Diagnostic and therapeutic issues of inflammatory diseases of the elderly

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Abstract

Inflammatory diseases of the central nervous system (CNS) mainly occur during early adulthood and multiple sclerosis (MS) represents the overwhelming majority of these disorders. Nevertheless, MS only rarely begins after 50 years and a diagnosis of late-onset MS should only be done when clinical as well as radiological and biological findings are typical of MS since the probability of misdiagnosis is higher in elderly patients. Indeed, in patients aged over 50 years, along with a relative decrease of MS incidence, other inflammatory diseases of the CNS but also differential diagnoses including neoplastic as well as infectious disorders should be thoroughly searched to avoid diagnostic mistakes and the prescription of inadequate and potentially harmful immunomodulatory/immunosuppressive therapies. Moreover, aging is associated with diverse immune changes also known as immunosenescence resulting in, notably, higher risk of comorbidities (including vascular diseases) and infections which need to be considered when planning medical treatments of elderly patients with inflammatory diseases of the CNS. Herein, therapeutic and diagnostic challenges faced by neurologists are reviewed to ease patient management.

Keywords : Multiple sclerosis, Neuromyelitis optica spectrum disorder, aging, elderly, differential diagnosis

Introduction

Inflammatory diseases of the central nervous system (CNS) represent a large variety of disorders that preferentially occur during early adulthood (i.e. between 20 and 50 years old)[1–3]. Multiple sclerosis (MS) is by far the most common of these disorders but it should be noted that diagnosis should only be applied in the presence of typical symptoms reminiscent of MS and in the absence of specific red flags (Table 1) suggesting the possibility of an alternative diagnosis[2,4–6]. Indeed, in the presence of such red-flags, other non-MS inflammatory diseases must be carefully searched since their prognosis and treatments markedly differ[7–9].

Advanced age is one of the most important red flags against MS[2,4]. Although MS can occur in elderly patients, this diagnosis should be considered with caution and no patient should be treated for a presumed MS unless clinical, imaging (including spinal cord magnetic resonance imaging (MRI)) and biological features are typical of MS since the probability of misdiagnosis is higher in this population[10–12].

Moreover, during their aging, people are exposed to multiple immune changes (namely inflammaging) that result in low-grade inflammation leading to defects of adaptive and innate immune systems[13–16]. Owing to inflammaging, patients can be exposed to severe complications of highly effective immune therapies including notably infections and cancer.

Herein, we review the diagnostic and therapeutic challenges associated with inflammatory disease of the CNS and provide diagnostic clues that could help to consider differential diagnoses

Main characteristics of inflammatory demyelinating diseases in the elderly

Multiple sclerosis

MS is the most common chronic inflammatory disease of the CNS with an estimated prevalence of 50-300 per 100000 persons and an average sex ratio of approximately 3 females to 1 male[1,3]. MS onset usually occurs between the third and fourth decades even if paediatric as well as late-onset cases have been described[17–20]. In young adults, at the beginning of the disease, MS is usually characterised by a relapsing remitting course (i.e. subsequent relapses with complete or almost complete recovery) in the absence of disease progression between relapses[1,21].

MS onset in patients aged over 50 years had been described under the term late-onset MS (LOMS). According to previous series, LOMS roughly represents 3 to 6% of MS cohorts and patients with onset after 60 years old are described in less than 0.5% of cases (some rare patients with onset > 70 years have been described)[22,23]. In these patients, MS more frequently follows a primary progressive course (from 8% to 55%) with or without superimposed relapses and no clear female to male predominance[22,24–26]. Moreover, MRI, as well as biological findings, can be slightly different in LOMS than in younger patients: indeed, it has been rarely described that LOMS can disclose lower percentage of gadolinium enhancing MRI-scan at onset (7% vs 36%) even if CSF results disclose similar proportion of patients with oligoclonal bands (OCBs) (from 50% to 98%)[25,27,28]. Additionally, it is important to understand that, even in patients with inflammatory disease, MRI interpretation is complicated by the association of age-related, vascular hyperintensities visible on T2/FLAIR-weighted imaging. Importantly, diagnosis of MS in patients over 50 years has been demonstrated to be delayed suggesting that MS diagnosis in this very specific population is harder than in younger patients.

A single series described the main characteristics associated with very late onset (>70 years-old) inflammatory disease of the CNS[11]. Only 9/25 patients finally had a MS diagnosis including 5/9 PPMS.

