Central nervous system infections: new diagnostic tools

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Abstract
Central nervous system infections are an emerging health problem with poor prognosis if treatment is not adequate. Thus, establishing a correct diagnosis is necessary to quickly start the appropriate treatment. This is a real challenge for the radiologist, as it frequently requires a multidisciplinary approach. The relatively low performance of diagnostic imaging is well known. While computed tomography (CT) is limited only to an initial structural assessment, magnetic resonance imaging (MRI) is the method of choice, despite its low specificity. However, this has been substantially modified in recent years with the introduction into daily practice of new magnetic resonance sequences that allow precise structural and functional analysis, and provide essential additional information for final diagnosis. Now, due to the techniques of diffusion, perfusion, and spectroscopy, among others, a more detailed analysis can be made in conjunction with clinical and laboratory studies that significantly improve the sensitivity and specificity of MRI in this complex patient group. The patterns of the most common infectious diseases of the nervous system are reviewed in this manuscript, highlighting the contributions of functional sequences in these complex patients.

Keywords: Brain abscess; Encephalitis; Diffusion; MRI perfusion; Spectroscopy

Introduction
Central nervous system infections (CNSI) are an emerging health problem given the sustained increase in the number of cases in recent years. Even if this increase is determined by the high number of patients with human immunodeficiency virus (HIV) infection, there are two other important factors: on the one hand, the significant migration flows worldwide and, on the other hand, the rise in the number of infectious agents that are resistant to standard therapy. The factor that most affects prognosis for survival in patients with CNSI is the identification of the causative agent. Such identification allows a rapid institution of a specific therapeutic strategy.

Among the tools available, magnetic resonance imaging (MRI) has undoubtedly changed the paradigm in the study of neurological diseases since its implementation. However, despite its high sensitivity for a final diagnosis, this method has some limitations at the time of establishing the agent involved. In this respect, MRI diffusion, perfusion and spectroscopy techniques have demonstrated effectiveness in the detection of various neurological conditions, particularly infectious diseases. The incorporation of these techniques into routine evaluation of the central nervous system (CNS) has substantially changed the overall performance of this method, and they have become essential tools.

The aim of this review is to highlight the role of new MRI techniques in the evaluation of patients with CNSI, discussing their scope and limitations and illustrating their role by presenting some cases from our site.

Significance: epidemiology
Nervous system involvement may occur due to infections caused by multiple agents (such as bacteria, viruses, fungi and parasites) and each of these agents has typical clinical and imaging features. Potentially involved pathogens vary based on the compartment or area involved, geographic location and immune status, vaccination and age of the patient, among other factors. In 2004, the World Health Organization (WHO) reported about 350,000 deaths from meningocencephalitis (ME), with an approximate incidence of 700,000 cases worldwide.
Despite multiple diagnostic advances, in most patients the causative agent of infection is still unknown. In the case of sporadic encephalitis, herpes simplex virus (HSV) is the most common, while in brain abscesses the most common causative microorganisms are Streptococcus and Staphylococcus species, accounting for approximately 35% and 20% of cases, respectively. Cerebral involvement is very important in most parasitoses, with cestodes (and within this group the agent causing cysticercosis) being the most frequent.

In our setting (Uruguay), it is difficult to know the exact figures of incidence and significance. Even if it is considered a rare condition, the most frequent infectious disease until 2002, according to the Ministry of Public Health, was ME, with a rate of 3.27 to 7 cases per 100,000 inhabitants in the country and an approximate mortality rate of 10-30%, depending on the agent involved and the patient’s age.

As regards brain abscesses (BAs), mortality has decreased worldwide from 40 to 10%, with an increase in full recovery from 33 to 70%.

In Uruguay, parasitic infections are rare, mainly in immunocompetent patients, unlike other neighboring countries, where neurocysticercosis is relatively common.

In immunocompromised patients, mainly in HIV-infected patients, parasites are the most common causative agents, with toxoplasmosis being the most common infection in this population, followed by JC virus infection.

Pathology: the basis of imaging findings

Predisposing factors or conditions are found in over 80% of patients with BA, mainly contiguous or distant foci from which dissemination originate.

