In infections diseases of the central nervous system

Jordi Ruscalleda,
Professor and Director, Servicio de Radiologia-Neuroradiologia,
Hospital de la Santa Creu I Sant Pau,
President –Elect of the E.S.N.R.
Barcelona, SPAIN

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 demielinated 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 physio-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)
HIV
Adenoviruses (infants)
Polioviruses types 1,2,3

Meningitis are classified according to inflammatory exudate, CSF exam and clinical evolution.
Acute piogenic (bacterial)
Aseptic (viral)
Chronic (parasitic and fungi)

3. - Role of imaging
The first purpose of CT or MRI is to detect possible complications of meningitis: Hydrocephalus and infarction.
Gd Contrast enhancement is positive in 55-70% of infectious cases but insensitive in viral meningitis.

4. - Bacterial meningitis
Acute bacterial (pyogenic) meningitis
Microorganism
- Neonates: escherichia coli and group B streptococci
- Infants, children: Haemophilus influenzae (basal)
- Adolescents: Neisseria meningitides 80% convexity
- Elderly: Streptococcus neumoniae. Lysteria monocytogenes
- Immunocompromised: klepsiella.
  Anaerobic agents. (Ventriculitis)
  Fungi.(Meningoencephalitis)

CSF cloudy or purulent. Meningeal vessels engorged.
Involvement of superficial arteries and veins, responsible of thrombosis and infarction.
Two patterns of contrast enhancement
  Dural enhancement: follows the inner contour of the calvaria
  Pia-subarachnoid enhancement: extends into the depths of the cerebral and cerebellar sulci and fissures.
Differential diagnosis with neoplastic subarachnoid dissemination (carcinomatosis), more irregular and nodular enhancement.

b. - Tbc Meningitis
Tbc is rising in the last two decades. 2-5% of patients with peripheral tbc have CNS tbc and in 10% of AIDS-related patients.
Pattern: diffuse meningoencephalitis with a predominant characteristic of leptomeningeal opacification and thick gelatinous infiltrates in the basal cisterns, sometimes with subarachnoid granulomas and blood vessels involvement (spasm, arteritis, and thrombosis).
Mechanisms of CNS infection:
  Rupture of subependymal or subpial granuloma into de CSF.
  Hematogeneous spread to the meningeal vessels.

c. - Neurosyphilis.
Basal predominance with obliterative endoarteritis.

d. - Neuroborreliosis (Lyme Disease)
Borrelia burgdorferi. Cranial nerve palsy, mild encephalopathy and polyneuropathy. Multiple unspecific foci of brain infarction or borrelia granulomas.

5. - Complications or manifestations of bacterial meningitis
a. - Hydrocephalus.
  Communicating hydrocephalus is the most frequent complication due to a leptomeningeal-ependymal fibrosis secondary to gelatinous exudates are the main cause and block of CSF resorption
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) Cryptococcus neoformans
      The most frequent fungus that enters the body via the respiratory tract, then spread hematogenously
      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 criptococcosas 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 de 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 reticuloendotelial 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
Coxackie, 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 demielination

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 pertechnenate 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.
Often bilateral involvement. Gyriform 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 Multiphocal Leucoencephalopathy (PML). JC-virus
HIC encephalitis
Tropical Spastic paraparesis (HTLV-1)
CMV encephalitis
Creutzfeldt-Jakob disease (proteinaceous particle: the prion)

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 astrocystosis, 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 ANS 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 sinusal 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.
1.5/10^5/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 leptomeningeal infection is called leptomeningitis.
Parenchymal tuberculomas is 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.

Ricketsiosis
Gram-negative nonmotile bacteria
  a) Rocky Monutain Spotted fever
    Ricketsia rickettsii spreads hematogenously producing vasculitis with damage to the endothelial blood vessels walls of any organ. Cutaneous rash (palms, soles and anterior aspects of distal extremities) and mialgias.
Brain lesions: perivascular accumulations of mononuclear cells (typhus nodule) with arterial infarction, cerebral edema and diffuse meningeal enhancement.
    Epidemic typhus (R. Prowazekii). Invades the endothelial cells of blood vessels.
Q fever (Coxiella burnetii)

Spirochetes (gram.negatives organisms)
- Syphillis
- Lyme Disease (borrelia burgdorferi)
- Leptospirosis

**PARASITES**
- Cerebral malaria
- Toxoplasmosisis gondii
- Amebiasis
- Neurocysticercosis

- Hematogeneous dissemination can reach the CNS.
- Brain abscesses caused by E. Histolytica are similar to those produced by bacteria, tuberculosis, nocardia with an hipodense central zone, a ring-enhanced capsule and marked surrounding edema.

Schistosomiasis
- More than 200 million in Asia, tropics and subtropic 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 ara 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 and abscess.
- The enhancement of the capsule is in relation to the immunity capacity of inflammatory reaction.
- Hyperintense masses on T2 represents areas of necrotizing encephalitis in early toxoplasmosis and the isointense masses, seen after treatment, probably represents organizing abscesses.
- Rapid response to treatment (12-15 days) confirms the diagnosis of toxoplasmosis and failure to respond to antibiotic treatment suggest another diagnosis. Is frequent that two different diseases may be occurring simultaneously.
- In AIDS differential diagnosis is between toxoplasmosis and lymphoma

Hydatidic disease
- Echinococcus granulosus and E. Multiloculares. Dog and carnivore is the definite host (intestinal).
- Eggs excreted and eaten by grazing animals and embrio released and through bowell wall go into the portal venous or lymphatic system. Liver the embrio 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.

Fungal Infections

Criptococcus neoformans
Coccidioidomycosis
Histoplasmosis
Blastomicosis
Candidiasis
Aspergillosis
Mucormycosis

With the advent of immunosuppressive therapy in organ transplant patients and HIV disease fungal infections have 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 aneurysms formations.
Histoplasmosis.
Candidiasis
Coccidioidomycosis
Cryptococcal infection: the most common in AIDS patients. Meningitis producing hydrocephalus.
Noenhncing lesions in the basal ganglia filling the Virchow-Robin spaces produced by mucoid
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.