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Neuro/Head and Neck Radiology PICTORIAL ESSAY

Psychiatric symptoms due to infectious and autoimmune-mediated central nervous system disorders: can brain MRI help to solve the riddle?

Danai Eleni Stefanou[1], Eleni Lazaridou[2], Demetrios Exarhos[2], Ioannis Kalogeropoulos[1]
[1]*Radiology Department, Evangelismos General Hospital, Athens, Greece*
[2]*Department of CT and MRI, Evangelismos General Hospital, Athens, Greece*

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ABSTRACT

A wide spectrum of organic diseases, including endocrine, metabolic and neurological disorders, may be the underlying cause of secondary psychiatric disorders. The diagnostic algorithm of a patient presenting with newly manifested psychiatric symptoms in the emergency department entails exclusion of possible organic disease as underlying cause of psychiatric symptomatology and relies on neurological evaluation, cerebrospinal fluid analyses and brain imaging. Brain magnetic resonance imaging is an indispensable diagnostic modality for the differentiation between primary and secondary psychiatric disorders. In this article, we focus on the differential diagnosis and MRI findings of infectious and immune-mediated central nervous system disorders in patients presenting with newly manifested psychiatric symptoms. We emphasise that accurate and prompt diagnosis of secondary psychiatric disorders is crucial in order to optimise treatment and improve clinical prognosis.

KEY WORDS: Brain MRI; Psychiatric symptoms; Encephalitis; Infectious diseases; Autoimmune

CORRESPONDING AUTHOR, GUARANTOR

Corresponding author: Danai-Eleni Stefanou, Radiology Department, Evangelismos General Hospital, 45-47 Ypsilantou Str., Athens, 10676, Greece, E-mail: danaistefanou@hotmail.com
Guarantor: Demetrios Exarhos, Director, Department of CT and MRI, Evangelismos General Hospital, 45-47 Ypsilantou Str., Athens, 10676, Greece, E-mail: jimexarhos@yahoo.com

1. Introduction

Psychiatric symptoms, including abnormalities of cognition, emotion and behaviour, have been well-studied in the context of primary psychiatric disorders. Nonetheless, over the last years, accumulating evidence suggests that a multitude of systemic and neurological disorders that follow the previous classification, often co-exist or are simultaneously manifested. According to the Diagnostic and Statistical Manual of Mental Disorders (DSM), a psychiatric presentation of a medical illness is a mental disorder due to a general medical condition [1]. Conversely, the diagnosis of a primary psychiatric disease requires prior exclusion of underlying or causally-relevant organic diseases.

Patients often present to the emergency department (ED) with neuropsychiatric and psychiatric symptoms and in about 10% of the cases an underlying medical cause is revealed [2]. The high rates of secondary psychiatric disorders among patients presenting with newly manifested psychiatric symptoms emphasise the importance of cautious medical evaluation, thorough history and physical examination, as well as laboratory and radiological investigations, including brain Computed Tomography (CT) and Magnetic Resonance Imaging (MRI) in order to rule out underlying organic disease.

Psychiatric symptoms alone or in combination with other neurological symptoms encompass a broad differential diagnosis. In accordance with recent literature, organic disorders that commonly present with psychiatric symptoms can be broadly classified into three categories: endocrine or metabolic disorders and deficiency states, systemic diseases and neurological disorders [2]. Although such classification schemes have been proven valuable in clinical practice and facilitate the differential diagnosis, a high degree of overlap between the diagnostic categories is noted. Systemic and neurological disorders that follow the previous classification, for example, often co-occur or may manifest sequentially. This is particularly the case with infectious and immune-mediated disorders, which may present both as systemic or purely neurologic disease.

In this article, we will focus on these two categories, i.e., infectious and immune-mediated central nervous system (CNS) disorders in patients with newly-manifested psychiatric symptoms. The aim of this article is to firstly provide a succinct description of imaging features of the most frequently encountered CNS disorders linked to psychiatric symptoms and secondly to raise awareness of the strengths and advantages of MRI in the prompt and accurate recognition of secondary psychiatric disorders.

2. CNS infections

CNS infections -bacterial, viral or fungal- are associated with extremely high rates of morbidity and mortality if they remain undiagnosed or untreated. Already during the stage of primary patient admission and care at the ED, a prompt diagnosis of a CNS infection is warranted in order to initiate immediate treatment and prevent short- and long-term neurological deficits or fatal outcome. The diagnosis of CNS infections is based on the patient's history, along with clinical and paraclinical investigations, including serological studies and cerebrospinal fluid (CSF) analysis. Furthermore, brain imaging is required for the differential diagnosis (see typical imaging findings below) or in order to exclude brain oedema or impending brain herniation prior to diagnostic lumbar puncture. CT is considered as first-line imaging modality, since its duration is significantly shorter compared to MRI (i.e., when lumbar puncture is acutely indicated). Also, CT is preferred as an imaging modality in patients presenting with agitation in the setting of CNS infection, or who are unable to undergo MRI without sedation [3]. Besides the aforementioned arguments, CT is also more widely available than MRI, especially in primary or secondary healthcare settings. Life-supporting equipment is compatible to the CT scanner, which is an advantage compared to MRI. With regard to the diagnostic utility, however, MRI is the modality of choice for diagnosis of CNS infections, with significantly higher sensitivity and specificity compared to CT [3]. Amidst the multitude of possible infectious CNS disorders, we discuss the specific MRI features suggestive of CNS infections in patients classically presenting with neuropsychiatric symptomatology.

2.1. Acute Meningitis

The majority of patients admitted with meningitis to the ED typically present with fever, neck stiffness and/or altered mental status [4]. Although psychiatric symptoms are rarely reported in uncomplicated men-

