Cognitive disorders in patients with neuroimmunological disease

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Purpose of review
Autoimmune diseases such as systemic lupus erythematosus (SLE), multiple sclerosis (MS), and autoimmune encephalitis can directly and indirectly affect brain function, leading to cognitive dysfunction or well characterized neurocognitive syndromes. However, these are often poorly characterized in the literature. Here, we review evidence on clinical manifestations, risk factors, their assessment and outcomes, and evidence for underlying mechanisms and associated biomarkers, if available.

Recent findings
Significant advances have been made in neurocognitive disorders associated with four categories of autoimmune disease: neurocognitive disorders due to autoimmune connective tissue diseases, neurocognitive disorders due to autoimmune demyelinating diseases of the CNS, neurocognitive disorders due to autoimmune encephalitis, and neurocognitive disorders due to cerebrovascular disease of autoimmune origin.

Summary
Autoimmune diseases should be considered as critical causal factors underlying new cases of neurocognitive disorder, especially in young patients. These diseases are mediated by immune system reactions involving antibody production, T-cell-mediated damage, and demyelination. Although the prognosis seems favourable in most conditions after immunotherapy, the magnitude of the therapeutic effect of immunotherapy on cognitive functioning remains unclear.

Keywords
autoimmune disease, cognitive impairment, neurocognitive disorders

INTRODUCTION

Some autoimmune diseases affect the brain and can be regarded as neuroimmunological conditions. In this review, we will address four categories: autoimmune connective tissue diseases, autoimmune demyelinating diseases, autoimmune encephalitis, cerebrovascular disease of autoimmune origin. We summarize the latest advances on how these diseases lead to cognitive dysfunction, including the identification of risk factors, underlying mechanisms, associated biomarkers, and outcomes [1▪,2–4].

COGNITIVE DISORDERS IN AUTOIMMUNE CONNECTIVE TISSUE DISEASES

Connective tissue diseases encompass a collection of multisystemic, chronic, and inflammatory autoimmune diseases, in which the immune system reaction involves an antibody or T cells that target self-antigens and ultimately results in tissue destruction and multisystemic damage. In this review, we will focus on systemic lupus erythematosus (SLE) [5].

Systemic lupus erythematosus

SLE is characterized by inflammation and immune-mediated injury, involving multiple organ systems. It affects 3.4 million people worldwide, with a female-to-male ratio of 7 : 1 to 15 : 1 before menopause and 8 : 1 in older adults [6,7]. Neuropsychiatric SLE refers to the central nervous system involvement, leading to seizures, focal neurological

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KEY POINTS

- Autoimmune diseases, such as systemic lupus erythematosus, multiple sclerosis, and autoimmune encephalitis, are associated with varying degrees of cognitive decline, from mild to major neurocognitive disorder.
- Autoimmune diseases should be regarded as potential etiological conditions underlying cases of neurocognitive disorder, especially in young patients.
- The pathogenesis of cognitive dysfunction in autoimmune diseases involves multiple mechanisms, including immune-mediated inflammation, blood–brain barrier disruption, and the presence of autoantibodies.
- Although the prognosis seems favourable in most conditions after immunotherapy, the size effect of immunotherapy on cognitive outcomes remains unclear.

dysfunction, psychosis, delirium, and subacute and chronic cognitive impairment [8,9].

Given the lack of consensus in screening tools for identifying cognitive impairment in SLE, the difficulty in attributing cognitive symptoms to SLE activity, and the lack of universal biomarkers explaining the causes of cognitive dysfunction, the prevalence rates of cognitive impairment in SLE are heterogenous, ranging between 3 and 88% [10]. Current research offers a more precise estimation. A systematic review focused on patients from Pakistan ($N = 2003$, mean age was 28.8 years, 76–96% were women), cognitive dysfunction had a pooled prevalence of 31.5% [95% confidence interval (CI)1.2–76.2%]. Other problems were headache (10.2%; 95% CI 0.0–33.4%), seizures (5.9%; 95% CI 3.8– 8.5%), and psychosis (3.6%; 95% CI 2.3–5.1%) [11▪]. A study from the Netherlands ($N = 357$, mean age 44 years, 86% women) showed that global cognitive function was impaired in 8% of patients [12]. A sample of 94 patients from Colombia [mean age: 37 years, interquartile range (IQR) 28–46.7] found a 15.95% prevalence of cognitive impairment [13]. In Northern India, 13.3% of the cases in a sample of 79 SLE patients had scores within the range of severe dementia [14].

