endothelium swelling of the local capillaries and migration of polymorphs, perivascular infiltration, focal oedema, and petechial hemorrhage displayed on MRI as a focal area of unspecific edema.

Progression to abscess occurs when a central zone of necrosis becomes better defined and liquefied with a peripheral collagen capsule. The collagen capsule is usually less well developed on the ventricular side likely related to differences in blood supply a weak point for daughter abscess formation.

Abscesses from Hematogeneous origin are mainly located at the grey-white matter junction.

MR imaging features of brain abscesses display the capsule as an iso to slightly hyperintense signal on T1 and hypointense on T2 probably due to the presence of paramagnetic free radicals. The capsule enhances with gadolinium. The centre of a mature abscess with necrotic material, displays on T1 a low signal higher than CSF and high signal on T2 similar to CSF or perilesional vasogenic edema.

Thallium-201 scanning may be useful in differentiating an abscess from a necrotic tumour because there is preferential uptake of thallium by tumors particularly of those of higher grade. (Not clear).

Differential diagnosis:

- Primary brain tumors
- Metastasis
- Septic and aseptic infarction
- Resolving hematoma
- Thrombosed aneurysms
- Arterio-venous malformations
- Tumefactive MS
- Lymphoma

### **MRE**

Abscess cavity with a lack of normal metabolites often contains amino acids and lactate, succinate and acetate that are not present in necrotic tumors.

### **CNS TUBERCULOSIS**

Incidence variable in different countries and population.

1.5/10<sup>5</sup>/year.

Hematogenous spread with small subpial or subependymal cortical focus of infection (Rich focus).

When such a focus ruptures it contaminates the subarachnoid spaces and cerebrospinal fluid and spreads along the cerebrospinal fluid pathways giving rise to tuberculous meningitis. Other manifestations are:

- Tuberculomas
- Tuberculous abscess
- Tuberculous cerebritis
- Pachymeningitis
- Spinal arachnoiditis
- Intraspinal tuberculoma

### **TBC meningitis**

Proliferative arachnoiditis and meningeal exudate predominantly in interpeduncular and pontomesencephalic cisterns progressively impeding CSF circulation (communicating hydrocephalus) and arteries and veins may become involved (vasculitis).

CT and MR imaging, obliteration of basal cisterns and contrast enhancement of basal meninges.

Hydrocephalus present in more than 50% of cases

Vasculitis by direct invasion of vessel wall may lead to spasm and thrombosis with hemorrhagic infarction mainly at the basal ganglia present in more than 25% of cases.

Granulomatous tuberculous meningitis is uncommon with diffuse or circumscribed granulomas in the basal cisterns.

A more diffuse chronic leptomenigeal infection is called leptomeningitis.

Parenchymal tuberculomas are thought to be secondary to an infective focus elsewhere in the body. They can be single or multiple, small or large and can be located anywhere in the cerebrum, brainstem and posterior fossa. Two forms a) noncaseating granulomas with or without contrast enhancement and only abnormal signal on MR or b) Caseating granuloma with a typical ring-enhancing lesion. A target sign with presence of central calcification in a hypodense center of a ring enhancing lesion is characteristic but not pathognomonic.

### **Rickettsiosis**

Gram-negative nonmotile bacteria

a) Rocky Mountain Spotted fever

*Rickettsia rickettsii* spreads hematogenously producing vasculitis with damage to the endothelial blood vessel walls of any organ. Cutaneous rash (palms, soles and anterior aspects of distal extremities) and myalgias.

Brain lesions: perivascular accumulations of mononuclear cells (typhus nodule) with arterial infarction, cerebral edema and diffuse meningeal enhancement.

Epidemic typhus (*R. prowazekii*). Involves the endothelial cells of blood vessels.

Q fever (*Coxiella burnetii*)

Spirochetes (gram-negative organisms)

Syphilis

Lyme Disease (*Borrelia burgdorferi*)

Leptospirosis

## PARASITES

Cerebral malaria

Toxoplasmosis *gondii*

Amebiasis

Neurocysticercosis

Amebiasis (*Entamoeba histolytica*). Fecal-oral transmission. Reproduction in the colon.

Hematogenous dissemination can reach the CNS.

Brain abscesses caused by *E. histolytica* are similar to those produced by bacteria, tuberculosis, nocardia with an hypodense central zone, a ring-enhanced capsule and marked surrounding edema.

Schistosomiasis

More than 200 million in Asia, tropics and subtropical areas.

*Schistosoma haematobium*, *japonicum* and *mansoni*.

Infected water. Skin of humans. Systemic veins and lymphatics and maturation of the larvae in the liver.

Brain imaging shows homogeneous or heterogeneous lesions with contrast enhancement and edema.