Radiology and pathology are inseparable at the time of understanding the phenomena causing nervous system infections. They are the basis for a large number of classifications: some based on the causative agent and others on topography of the infection (intraextra-axial). However, one of the most important classifications divides infections into focal, multifocal or diffuse depending on the type of involvement. Each of these groups is associated with specific agents and processes.

The response of the nervous system is highly restricted despite the interaction of multiple cell populations. There is a limited inflammation with blood-brain barrier (BBB) abnormalities and cerebrospinal fluid (CSF) involvement. Thus, a predominantly vasogenic edema develops, though with variable degrees of cytotoxicity and necrosis in different forms, hemorrhagic sites and changes in BBB permeability. All these changes translate into typical imaging findings and constitute the basis for an adequate interpretation.

Infections and their alterations (and, therefore, findings) depend on different factors. The leading factors include: the agent involved, the patient’s immune status and the route through which the infectious agent reaches the system.

Agents may be differentiated into pathogens proper (including bacteria and most viruses) and opportunistic pathogens, which are those requiring an immunosuppression status to cause harm (e.g., fungi).

The routes of infection are diverse. The most common route is hematogenous, but direct spread from contiguous sites can also occur, e.g. in trauma, or there may be cases of retrograde perineural spread.

We should bear in mind the huge variety of associated pathologic processes, which are not directly caused by the infectious agent but are triggered by this agent: for example, vascular abnormalities (such as vasculitis or vein thrombosis), circulatory disorders and reabsorption of the CSF, and direct or autoimmune demyelinating phenomena.

Magnetic Resonance Imaging: study protocol and advanced techniques

MRI is the method of choice in the evaluation of patients with CNSI, but it is essential to assess images together with the patient’s age, socioeconomic and immune status, as well as much clinical data as available. This technique helps to establish the presence of an infection, to rule out differential diagnoses, analyze the mechanism of infection and provide guidance about the etiologic agent, in addition to being helpful in follow-up and treatment monitoring. However, it is also essential to have a CSF study available and to know whether or not there is suspicion of an extra-neural focus of infection, as this contributes to an early diagnosis. We should bear in mind that an early diagnosis and initiation of a specific therapy are the most important factors having the greatest impact on mortality from infectious diseases.

Any study protocol should include basic sequences in all 3 planes: T1- and T2-weighted sequences, CSF suppression sequences (FLAIR) and T1-weighted sequences after the administration of gadolinium-based paramagnetic contrast medium. In recent years, usefulness of functional techniques has also been confirmed. These techniques provide information about the baseline process and pathophysiologic abnormalities (previously reviewed); therefore the protocol should include diffusion-weighted imaging (DWI) and an apparent diffusion coefficient (ADC) map, both essential for the study of this pathology. The use of perfusion-weighted imaging (PWI) and spectroscopy, as well as of other modalities, is also relevant.
Post-contrast FLAIR sequence

Post-contrast T2 FLAIR sequence is used with an inversion pulse that nulls the signal intensity of CSF. This increases its sensitivity to detect lesions and edema. Post-contrast FLAIR imaging constitutes an essential part of the basic study protocol for brain conditions when potential infection is being evaluated, mainly because of the ability of this sequence to recognize the edema associated with most bacterial and viral infections of the brain parenchyma.

In recent years, the importance of using this sequence with fat saturation pulses and after contrast administration has been highlighted: while the former increases contrast between grey and white matter, with a consequent improvement in resolution, post-contrast images have higher sensitivity for detecting meningeal abnormalities, both fluid collections (mainly subdural empyema) and leptomingeal involvement seen in meningitis of various etiologies8-10 (fig. 1).

Some authors suggest that post-gadolinium FLAIR images have identical sensitivity but a higher specificity compared to T1-weighted images for the diagnosis of infectious leptomeningitis10. Moreover, other authors, namely Splendiani et al11, have shown the usefulness of MRI with post-contrast FLAIR sequences in the early diagnosis of infectious meningitis. Nevertheless, in spite of these studies and the fact that our experience is very similar in a significant number of patients, we should emphasize that conventional contrast-enhanced T1-weighted images cannot be substituted in this population.