Neuromyelitis optica spectrum disorder (NMOSD)

NMOSD is a rare disease that predominantly affects the optic nerve and spinal cord and is characterised by severe relapses with characteristic MRI findings and OCBs in less than 10% of patents[7,29,30]. The identification of specific anti-AQP4 and, more recently, anti-MOG autoantibodies has allowed a more precise delineation of these disorders and an expansion of the phenotype from typical neuromyelitis optica to more complex features (Table 2/ Fig. 1)[31,32]. Although the age of onset of NMOSD is typically between the third and fourth decades, late-onset NMOSD is relatively more common than late onset MS[33–36].

AQP4-positive NMOSD is mainly characterised by longitudinally extensive transverse myelitis (LETM), severe optic neuritis, NMO or characteristic brain (or brainstem) episodes[37–39]. On MRI, LETM is characterised by an extensive T2-hyperintensity spanning ≥ 3 spinal cord segments and some specific features have been suggested[38,40,41]…

Similarly, optic neuritis is different from MS-associated optic neuritis: it is usually severe and/or bilateral, with classical involvement of the intracranial segment (including the chiasma) of the optic nerve and relative extension to the intraorbital segment[39,42,43]. Although NMO has been initially described in patients with normal brain MRI, it is noticeable that brain/brainstem syndrome can occur in AQP4-IgG positive NMOSD: even if supratentorial lesions can occur, they are mainly

characterised by area postrema syndrome and diencephalic syndrome[44,45]. Importantly, a comparison between anti-AQP4 IgG positive NMOSD patients with age at onset > 50 years and < 49 did not evidence significant differences between young and late NMOSD[12].

Following the identification of MOG-IgG as the specific antigen in series of seronegative NMOSD, MOG-IgG-associated disorders (MOGAD) spectrum has been progressively expanded[34,35]. It currently represents a broad spectrum of (recurrent) optic neuritis, myelitis, NMOSD, acute disseminated encephalomyelitis (ADEM) as well as other encephalitis (Table 3). Apart from ADEM, that seems to be more common in adolescents, all the different clinical presentations of MOGAD seem to occur at various ages including in the elderly[46–48]. Since the precise extent of the disease is still expanding, it is important to consider this disease in a large variety of situations[49].

Other inflammatory diseases of the CNS (figure 2)

Autoimmune encephalitis

Thanks to the recent discovery of several autoantibodies targeting multiple neuronal and glial antigens, autoimmune encephalitis is an increasingly recognised, and potentially treatable condition[50,51]. While classical causes of paraneoplastic encephalitis (mainly related to intracellular antigens: Yo, Hu, Ri, Ma2…) were initially identified in the context of cancer, most of the recently identified autoimmune encephalitis cases (related to synaptic/cell surface antigens: NMDAr, LGI1, CASPR2, GFAP) are more commonly termed “idiopathic”. Autoimmune encephalitis should be suspected in the presence of a subacute neurological deficit with predominant short-

term memory loss or psychiatric symptoms associated with either evidence of CSF pleocytosis and/or bilateral medial temporal lobe T2-hyperintensities on brain MRI. In the elderly, although NMDAr encephalitis is less common, one should note that almost all of the autoimmune encephalitis have been described. As a consequence, a broad workup looking for all the autoantibodies (synaptic/cell membrane antibodies in the CSF, intracellular antibodies in the blood) and associated cancer is usually needed[52].Acute disseminated encephalomyelitis (ADEM) is an immune-mediated demyelinating disease of the CNS that preferentially occurs during childhood[53–55]. Clinically, it is mainly characterised by multifocal neurologic symptoms and a variable degree of encephalopathy[56]. Imaging features commonly include T2-weighted and FLAIR multiple, asymmetric hyperintensities usually involving white matter as well as cortical and deep grey matter[55,57,58]. Although ADEM usually follows a monophasic course, some patients with multiple, recurrent episodes have been described[54]. It should also be noted that AQP4 (rarely) and more frequently MOG-IgG have been found in the context of ADEM and should thus systematically screened[7,59,60].