Current research on neuropsychological patterns shows a multidomain cognitive disturbance in SLE [15]. A sample from Brazil (103 patients and 93 controls) showed deficits in the visuospatial ($P = 0.03$), abstraction ($P = 0.002$), language ($P = 0.002$), and spatial orientation domains ($P = 0.01$) [16]. A study of 95 patients with SLE and 48 controls showed a neuropsychological pattern, involving verbal fluency, working memory, and attention [15]. In SLE of childhood onset ($N = 39$), attention, executive functioning, and memory are frequently affected [17].

Mild to moderate SLE-related cognitive dysfunction may occur in the absence of active systemic lupus, but patients with overt neuropsychiatric systemic lupus erythematosus (NPSLE) tend to have more profound cognitive impairment. Immune system dysregulation and vascular abnormalities lead to structural and functional brain connectivity changes. The presence of N-methyl-D-aspartate receptor (NMDAR) antibodies may have a causal role in a subset of patients, and antiribosomal-P antibodies increase the likelihood of NPSLE [9]. Importantly, current research provides insights into understanding cognitive impairment resulting from blood–brain barrier (BBB) leakage. In a study from Canada ($N = 77$), BBB leakage was associated with cognitive impairment. Abnormalities in functional connectivity accounted for 64% of the association between BBB leakage and cognitive impairment, involving the language/memory, attention/executive, and sensory functional networks [18]. Also, a study of 290 patients with SLE showed that 40% had cognitive impairment; serum levels of the S100A8/A9 protein ($P = 0.006$) and MMP-9 proteases ($P = 0.036$) were significantly higher in patients with SLE with cognitive impairment compared to patients without cognitive dysfunction.

Prospective cohort studies have reported complete resolution of cognitive dysfunction in most patients with SLE over a 1–10 year follow-up [19,20]; few studies have reported a persistently low but stable cognitive dysfunction [21]. Although there is increasing interest in the pharmacological treatment of cognitive dysfunction in SLE, randomized control trials are lacking. However, observational research suggests that some immunological treatments could have a therapeutic effect on cognition. A prospective study ($N = 300$) assessed the effects of two treatments (azathioprine and mycophenolate). The cumulative azathioprine dose was associated with reduced odds of cognitive dysfunction [odds ratio (OR) = 0.76, 95% CI 0.58–0.98]. Mycophenolate use was not associated with benefits or harms in terms of cognitive dysfunction [22▪].

COGNITIVE DYSFUNCTION IN AUTOIMMUNE DEMYELINATING DISEASES OF THE CENTRAL NERVOUS SYSTEM

Autoimmunity plays a major role in CNS demyelination, which results in poor conduction of action potentials, impaired neuronal signalling, and, in some cases, neuronal loss [2]. Here we focus on multiple sclerosis (MS), neuromyelitis optica spectrum

Table 1. Cognitive impairment in autoimmune demyelinating diseases of the central nervous system

	Classical syndrome	Cognitive impairment
Multiple sclerosis	Classic features include unilateral optic neuritis, partial myelitis (extremity and torso impaired sensation or weakness), focal sensory disturbance [limb paresthesias, abdominal or chest banding (dysesthesia)], or brainstem syndromes (intranuclear ophthalmoplegia, vertigo, hearing loss, facial sensory disturbance)	Deficits in processing speed, attention, and working and episodic memory. Patients with relapsing–remitting MS have a prevalence of cognitive impairment was 32.5% [25]. 70% of the patients with progressive multiple sclerosis have cognitive impairment [24].
Optic neuromyelitis	Optic neuritis in rapid succession or bilateral simultaneous optic neuritis: myelitis is symmetrical and involves three or more vertebral segments in length, area postrema syndrome and other brainstem or diencephalic syndromes.	47% of the NMOSD patients (47%) show cognitive impairment, with a pattern of executive dysfunction, correlated with the degree of physical disability [34].
MOGAD	Overlaps phenotypically with NMO and MS; more commonly presents as optic neuritis, myelitis, and acute disseminated encephalomyelitis (ADEM)	Reduced visuomotor processing speed and semantic fluency [39▪].

disorders (NMOSD), and myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD). Table 1 summarizes some of the current concepts on cognition in MS as well as other demyelinating diseases of the CNS.