Diffusion (DWI)

The diffusion technique allows an analysis of the motion of water molecules in brain tissue and provides unique information in the study of infections18.

The presence of intense restricted diffusion has been reported in the central part of nonspecific bacterial BAs, which has been related to the poor cellularity and viscosity of pus18,19 (fig. 2). The presence of restricted diffusion within a ring-enhancing lesion allows diagnosis of bacterial BA (with near 100% specificity) and differentiates this entity mainly from necrotic or cystic tumors18,20,21 (fig. 4). This finding has even been reported to be pathognomonic for BA, in spite of the fact that it may be found in other types of lesions, such as some metastases with high viscosity or glioblastomas with hemorrhage22.

In the early stages of bacterial infection, cerebritis and early capsule stage, diffusion restriction is not so marked, and therefore there are difficulties at the time of making differential diagnosis15,18.

In practice, it is very complex to distinguish among the various types of BAs using only conventional sequences. By using DWI in combination with a detailed assessment of the morphology of lesions, clinical data and the patient’s immune status, a more accurate diagnosis can be reached.

In fungal or tubercular brain abscesses diffusion restriction is not as homogeneous as in bacterial brain abscesses, with areas of restricted diffusion and areas of no restriction; therefore DWI is an essential tool in diagnostic assessment23. Fungal BAs show restriction of diffusion in the wall with values similar to those of bacterial BAs, but also in the projections, which are usually directed centrally, with low signal on DWI23,24.

The phenomenon of restricted diffusion related to the presence of pus occurs independently of the compartment where pus is found. Therefore, this phenomenon may be seen both in extradural or subdural suppurative collections (empyemas) or within the ventricular system, as in ventriculitis25,26 (fig. 5). Finally, a very interesting point is the use of DWI in the fol-
Figure 1. Patient with documented tuberculous meningitis. The figure shows the utility and findings of FLAIR imaging after contrast administration. (a, b and c). Axial slices show strong enhancement and occupation of the Sylvian cistern on the right side by granulomatous material deposition (typical of this pathology). (d, e and f) Same patient: contrast-enhanced sagittal and axial T1-weighted SE images show findings clearly identified in the previous sequence.
low-up of patients with BA treated with antibiotics and no surgical drainage. This is one of the most important tools for assessing success of the selected therapy, as there is a decrease in central signal intensity if antibiotic therapy has the expected effect, and total disappearance if completely surgically drained27 (fig. 6).

In viral infections, DWI also plays an essential role16,18. Herpetic encephalitis by herpes simplex virus type 1 is the most common infection in this group, with a high mortality1,18. The classical finding is cortical restricted diffusion with a gyral pattern from the initial stages of disease (48 hours after the onset of symptoms), which allows establishing diagnosis18,28,29 (fig. 3).

In all viral infections, it is common to find high signals on DWI, with variable degrees of diffusion restriction, in different anatomical regions depending on the causative agent. This allows establishing diagnostic suspicion with adequate levels of sensitivity18,30 (Fig. 7). DWI has even been reported to have high sensitivity for detecting areas of viral activity in the early stages of encephalitis in relation to the onset of symptoms. This is shown by areas of cortical restricted diffusion not identified on other sequences (clinical-radiological dissociation) (fig. 8).

