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REVIEW ARTICLE

Neuropsychiatric Systemic Lupus Erythematosus in Older Adults: Diagnosis and Management

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Abstract

Systemic lupus erythematosus (SLE) is a multisystem chronic autoimmune disease with variable clinical manifestations. Neuropsychiatric systemic lupus erythematosus (NPSLE) includes the neurologic syndromes of the central, peripheral and autonomic nervous system and the psychiatric syndromes observed in patients with SLE. Neuropsychiatric systemic lupus erythematosus events may present as an initial manifestation of SLE or may be diagnosed later in the course of the disease. Older adults with NPLSE include those who are ageing with known SLE and those with late-onset SLE. The diagnosis of NPSLE across the lifespan continues to be hampered by the lack of sensitive and specific laboratory and imaging biomarkers. In this review, we discuss the particular complexity of NPSLE diagnosis and management in older adults. We first discuss the epidemiology of late-onset NPSLE, then review principles of diagnosis of NPSLE, highlighting issues that are pertinent to older adults and that make diagnosis and attribution more challenging, such as atypical disease presentation, higher medical comorbidity, and differences in neuroimaging and autoantibody investigations. We also discuss clinical issues that are of particular relevance to older adults that have a high degree of overlap with SLE, including drug-induced lupus, cerebrovascular disease and neurocognitive disorders. Finally, we review the management of NPSLE, mainly moderate to high- dose glucocorticoids and immunosuppressants, again highlighting considerations for older adults, such as increased medication (especially glucocorticoids) adverse effects, ageing-related pharmacokinetic changes that can affect SLE medication management, medication dosing and attention to medical comorbidities affecting brain health.

1 Introduction

Systemic lupus erythematosus (SLE) is a multisystem chronic autoimmune disease with variable clinical manifestations characterised by the production of autoantibodies to nuclear antigens [1]. Women of childbearing age are particularly affected; however, late-onset lupus, usually defined in the literature as onset at age ≥ 50 years, is reported to occur in 3–18% [2–5]. Systemic lupus erythematosus in older patients, with disease onset at age 65 years and older is rare [4, 6, 7]. There is no strict definition of late-onset SLE, and different age cut-offs (50, 55, 60, 65 and even 45 years) are used in the various studies [8, 9]. Late-onset SLE represents a distinct phenotype, irrespective of the chosen cut-off, in terms of clinical presentation, disease course, response to treatment and prognosis [10]. In general, patients with late-onset SLE experience a more insidious onset of SLE, delayed diagnosis and a less common occurrence of severe manifestations, but with higher damage accrual and a lower survival rate compared with patients with early-onset SLE [9, 11]. The combination of altered disease presentation and course with a broader differential diagnosis, comorbidities and polypharmacy in patients with late-onset SLE, and particularly neuropsychiatric lupus, presents a challenge in the diagnosis and management of the disease [12].

Neuropsychiatric systemic lupus erythematosus (NPSLE) includes the neurologic syndromes of the central, peripheral and autonomic nervous systems and the psychiatric syndromes observed in patients with SLE. There are two separate and potentially complementary autoimmune pathogenic

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Key Summary Points

Neuropsychiatric systemic lupus erythematosus encompasses a total of 19 syndromes: central, peripheral and autonomic nervous system and psychiatric syndromes.

The diagnosis of neuropsychiatric systemic lupus erythematosus is challenging, particularly in older adults.

The treatment of neuropsychiatric systemic lupus erythematosus events attributed to systemic lupus erythematosus in older adults does not differ significantly from adults in general.

Older adults are more vulnerable to the development of adverse events to glucocorticoids and immunosuppressants, which can render the management more challenging.

mechanisms for NPSLE. The first mechanism implicates vascular injury to large and small blood vessels, mediated by antiphospholipid antibodies, immune complexes and leucoagglutination. The second mechanism involves autoimmune inflammation injury, with increased permeability of the blood–brain barrier, intrathecal formation of immune complexes, and production of interferon-α and other inflammatory mediators [13–15]. The 19 neuropsychiatric (NPSLE) syndromes defined by the American College of Rheumatology (ACR) include: aseptic meningitis, cerebrovascular disease (CVD), demyelinating syndrome, headache, movement disorder (chorea), myelopathy, seizure disorders, acute confusional state, anxiety disorder, cognitive impairment, mood disorder, psychosis, acute inflammatory demyelinating polyradiculoneuropathy (Guillain–Barré syndrome), autonomic disorder, mononeuropathy single/multiplex, myasthenia gravis, cranial neuropathy, plexopathy and polyneuropathy [16, 17]. Headache and mood disorders are the most frequent neuropsychiatric complaints overall in patients with SLE, but seizure disorders, CVD, acute confusional states and neuropathies are the most common neuropsychiatric syndromes attributed to SLE [13]. Mood disorders include depressive and related disorders, and bipolar and related disorders. However, the most prevalent psychiatric disorders in SLE are depression and anxiety [18, 19]; bipolar disorders were present in less than 0.05% of an inception cohort of 1827 with SLE [20].