More recently, autoimmune encephalitis related to GFAP-IgG autoantibodies have been described in patients with acute/subacute meningoencephalomyelitis[61,62]. Although this entity has only recently been described, GFAP autoimmune astrocytopathy can arise in geriatric patients and is mainly characterised by one or more of encephalitis, myelitis or meningitis[63,64]. CSF analysis usually discloses pleocytosis and elevated protein and OCBs are found in > 50% of patients[61]. On MRI a striking pattern of radial perivascular gadolinium enhancement is observed although more recent series suggest a broader spectrum of MRI abnormalities.

Primary angiitis of the central nervous system (PACNS)

PACNS is a rare disease characterised by vessel wall inflammatory infiltrate restricted to the CNS[65–67]. Diagnosis requires the identification of histological evidence of vascular lesions with angiocentric transmural inflammatory infiltrates and vessel wall damage or angiographic evidence of typical segmental stenoses/dilatations[68,69]. Most patients present several clinical manifestations including headaches, transient ischaemic attacks, stroke, seizures of altered cognition. CSF analysis is abnormal in more than 50% of patients revealing an elevated leukocyte count and/or raised protein concentration[66]. MRI usually shows findings suggestive of PACNS typically evidencing disseminated infarcts usually involving subcortical structures associated with gadolinium enhancing FLAIR hyperintensities[69,70]. Susceptibility imaging is of importance since hemosiderin deposits are highly suggestive of a vascular phenomenon[71,72]. Rarely, PACNS can present with an isolated cerebral lesion mimicking brain tumour. Computed tomographic (CT) or magnetic resonance (MR) angiography usually disclose alternating stenoses and dilatations highly suggestive of the diagnosis but, in some cases, histopathological analysis is necessary. Although PACNS is a rare disease, it should be considered in the differential diagnosis of all inflammatory diseases of the elderly since nearly one quarter of the patients are older than 50 years[66].

It is noticeable that other inflammatory diseases with CNS involvement exist, they mainly include neurosarcoidosis, systemic lupus and Sjogren syndrome[73–75]. The main causes are disclosed in Table 2.

Differential diagnosis (Fig. 3)

The spectrum of differential diagnoses of inflammatory diseases of the CNS in the elderly is broad[73]. Notably, in the context of acute/subacute neurological deficits, it includes CNS tumours and, more rarely, infectious diseases. Indeed, it can be complicated to distinguish inflammatory diseases from CNS lymphoma and brain biopsy is sometimes needed[76,77]. The main radiological clues that help to differentiate these two diseases include CT-scan and diffusion-weighted imaging (DWI) hyperintensities associated with punctate and curvilinear or nodular central enhancement that are rarely found in inflammatory demyelinating disorders[77,78]. Moreover, it has been recently shown that CSF IL-10 levels were elevated in CNS lymphoma and could be of additional diagnostic value in this context[79].

In the context of progressive worsening of gait and/or cognitive disturbance, one of the main issues is to differentiate chronic microangiopathy from inflammatory demyelinating disorders (mainly MS). A thorough analysis of MRI features is mandatory since, in patients over 50 years and especially thosewith vascular risk factors, inflammatory and microangiopathy lesions can coexist[80]. This analysis can help to distinguish those two conditions (table 3):

- Central pons, temporal pole, deep basal ganglia and external capsule involvement as well as cerebral microbleeds and calcifications are in favour of a vascular process.
- Juxtacortical, cortical and periventricular lesions (perpendicular to lateral ventricles) as well as open ring gadolinium enhancement strongly argues in favour of MS.

Finally, some very rare diagnoses including progressive multifocal leukoencephalopathy (PML), chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids (CLIPPERS) and some other rare

diseases can be considered in the differential diagnosis of inflammatory diseases in the elderly[81–83]. They are listed in Table 3.

What are the main diagnostic clues?

Even though the number of published studies focusing on inflammatory diseases of the CNS in elderly patients is very low, it seems to be clear that the overwhelming overrepresentation of MS among all these diseases does not remain after 50 years old and more so over after 60 or 70 years old[11]. This was well described by Lavandier et al., who presented a series of 25 cases of which only nine were finally diagnosed as MS. It is therefore of importance to perform a complete imaging and biological workup searching for evidence of an alternative diagnosis (Table 3).

After a complete workup is done, there are important imaging diagnostic clues that need to be considered:

- Acute partial myelitis notably involving the external part of the spinal cord, evidence of asymptomatic optic nerve involvement (on visual evoked potential and/or optic coherence tomography) as well as presence of ≥ 2 oligoclonal bands are highly in favour of MS.
- Acute transverse myelitis and severe optic neuritis strongly suggest either AQP4- or MOG-IgG associated disease. If antibody screening is negative, it should be renewed (AQP4) and research should be done within the CSF (MOG)[84–86].