Multiple sclerosis

MS causes demyelination and neuronal injury, resulting in a multitude of signs and symptoms. Cognitive dysfunction affects around 30–40% of patients with MS, interfering with their functionality and quality of life [23,24]. In patients with relapsing–remitting MS, current research shows that the pooled prevalence of cognitive impairment was 32.5% (95% CI 29.3–36.0%) across 5859 participants in a systematic review and meta-analysis; age and disease duration were the most reliable predictors of cognitive impairment [25]. Patients with progressive multiple sclerosis have rates of cognitive impairment as high as 70% [24]. Figure 1 presents a clinical and neuroradiological vignette of this problem.

Different neuropsychological tools have been developed for the evaluation of MS. For screening, the accepted tools include the Multiple Sclerosis Neuropsychological Questionnaire, the Symbol Digit Modalities Test, and the PASAT-3 (3-s Paced Auditory Serial Addition Task). If a more extensive evaluation is necessary, the Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS), the Brief Repeatable Battery-Neuropsychology (BRB-N), and the Minimal Assessment of Cognitive Function in Multiple Sclerosis (MACFIMS) have demonstrated higher sensitivity in the detection of cognitive impairment in MS [23] (Fig. 2).

Cognitive impairment in MS is defined by a performance below 1.5 or 2 SD in at least two cognitive domains. Processing speed, attention, working and episodic memory are the major cognitive domains affected by MS [23,26]. A dysexecutive neuropsychological profile is usually associated with progressive forms of MS, while an amnestic neuropsychological profile is often seen in relapsing–remitting MS. In a sample of 243 patients and 158 controls, the neuropsychological patterns of MS were reduced into five cognitive phenotypes: 56% of the patients had preserved cognition, whereas 15% had mild single-domain impairment, 9% suffered from mild multidomain impairment, 12% had significant single-domain impairment, and 8% had significant multidomain impairment [27]. Social cognition and emotional processing are frequently involved as well with current research showing a pathological level of alexithymia in 34% of patients with radiologically isolated syndrome and 51.7% with remitting–relapsing MS [28].

Disease-modifying therapies (DMTs) for MS have shown beneficial effects, delaying and perhaps improving cognitive function by arresting the course of the disease and preventing relapses. Whether or not they directly improve cognition is still controversial. The BENEFIT trial, which included 464 patients with clinically isolated syndrome (CIS), showed significant improvement in the PASAT-3 after 2 years of treatment with interferon beta-1b relative to placebo. Similarly, in the AFFIRM study, patients who received natalizumab reduced the rate of PASAT score decline compared to placebo [2]. However, it has been suggested that volumetric measures in the MRI are stronger predictors of cognitive performance than relapse activity, which highlights the relevance of assessing cortical thickness, grey matter, and deep grey matter, especially in late relapsing–remitting and progressive multiple sclerosis [29,30]. Also, a systematic review and meta-analysis concluded that neurofilament light

