MR imaging of adult acute infectious encephalitis

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IRM des encéphalites aiguës infectieuses de l'adulte

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Summary

Background. **-** Imaging is a key tool for the diagnosis of acute encephalitis. Brain CT scan must be urgently performed to rule out a brain lesion with mass effect that would contraindicate lumbar puncture. Brain MRI is less accessible than CT, but can provide crucial informations in patients with acute encephalitis.

Method. - We performed a literature review on PubMed on April 1, 2015, with the search terms “MRI” and “encephalitis”.

Results. – We first describe the various brain MRI abnormalities associated with each pathogen of acute encephalitis (HSV, VSV, other viral agents targeting immunocompromized patients or travelers; tuberculosis, listeriosis, other less frequent bacterial agents). Then, we identify specific patterns of brain MRI abnomalies that can suggest a particular pathogen. Limbic encephalitis is highly suggestive of HSV; it also occurs less frequently in encephalitis due to HHSV6, Syphillis, Whipple disease and HIV primoinfection. Rhombencephalitis is suggestive of tuberculosis and listeriosis. Acute ischemic lesions can occur in patients with severe bacterial encephalitis, tuberculosis, VZV encephalitis, syphilis and fungal infections.

Conclusion. - Brain MRI plays a crucial role in the diagnosis of acute encephalitis: it detects brain signal changes that reinforce the clinical suspicion of encephalitis, especially when the causative agent is not identified by lumbar puncture; it can suggest a particular pathogen based on the pattern of brain abnormalities; it rules out important diffential diagnosis (vascular, tumoral or inflammatory causes).

Résumé

***Introduction.* –** L'imagerie cérébrale est essentielle au diagnostic d'encéphalite aiguë. Le scanner cérébral doit être réalisé en urgence afin d'exclure une lésion cérébrale avec effet de masse qui contre-indiquerait la ponction lombaire. L'IRM cérébrale est moins accessible que le scanner, mais peut apporter des informations importantes pour la prise en charge des patients ayant une encéphalite aiguë.

***Méthode.* –** Revue de la littérature sur PubMed le 1er avril 2015, avec les mots clés « IRM » et « encéphalite ».

Résultats. Nous décrivons tout d'abord les différentes anomalies IRM associées à chaque agent pathogène de l'encéphalite aiguë (HSV, VSV, autres virus ciblant les patients immunodéprimés ou voyageurs ; tuberculose, listériose et autres agents bactériens moins fréquents). Ensuite, nous identifions des patterns spécifiques d'anomalies IRM qui peuvent orienter vers un pathogène en particulier. L'encéphalite limbique est très évocatrice de l'HSV ; elle survient aussi moins fréquemment dans les encéphalites dues au HHSV6, à la syphilis, à la maladie de Whipple et à la primo-infection par le VIH. Une rhombencéphalite doit fait rechercher la tuberculose et la listériose. Des lésions ischémiques aiguës peuvent survenir chez des patients atteints d'encéphalite bactérienne grave, de tuberculose, d'encéphalite à VZV, de syphilis et d'infections fongiques.

Conclusion. – L'IRM cérébrale joue un rôle crucial dans le diagnostic des encéphalites aiguë : elle permet de détecter des anomalies de signal cérébrales qui renforcent la suspicion clinique d'encéphalite, en particulier lorsque l'agent causal n'est pas identifié par la ponction lombaire; elle peut suggérer un pathogène particulier en fonction du pattern des anomalies cérébrales ; elle permet d'éliminer des diagnostics différentiels importants (causes vasculaires, tumorales ou inflammatoires).

Introduction

Acute infectious encephalitis can be a life-threatening condition, and may sometimes be cured if an early and appropriate treatment is initiated. Acute infectious encephalitis is caused by a large number of pathogens [(1–3)]. Diagnosis is suspected on the basis of acute neurological symptoms and infectious signs, but it can be challenging in cases of atypical presentations. Brain imaging is crucial for the diagnosis of acute encephalitis. A brain CT scan must urgently be performed to rule out a brain lesion with mass effect that would contraindicate lumbar puncture. After lumbar puncture is performed, brain MRI is the modality of choice for acute encephalitis [(4)]. Brain MRI allows for detecting abnormalities suggestive of the diagnosis, and sometimes even suggestive of the pathogen; it also estimates the extent of brain damage, that will condition the prognosis; finally, it rules out important differential diagnoses, such as cerebral venous thrombosis, stroke, posterior reversible encephalopathy syndrome, or brain tumor [(1)]. In the present work, we reviewed the various MR findings in brain encephalitis using two successive and complementary approaches: we first reviewed the various MR abnormalities that can be associated with each pathogen, and we then reviewed the various pathogens that can be suspected for particular pattern of brain involvement on MRI.