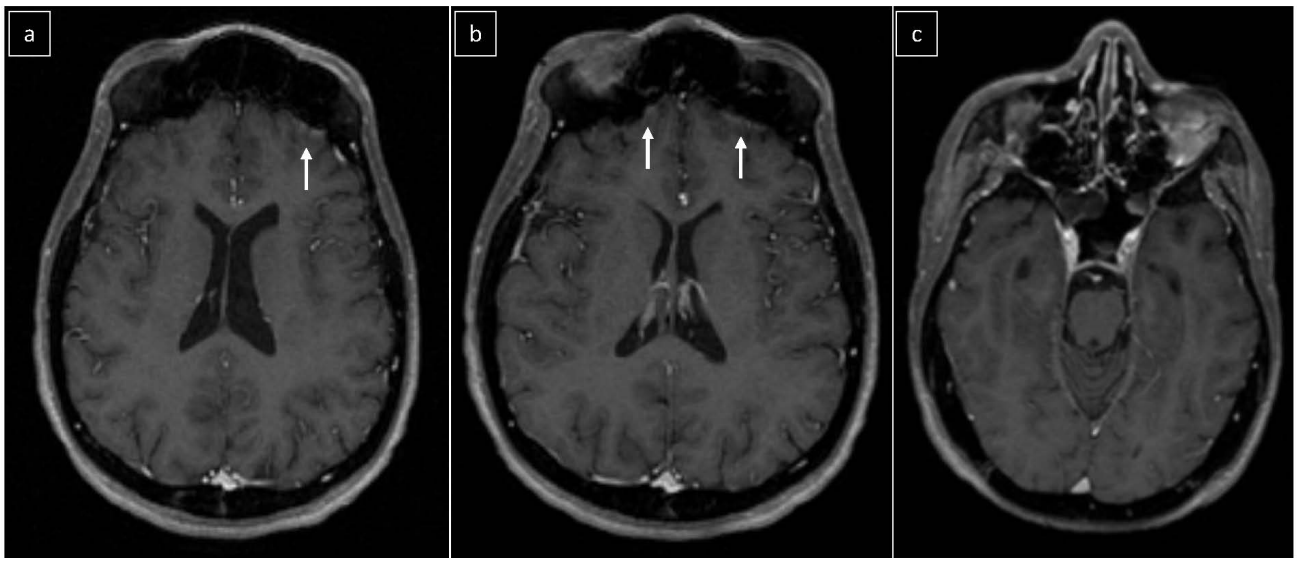

Fig. 1. *A 20-year-old male presented to the ED with headache, fever, confusion and somnolence. On gadolinium-enhanced T1W MR image* ***(a, b)*** *mild focal dural enhancement bilaterally in the frontal extra-axial region was depicted (arrows in* ***a, b****). These findings proved to be suggestive of bacterial meningitis in a complicated case of sinusitis, where endoscopic approach had been preceded.* ***(c)*** *Hyperintense sphenoid and left paranasal sinus opacification is depicted corresponding to residual sinusitis.*

ingitis cases, non-specific psychiatric manifestations, including confusional psychosis and mood disorders (hypomania) have been reported in the literature [5]. Although it remains currently unclear to what extent these psychiatric symptoms may indicate concomitant encephalitis in the setting of advanced meningeal inflammation, we report some distinct imaging findings of infectious meningitis in patients with neuropsychiatric symptoms.

2.1.1. Imaging Findings

Neuroimaging is not necessary in uncomplicated cases of acute meningitis because the diagnosis is based on the combination of clinical and CSF findings. Imaging findings typically depend on the stage of the meningeal infection.

In early disease, neuroimaging studies may be normal. In uncomplicated cases, even on gadolinium-enhanced MR scans, up to 50% of patients with meningitis have no imaging abnormalities [6]. CT may show enlargement of the ventricles and basal cisterns, but these findings are considered non-specific. On brain MRI, abnormal asymmetrical arachnoid and pia materenhancement is seen in approximately 50% of affected patients. However, high rates of false positive MRI findings are reported, as prominent enhancing vascular structures may be frequently mistaken for abnormal meningeal enhancement. Regarding the morphological features of gadolinium enhancement on brain MRI, a thin and linear leptomeningeal pattern has been associated with bacterial or viral meningitis, while a thick, lumpy or nodular pattern is usually suggestive of fungal meningitis [7, 8]. Current imaging guidelines suggest that contrast-enhanced 3D fluid-attenuated inversion recovery (FLAIR) is superior to conventional post-contrast 3D T1-weighted (T1W) MR imaging in depicting meningeal enhancement [9].

At a later stage, brain MRI is performed to exclude or depict complications of established meningitis, including communicating hydrocephalus, cerebritis, abscess, infarction, subdural effusion or empyema and impending brain herniation. On FLAIR, a high signal intensity is noted in the subarachnoid spaces and ventricles due to CSF accumulation, which is caused by inflammatory cascades that lead to abnormal CSF production with high protein levels [7-9]. In meningitis, elevations not only in protein but also in cellular concentrations appear as hyperintensity of CSF on FLAIR sequence. Although this sign is non-specific, as it may also occur in other CNS disorders, including subarachnoid haemorrhage, met-

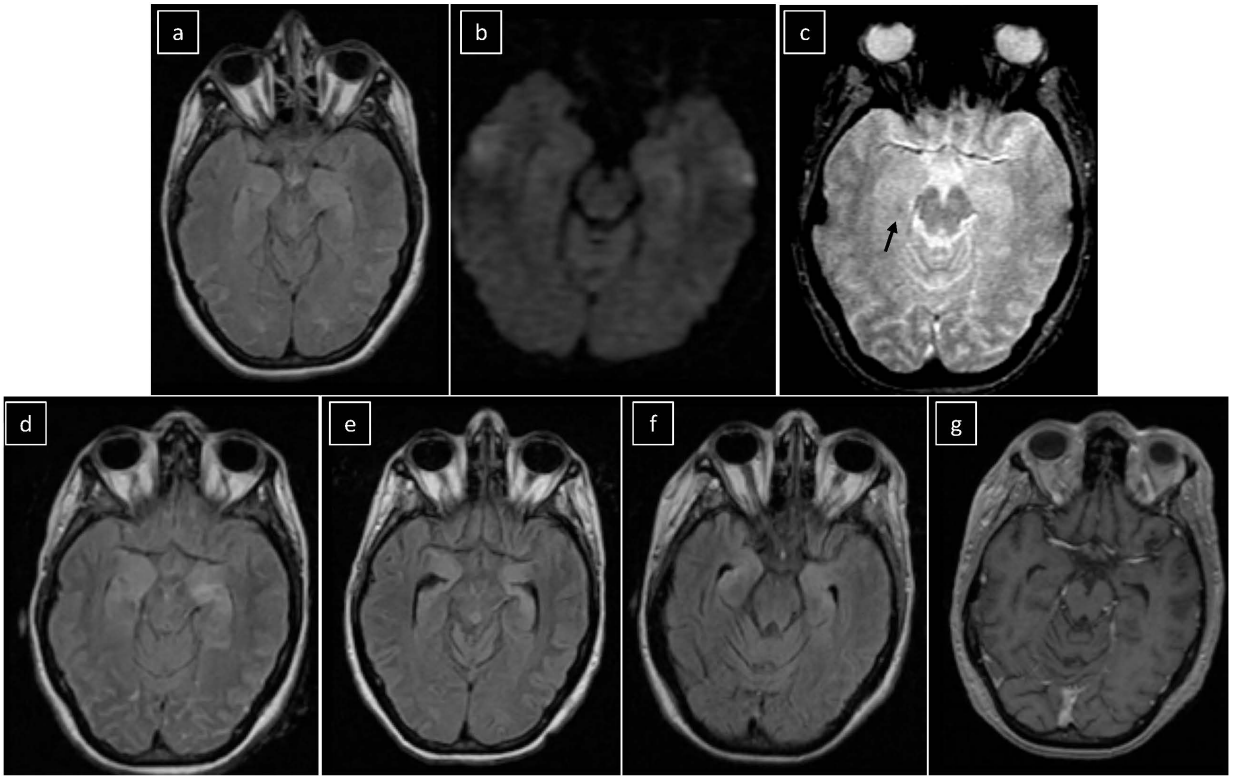

Fig. 2. *A 36-year-old woman presented to the ED with visual hallucinations, confusion and fever. On FLAIR* ***(a)*** *both medial temporal lobes are hyperintense with mild restriction on DWI* ***(b)****. Two weeks later, on the T2* axial MR image* ***(c)****, right sided hypointense lesions (arrow) corresponding to micro-haemorrhage are noted in the hippocampus, a finding typical for HSV-1 encephalitis. CSF analysis revealed HSV-1. Prominent FLAIR hyperintensity is noted on both medial temporal lobes* ***(d)****. One month later, the patient clinically deteriorated. Persistent FLAIR hyperintensities without cortical oedema are seen on follow-up scans* ***(e, f)****. On gadolinium-enhanced T1W MR image* ***(g)****, no enhancement is depicted in this patient, even though HSV-1 encephalitis may be accompanied by intraparenchymal or meningeal foci of enhancement.*

astatic disease, neurosarcoidosis and lymphoma [7], it should not be missed in a patient with meningitis. Assessment of the ventricles is crucial, as ventriculitis or ventricular dilatation (e.g. in cases of communicating hydrocephalus due to impaired CSF absorption) should be promptly acknowledged due to the detrimental implications of these complications on the patient's clinical course **(Fig. 1)**. On diffusion-weighted imaging (DWI), the ventricles may appear hyperintense, reflecting the purulent fluid that causes restricted diffusion - a finding that is most commonly encountered in cases of bacterial meningitis. Sulcal hyperintense lesions may also be seen on DWI (e.g. in meningitis caused by Streptococcus pneumoniae). Frontal lobe subarachnoid hyperintensities on DWI have been related to poor prognosis [10]. Additionally, DWI, MR-angiography (MRA) and venography (MRV) play a major role in the diagnosis of arterial or venous infarction, especially in cases of bacterial meningitis.