No specific signs.

Toxoplasmosis. *Toxoplasma gondii*.

Intrauterine infection: chorioretinitis, encephalomyelitis, hydrocephalus and microcephaly.

AIDS. 28% of patients have toxoplasmosis.

Lesions typically located in the corticomedullary junction and in the basal ganglia.

CT and MR are useful for diagnosis and follow-up. Lesions display typical pattern of an abscess.

The enhancement of the capsule is in relation to the immunity capacity of inflammatory reaction.

Hyperintense masses on T2 represent areas of necrotizing encephalitis in early toxoplasmosis and the isointense masses, seen after treatment, probably represent organizing abscesses.

Rapid response to treatment (12-15 days) confirms the diagnosis of toxoplasmosis and failure to respond to antibiotic treatment suggests another diagnosis. It is frequent that two different disease processes may be occurring simultaneously.

In AIDS differential diagnosis is between toxoplasmosis and lymphoma

Toxoplasmosis Lymphoma CT Hyperdense noncontrast CT

Subependymal spread SPECT

PETNO increased uptake Hypermetabolism, resulting in increased tracer activity MRE Increased lipid and lactate peaks and a decreased in other metabolites Mild-moderate increase in lipid and lactate but a large increase in choline peaks.

Hydatidic disease

*Echinococcus granulosus* and *E. multilocularis*. Dog and carnivore is the definite host (intestinal).

Eggs excreted and eaten by grazing animals and embryo released and through bowel wall go into the portal venous or lymphatic system. Liver the embryo matures into a cyst.

Cerebral hydatidic cyst usually unilocular. CT shows a well-defined, smooth, thin-walled, homogeneous cystic lesions similar in density to CSF. Capsule is difficult to be seen an enhancement in uncommon. Edema rare. With MR the capsule is better seen.

## Cysticercosis

Wide variety of neurologic syndromes induced by CNS infestation of cysticerci, the larva of *Taenia Solium*.

Endemic in many areas (South America, Africa, Asia, East Europe).

The CNS is involved in 60-90% of patients with cysticercosis.

Parenchymal lesions of 10mm or less. Central hemisphere and basal ganglia.

Subarachnoid lesions: cortical sulci, basal cisterns, intraventricular.

Imaging Escobar's Stages

1.- Vesicular stage: the larva is seen as a small marginal nodule into a small cyst containing clear fluid. The parasite may remain in this stage for years. No contrast enhancement.

2.- Colloidal vesicular stage. The larva begins to degenerate as a result of host's immune response. Scolex shows signs of hyaline degeneration and gradual shrinkage. Fluid becomes turbid and the capsule thicker. Surrounding edema. Contrast enhancement and hyperdense contents.

3.- Granular nodule stage. Capsule thickens and scolex mineralise. Edema regresses.

4.- Nodular calcified stage. Lesion completely mineralized.. No edema.

## FUNGAL INFECTIONS

*Cryptococcus neoformans*

Coccidioidomycosis

Histoplasmosis

Blastomycosis

Candidiasis

Aspergillosis

Mucormycosis

With the advent of immunosuppressive therapy in organ transplant patients and HIV disease fungal infections has become less rare.

Fungi may exist as single cells (yeast) or in colonies (hyphal form) and may coalesce and form micelia.

Hematogenous spread.

Yeast forms: blastomyces, *Candida*, *Coccidioides*, *Cryptococcus*, *histoplasma* and *torulopsis*.

Hyphal forms: *Aspergillus*, *mucormycosis*, *pseudallescheria*.

### Aspergillosis

Aspergillomas are close to the paranasal sinuses, and display abscesses not specific from other causes. 50% cases associated hemorrhage

Low density due to the presence of calcium, magnesium, manganese and iron and decreased signal intensity on T2w.

### Mucormycosis

Diabetes high risk.

The triad of diabetic ketoacidosis, meningoencephalitis and naso-orbital infection highly suggest the diagnosis of mucormycosis.

Other risk factors: metabolic acidosis: sepsis, severe dehydration, chronic renal failure.

Propensity for vascular structures: arteritis, ischemic changes, hemorrhagic infarcts and aneurysm formations.

Histoplasmosis.

Candidiasis

Coccidioidomycosis

Cryptococcal infection: the most common in AIDS patients. Meningitis producing hydrocephalus.

Nonenhancing lesions in the basal ganglia filling the Virchow-Robin spaces produced by mucoid

material.

CNS infections in Pediatric population.

Intrauterine and neonatal: malformations

Infants: destructive lesions

Congenital are infections transmitted from the mother. Neonatal the first 4 weeks of life. The immune system is not fully developed. TORCH infections.