Material and methods

We performed a PubMed search on April 1, 2015, using the search terms « MRI » and « encephalitis ». We retrieved 5,436 articles published between 1982 and 2015. We first reviewed the most recent 1,500 articles (i.e., from mid-2010 to 2015) to compile a list of pathogens involved in acute encephalitis and for which brain MRI studies were available. We then reviewed the articles that included the name of each pathogen. We excluded from this review the articles on differential diagnoses (paraneoplastic encephalitis, autoimmune or inflammatory encephalitis), those limited to neonate or children cases, those in which the infectious agent had not been formally identified, and those without MR imaging data. We also excluded non-original works (i.e., editorial, opinions). We also did not take into consideration articles focusing on HIV-related opportunistic infections, which are beyond the scope of our review. The final choice of articles and the references included are based on our judgment of their relevance to this subject.

Results

1. MRI findings in acute encephalitis: a pathogen-based approach

a. Viral encephalitis

1. Herpes simplex virus (HSV) encephalitis

HSV encephalitis (HSVE) is the most common cause of infectious encephalitis [(1)]; it is a severe condition with 10-20% case fatality and a high rate of sequelae [(5,6)]. Rapid diagnosis of HSVE is crucial, as delayed treatment is associated with poor outcome [(5)]. Delay in brain imaging has been reported as an independent factor for delayed treatment [(7)]. HSVE is predominantly caused by HSV type 1 in adults and by HSV type 2 in neonates. Recent studies have shown that brain MRI has a high sensitivity for the diagnosis of HSVE, showing brain abnormalities in 80 to 100% of cases [(1,6,8–10)]; however, a normal brain MRI does not rule out HSVE diagnosis. Patients suspected of having HSVE may initially have a negative PCR for HSV but suggestive lesions on brain MRI, thus reinforcing the diagnosis of HSVE [(6,9–11)]. HSVE typically affects the limbic system: most frequently the medial temporal lobes [(9)], but also the insular, cingulate and frontobasal cortex; lesions are unilateral in 64-68% of cases [(6)]. Brain MRI typically shows area of T2 and FLAIR hyperintensities involving both the cortex and the white matter; areas of contrast enhancement can also be present. Basal ganglia are usually spared, although a few cases of basal ganglia involvement have been reported in HSVE [(12,13)]. The frequent seizures associated with HSVE may also lead to reversible hyperintense FLAIR signal in the thalamus of patients [(14)]. Isolated brainstem involvement is rare [(15)]. Diffusion-weighted imaging (DWI) seems to be the most sensitive sequence for detecting HSV encephalitis at the acute phase, typically showing hyperintense lesions with restricted apparent diffusion coefficient (ADC) [(16–21)]. In the subacute phase of treated HSVE (>10 days), the ADC decreases and DWI seems less sensitive than T2 and FLAIR imaging for lesion depiction [(19,21,22)]. Severe presentations of HSVE show cortical and subcortical hemorrhagic necrosis, characterized by hypointense T2* signal and T1 hyperintense laminar necrosis. Lobar hematoma is rare [(23–26)]. Extensive lesions on MRI are associated with a poor prognosis [(6)].

2. Varicella-zoster virus (VZV) encephalitis

VZV encephalitis affects both immunocompetent and immunocompromised patients. Immunocompetent individuals primarily affected by VZV encephalitis are the children and the elderly [(27)]. VZV encephalitis occurs after zoster or varicella, although there is no evidence of cutaneous rash in about 30% of patients [(28)]. The typical presentation of VZV encephalitis is a vasculopathy causing ischemic infarction and arterial stenosis. It can be either unifocal or multifocal and can affect both large and small arteries (most frequently both) [(28)]. In cases with large artery involvement, brain MRI can show large ischemic lesions and arterial stenosis, with a frequent localization at the M1 segment of the middle cerebral artery, and at the termination of the carotid artery [(29)]. High-resolution MRI sequences dedicated to vessel wall imaging can show contrast enhancement within the arterial wall [(29–31)], which may or may not regress after treatment [(29)]. In cases with small artery involvement, brain MRI shows small ischemic lesions at the grey-white matter junction and in the deep territories, without evidence of arterial stenosis [(28,32)]. Less frequently, VZV vasculopathy can also present as subarachnoid and cerebral hemorrhage [(33,34)], aneurysms [(35,36)], and carotid artery dissection [(37)]. The exact sensitivity of brain MRI in VZV encephalitis is difficult to estimate as literature data is scarce, and because most studies report case patients who either did not have brain MRI systematically performed [(38)] or were selected on the basis of vasculopathy on MRI [(28)]. It should be emphasized that a negative angiogram does not rule out VZV vasculopathy, as arterial stenosis cannot be depicted when only small arteries are affected [(28)].

3. Viral encephalitis of the immunocompromised patient

HIV primary infection may present as acute encephalitis. Brain MRI is usually unremarkable [(39,40)], although there are a few case reports of HIV primary infections presenting as acute limbic encephalitis [(41,42)] or acute cerebral vasculitis with ischemia [(43)].

HHV6 is the causative agent of exanthema subitum. It can cause encephalopathy either during primary infection in children or during reactivation in immunocompromised patients, most frequently after allogeneic hematopoietic stem cell (AHSC) transplantation. These

reactivations are frequent; they occur in almost 40% of cases after AHSC transplantation, and cause acute encephalitis in only 6% of cases after AHSC transplantation [(44)]. Patients usually present with memory deficits, cognitive deficits, fever, and seizures [(45)]. Brain MRI shows hyperintense T2 and DWI lesions often limited to the mesial temporal lobes, that may reverse on follow-up imaging [(46)]. Enhancement and hemorrhagic necrosis is usually absent [(45)]. Early brain MRI may be normal [(45)].