2.2. Encephalitis-Abscess

Inflammation of the brain parenchyma is defined as encephalitis. It can present with a wide spectrum of clinical manifestations, including altered level of consciousness, memory loss, psychiatric changes and epileptic seizures. The most frequent causes of encephalitis can be classified into two broad categories; infectious (viral, bacterial or parasitic) and non-infectious (immune-mediated) [11]. In the ED, encephalitis should always be suspected when a patient presents with newly-mani-

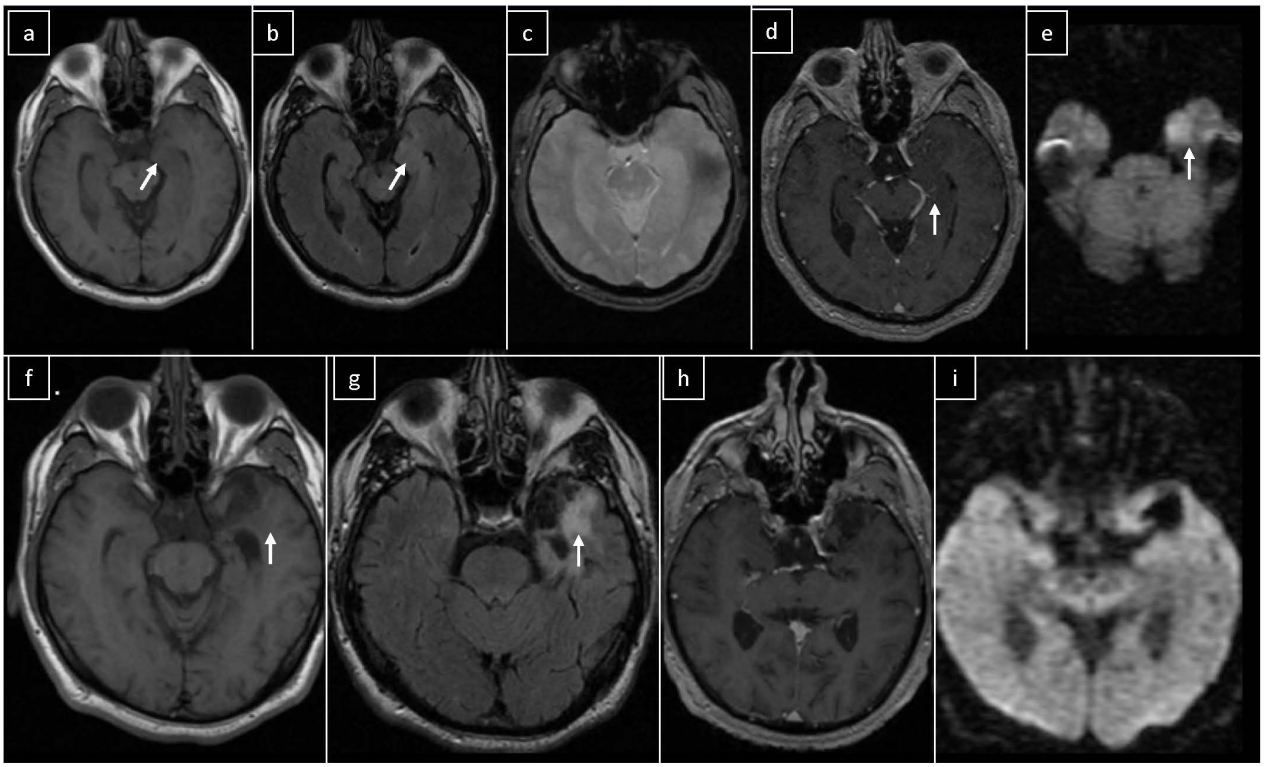

Fig. 3. *A 68-year-old male presented to the ED with personality changes and psychosis. On axial T1W* ***(a)*** *and FLAIR MR images* ***(b)*** *bilateral (mostly left-sided) oedema in the medial temporal lobes is noted (arrows in* ***a, b****), without haemorrhagic signs on the corresponding T2* MR image* ***(c)****. On gadolinium-enhanced T1W MR image* ***(d)****, mild leptomeningeal enhancement is shown (arrow), with restricted diffusion in the temporal lobes on DWI (arrow in* ***e****). CSF analysis revealed HSV-1. On 2-month follow-up, signs of gliosis in the left temporal lobe are shown, corresponding to hypointensity on T1W (arrow in* ***f****) and hyperintense signal on FLAIR (arrow in* ***g****) MR images. Neither enhancement on gadolinium-enhanced T1W* ***(h)*** *nor restricted diffusion on DWI* ***(i)*** *are noted in the temporal lobes.*

fested neuropsychiatric symptoms or seizures. Typically, the clinical findings correlate with the region of the affected brain parenchyma. For example, temporal lobes are most commonly affected in patients presenting with psychiatric symptoms, including personality changes, psychosis and hallucinations and temporal lobe affection is typically noted in Herpes Simplex Virus (HSV) encephalitis [12].

As the overlapping clinical manifestations preclude a definite distinction between infectious and non-infectious encephalitis on clinical grounds, numerous diagnostic modalities (including serological and CSF analyses) are employed to facilitate the differential diagnosis. With respect to neuroimaging, conventional MRI sequences can be combined with complementary advanced MRI techniques and occasionally electroencephalography (EEG) studies [13].

2.2.1. Imaging Findings

Four well-defined stages have been described concerning the imaging appearance of cerebritis and brain abscesses: early cerebritis (1-3 days), late cerebritis (4-9 days), early capsule formation (10-13 days) and late capsule formation (14 days and later) [13, 14].