Finally, the role of DWI in the diagnosis of progressive multifocal leukoencephalopathy (PML) in HIV/AIDS patients should be highlighted. In cases of severe immunosuppression it is essential to establish a diagnosis based on the study of C-
Figure 3 Herpetic encephalitis (VHS 1) in a 2-year-old male patient with diagnosis confirmed by cerebrospinal fluid study. (a) FLAIR imaging, (b) diffusion-weighted imaging, (c) T2-weighted FSE image, (d) GRE T2*, (e) T1-weighted SE image and (f) contrast-enhanced imaging. Findings are typical of this entity: intense cortical restricted diffusion with a gyral pattern, similar to the distribution of the edema caused by this entity and to the enhancement pattern. (d) The gradient echo image shows the deep cortical hemorrhagic component.
Figure 4 Nonspecific bacterial brain abscesses. Patients with bacterial cerebellar BA (a and d), subcortical brain abscess (b and e) and multiple bilateral superficial and deep BAs (e and f). The typical behavior of these lesions is illustrated by the classical ring enhancement in (a, b and c) contrast-enhanced T1-weighted images and (d, e and f) the intense restricted diffusion in the necrotic center in diffuse-weighted images, typical of these lesions.
Figure 5. Bacterial infections with involvement of different compartments. This figure illustrates the usefulness of diffusion-weighted imaging for the assessment of bacterial involvement of the various compartments affected. (a) contrast-enhanced T1-weighted SE image and (d) diffusion-weighted image show an open BA partially ruptured into the lateral ventricle with pus (which accounts for restricted diffusion within) (b and e) Extradural empyema in right anterior frontal region, secondary to infection in the sinonasal cavity, with (b) classical enhancement on contrast-enhanced T1-weighted image and (e) restricted diffusion. Finally, we present a subdural empyema with the same behavior as described above: (c) contrast-enhanced T1-weighted SE image and (f) diffusion-weighted image.
Figure 6. Bacterial brain abscess treated with antibiotics: follow-up. Patient treated with triple antibiotic (ATB) regimen because of the absence of neurological focus and the size of the abscess. The diagnostic scan shows the typical appearance of the lesion: (a) edema on FLAIR imaging, (b) ring enhancement on contrast-enhanced T1-weighted imaging and (c) intense restricted diffusion. The follow-up MRI performed 15 days later shows (d) reduced size of the lesion and edema, (e) an area of persistent enhancement and (f) total absence of restricted diffusion, which confirms an excellent response to treatment.
Figure 7. Arbovirus encephalitis: multimode MRI. (a) T2-weighted and (b) FLAIR images show edema on the left hemisphere, consistent with intense restricted diffusion with a gyral pattern and (c) cortical edema on diffusion-weighted image (which is common in viral infections). (d) Contrast-enhanced T1-weighted imaging shows cortical enhancement while (e) perfusion-weighted imaging shows that the pathologic area has, despite enhancement, a decrease in regional cerebral blood volume, delimiting the affected area as an area of hypoperfusion. (f) Spectroscopy shows the pseudotumoral metabolic pattern, with a decrease in N-acetylaspartate and creatinine, an increase in choline levels and a small lactate peak (arrow).
Figure 8 Encephalitis confirmed by cerebrospinal fluid study. This figure illustrates the special usefulness of diffusion-weighted imaging in the early diagnosis of viral infections. (a, b and c) FLAIR image interpreted as normal 3 days after the onset of symptoms. (d, e and f) Diffusion-weighted image from the same scan shows extensive areas of cortical restricted diffusion at the level of the right hemisphere, with associated insular involvement, and no significant edema or mass effect.
Figure 9 Multimodal MRI in an HIV-positive patient with progressive multifocal leukoencephalopathy. Extensive pathological area on the left anterior frontal region, with mass effect and edema on (a) FLAIR imaging and (b) classical pattern on diffusion-weighted imaging with high signal halo and hypointense center. (c) No enhancement on contrast-enhanced imaging. (d) Spectroscopy shows a pseudotumoral pattern represented by decreased N-acetylaspartate and increased choline levels, and a very significant presence of lactates (arrow) visible on (e) the metabolic map as an inverted double peak at 1.3 and (f) which shows low cerebral blood volume on perfusion weighted-imaging. The presence of the JC virus, the causative agent of this condition, was confirmed by the cerebrospinal fluid study.
reactive protein (CRP) in CSF and imaging findings, with the purpose of changing immediate prognosis31. PML is a subacute demyelinating disease caused by reactivation of the JC virus. Because of the progressive nature and poor prognosis of this disease, treatment and evaluation of response are essential31,32. Recently, multiple studies have used DWI to detect areas of activity in patients with PML and monitor their response to treatment18,33. In these cases, lesions on DWI are characterized by a low signal in the center of lesions and a high signal in the periphery, which is indicative of activity. This is the area that is susceptible of response to antiretroviral therapy34 (fig. 9).