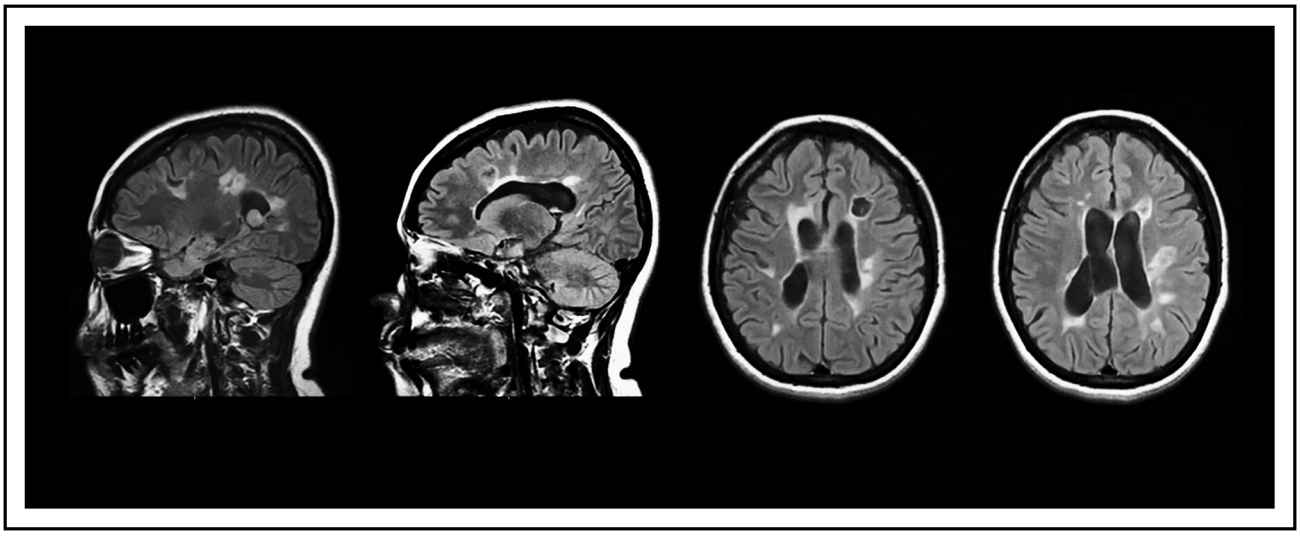

FIGURE 1. Structural magnetic resonance imaging of a 35-year-old woman with a diagnosis of neuropsychiatric systemic lupus erythematosus, who suffers from cognitive disturbance (verbal and visual memory abnormalities as well as executive dysfunction) leading to academic failure, which prevented her from completing her university education. She also presents a psychopathological pattern characterized by depressive symptoms, affective dysregulation, and suicidal ideation. The T2 FLAIR axial and sagittal projections shows multiple periventricular, hyperintense lesions (the largest one with a hypointense component) on both cerebral hemispheres, which are compatible with chronic ischaemic changes.