CMV reactivation in immunocompromised patients manifests as acute ventriculitis. T2 hyperintensities and contrast enhancement are present along the wall of the ventricles [(47)], but may be difficult to depict; DWI may facilitate the detection of periventricular abnormalities, suggesting the diagnosis [(48)].

JC virus reactivation in immunocompromised patients causes progressive multifocal leukoencephalopathy (PML), a severe demyelinating disease of the brain. It mostly affects 1) AIDS patients 2) multiple sclerosis (MS) patients treated with natalizumab, a humanized monoclonal antibody against α4 integrin used in severe presentations of MS, but it can also occur in other causes of immunosuppression (after organ transplantation, bone marrow transplantation, leukemia) [(49)]. Clinical symptoms are not those of acute encephalitis: they include progressive neurological deficits and cognitive dysfunction, in the absence of systemic inflammatory signs [(49)]. Brain MRI typically shows subcortical white matter lesions with no or minimal mass effect, high signal on T2WI, very low signal on T1WI, no or minimal peripheral contrast enhancement, and a suggestive peripheral hyperintense ring on DWI [(50)].A punctate pattern of T2 hyperintensities, and the presence of SWI hypointensities within the adjacent grey matter, are suggestive of the diagnosis (51,52). MR spectroscopy in PML lesions shows increased choline and myo-inositol, decreased N-acetylaspartate (NAA), and presence of lactates [(53)].

BK virus is a rare cause of encephalitis in immunocompromised patients. It can be suspected when neurological symptoms are associated with urological manifestations [(54)]. Brain MRI may show limbic encephalitis [(55)] or diffuse T2 and DWI hyperintensities in the white matter, associated with restricted diffusion [(54)].

4. Viral encephalitis of the traveler

These various pathogens do not require the administration of a specific treatment; thus, an MRI diagnosis is not as crucial as for other types of viral encephalitis.

Eastern Europe

Tick-borne encephalitis is caused by a *flavivirus*. On brain MRI, lesions predominate within the basal ganglia and the cerebellum [(56)]. Reversible splenial lesions on DWI have been reported [(57)].

Tropical and subtropical areas

Dengue is the second cause of mosquito-borne disease in humans, after malaria. When symptomatic, dengue fever is associated with neurological features in 1 to 20% of cases [(58)]. Patients presenting with dengue encephalitis may have a normal brain MRI, or nonspecific changes such as edema and meningeal enhancement with variable pattern (either supratentorial, infratentorial, limbic, within the basal ganglia or the splenium of corpus callosum) [(58–62)]. Hemorrhages or microhemorrhages may occur [(62,63)]. Areas of DWI hyperintensities with restricted ADC can be present [(60)].

Chikungunya virus infection usually manifests as acute febrile arthralgia in patients who recently travelled to an area of outbreak. Chikungunya infection can also cause acute encephalitis; brain MRI is usually normal [(64)], except for a case report of multiple small stroke-like lesions in the white matter [(65)].

Asia

Japanese encephalitis is a mosquito-borne disease caused by a *flavivirus*. The MRI most frequently shows bilateral areas of high T2 intensity within the basal ganglia, thalamus, substantia nigra, and midbrain, but abnormalities can also be observed within the hippocampus and cortex [(66)]. Meningeal enhancement may be present [(67)]. Hemorrhages, however, are rare [(68)]. Reversible splenial lesions on DWI have been reported [(69)].

Nipah virus is transmitted to human by mammals, especially pigs, and causes outbreaks in Malaisia, Bangladesh and India(70). Brain MRI show small, multiple, corticosubcortical FLAIR-

hyperintense lesions, sometimes hyperintense on DWI, sometimes hemorrhagic with hypointensities on T2-weighted images and hyperintensities on T1-weighted images(71,72).

Australia

Hendra virus is transmitted to human by horses. Brain MRI shows multiple T2 and DWI hyperintensities with restricted ADC, predominating in cortical and subcortical areas; meningeal enhancement may occur [].

Murray Valley virus causes a mosquito-borne disease. Brain MRI shows bilateral T2 hyperintensity of the basal ganglia and thalamus, that can extend to the temporal lobe [(73)], midbrain, and cerebellum in severe presentations [(74)]. Meningeal enhancement may be present [(74)].

America / Caribbean

West Nile virus is a mosquito-borne disease caused by a *flavivirus*. Brain MRI may be normal [(75,76)] or demonstrate increased T2 signal intensity within the basal ganglia, the pons, the mesial temporal lobe, and the anterior horns or the spinal cord; leptomeningeal enhancement can also be present [(76–78)]. West Nile virus is endemic in the United States [(78)] and recent outbreaks have been reported in Europe [(79–81)].

Eastern equine encephalitis is a rare and severe mosquito-borne disease [(82)]. Brain MRI classically demonstrates symmetrical T2 hyperintensities which predominate in the basal ganglia and the thalamus [(82,83)], and may be enhanced with contrast agent injection [(82)].