The prevalence of NPSLE is variable, with a range from 21 to 95% in patients with SLE [13]. Most NPSLE events (50–60%) occur at SLE onset or within the first year after SLE onset [21]. Neuropsychiatric systemic lupus erythematosus is associated with reduced health-related quality of life [22, 23], and several studies imply an increased mortality rate compared with patients with SLE without NPSLE [24–26]. In this review, we highlight the complexity in the diagnosis and the treatment of NPSLE in older patients, with both early and late-onset SLE.

2 Epidemiology of Late-Onset NPSLE

Studies have provided conflicting results regarding the difference in prevalence of NPSLE syndromes in late-onset SLE. The reasons for this inconsistency are likely multifactorial, with relatively small cohort sizes, retrospective data collection, diverse ethnicities, inconsistent age definitions of late-onset SLE and variability in NPSLE definitions [6, 8, 27] (Table 1). Definitions of NPSLE vary among studies, some including only the 1982 revised ACR SLE classification criteria [28] neurologic manifestations (i.e. psychosis and seizures), some including only the neurologic manifestations attributed directly to SLE and some including all 19 NPSLE syndromes. However, most studies indicate a lower frequency of NPSLE in late-onset SLE compared with early-onset SLE. Two meta-analyses of late-onset SLE reported lower rates of NPSLE compared with younger patients. A meta-analysis by Ward et al. [8] from 1989 included nine studies, seven of which included NPSLE manifestations, with different age cut-off points (45–60 years), and showed a pooled odds ratio for neuropsychiatric manifestations of late-onset SLE of 0.52 (95% confidence interval 0.33–0.80). In their review, Boddaert et al. [9] included 23 studies examining neuropsychiatric manifestations in late-onset SLE with a different age cut-off point (45–60 years) and showed that NPSLE occurred less frequently in late-onset SLE compared with early onset (15.3% vs 20.2%; $p = 0.025$). More recent studies, from the last decade, are in agreement with these findings [11, 27, 29–32], though other reports show no differences in the prevalence of NPSLE in late-onset SLE compared to early-onset SLE [10, 33–38]. One study found more frequent NPSLE events in late-onset SLE compared to patients with early-onset SLE [39]. The authors acknowledge that their results do not align with previous studies, and that the increased rate of NPSLE syndromes might be explained by their inclusion of neurological manifestations independent of their attribution, and included cognitive impairment and headaches, while other studies excluded these manifestations [39].

3 Diagnosis

3.1 Principles of NPSLE Diagnosis

Neuropsychiatric systemic lupus erythematosus may be present as an initial manifestation of SLE or may be diagnosed

Table 1 Studies including comparison of prevalence of late vs. early-onset NPSLE

	References	Study type	Age cut-off, years	NPSLE definition	Number of patients late/early-onset SLE	Length of follow-up	Frequency of late-onset vs. early-onset NPSLE
1	Ward [8]	Meta-analysis of 7 R + P studies	45–60 (mostly 50)	Variable	170/1612	Variable	Lower Pooled OR 0.52 (95% CI 0.33–0.8)
2	Boddaert [9]	Meta-analysis of 23 R + P studies	45–60 (mostly 50)	Variable	714/4700	Variable	Lower 15.3% vs. 20.2%, $p = 0.025$
3	Webb [30]	P cohort	50	ACR SLE criteria[a§]	168/1068	NA	Lower OR 3.02 for seizures (95% CI 1.21–7.55) for early-onset vs late- onset
4	Aljohani [11]	P cohort	50	ACR SLE criteria[a§]	86/169	5 years	Lower 3.5% vs. 12.4%, $p = 0.003$
5	Budhoo [31]	R cohort	50	ACR SLE criteria[a§]	59/338	Median 48 months	Lower 1.7% vs. 9.5%, $p = 0.028$ for psychosis 1.7% vs. 11.5%, $p = 0.02$ for seizures
6	Chen [37]	R cohort	60	ACR SLE criteria[a§]	19/50	NA	No difference 15.8% (3 patients) vs. 6.0% (3 patients), p = NS
7	Alonso [10]	R cohort	50	ACR SLE criteria[a§]	59/91	Mean 7.7 years	No difference 3.4% (2 patients) vs. 5.5% (5 patients), $p = 0.71$
8	Tomic-Lucic [29]	Case-control	50	Seizures, psychosis, multiple CVAs, cranial/peripheral neuropathy; only if attributable to lupus (other causes excluded)	30/30	Median 37 months	Lower 6.6% vs 36.6%, $p < 0.05$
9	Ambrose [27]	P cohort	50	19 ACR NPSLE syndromes[¶c] (excluding headaches)	44/467	Median 15 years	Lower 2% vs 20% (approximate numbers), $p < 0.01$
10	Feng [33]	R cohort	45	Almost identical 19 ACR NPSLE syndromes [¶*b,c]	195/1444	NA	No difference 8.2% vs 6.1%, $p > 0.05$ Deaths caused by NPSLE 1.5 vs. 1.4, $p > 0.05$
11	Catoggio [35]	P cohort	50	Any NPSLE syndrome described	102/1378	Mean 3.6 years	No difference 39% vs. 35% $p = 0.413$