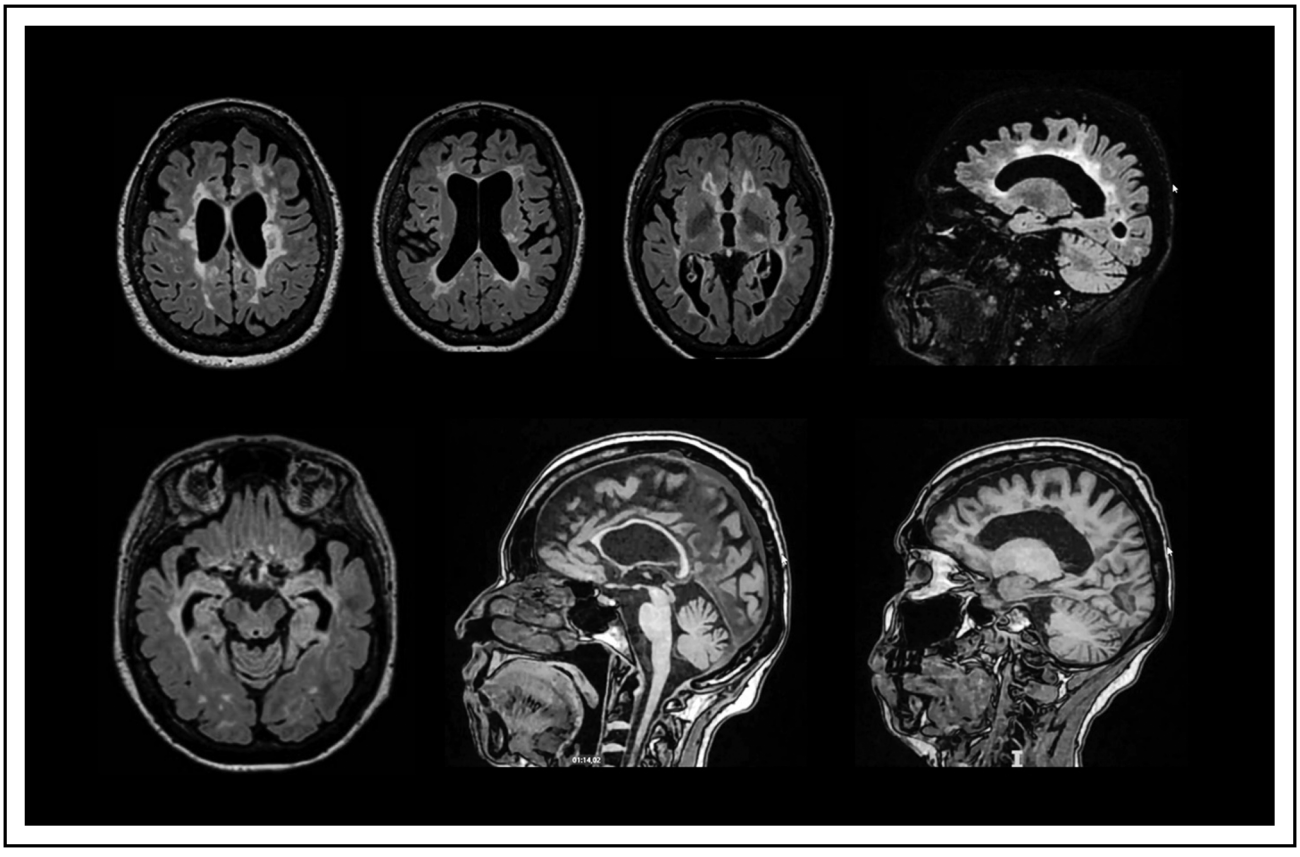

FIGURE 2. Structural Magnetic resonance imaging in the case of a 58-year-old woman suffering from secondary progressive multiple sclerosis, showing extensive white matter damage and loss of volume in both hemispheres with increased ventricular size. In T2 FLAIR sagittal projection, the Dawson fingerprint is present. Prominent demyelination and loss of cortical volume can be observed in the medial temporal lobes, bilaterally. The patient suffered from severe cognitive dysfunction affecting memory (visual, episodic, and semantic) and executive functioning (processing speed, planning, and inhibitory control).

chain, a neuroaxonal cytoskeletal protein increasing in serum with acute and chronic lesions, is the most significant biomarker related to cognitive impairment in MS [31].

Neuromyelitis optica spectrum disorders

NMOSDs are inflammatory diseases usually associated with autoantibodies targeting aquaporin 4 (AQP4), a water channel protein expressed in astrocytes, with diverse clinical presentation, including optic neuritis, acute myelitis, narcolepsy, area postrema syndrome, and other diencephalic and cerebral syndromes. NMOSD commonly affects young adults (with a more significant proportion of women affected) with a mean age of onset of 40 and has a relapsing course that may result in severe disability [32]. NMOSD has been more consistently associated with significant cognitive impairments in information processing speed and attention, affecting 30–70% of the patients with deficits in learning and memory also reported [33]. A recent study in Mexico found that about 50% of patients with NMOSD have some degree of cognitive impairment, affecting especially the executive domain [34].

Myelin oligodendrocyte glycoprotein antibody-associated disease

MOGAD is also an autoimmune demyelinating disease that affects the CNS, has heterogeneous clinical manifestations, and is associated with MOG antibodies. It may be monophasic or relapsing with children usually presenting as acute disseminated encephalomyelitis and adults commonly presenting with optic neuritis [32]. It affects children and young adults with a slight female predominance. Unlike NMOSD, long-term studies have demonstrated a favourable course, with many patients experiencing complete lesion resolution and minimal disability [32]. In an international survey of 204 patients, Santoro *et al.* [35], found that 26 and 19% of the sample reported memory difficulties and confusion, respectively. Supporting this, Li *et al.*, described cognitive functioning in nine patients with MOGAD with a median age of 33. Almost half their sample demonstrated impaired performance in at least on cognitive domain, verbal memory, visual memory, confrontation naming, verbal fluency, auditory working memory, visuospatial abilities, processing speed, and executive function [36].