5. Other less frequent ubiquitous viral pathogens

Influenza virus is a common pathogen that rarely causes encephalitis. Brain MRI may be normal or show non-specific changes within the cortex, white matter, basal ganglia, brain stem, and cerebellum. Patients present with acute necrotizing encephalopathy [(84–88)]. Reversible splenial lesions have been reported [(87,89)]. MRI findings do not appear to be strain-specific, as similar abnormalities have been observed during the recent H1N1 outbreak [(90–93)].

Hepatitis A virus may cause acute encephalitis. MRI findings occasionally show reversible splenial DWI hyperintensity with restricted diffusion in these patients [(94,95)]. Meningeal enhancement has also been reported [(96)].

Epstein-Barr virus (EBV) infection, or reactivation in immunocompromised patients, can cause acute encephalitis. Brain MRI can be normal [(97)], or demonstrate areas of T2 hyperintensities within the cortex and/or the basal ganglia and substantia nigra [(98–102)]. Areas of hyperintensities on DWI with restricted ADC may be present [(103)]. White matter reversible lesions [(104,105)] and hemorrhagic leukoencephalitis [(106)] have also been reported.

Subacute sclerosing panencephalitis is a rare and fatal complication occurring years after measles virus infection. Brain MRI usually shows multiple T2 hyperintensities in the white matter and grey matter of patients [(107,108)], with increased ADC [(109)]. Lesions may look like pseudotumors [(110,111)], or suggest an inflammatory demyelinating disease [(110,112)]. Limbic [(113)] or brainstem [(114)] involvement is also possible.

Rubella is a rare cause of encephalitis in adults. Reversible splenial lesions on DWI have been reported [(115)].

Mumps is a rare cause of encephalitis in adults. Reversible splenial lesions on DWI have been reported [(116,117)]. Claustrum hyperintense lesions [(118)] and deep necrotic lesions [(119)] have also been reported.

Rabies encephalitis is a fatal infectious disease, transmitted through bites by rabid animals. Rabies occurs in Africa and Asia, and has recently re-emerged in Southern Europe [(120)]. Brain MRI usually demonstrates symmetrical T2 hyperintensities within the grey matter nuclei of the basal ganglia, thalamus, midbrain, and pons [(121)].

b. Bacterial encephalitis

1. Tuberculosis

Tuberculosis (TB) is the 3rd cause of acute infectious encephalitis [(1,2)].

MRI findings evocative of cerebral TB comprise:

- **Basal meningitis**. Leptomeningitis can be depicted on MRI as spontaneously hyperintense leptomeningeal spaces on FLAIR sequence, enhancing after gadolinium injection on T1 and FLAIR sequences. TB leptomeningitis predominates in the basal cisterns and Sylvian fissures, but can later extend to the convexity [(122)]. Leptomeningeal enhancement can be associated with cranial nerve enhancement and citernal necrotic abcesses [(122)]. Pachymeningitis may also occur in TB, mimicking a meningioma [(123,124)].
- **Hydrocephalus.** Hydrocephalus during TB is most commonly non-communicating, caused by obstruction to CSF flow in the basal cisterns by inflammatory exudates. Obstructive hydrocephalus may also occur as a result of the mass effect of a tuberculoma or ventriculitis [(125)].
- **Vasculitis**. TB vasculitis is a consequence of the inflammatory changes of the leptomeninges of basal cisterns, which surround the arteries of the circle of Willis. Narrowing or occlusion of intracranial arteries is most frequently proximal (basilar artery with its perforant branches, internal carotid atery, proximal parts of the anterior, middle and posterior cerebral arteries with their perforant branches), and affects more frequently the anterior circulation [(126,127)]. They can be depicted on conventional angio-MRI (magnetic resonance angiography imaging) or angio-CT (computed tomography angiography). Acute infarcts are observed in 25-60% of patients presenting with CNS tuberculosis [(127,128)]; they are most frequently multiple and located within the deep territories of perforant branches.
- TB cerebritis may present as area of high T2 signal in the brain parenchyma, often adjacent to the areas of leptomeningeal enhancement [(122)]. In later stages, tuberculomas or abscesses can form in the parenchyma. They initially appear as solid-enhancing lesions, and later as ring-enhancing lesions with central necrosis. They may be caused either by a spread of TB from the leptomeningeal spaces to the

adjacent parenchyma via the perivascular spaces, or by a hematogenous spread in cases of miliary TB. High T1 signal and low T2 signal within the solid portions of tuberculomas are suggestive of TB, but non-specific (also observed in fungal infections, lymphoma, and tumors with a high CSF cell count). The presence of lipid peaks on spectroscopy in necrotic TB lesions is non-specific (also observed in metastasis, glioblastoma, pyogenic abscess).

However, a normal brain MRI does not rule out acute TB encephalitis. The authors of a recent prospective study of encephalitis observed that 55% (6/11) of patients presenting with acute TB encephalitis for whom brain MRI was available had normal MRI findings (no abnormality, or non-specific FLAIR hyperintensities in the parenchyma) [(129)]. This low sensitivity of brain MRI could probably be improved using appropriate sequences (contrast-enhanced FLAIR sequence for detecting subtle meningeal enhancement, DWI sequence and 3D time of flight (3DTOF) for detecting acute ischemia and arterial stenosis).