Table 1 (continued)

	References	Study type	Age cut-off, years	NPSLE definition	Number of patients late/early-onset SLE	Length of follow-up	Frequency of late-onset vs. early-onset NPSLE
12	Choi [36]	P cohort	50	ACR SLE criteria[a§]	25/149	1.7 years	No difference 4% vs 11.4%, $p = 0.276$
13	Martinez-Barrio [34]	P cohort	50	Any NPSLE syndrome described	77/276	Mean 10 years	No difference 26% vs. 27.2%
14	Bertoli [137]	Case-control	50	Any NPSLE syndrome described, independent of the cause	73/144	Mean 63.4 months	Higher 53% vs. 32%, $p = 0.003$ OR 2.82 (95% CI 1.12–6.79)

ACR American College of Rheumatology, *CI* confidence interval, *CVA* cerebrovascular accident, *NA* not available, *NPSLE* neuropsychiatric systemic lupus erythematosus, *OR* odds ratio, *P*: prospective, *R*: retrospective, yrs: years, *mos*: months, *NA:* not available *SLE* systemic lupus erythematosus

[a§]Including psychosis and seizures

[b]*Cerebral vasculitis and cerebellar ataxia instead of Guillain–Barré syndrome GBS and myasthenia gravis MG

[¶c]19 ACR NPSLE syndromes include: aseptic meningitis, cerebrovascular disease (CVD), demyelinating syndrome, headache, movement disorder (chorea), myelopathy, seizure disorders, acute confusional state, anxiety disorder, cognitive impairment, mood disorder, psychosis, acute inflammatory demyelinating polyradiculoneuropathy (Guillain–Barré syndrome), autonomic disorder, mononeuropathy single/multiplex, myasthenia gravis, cranial neuropathy, plexopathy and polyneuropathy

later in the course of the disease [13]. The diagnosis of NPSLE across the lifespan relies mainly on clinical assessment, appropriate history and physical examination, and a thorough interpretation of laboratory results by an appropriately trained rheumatologist. Neuropsychiatric systemic lupus erythematosus events can be attributed to SLE activity but can also occur independently of SLE activity and be associated with other aetiologies. The attribution of NPSLE events to SLE has an implication on the management particularly treatment and prognosis. The diagnosis of NPSLE events requires the establishment of a SLE diagnosis, and the exclusion of other causes (i.e. infection, metabolic disorders, malignancy, medication side effects and others), and the selection of appropriate investigations directed by clinical assessment. Such investigations may include measurement of autoantibodies, analysis of cerebrospinal fluid, electrophysiological studies, neuropsychological assessment and neuroimaging.

3.1.1 Measurement of Autoantibodies

Anti-nuclear antibodies (ANA), anti double-stranded DNA (dsDNA), anti-Smith (Sm), anti-Ro, anti-La and anti-histone are not specific for NPSLE but are used to establish the diagnosis of SLE [1, 40]. Anti-ribosomal P antibodies have been reported to be associated with psychosis [41, 42] and with severe depression [43, 44]; however, a meta-analysis showed that anti-ribosomal P antibodies have low sensitivity (20%) and acceptable specificity (80%) for NPSLE. Antiphospholipid antibodies (persistently positive moderate-to-high anticardiolipin antibodies or anti-β2-glycoprotein IgG/IgM titres or the lupus anticoagulant) [45–48] have been associated with CVD, seizure disorder [49, 50], moderate-to-severe cognitive impairment [48, 51], myelopathy [52–54] and movement disorder [55, 56]. Patients with myelitis should be evaluated for AQP4 antibodies in the serum given the high risk of relapse when AQP4 IgG is present [57, 58].

3.1.2 Analysis of Cerebrospinal Fluid

Cerebrospinal fluid analysis is used mainly to exclude central nervous system infection, but could be also abnormal in cases of aseptic meningitis, vasculitis and transverse myelitis.

3.1.3 Electrophysiological Studies

Electrophysiological studies may help to diagnose underlying seizure disorder or peripheral neuropathy.

3.1.4 Neuropsychological Assessment

Neuropsychological assessment is required when there is a clinical suspicion of cognitive impairment [51, 59–61].