Moreover, the ADC map has also been reported to be helpful in differentiating between rapid responders and non-responders, with poor progress and the possibility of developing an immune reconstitution inflammatory syndrome (IRIS)35.

**Perfusion**

PWI techniques allow a functional and hemodynamic assessment of cerebral circulation, including capillary bed status, indemnity or not of the BBB and presence or absence of angiogenesis 36. Through a dynamic injection of contrast medium, different functional maps can be generated (e.g., cerebral blood flow [CBF]) or cerebral blood volume [CBV]). Even if the role of PWI has been well established for the evaluation of stroke or nervous system tumors, it is a tool of special interest in patients with infection 37. Because of the constitution of the brain abscess capsule, rich in collagen and with decreased vascularity, it is easy to distinguish these lesions from tumors that may have a similar appearance on conventional imaging 38,39. Thus, on PWI CBV values are low, with no alterations of permeability in the area of maximum enhancement (i.e., in the capsule of the lesion)39 (fig. 10). For CBV values found in the necrotic center of tumors and in BAs there are no significant differences; therefore, it is necessary to make a correct assessment of the various areas of the lesion40.

PWI is an effective tool for differentiating between brain abscesses and necrotic tumors, which --as previously mentioned-- may show restricted diffusion in the center of the lesion. Chan et al have shown that relative CBV values (rCBV) on the walls of various types of cystic or necrotic tumors are higher than those of normal white matter, relative to those of the BA wall41. The perfusion technique may be used in all CNSIs, since as a general rule, these are lesions with low CBV values, i.e., they demonstrate hypoperfusion (figs. 7 and 9).

Different authors have confirmed that PWI is very useful in patients with HIV/AIDS to differentiate between toxoplasmosis and primary cerebral lymphoma, as the latter shows high rCBV values as compared to the decrease observed in infectious lesions42 (fig. 11).

**Spectroscopy**

Spectroscopy is a technique that allows noninvasive assessment of the metabolic behavior of normal and pathologic tissues. Even if its interpretation may be complex, it has a good diagnostic performance in a wide range of CNS disorders43. The major contribution of spectroscopy has been in tumors, but the usefulness of this modality in infectious lesions is undeniable44.

For ring-enhancing lesions, spectroscopy provides very important data to differentiate between infectious lesions and other entities, and it even provides information about the infective agent probably involved44-46.

The presence of succinate, acetate, alanine, leucine and valine in some cases is considered specific for pyogenic BA, even in the absence of restricted diffusion on DWI44,47. Some indexes, such as the acetate / succinate ratio even allow distinguishing between bacterial and parasitic lesions48 (fig. 12). If amino acids are present, a BA can be differentiated from a tumor with adequate sensitivity and specificity levels48.

In the case of viral encephalitis, there is no clear evidence about the overall performance of this method.

In patients with acute HSV, in the initial stages there is a decrease in the levels of N-acetylaspartate (NAA) and an increase in choline (Cho) with a decrease in the NAA/Cr (creatine) ratio and variable peaks of lactate, usually high49. However, this pattern is not very specific and, as it can be seen in multiple viral agents, it may be interpreted as tumoral (pseudo-tumoral pattern), compromising the specificity of the method (figs. 7, 9 and 13).

Some authors have suggested the usefulness of spectroscopy for the evaluation of infectious lesions in cases of HIV/AIDS, but its interpretation is complex and it has some difficulties50 (fig. 14). In HIV patients, CNS tuberculosis is one of the emerging pathologies and, among the forms of involvement of this condition, meningitis is the most common, while tuberculoma constitutes a real diagnostic challenge.

Tuberculomas are lesions with a caseating center, which results in the typical low signal on T2-weighted imaging51. These lesions show no restricted diffusion and have low CBV, as it occurs in previously discussed cases with specific agents50,51. Metabolic spectra usually show a very significant lipid/lactates peak. Even if this is a nonspecific finding, when assessed in conjunction with the information available, it allows suspicion of the final diagnosis51 (fig. 15).