2. *Listeria monocytogenes*

Listeria monocytogenes is a Gram-positive intracellular bacterium that penetrates the intestinal, blood–brain, and fetoplacental barriers. It has a specific affinity for the central nervous system, especially in cell-mediated immunodeficient individuals [(130)]. It may present as acute meningitis and/or encephalitis. About half of the patients presenting with acute *Listeria* encephalitis have an underlying comorbidity (diabetes, chronic renal failure, alcoholism, cirrhosis, pregnancy, chemotherapy, or corticoid therapy) or underlying immunosuppression (hematologic malignancy, transplantation, HIV infection) [(131)]. Brain MRI is abnormal in 64% of neurological *Listeria* cases (either meningitis or encephalitis) [(131)]. In one-third of cases, brain MRI demonstrates rhombencephalitis, i.e. increased T2 signal and mass effect [(131–133)]. Parenchymal microabscesses or true abscesses may occur; they are most frequently located within the brainstem [(133)], but they can also be observed within the hemispheres [(134,135)]. Non-specific sign of meningitis may also be observed (i.e., hyperintense leptomeningeal spaces on FLAIR sequence, enhancing after gadolinium injection on T1 and FLAIR sequences). Hydrocephalus occurs in 20% of cases [(131)].

3. Other less common bacteria

Borrelia burgdorferi is the causal agent of Lyme disease, a multisystem disorder predominantly affecting the skin, but it may also involve the central nervous system. Neurological Lyme disease manifests as painful lymphocytic meningoradiculitis; encephalitis remains a rare complication [(136)]. Brain MRI may show leptomeningeal and cranial nerve enhancement.

Treponema pallidum is the causal agent of syphilis. Neurosyphilis has been reported to cause limbic encephalitis, with T2 and FLAIR hyperintensities within the mesiotemporal lobes, sometimes extending to the insula [(137–139)], mimicking HSV encephalitis. Acute ischemic lesions have also been reported.

Tropheryma whipplei is the causal agent of Whipple's disease. Neurological manifestations of Whipple's disease are rare complications that appear most frequently in patients whose treatment did not include antibiotics able to cross the blood-brain barrier [(140)]. Brain MRI can demonstrate hyperintense T2 lesions within the medial temporal lobes, hypothalamus, and pons [(141–143)].

Bartonella henselae is the causal agent of cat scratch disease (CSD). CSD typically presents in children and young adults as febrile lymphadenitis 1 to 3 weeks after scratch, bite, or lick from a cat [(144)]. Acute encephalopathy occurs in up to 3% of all CSD cases [(145,146)]. Seizures are frequent and sometimes severe, and many reported brain MRI abnormalities (cortical and thalamic T2 hyperintensities, meningeal enhancement) could have been induced by repeated seizures [(147,148)]. Non-enhancing corticosubcortical nodular lesions [(149)] and pachymeningeal enhancing mass [(150)] have been reported, both with complete regression after antibiotic treatment.

Salmonella infections are frequently associated with non-infectious neurological complication, including encephalopathy. Acute cerebellitis may be observed on brain MRI [(151,152)]. Diffuse white matter hyperintensities have been reported, hyperintense on DWI and corresponding to restricted ADC [(153)]; they may reflect the consequences of the septic shock syndrome rather than specific pathogen-induced lesions. Reversible splenial lesions on DWI have also been reported [(154,155)].

Mycoplasma pneumoniae is a frequent cause of acute pneumonia, especially in children, and may cause encephalitis. Brain MRI is frequently abnormal, with preferential involvement of the brainstem, cerebellum, and basal ganglia [(156)].

2. MRI findings in acute encephalitis: a pattern-based approach

a. Limbic encephalitis

HSV1 encephalitis is a frequent cause of limbic encephalitis, and early treatment is crucial for its long-term prognosis. Thus, HSV1 should first be considered in any patients presenting with acute limbic encephalitis.

HHV6 encephalitis may also be suspected in case of acute limbic encephalitis in patients who underwent allogeneic hematopoietic stem cell transplantation. HHV6 encephalitis lesions are usually less severe than HSV1 encephalitis lesions; they are often limited to the mesial temporal lobes; contrast enhancement and necrotic and hemorrhagic changes are usually absent. Lesions may reverse on follow-up imaging, even in cases of decreased ADC on initial imaging [(45,46)].

Neurosyphilis, Whipple's disease, and HIV primary infection are rare causes of limbic encephalitis that can benefit from a specific treatment.