- Susceptibility weighted imaging (either SWI or T2-GRE) and CT-scan can identify microhaemorrhages and/or calcifications that suggest a vascular process. In all the cases, when no cause is obvious, a minimal vascular workup is needed to explore extracranial and intracranial vessels[71].
- Punctate and curvilinear gadolinium enhancement are more frequent in lymphoma, CLIPPERS, vasculitis and systemic diseases[87]. Their identification should lead to appropriate complementary workup including at least CSF IL10/IL6 assessment, whole body PET-FDG and a minimal workup looking for systemic involvement.
- New MRI techniques, including the identification of central vein on SWI/FLAIR* will probably help to separate MS from other inflammatory diseases of the CNS but their relevance in elderly patients (notably due to the association of age-related vascular changes) is not known[4,88,89]

A careful analysis of all the clinical and radiological findings should normally help to identify the exact diagnosis. Nevertheless, in some cases, brain biopsy can be required to identify the exact mechanism.

Treatment specificities in elderly patients

Aging is associated with immune changes including thymic involution, reduced repertoire diversity, loss in naïve T cells as well as epigenetic changes and circulating cytokines increase that results in chronic low-grade inflammation also named inflammaging[90,91]. Moreover, elderly patients are exposed to multiple comorbidities including cardiovascular risk factors[92]. These considerations are of importance in patients who may suffer from advanced disability that can also increase the risk of

potentially life-threatening medication-related adverse effects including notably infections[93].

In the context of MS for example, most infections (including opportunistic infections) in the context of disease modifying therapies occur preferentially in patients over 50 [94,95]. Moreover, natalizumab-associated primary multifocal leukoencephalopathy risk has been shown to increase in elderly patients[96]. Recently, leflunomide (the teriflunomide metabolite) has been shown to be associated with pulmonary arterial hypertension in patients > 50 years[97]. Even if teriflunomide has not been associated with a similar adverse effect, ageing patients should be more closely monitored since they are probably more prone to develop potentially severe adverse effects than younger people. Finally, one should note that patients > 50 years are at higher risk of having previous history of stroke or myocardial infarcts, having atrioventricular blocks and being under treatments that either contraindicate or require specific consideration before considering a treatment like fingolimod[98].

Taken together, all these changes that occur in ageing patients absolutely need to be considered when planning medical management (including potentially highly effective immunotherapies) of patients with suspected inflammatory disease.

Conclusion

Whereas MS is by far the most common cause of inflammatory diseases of the CNS in young adults, one should note that, in elderly patients, the probability of having MS is markedly reduced and should prompt complete biological and radiological workup to identify specific clues as well as major red flags that can help to recognise alternative diagnoses.

Owing to immune changes that occur along with ageing exposing patients to higher probability of infections along with the presence of multiple comorbidities, it is also noticeable that therapeutic management in this particular population needs to be thoroughly considered in order to maximize the benefit/risk ratio and reduce the number of potentially severe adverse effects.

In this review, we try to focus on the main diagnostic clues that should help clinicians to accurately identify specific red flags for MS and then reconsider the diagnosis. We also give a rapid overview of the main differential diagnoses of inflammatory disease of the CNS and underline the important need for complete biological and radiological workup that is essential to avoid misdiagnosis and the initiation of potentially inadequate treatments.

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TABLES :

Table 1: Atypical features for MS (“red flags”)

Red flags
Clinical
Age at onset > 50 years or age at onset < 20 years
Optic neuritis: severe, bilateral or poor recovery
Myelitis: bilateral, severe motor weakness
Abrupt onset, rapid cognitive decline at onset, headaches
History of systemic disease, aphtosis, retinal vasculitis, hearing loss
Laboratory (CSF)
Absence of OCB
White blood cell count > 50 cells/mm^3
Proteinorrhachia > 100 mg/dL
Imaging
Atypical morphology/distribution of brain white matter lesions
Longitudinal extensive transverse myelitis
Extended/posterior and/or bilateral optic neuritis