An essential concept that we should bear in mind is that met-
Figure 10  Bacterial brain abscesses: appearance on perfusion-weighted imaging. MRI in selected sequences, in the 2 patients with bacterial BA confirmed after surgical drainage shows (a and d) the classical restricted diffusion and (b and e) an ADC map with (c and f) low cerebral blood volumes on perfusion weighted images.
Figure 11 Multimodal MRI in HIV-positive patient with cerebral toxoplasmosis. A large-volume lesion in the right basal ganglia with necrosis, edema and mass effect is seen on (a) T1-weighted images and (C) FLAIR images. Central areas of hemorrhage on (b) T2-weighted images and (d) a strong heterogeneous enhancement. (e) No restricted diffusion in the center of the lesion, which differentiates it from bacterial brain abscess and lymphoma, with projections directed inwardly in the form of septa with high signal (common in atypical agents). (f) Perfusion-weighted imaging typically shows decreased cerebral blood volume (area of hypoperfusion).
Abolic spectra should be interpreted in conjunction with the whole set of images and sequences obtained, in order to allow adequate diagnosis and potential differential diagnoses.

**Recommendations and final concepts**

CNS infections constitute a real health problem, with high mortality rates in cases of late diagnosis. The interpretation of images is a challenge, but among diagnostic methods, MRI is the method of choice because it has demonstrated a positive impact in this group of patients: not only does it help to determine an approximate diagnosis, to rule out differential diagnoses and to analyze both the agent most likely involved as well as the etiopathogenic mechanism, but it also allows a strict follow-up of the selected therapeutic management.

For an improved performance of this method, images should be interpreted in conjunction with clinical data, the course of disease and the patient’s immune status, as well as any relevant epidemiological information (known contact with agents, recent trips, etc.) and laboratory tests, mainly blood and CSF tests.

An early diagnosis reduces mortality, as it allows the rapid institution of specific treatment. To achieve this, it is imperative...
Figure 13 Spectroscopy in a patient with documented arbovirus encephalitis and extensive left frontal pathological area, (b) with edema not significantly reflected in diffusion, and (f) areas of heterogeneous enhancement. (d and e) Metabolic spectrum shows a pseudo-tumoral pattern with very high levels of lactates (arrow). (a) FLAIR imaging and (c) non-contrast enhanced T1-weighted SE imaging complement the study.
to perform an adequate MRI, which should include conventional, FLAIR, T2- and T1-weighted imaging, and contrast-enhanced images. The use of new imaging modalities, mainly diffusion- and perfusion-weighted imaging, is essential. Thus, a final diagnosis can be established with near 100% sensitivity and specificity.

Conflict of interests
The author declares a possible conflict of interest as a member of the International Advisory Board of Revista Argentina de Radiología.

References

Figure 14 Perfusion and spectroscopy in HIV-positive patients with cerebral toxoplasmosis. (a) Right frontal focal lesion with a ring- and target-shaped enhancement pattern, with an eccentric nodule on contrast-enhanced T1-weighted imaging. Functional imaging shows the following typical findings: (b) decreased cerebral blood volume and (c) spectrum of metabolites with normal concentrations of N-acetylaspartate and creatine, increased levels of choline and a very significant peak of lactates (arrow). This pattern is clearly different from that of lymphoma, the most common nervous system tumor in this group of patients.
Figure 15. Multimodal MRI in an HIV-positive patient with brain tuberculoma diagnosed by pathological examination of the surgical specimen. (a) Left superficial parietal focal lesion with associated edema on FLAIR imaging, (b) low signal on T2-weighted imaging (typical of these lesions) and (c) ring enhancement on contrast-enhanced T1-weighted imaging. (d) On diffusion-weighted imaging, no restriction in the center of the lesion. (d) perfusion-weighted imaging and (f) spectroscopy show the typical characteristics of infectious lesions, with an elevated lipids/lactates peak (arrow).