Autoimmune/paraneoplastic limbic encephalitis and HSV1 encephalitis presentations may be very similar. They can manifest as acute symptoms including fever, seizures, neurological deficits, and memory impairment. Lumbar puncture shows lymphocytic pleocytosis and elevated protein levels, and MRI demonstrates T2 hyperintensities within the limbic system. MRI abnormalities can be asymmetrical or unilateral, and contrast enhancement may be

present [(157–159)]. Thus, HSV1 encephalitis should first be considered in this setting. Subtle differences have been reported between the two groups, yet none of them can rule out HSVE [(157)]:

- psychiatric symptoms are more frequent in patients with autoimmune/paraneoplastic encephalitis patients than in patients wirth HSVE;
- acute onset, fever, and aphasia are more frequent in patients with HSVE than in patients with autoimmune/paraneoplastic encephalitis;
- a normal brain MRI is rare in patients with HSVE, but frequent (40%) in patients with autoimmune/paraneoplastic encephalitis;
- on MRI, diffuse insular and temporal lobe involvement, necrotic and hemorragic changes, sparing of basal ganglia are more frequent in patients with HSVE than in patients with autoimmune/paraneoplastic encephalitis;
- on MRI, symmetrical lesions are more frequent in autoimmune/paraneoplastic encephalitis than in HSVE .

However, none of these findings can rule out HSVE.

Recently, it has been reported that HSVE patients may present a neurological relapse 1 to 3 months after the initial encephalitis, due to HSVE-induced autoimmune encephalitis associated with anti-N-methyl- d-aspartate receptor (NMDA-R)(160,161). This rare complication is important to diagnose, as it may be confused with a true HSVE relapse, but it requires specific immunotherapeutic treatments.

Glioma or gliomatosis cerebri may present as acute neurological symptoms and may mimic limbic encephalitis [(157,162,163)]. HSV1 encephalitis should always be considered on initial MRI. Lumbar puncture showing isolated mild pleocytosis, together with clinical and radiological follow-up, can correct the diagnosis.

b. Rhombencephalitis

The two most frequent infectious agents causing rhombencephalitis are ***Listeria monocytogenes*** and ***Mycobacterium tuberculosis*** [(164)]. They should first be suspected in acute rhombencephalitis because of the need to initiate a specific treatment. The presence of leptomeningeal enhancement and/or brainstem abscesses reinforces the suspicion of *Listeria* or TB. The association with focal arterial narrowing and strokes specifically favors a suspicion of tuberculosis. Rhombencephalitis have also been reported in encephalitis due to Mycoplasma pneumoniae, HSV1 and HHV6(15,156).

Behçet's disease is a frequent cause of acute rhombencephalitis and the main differential diagnosis of infectious rhombencephalitis [(164)].

Neuromyelitis optica spectrum disorder should be included in the differential diagnosis of acute rhombencephalitis as isolated brainstem involvement is possible [(165)]. The classic "area postrema syndrome" manifests as uncontrollable nausea and vomiting, corresponding on brain MRI to hyperintense lesions in the dorsal brainstem [(165)].

Posterior reversible encephalopathy syndrome sometimes present as isolated brainstem/cerebellar involvement, and should be included in the differential diagnoses of rhombencephalitis [(166)].

Neurosarcoidosis, other **granulomatosis,** and **histiocytosis** can involve the brainstem and cause T2 hyperintensities, mass effect, and contrast enhancement [(167)].

c. Acute encephalitis with ischemic lesions

The presence of acute ischemic lesions on brain MRI in patients with a suspicion of acute infectious encephalitis should first raise the possibility of an acute endocarditis.

Bacterial encephalitismay be associated with acute ischemic lesions [(168)]. Tuberculosis is a common cause of arteritis and may lead to small ischemic lesions [(122)]. VZV encephalitis

can be associated with acute ischemic stroke, especially in the territory of the middle cerebral artery [(28)]. In immunocompromised patient, acute encephalitis with acute ischemic lesions observed should raise the suspicion of fungal infection, especially cerebral aspergillosis and candidiasis; or neurosyphilis [(103,169)].

d. Splenial reversible DWI hyperintensity (MERS)

Mild Encephalopathy with Reversible Splenial Lesion (MERS) is a clinical and radiological syndrome associating a mild encephalopathy (behavioral changes, altered consciousness, seizures) and an oval-shaped, well-limited signal abnormality within the splenium of corpus callosum, hyperintense on T2WI and DWI, corresponding to restricted ADC. Both clinical and radiological abnormalities spontaneously resolve within days or weeks. The mechanism of MERS remains unknown.

MERS has been linked to numerous infectious agents, either bacterial (*Legionella pneumophila* [(170)], *Enterococcus faecalis* [(171)], *Escherichia coli*, *Staphylococcus aureus*, *Salmonella enteritidis* [(154,155)]), or viral (CMV, influenza, mumps, rubella, hepatitis A, adenovirus, flavivirus [(57,69,115,172)]). However, MERS can also be caused by many non-infectious conditions such as seizures, antiepileptic drugs, hypoglycemia, high-altitude brain injury, and acute axonal injury.

Conclusion

Brain MRI plays a crucial role in the diagnosis of acute encephalitis. It can demonstrate brain signal abnormalities and contrast enhancement, and reinforce a clinical suspicion of encephalitis, especially when identification of the causal agent by lumbar puncture is lacking. A good knowledge of the MRI patterns of brain involvement can also help physicians in suspecting a particular pathogen. However, MRI patterns must be interpreted in light of the clinical context (frailty, immunosuppression, recent travel), and should always integrate the differential diagnoses, mainly related to vascular, tumoral and inflammatory causes.