In early cerebritis, the imaging abnormalities correspond to infected sites of the brain which are typically inflamed and oedematous [14]. CT may be normal or may show hypodense parenchymal lesions. Brain MRI is more sensitive than CT being abnormal in approximately 90% of early encephalitis cases [15]. The lesions appear with low signal intensity T1W and high signal intensity on T2-weighted imaging (T2W) and FLAIR MR

images. Encephalitic lesions are typically surrounded by perifocal oedema. The oedema may cause mass effect, depending on its extent. These non-specific imaging findings are often difficult to pick up and the differential diagnosis is extensive, including brain tumours or infarctions. Thus, clinical information should always be taken into account when assessing imaging findings. Localisation of MRI abnormalities is also extremely useful, as certain MRI patterns have been uniquely associated to specific underlying aetiologies:

- HSV-1, for example, is the most common viral pathogen presenting with T2W hyperintense lesions, typically localised in the medial temporal lobes or the orbital surfaces of the frontal lobes. HSV-1 can affect one or both lobes, while the distribution is usually asymmetric. Another typical characteristic of HSV-1 encephalitis is the sparing of the basal ganglia. Haemorrhage is a typical feature of HSV encephalitis, while T2* sequences are highly sensitive in revealing microhaemorrhages, that are depicted as patchy areas of low signal corresponding to sites with haemoglobin degradation products [16] **(Figs. 2, 3).**
- Deep grey matter (basal ganglia and thalamus) abnormalities are commonly seen in a wide spectrum of viral encephalitides, including West Nile virus, Japanese virus, enteroviruses and rabies [12].
- Brainstem and cerebellum abnormalities are often encountered in encephalitis caused by Listeria monocytogenes, Brucella, Arboviruses and Enteroviruses [12].
- White matter abnormalities along with lesions at the grey-white matter junction may be seen in cases of Varicella zoster virus (VZV) [12, 17].

In late cerebritis, imaging findings of coalescing central lesion necrosis are depicted, shown as hypodense lesions on CT, hypointense lesions on T1WI and hyperintense lesions on T2W and FLAIR MRI sequences. DWI may show increased signal intensity within the lesion centre, while late rim enhancement may be shown after gadolinium injection. Furthermore, vasogenic oedema and mass effect may be noted in late, but not early cerebritis [12, 14, 17].

Early capsule: At this stage, brain abscess will be recognised as a round/oval walled mass with a T1W hypointense and a T2W hyperintense core corresponding to the central necrosis, a three layered T2W hypointensity and iso-hyperintense T1W capsule (due to the presence of collagen fibres, reticulin and macrophages), prominent perifocal oedema and smooth, thin ring-like enhancement on post-contrast T1W. On DWI, the cavity shows homogeneous high signal with low ADC values, as restricted diffusion is due to the high viscosity of the content that contains proteins, bacterial and cellular debris.

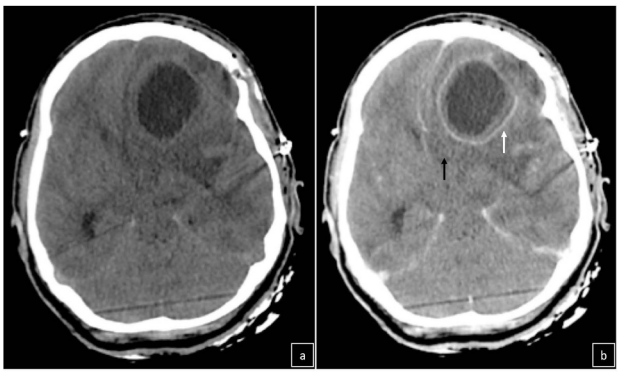

Fig. 4. *A 23-year-old female with confusion and fever underwent brain CT on admission to the ED. Pre-contrast* ***(a)*** *and post-contrast* ***(b)*** *CT revealed an oval ring-like enhancing mass in the left frontal lobe with a thick wall, a dual rim sign (white arrow) and intense perifocal oedema (black arrow) causing mass effect. Concomitant sinusitis was diagnosed (images not shown), suggestive of a brain abscess as a sequel. Microbiological analyses revealed Staphylococcus epidermidis and Enterobacter aerogenes.*

Late capsule: The capsule is better defined than in previous stages, is thicker and multilobulation may be present. Since decreased blood supply is noted in the core compared to the surrounding grey matter, gadolinium enhancement is prominently noted in the periphery (i.e. at the rim of the abscess closest to the grey matter). Ventriculitis or ependymitis may occur as a consequence of intraventricular rupture of the abscess. Finally, haemorrhage in the wall of the abscess is infrequently noted, and typically results from rupture of newly formed fragile vasculature around the abscess **(Fig. 4)**.

Advanced MRI techniques, including DWI, susceptibility weighted images (SWI), spectroscopy (MRS) and perfusion (PWI) give information about structural, morphologic and haemodynamic features that help in the differential diagnosis between the different bacterial causes of an abscess, but also in the differentiation of bacterial abscesses from

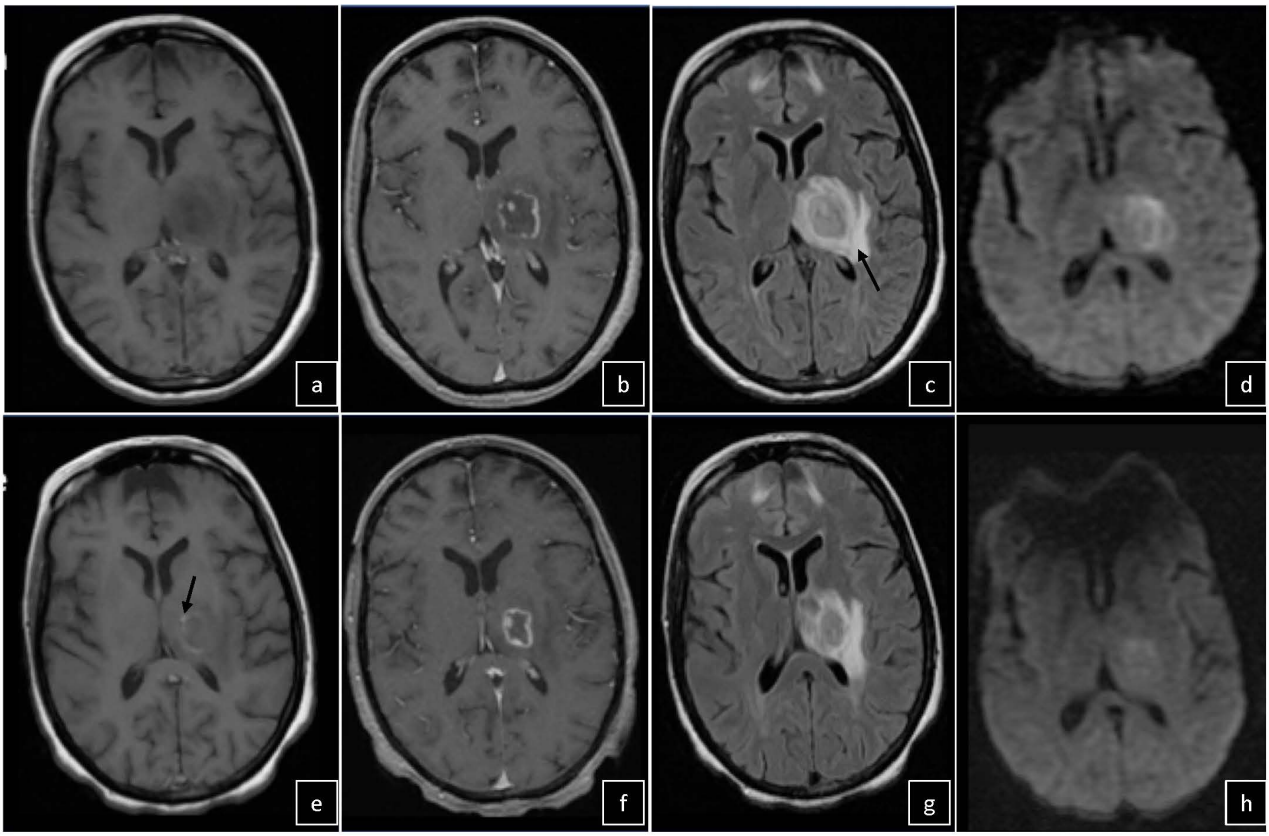

Fig. 5. *Cerebral toxoplasmosis in a 35-year-old patient with newly diagnosed HIV infection. A ring-like enhancing parenchymal lesion and an eccentric nodule along the wall on T1W and contrast-enhanced T1W MR images* ***(a, b)*** *are shown at the level of left thalamus. Surrounding vasogenic oedema (arrow in* ***c****) and mild mass effect on the third ventricle are seen on the FLAIR image* ***(c)****. The lesion shows restricted diffusion on DWI* ***(d)****. A follow-up post-treatment scan a month later revealed microhaemorrhage on T1W (arrow in* ***e****). The remaining findings were stable but showed mild regression after treatment* ***(f-h)****.*

other causes of ring-like enhancing focal brain lesions, such as cystic or necrotic tumours [18].