Table 2: Main features differentiating MS from NMOSD in adults

	MS	AQP4-IgG NMOSD	MOGAD
Clinically	Acute partial myelitis Unilateral optic neuritis Typical brain/brainstem syndrome	Longitudinally extensive transverse myelitis Recurrent, bilateral & severe optic neuritis with limited recovery NMO Brainstem syndrome	Longitudinally extensive transverse myelitis Recurrent, bilateral & severe optic neuritis, Steroid responsiveness ADEM, Steroid responsive epileptic encephalopathies
Biological	OCBs in > 90% Normal WBC	OCBs in 10-20% Slightly elevated WBC count	OCBs in +/- 5% Markedly elevated WBC count
Brain MRI	Periventricular lesion centered by a small central vein (Dawson's finger) Cortical lesions ≥ 9 lesions	Brain lesion around subependymal area, Area postrema, medulla oblongata involvement	Fluffy lesions No lesion adjacent to the lateral ventricle, Pons, thalamus involvement
Optic nerve MRI	Canalicular, unilateral, Short	Intracranial, chiasmal, Bilateral	Optic nerve head swelling, Bilateral, Perineural gadolinium enhancement
Spinal cord MRI	Short partial myelitis Multiple lesions	LETM Bright spotty lesion	LETM Multiple lesions H sign, Linear sagittal hyperintensity Conus involvement

Table 3: Other inflammatory disease of the CNS and differential diagnosis: main differentiating features

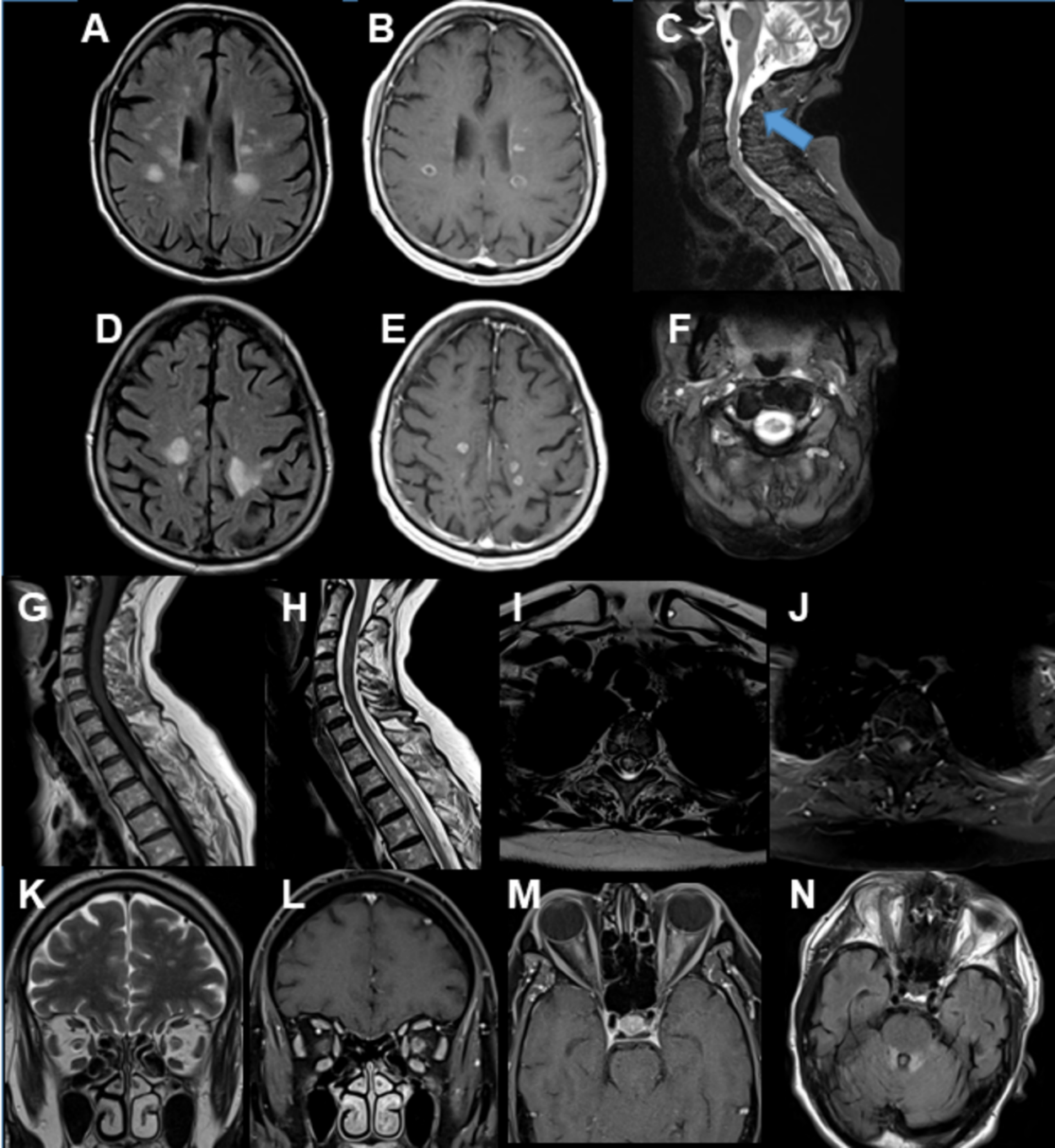
	Clinical findings	Main MRI findings	CSF	Diagnostic clues
CNS vasculitis	Headaches, transient ischaemic attacks/strokes, encephalopathy	Punctate Gd+ lesions, Small ischemic dots Hemorrhages	WBC count ↗	Angiography, biopsy
Acute disseminated encephalomyelitis	Multifocal CNS involvement, encephalopathy	Multiple FLAIR WM hyperintensities, most of the lesions Gd+	OCBs usually absent	Absence of clinical/radiological evolution after 3 months, MOG, AQP4 Abs
Autoimmune encephalitis	Limbic encephalitis, psychiatric symptoms, seizures, FBDS…	Temporal lobe T2-hyperintensities	Variable	Cell-surface/synaptic Abs (CSF), Intracellular Abs (serum)
GFAP encephalitis	Encephalomyelitis, Meningitis	Radial enhancement Punctate and curvilinear enhancement,	OCBs in >50% WBC count ↗	GFAP-IgG testing (serum/CSF)
Neurosarcoidosis	Facial palsy (bilateral), systemic involvement	Predominantly meningeal involvement	OCBs rare	PET-scan, thoracic imaging, biopsy
Connective tissue disorder	Predominantly systemic involvement	Variable	OCBs usually absent	Systemic features
CNS lymphoma	Variable	Punctate or nodular Gd+ lesions	OCBs usually absent, WBC count ↗	FDG PET-Scan, Raised IL10/IL6
CLIPPERS	Brainstem symptoms Steroid responsive steroid dependent	Punctate brainstem Gd+ lesions	OCBs sometimes present	Brain biopsy
Cerebral microangiopathy	Progressive walking and cognitive difficulties	Variable white matter hyperintensities, Small ischemic dots, haemorrhages		Vascular risk factors (age, HBP)