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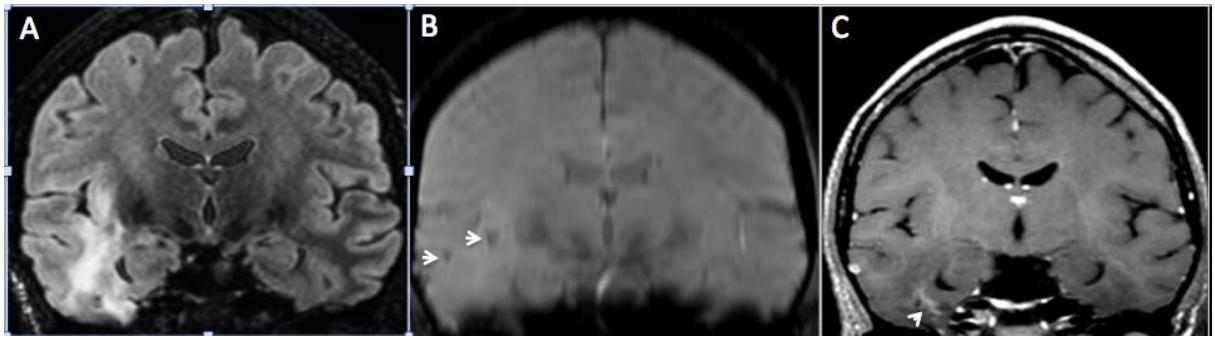
Figure 1. HSV encephalitis.

Figure 1. Encéphalite herpétique.



A: coronal FLAIR-weighted image demonstrates hyperintensities affecting the cortex and the white matter of right temporal and insular lobes.

B: T2* coronal image demonstrates small areas of parenchymal hemorrhage.

C: post-contrast coronal T1-weighted sequences shows areas of contrast enhancement within the right temporal lobe.

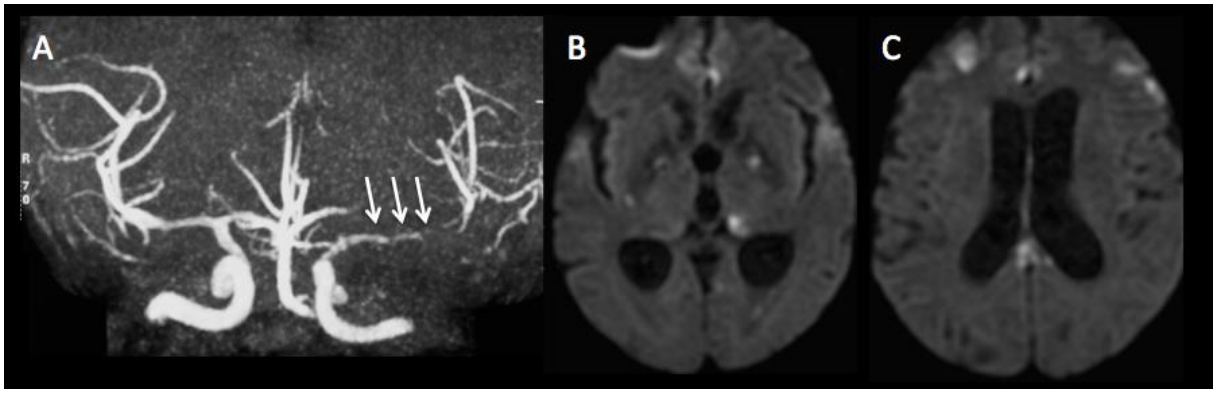
A : Coupe coronale en pondération FLAIR montrant des hyperintensités au niveau du cortex et de la substance blanche du lobe temporal droit et de l'insula.

B : Coupe coronale en pondération T2* montrant de petites zones d'hémorragies parenchymateuses.

C : Coupe coronale en pondération T1 après injection de produit de contraste, montrant des zones de rehaussement au niveau du lobe temporal droit.

Figure 2. VZV encephalitis.

Figure 2. Encéphalite à VZV.



A: severe stenosis along the M1 segment of the left middle cerebral artery.

B: multiple, bilateral, small ischemic lesions in another case of severe VZV encephalitis affecting small arteries.

A : sténose serrée le long du segment M1 de l'artère cérébrale moyenne gauche.

B : multiples petites lésions ischémiques bilatérales chez un autre patient atteint d'encéphalite grave à VZV touchant les petites artères.