SWI in a pyogenic brain abscess will reveal the "dual-rim" sign corresponding to two concentric rims, the inner one hyperintense and the outer hypointense (compared to the cavity contents) that surround the necrotic central area [19, 20].

MRS in the central part of a pyogenic abscess shows peaks of succinate, acetate, lactate and amino acid, without peaks of N-acetyl-aspartate and choline that would be noted in healthy neural tissue. Bacterial glycolysis and fermentation lead to the presence of lactate, acetate and succinate, while amino acids are the products of proteolysis from enzymes released from neutrophils [21]. Furthermore, MRS may be useful in differentiating between anaerobic and aerobic pathogens as the cause of a brain abscess. Presence of succinate and acetate highly suggests anaerobic agents [22]. Also, MRS should be performed before treatment initiation, because peaks that occur after treatment may misguide in the differential diagnosis from cystic tumours [21, 22].

PWI is believed to be proportional to the maturity of the brain abscess capsule, as it provides information about cerebral haemodynamics. In the stage of early capsule formation, increased capillary density will produce increased regional cerebral blood volume (rCBV), whilst in late capsule, when decreased neovascularity is found and more amounts of mature collagen are illustrated, low rCBV is displayed [23, 24].

Conventional MRI sequences cannot differentiate between pyogenic brain abscess and other rim-like enhancing lesions such as cystic glioblastoma or metas-

tases. Yet, the use of complementary MRI sequences may facilitate the differential diagnosis. For example, low ADC is typically noted in pyogenic abscesses and helps to exclude cystic tumours, while an increase in rCBV suggests a necrotic tumour rather than a capsule of an abscess. Furthermore, MRS peaks will help in distinguishing abscesses from malignant brain lesions.

2.3. Infections in immunocompromised patients

A wide spectrum of CNS infections has been described in immunosuppressed patients. Although in the ED immunocompromised patients may complain about symptoms suggestive of CNS infection, in some cases an indolent disease course that complicates the diagnosis may be noted. The most common CNS infections in immunocompromised patients include aspergillosis, cryptococcosis, parasitic infections (e.g. toxoplasmosis), VZV, Cytomegalovirus (CMV) and herpes encephalitis, mycobacterial infection, progressive multifocal leukoencephalopathy (PML) and meningovascular syphilis [25].

- Toxoplasmosis is the most common opportunistic CNS infection in patients with acquired immune deficiency syndrome (AIDS) and CD4<200 cell/mm^3 and patients who have undergone bone marrow transplantation. CNS toxoplasmosis typically presents with multiple nodular or ring-like enhancing parenchymal lesions with surrounding vasogenic oedema. Frequently involved locations include the basal ganglia, followed by white matter and cortical lesions. In 30% of the cases an eccentric nodule along the wall is present, while less frequently a "concentric target sign" on T2W MR images is seen. On follow-up MRI, after the treatment has been completed, the abscesses may show haemorrhage and calcifications. Diagnostically it remains challenging to differentiate between cerebral toxoplasmosis and lymphoma by conventional contrast-enhanced MRI. Advanced MRI techniques or 18F-FDG PET/CT may be useful [26-29]. The findings on DWI may overlap but the ADC values are over 1.6 times that of contralateral normal white matter favouring toxoplasmosis and less than 0.8-1.0 times in cases of lymphoma. Choline values derived from MRS and rCBV values obtained from PWI are helpful for distinguishing between the abovementioned entities. Choline levels are reduced in cases of toxoplasmosis compared to increased levels in cases of lymphoma and the average mean rCBV for toxoplasmosis lesions are typically lower than those for lymphoma lesions [26-29] **(Fig. 5).**
- Invasive fungal infections, including Cryptococcus and Aspergillus, are a major cause of morbidity and mortality among immunosuppressed patients. The main radiological presentations of CNS cryptococcosis include signs of meningitis with high signal intensity subarachnoid spaces on FLAIR images, as well as leptomeningeal enhancement on contrast-enhanced T1W or on post-contrast FLAIR MR images, which demonstrates meningeal pathology with higher sensitivity and specificity [30-32]. More specific features, such as gelatinous (mucoid material) pseudocysts arising from dilated Virchow-Robin spaces and the so-called "hazy brain base" sign on T2W MR images, corresponding to ill-defined hyperintensities in the basal ganglia due to diffuse oedematous changes [30-32], can be noted. Differential diagnosis includes toxoplasmosis, primary CNS lymphoma and CMV encephalitis in cases where abnormal enhancement in the basal ganglia or in the subependymal spaces is noted. Aspergillus on the other hand presents mainly as multiple abscesses and fungal aneurysms [30-32] **(Fig. 6).**
- PML is the sequel of reactivation of latent John Cunningham (JC) virus. On T2W MR images, the lesions in the subcortical and deep white matter are hyperintense, while on DWI there is low signal (except from the lesion periphery, where patchy restriction is noted). Typical imaging findings of PML are also lack of mass effect and involvement of U-fibers (scalloping), as well as the crescent shape of the cerebellar lesions. Commonly, there is no gadolinium enhancement, but when this is noted, it is usually suggesting the manifestation of Immune Reconstitution Inflammatory Syndrome (IRIS), after initiation of Highly Active Antiretroviral Therapy (HAART) or in patients with multiple sclerosis treated with natalizumab [33, 34] **(Fig. 7).**
- Intracranial mycobacterial infections present most frequently as meningitis (basal meningitis with nodular enhancement) and in 25% with tuberculomas that affect the corticomedullary junction and have a smaller diameter and less perifocal oedema than abscesses. The imaging features of tuberculomas are also dependent on the stage of infection [35, 36].