COGNITIVE DYSFUNCTION IN AUTOIMMUNE ENCEPHALITIS

Cognitive dysfunction is common and often severe in patients with autoimmune encephalitides. Autoimmune encephalitides are conditions of brain inflammation mediated by neuronal surface antibodies directed to neuronal surface epitopes, or by intracellular antibodies in the context of paraneoplastic encephalitis. Autoimmune encephalitides is being recognized as an important cause of rapidly progressive dementia [37,38]. To know more about the concept of autoimmune dementia, the reader is referred to the excellent review by Alessandro Dinoto and Eoin P. Flanagan in this same volume of *Current Opinion in Psychiatry*. This review will discuss cognitive dysfunction related to the most frequent antibody-mediated encephalitis: anti-NMDAR and anti-LGI-1. However, Table 2 summarizes the features of cognitive impairment associated with other forms of neuronal autoantibody-associated encephalitis, before and after treatment.

Anti-NMDAR encephalitis

Anti-NMDAR encephalitis (ANMDARE) is the most common form of Autoimmune encephalitides, often heralded by a viral prodrome, and characterized by a subacute onset of neuropsychiatric symptoms and severe cognitive dysfunction, accompanied by seizures, movement abnormalities, and autonomic dysfunction [40]. The profound cognitive impairment in the acute phase has been classified as delirium, or described as severe and disproportionate cognitive dysfunction in the context of psychosis [41,42]. Objective neuropsychological testing is often challenging to obtain during the acute or subacute episode, and most studies on cognition have focused on the persistent cognitive symptoms evident even after immunotherapy. According to Heine *et al.*, moderate to severe cognitive impairments persisted for an average of 2.3 years after ANMDARE onset, mainly compromising memory and executive function. In the same study, significant improvements were observed in neuropsychological performance after 4.9 years, but two of three of patients still had moderate to severe cognitive deficits [43]. Galioto *et al.* [44▪] found that cognitive deficits in patients with ANMDARE were most common in verbal memory (92%), visual memory (71%), attention/working memory (auditory – 91%, visual – 60%), and processing speed (80%); language is less frequently affected (20–40%). Bayliss *et al.* [45] described the cognitive outcomes in ANMDARE patients, and revealed an improvement in global cognition at 12 months after hospital discharge, with complex attention fluctuating throughout the first year and executive functions not recovering completely during the follow-up. Timely immunotherapy is the most critical factor determining positive neuropsychological outcomes [46].

Table 2. Cognitive impairment in autoimmune encephalitis

Antigen	Classic syndrome	Cognitive impairment before treatment (acute phase)	Cognitive outcome after treatment (follow-up)
NMDAR (NR1 subunit)	Flu-like prodrome followed by psychiatric symptoms, cognitive impairment, seizures, movement disorders, autonomic dysfunction and reduced level of consciousness	Deficits in across all domains; memory, information processing, attention, executive function, language, visuospatial processing all impaired. *Cognitive testing during acute stages is complex.	Most recover global cognition performance. Episodic memory, processing speed, and executive function may remain impaired
LGI1	Amnesia and seizures, including FBDS are the most common hallmarks. Psychiatric symptoms, sleep disturbances, and hyponatremia are also frequent.	Memory impairment dominates acute stages; spatial disorientation *Cognitive testing during acute stages is complex.	Only few return to baseline Neuropsychological performance. Prominent memory deficits may remain with spatial disorientation
CASPR2	Diverse clinical presentation with features of limbic encephalitis including changes in personality, cognitive impairment, and seizures. Associated with neuromyotonia, autonomic dysfunction, and Morvan's syndrome	Cognitive dysfunction is common with memory deficits affecting anterograde episodic memory.	Long-term cognitive outcomes for CASPR2 encephalitis have not been clearly elucidated
GABAAR	Features of limbic encephalitis. Seizures almost always present and cognitive/behavioural symptoms in more than 60% of patients.	Memory deficits and other cognitive impairments have been less commonly described.	Long-term neuropsychological outcomes for GABA-A R encephalitis have not been published.
AMPAR	Prominent memory impairment, confusion, and seizures as limbic encephalitis	Impaired memory is the most common deficit, often with confusion and executive dysfunction	Memory deficits persist in some, worst outcomes in those presenting with fulminant encephalitis