Figures legend:

Figure 1: MRI features in MS (A-F), AQP4-IgG positive NMOSD (G-J) and MOGAD (K-M). Axial FLAIR (A, D) and T1-post gadolinium injection (B, E) disclose multiple gadolinium enhancing periventricular and juxtacortical hyperintensities suggestive of MS. Sagittal (C) and Axial (F) T2 spinal cord MRI reveal acute partial myelitis. An acute transverse myelitis with extensive longitudinal (G, H) and axial (I, J) involvement is in favour of a NMOSD. It is noticeable that T2 hyperintensity is heterogeneous with areas of marked hyperintensities (brighty spotty lesions). In MOGAD patients, optic neuritis (K-L) are typically extensive with diffuse intraorbital involvement and perineural gadolinium enhancement (K-M). Posterior fossa involvement and notably cerebellar peduncle hyperintensities (N) are also common in MOGAD.

Figure 2 : MRI abnormalities in other inflammatory diseases of the CNS. Temporal medial lobe hyperintensities (A-C) are highly suggestive of an immune-mediated encephalitis. They can be subtle (A, in a patient with anti-LGI1 autoantibodies) or more diffuse (B, C, in a patient without specific autoantibody). In ADEM (D-G), cortical, juxtacortical and posterior fossa hyperintensities (D, F) are common. Most of the lesions are gadolinium-enhancing (E, G). In patients with GFAP encephalitis (H, I), abnormalities are more common on T1-weighted postgadolinium sequences (H) than on FLAIR imaging (I). The pattern is typically perivascular with linear, radial or punctate enhancement. In PACNS (J-L), cortical and juxtacortical hyperintensities (J) are common with punctate and/or nodular enhancement (K). susceptibility imaging including T2* is of diagnostic value when it shows cerebral microbleeds.