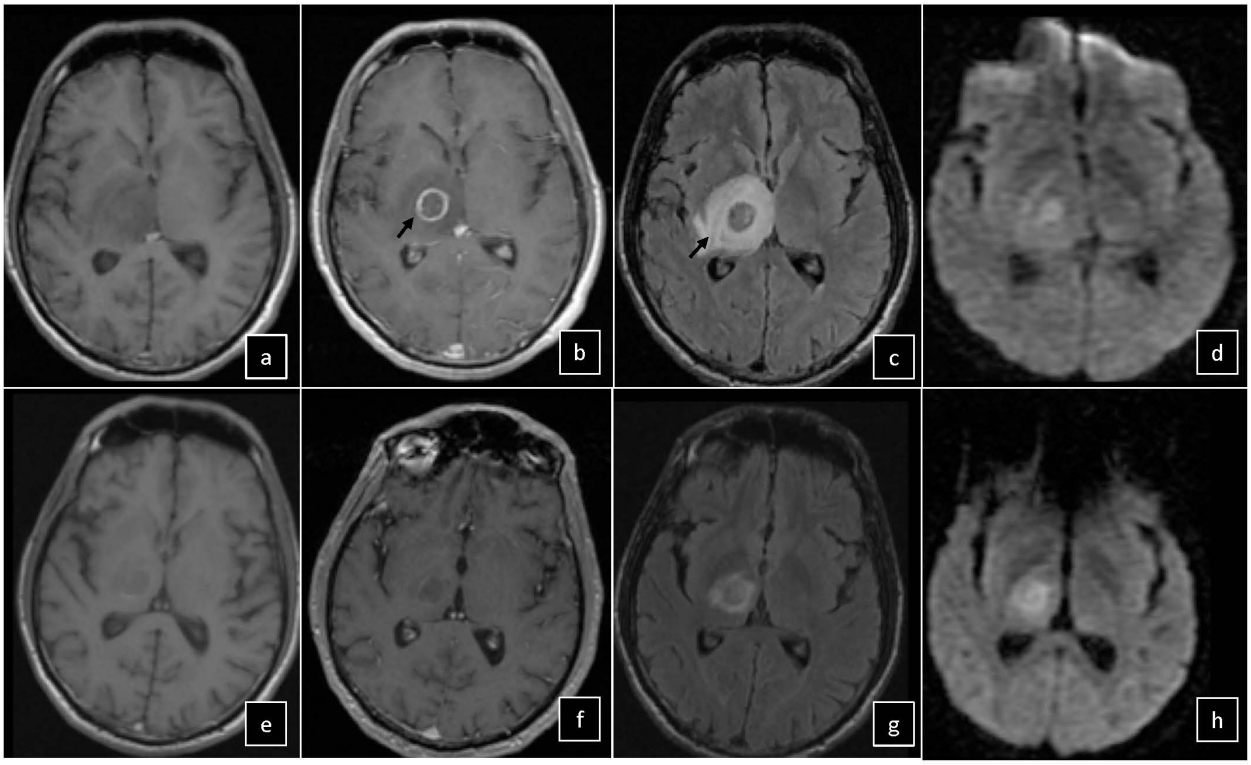

Fig. 6. *A 38-year-old patient with HIV infection showed on T1W MR images* ***(a)*** *a hypointense intraparenchymal focal lesion at the level of the right thalamus with a thick ring-like enhancement after contrast injection (arrow in* ***b****), suggestive of a brain abscess. On FLAIR MR imaging* ***(c)*** *there is perifocal oedema (arrow). Restricted diffusion is seen on DWI* ***(d)****. Serological analyses revealed antibodies against Cryptococcus. A post-treatment follow-up scan showed microhaemorrhage on plain T1W MR image* ***(e)*** *with less prominent imaging findings and limited perifocal oedema on contrast-enhanced T1W, FLAIR and DWI MR images* ***(f-h)****.*

3. Autoimmune-mediated encephalitis (AE)

Several immune-mediated CNS disorders, including multiple sclerosis, acute disseminated encephalomyelitis (ADEM), CNS vasculitis, rheumatologic conditions, including systemic lupus erythematosus and Behcet's disease, to name only a few, may present with neuropsychiatric deficits. A thorough analysis of the imaging findings of all immune-mediated CNS diseases is beyond the scope of the present article. Here, we focus on the recently discovered nosological entity of autoimmune-mediated encephalitis (AE), which has been linked to a predominantly encephalopathic and psychiatric clinical phenotype and has been shown to be causally related to antibodies against neuronal cell-surface or synaptic proteins. AE is believed to account for up to 1/3 of adult patients with new onset of epilepsy [37]. Yet, among AE patients, psychiatric symptoms, including newly-developed irritability, depression, sleep disturbances, hallucinations, and short-term memory loss are most frequently encountered in patients with limbic encephalitis, a form of AE affecting the limbic system. The limbic system comprises cortical structures, including the olfactory cortex, parahippocampal gyrus, hippocampus, cingulate gyrus and subcallosal gyrus, along with subcortical regions, including the amygdala, hypothalamus, anterior thalamic nuclei, mamillary bodies and parts of the basal ganglia [38]. Limbic encephalitis predominantly affects young and female patients (median 20 years) [39]. Clinical symptoms develop subacutely, within days or up to 12 weeks. Thus, a recent history of mood changes, delusional thoughts, paranoid ideation and short-term memory deficits in a patient admitted to the ED should promptly lead the physician to suspect an underlying limbic encephalitis [40]. Recent evidence suggests that the severity of psychiatric