Anti-LGI1 encephalitis

This disease typically presents as a limbic encephalitis. Faciobrachial dystonic seizures, unique to LGI1 encephalitis, usually precede cognitive symptoms characterized by prominent disturbance of recent episodic memory and autobiographical memory with disorientation [47]. According to Galioto *et al.*, the cognitive impairment in patients with anti-LGI1 affects multiple cognitive domains but more often verbal and visual memory (100 and 80%, respectively). Persistent memory deficits and psychiatric disturbances are the most prevalent longitudinal symptoms in patients with anti-LGI-1. Cognitive impairment at baseline measured by MoCA is an essential determinant of disability outcomes in this population [48].

COGNITIVE DYSFUNCTION IN CEREBROVASCULAR DISEASE OF AUTOIMMUNE ORIGIN

Autoimmune vasculitis

Vasculitis of the CNS can be a localized process, such as primary vasculitis of the CNS. Secondary CNS vasculitis may arise when vasculitis is active elsewhere, and it has been documented in ANCA-positive and ANCA-negative cases. Primary central nervous system vasculitis is rare. When there is a small-vessel involvement, patients often present with cognitive dysfunction, and MRI can reveal leptomeningeal enhancement and variable parenchymal lesions [49]. In a recent systematic review, including 24 case series of patients with primary central nervous system vasculitis, Sarti *et al.* found that 42.7% (190/445) reported cognitive impairment [50]. ANCA-associated vasculitis, particularly granulomatosis with polyangiitis, can affect the brain in a minority of patients, with around 30% of patients showing subclinical cognitive impairment characterized by mild deficits in abstraction, memory, and processing speed [49,51].

Susac syndrome

Susac syndrome is a rare autoimmune condition affecting young adults. It is often recognized by the clinical triad of encephalopathy, visual disturbances (caused by branch retinal artery occlusions), and neurosensorial hearing loss caused by the autoimmune-mediated occlusion of microvessels in the brain, retina, and inner ear [52]. Progressive

cognitive impairment has been reported in 48–64% of patients, with memory, attention, and executive function being the most frequently affected domains. However, recent prospective studies, including neuropsychological testing, have started to document better cognitive outcomes in patients with Susac syndrome than previously thought [52]. For example, Machado *et al.*, evaluated 19 patients (median age 37.5) with Susac syndrome and found largely preserved global cognitive functions (MoCA scores 25.1 ± 3.6) but significant processing speed slowing (TMT version A: 43.1 ± 16.2 s; version B: 95.5 ± 67.9 s; reaction time: 314.6 ± 79.6 ms) [53]. Similarly, Vrekhem *et al.*, in a follow-up study including 13 patients with Susac syndrome (mean age 39.5), found normal neuropsychological scores at a group level, both at baseline and follow-up testing 2 years later. Individual test results, however, exhibited interindividual variability at baseline, particularly in attention, executive functioning, and language, which improved after 2 years [54].

CONCLUSION

Neuroimmunological diseases are associated with varying degrees of cognitive decline, from delirium to major neurocognitive disorder, and should be regarded as etiological factors, underlying cases of neurocognitive disorder, especially in young patients. The pathogenesis of cognitive dysfunction in autoimmune diseases involves multiple mechanisms, including immune-mediated inflammation, BBB disruption, and the presence of autoantibodies, which interact with functional networks supporting cognition. Understanding these mechanisms is essential for developing targeted and effective evidence-based treatments. Emphasis on early diagnosis and intervention and comprehensive management plans may improve cognitive outcomes and overall quality of life for patients with autoimmune diseases. While the prognosis seems favourable in most cases, the size effect of immunotherapy on cognitive outcomes remains unclear. However, a subset of patients with SLE, MS, autoimmune encephalitis, and Susac syndrome has a poor prognosis. The identification of predictive and modifiable factors is of great importance.

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Conflicts of interest

There are no conflicts of interest.

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- ■ of special interest
- ■■ of outstanding interest

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