Figure 3: Disorders that can mimic inflammatory disease of the central nervous system. CNS lymphoma (A, D) lesions can evoke inflammatory lesions. Nevertheless, the presence of punctate enhancement pattern (B, D) and the diffuse infiltration of the corpus callosum (C) as well as rapid progression (1 month between images A-B and C-D) suggest alternative diagnosis. In some patients, brain cerebral microangiopathy (E-H) can be misdiagnosed as inflammatory lesions. Nonetheless, the absence of typical periventricular and cortical/juxtacortical lesions (E) as well as the presence of central pons (F) and temporal (G) involvement suggest a vascular disease. Cerebral microbleeds (H) are also in favour of a microangiopathy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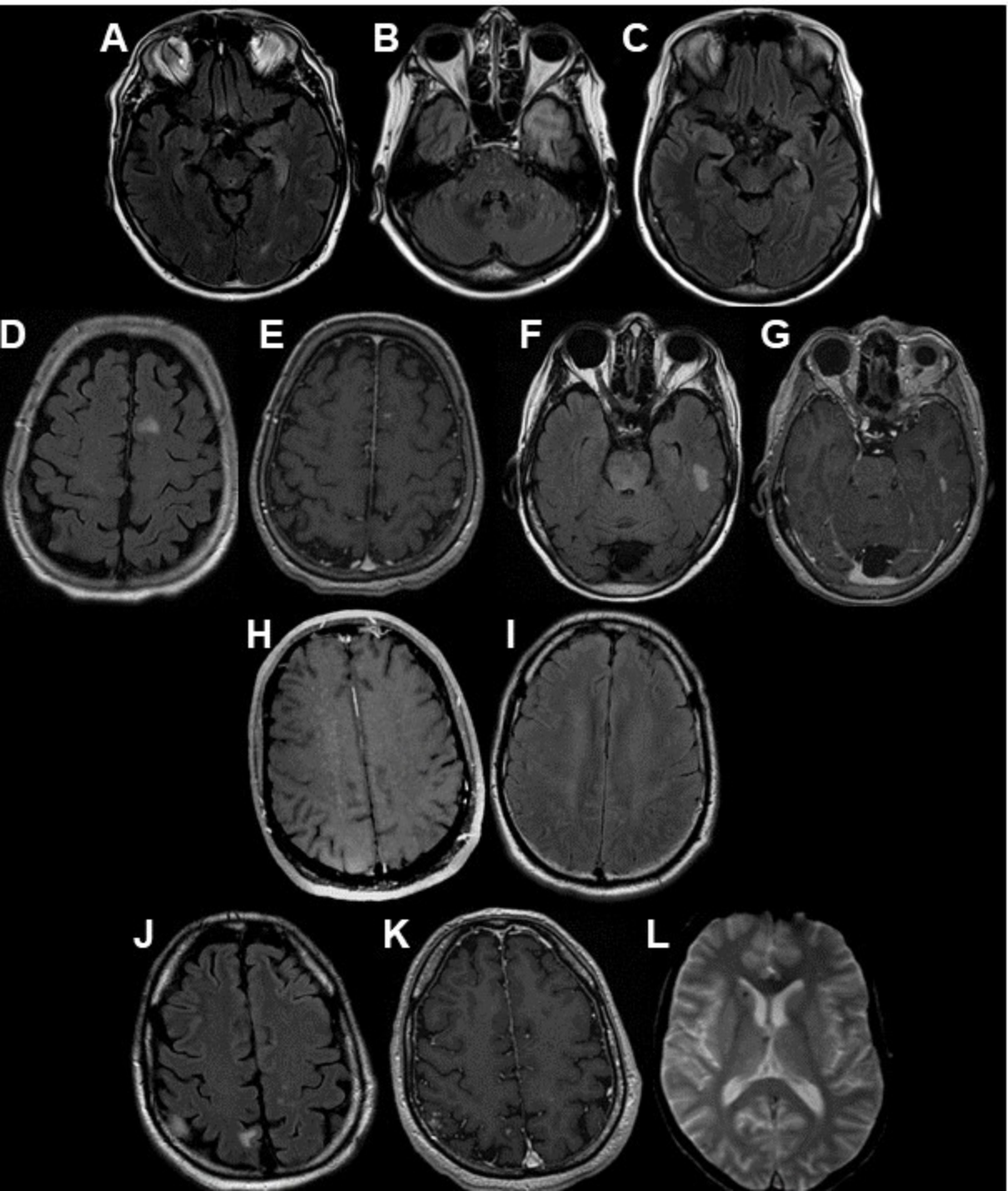
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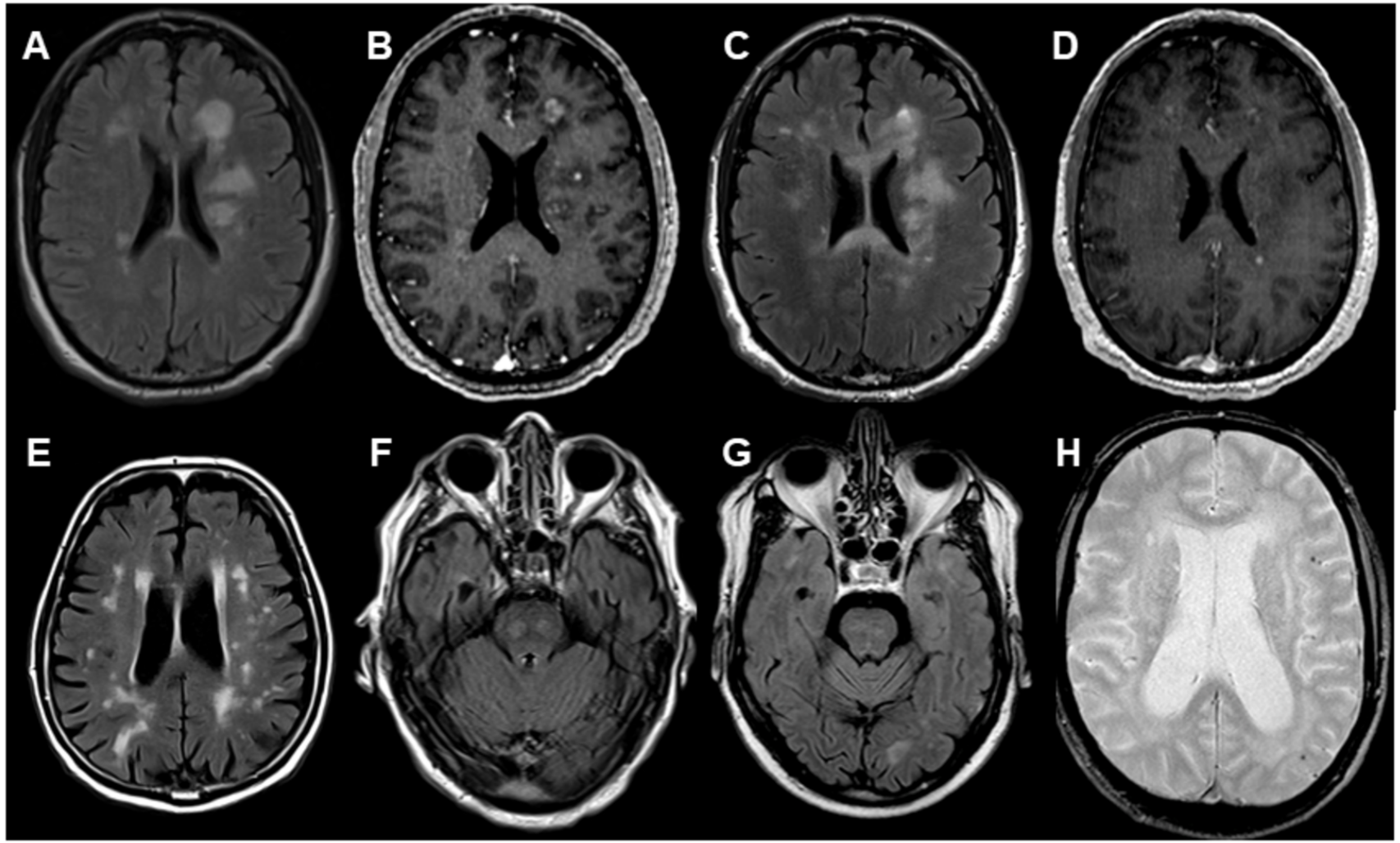
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