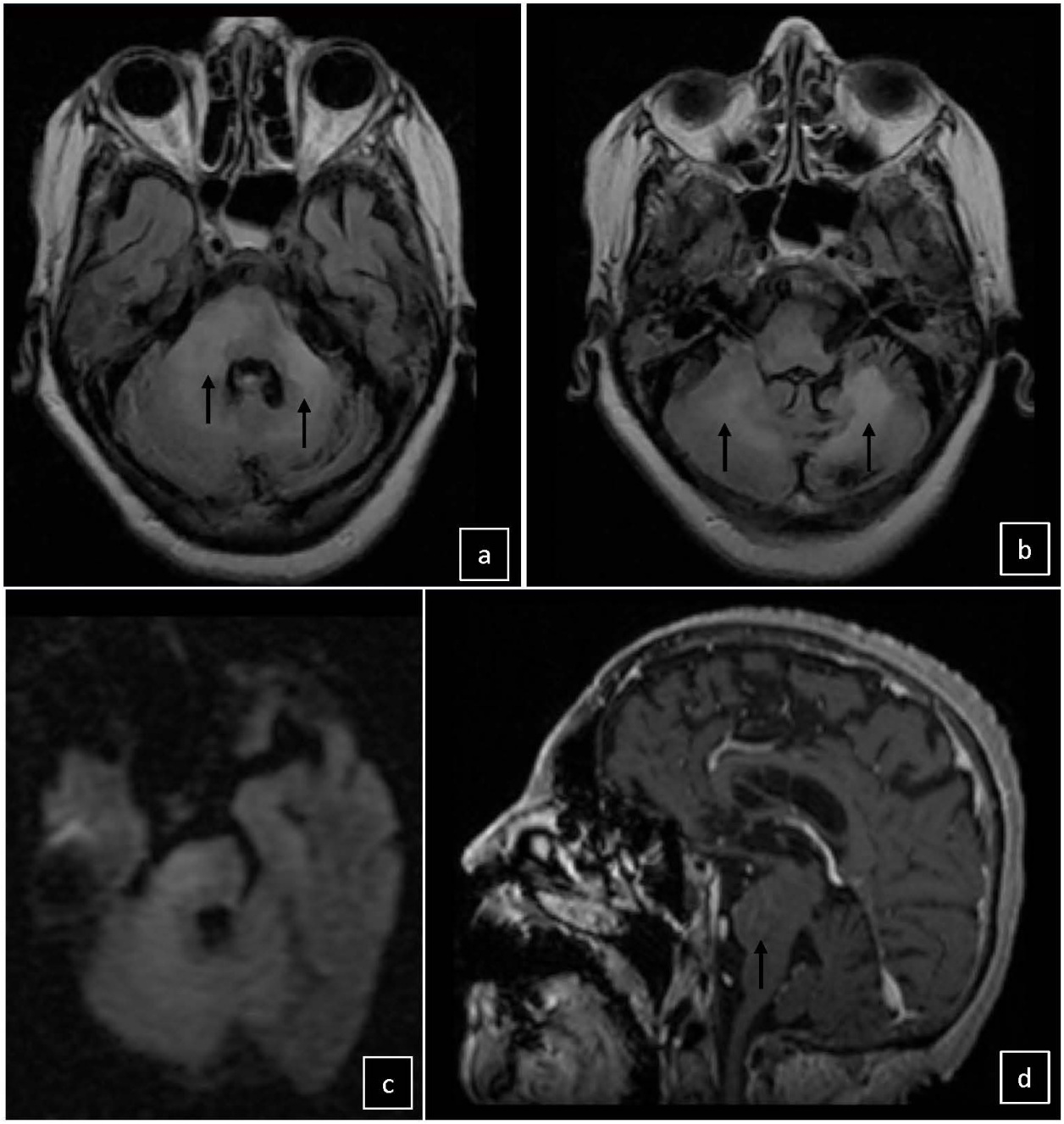

Fig. 7. *A 71-year-old patient with multiple sclerosis under natalizumab treatment was diagnosed with PML-IRIS. Hyperintense cerebellar and pontine lesions are noted on FLAIR MR images (arrows in* ***a, b****) with mild focal restricted diffusion on DWI* ***(c)*** *and mild gadolinium enhancement mostly in the pons on sagittal post-contrast T1W MR image (arrow in* ***d****).*

symptoms is often related to the levels of circulating antibodies, although different types of antibodies may be associated with distinct clinical phenotypes [41]. For example, anti-NMDA-receptor encephalitis is frequently associated with psychosis, dyskinesia, seizures, and/or catatonia in affected patients [42]. Besides psychiatric manifestations, anti-NMDA-receptor encephalitis (along with most types of limbic encephalitis) is also characterised by epileptic seizures, which can be diagnosed as epileptic activity in the

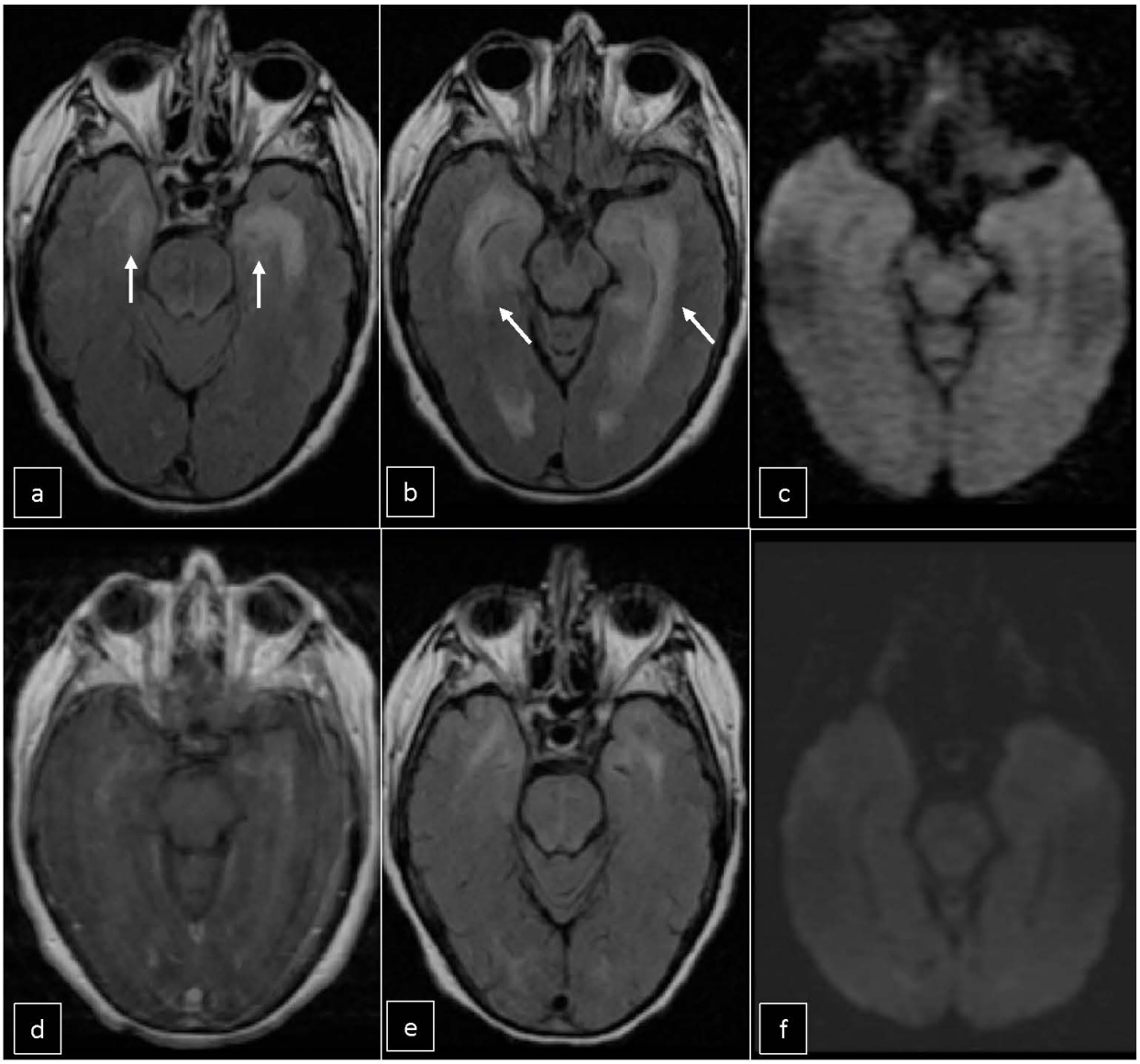

Fig. 8. *A 70-year-old female presented to the ED with rapid progressing dementia and emotional changes. On axial FLAIR* ***(a, b)*** *bilateral oedema and cortical thickening in the medial temporal lobes (arrows) are noted with no restricted diffusion on DWI* ***(c)****, suggesting limbic encephalitis. Serological CSF analysis revealed anti-GFAP Abs. A follow-up scan post-treatment showed less prominent imaging lesions on axial contrast-enhanced T1W* ***(d)****, FLAIR* ***(e)*** *and DWI MR images* ***(f)****.*

temporal lobes by EEG [43]. Besides the NMDA-receptor antibodies, several antineuronal antibodies (Abs) that target either intracellular or neuronal surface antigens have been discovered over the past years, and they have been associated with different types of AE of paraneoplastic or non-paraneoplastic origin. Abs against intracellular antigens have been frequently associated with malignancy and include the Hu, Yo, Ma/Ta, CV2, GAD Abs, whereas Abs against cell-surface antigens, including NMDA, VGKC, VGCC, GABAr Abs, have been associated to a variable (although lesser) extent with underlying malignancies. Crucially, one-third of the patients with AE have an underlying tumour, with ovarian teratoma being the most common in women of reproductive age (commonly associated with NMDA-receptor Abs) [44, 45].