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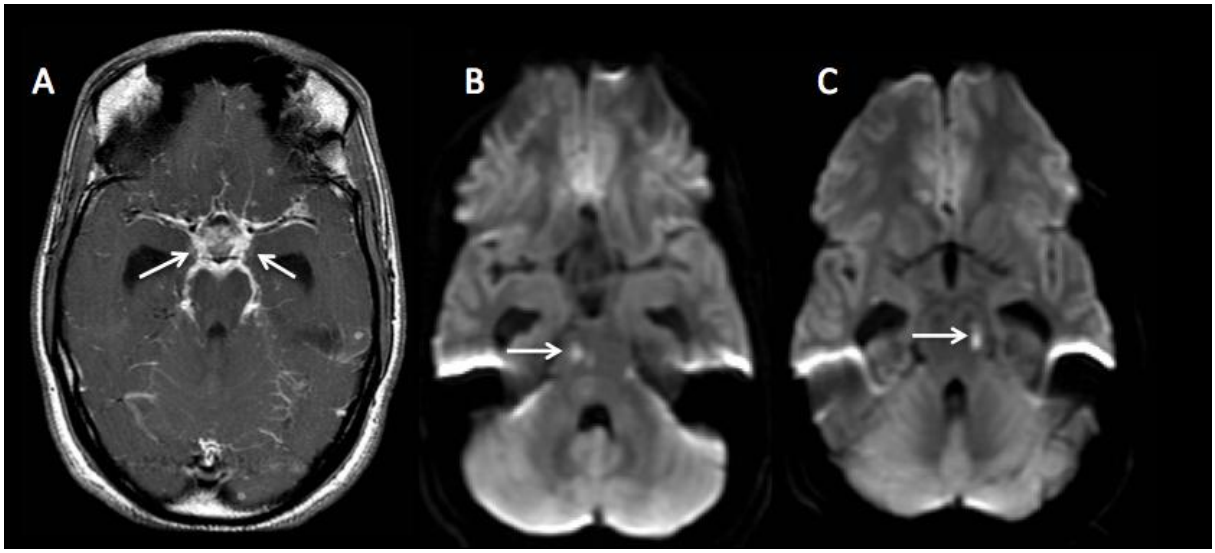
Figure 3. Neuromeningeal tuberculosis.

Figure 3. Tuberculose neuro-méningée.

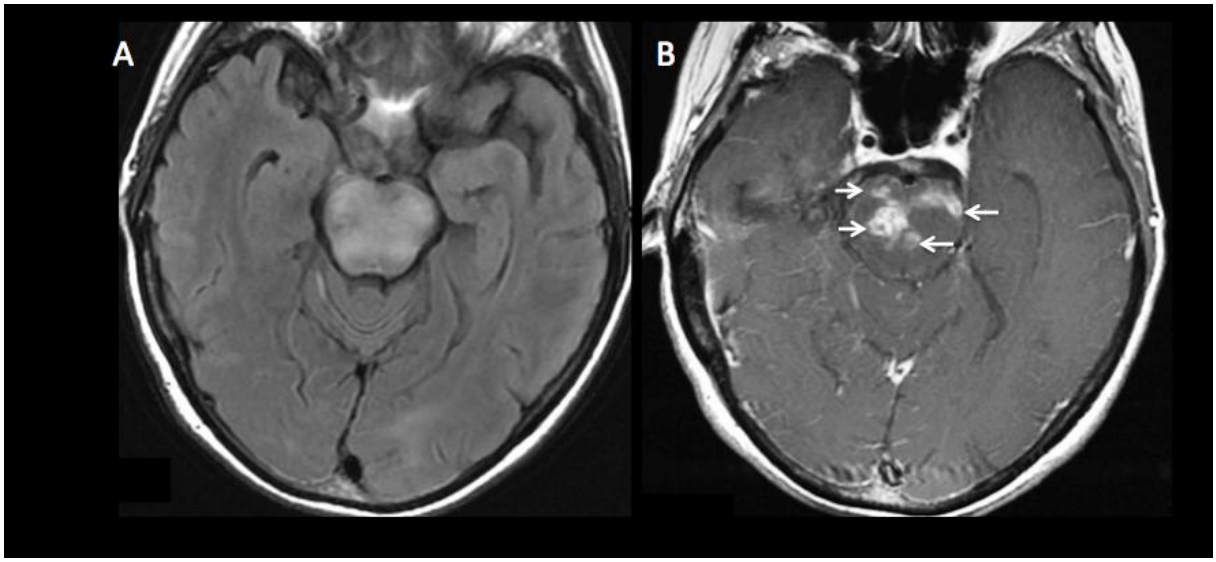


A: post-contrast axial T1-weighted image shows marked leptomeningeal enhancement in the basal cisterna, surrounding the arteries of the circle of Willis (arrows).
B&C: DWI shows small, punctate ischemic lesions within the brain stem, in the territories of the perforating arteries (arrows).

A : coupe axiale pondérée T1 après injection de produit de contraste montrant un important rehaussement leptoméningé marqué des citernes de la base, autour des artères du polygone de Willis (flèches).
B & C : l'imagere de diffusion montre de petites lésions ischémiques punctiformes du tronc cérébral, dans le territoire des artères perforantes (flèches).

Figure 4. Neuromeningeal listeriosis.

Figure 4. Listériose neuro-méningée.



A: axial FLAIR-weighted image shows diffuse edema of the pons, reflecting acute rhombencephalitis.

B: post-contrast axial T1-weighted image shows multiple small abscesses within the pons, with peripheral ring-enhancement (arrows).

A : coupe axiale pondérée FLAIR montrant un œdème diffus du pont, témoignant d'une rhombencéphalite aiguë.

B : coupe axiale pondérée T1 après injection de produit de contraste montrant de multiples petits abcès du pont, avec un rehaussement annulaire (flèches).