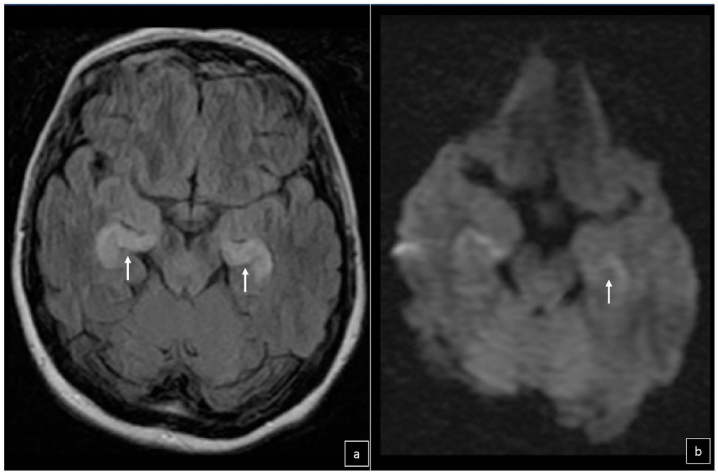

Fig. 9. *A 58-year-old female presented to the ED with personality and emotional changes. On axial FLAIR* ***(a)*** *bilateral oedema and cortical thickening in the medial temporal lobes are noted (arrows in* ***a****) with restricted diffusion on DWI (arrow in* ***b****). CSF analysis did not reveal HSV-1 infection or presence of antineuronal antibodies, though the imaging study was more suggestive of limbic encephalitis. The patient under immunosuppressive treatment showed clinical improvement.*

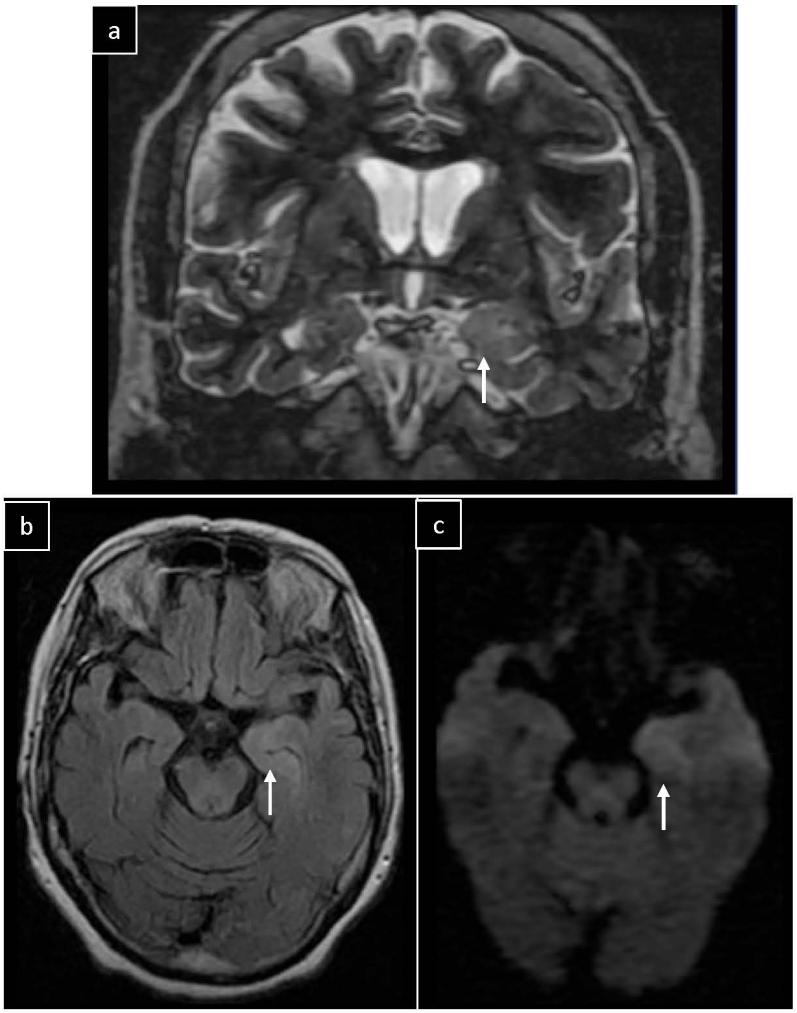

Fig. 10. *A 69-year-old female presented to the ED with emotional changes and visual hallucinations. On coronal T2W* ***(a)*** *and axial FLAIR MR images* ***(b)*** *bilateral (mostly left-sided) oedema and cortical thickening in the medial temporal lobes are noted (arrows in* ***a, b****) with restricted diffusion on DWI (arrow in* ***c****). CSF analysis did not reveal HSV-1 infection or antineuronal antibodies, though the imaging study was more suggestive of limbic encephalitis. PET/CT scan was negative with no evidence of paraneoplastic limbic encephalitis. The patient under immunosuppressive treatment showed clinical improvement.*

3.1. Imaging findings

Neuroradiological studies, including MRI and fluorodeoxyglucose positron emission tomography (FDG-PET), are extremely useful in the early diagnosis of AE. Importantly, imaging abnormalities may be noted at early disease stages and may precede the Abs detection. Additionally, recent studies suggest specific correlations between radiological findings, clinical phenotypes and the antigen/Abs profiles in AE [46].

In limbic encephalitis, MRI abnormalities are detected in approximately 70% of affected patients and typical findings involve signal and volume abnormalities of the amygdalae and hippocampi [47]. Asymmetric bilateral or unilateral T2 hyperintense lesions in the amygdalae and hippocampi are considered radiological features highly-suggestive of limbic encephalitis **(Figs. 8-10)**. These findings may evolve over the course of disease. The oedema may progress within the first 2 weeks. Significant atrophy may present at later stages, which in turn may or may not be reversible under immunosuppressive treatment. In practice, there is a long list of differential diagnoses of amygdala and hippocampus enlargement with abnormal T2 hyperintensities, including diffuse infiltration glioma, infectious encephalitis, Creutzfeld - Jakob disease, lesions associated with neurofibromatosis type 1, systemic lupus erythematosus, ADEM, Susac's syndrome, CNS angiitis and Rasmussen's encephalitis [48]. For purposes of differential diagnosis, further MRI studies including DWI and gadolinium-enhanced sequences are warranted to differentiate AE from other CNS disorders with limbic involvement. In limbic encephalitis, DWI has a pattern similar to cytotoxic oedema. However, ADC values are within normal limits [49, 50]. A diffuse loss of grey-white matter differentiation or concomitant involvement of subcortical grey matter in the presence of Abs may be noted [47]. Contrast enhancement is mainly seen in cases of paraneoplastic limbic encephalitis [51]. Finally, FDG-PET appears to be more sensitive than brain MRI in the diagnosis of acute limbic encephalitis and is considered useful as a follow-up method [52]. Radiologists should bear in mind that the diagnosis of a paraneoplastic limbic encephalitis should always lead to further diagnostic work-up, including whole-body CT or PET/CT scan for the detection of the primary site of cancer (e.g. lung, ovaries, thymus) [51].

4. Conclusion

Brain MRI is an indispensable tool for the diagnosis of underlying organic disease and for differentiating between primary and secondary psychiatric disorders in patients with newly-manifested neuropsychiatric symptoms. Conventional MRI sequences, along with advanced imaging modalities, can facilitate the early detection of infectious or immune-mediated CNS disorders, that may often masquerade as "mental disease". We suggest that MRI should be considered as an integral part of the diagnostic algorithm for patients presenting with psychiatric symptomatology in the ED, as accurate and prompt diagnosis of an underlying CNS disease is crucial for therapeutic management and clinical prognosis. **R**

Conflict of interest

The authors declared no conflicts of interest.

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