3.1.5 Neuroimaging

A number of neuroimaging methods are available [62] to evaluate brain structure and function that may detect NPSLE involvement and exclude other (neurosurgical, infectious) causes. The imaging technique of choice is magnetic resonance imaging (MRI), which is more likely to show abnormalities if there are focal neurologic defects, seizures or thrombotic events related to antiphospholipid syndrome, and less likely to show abnormalities in patients with mood disorders, confusional states, cognitive impairment or headache [62]. The most frequent structural pathological pattern is the non-specific, small punctate, hyperintense T2-weighted focal lesions in subcortical and periventricular white matter, and in the frontal-parietal regions [63, 64] as well as white matter hyperintensities [65, 66]. However, the correlation between structural changes and clinical NPSLE is low [17, 67], and white matter hyperintensities are present in many older adults, in both healthy cohorts and various clinical samples [68, 69]. Of the available MRI neuroimaging modalities [70, 71], functional MRI and diffusion weighted imaging may eventually provide neural biomarkers, such as abnormal hippocampal or parahippocampal activation on functional MRI or specific white matter microstructural abnormalities on diffusion weighted imaging, for cognitive impairment in SLE [72–74]. Other neuroimaging modalities may be used to examine activity in particular brain regions relevant to cognitive impairment in SLE, including radionuclide brain scanning (single photon emission computed tomography) [75, 76] and positron emission tomography [13, 55, 73, 77, 78].

3.2 Attribution of NPSLE Events in SLE

The attribution of NPSLE events to SLE disease activity (SLE related) as opposed to other SLE-unrelated mimicking conditions (such as metabolic changes, medications side effects, infection, neoplasm and others) presents a challenge as it is hampered by the lack of sensitive and specific laboratory and imaging biomarkers. More importantly, there is currently no objective biomarker to distinguish between different SLE-related pathogenesis mechanisms (inflammatory/immune vs thrombotic/ischaemic-vascular injury) that require qualitatively different intervention strategies and different management approaches. The 1999 ACR nomenclature criteria of the 19 NPSLE syndromes [16] listed exclusion criteria to assist in the attribution to SLE-related or SLE-unrelated conditions. Several decision algorithms have been developed to assist in the determination of the attribution of NPSLE to SLE disease activity or alternative aetiologies. In 2001, a further modification of the 1999 ACR nomenclature criteria by Ainiala et al. [79] was made in an attempt to improve the attribution to SLE disease activity. The revised criteria by Ainiala et al. excluded anxiety, headache, mild depression, mild cognitive impairment (deficits in < 3 of eight ACR cognitive domains) and polyneuropathy unconfirmed by electrophysiological studies; resulting in improved specificity. The Systemic Lupus International Collaborating Clinics group, led by Hanly et al. [80], introduced the attribution models for SLE disease activity, Model A (more stringent) and Model B (less stringent). Monov and Monova divided NPSLE syndromes into a major and a minor group and proposed an approach to facilitate early diagnosis of NPSLE events [81]. More recently, the Italian Study Group for NPSLE developed a new attribution model with four domains including several items with different weight scores, where a total score > 7 confirms the attribution of the NPSLE event to SLE disease activity and a score < 3 confirms the lack of attribution to SLE [82].

3.3 Diagnosis of Late-Onset NPSLE

The diagnosis of NPSLE is more challenging in the older population. Atypical disease manifestations, in combination with age-related comorbidities and increased production of autoantibodies [83] and pathologic imaging studies (e.g. unrelated white matter hyperintensities on MRI) complicate the clinical picture and may theoretically result in both under-diagnois and over-diagnosis.

As with the general adult SLE population, the diagnosis of late-onset NPSLE begins with confirmation of the SLE diagnosis. The most commonly used classification criteria for SLE are the 1982 revised ACR SLE classification criteria [28] and their 1997 revision [84] and, more recently, the European Alliance of Associations for Rheumatology/ACR SLE classification criteria [85]. Although classification criteria are developed to identify a relatively homogenous patient population for clinical research and trials and not for the diagnosis of an individual patient; they can be used as a guide in clinical practice. The ACR SLE classification criteria were developed primarily using SLE cohorts with long-standing SLE [86, 87] and their utility in late-onset SLE is not well studied. Studies show that patients with late-onset SLE tend to have less ACR criteria at presentation [9, 88] and therefore the 1982 revised criteria [28] and their 1997 revision [84] may not be appropriate for the study of an illness of insidious onset with a paucity of classic features at presentation, as seen in elderly patients [89]. Consequently, the diagnosis of SLE in older adult patients is often delayed because of its insidious onset, lower number of cumulative SLE manifestations at presentation, nonspecific presentation and lack of awareness [7, 29, 35, 88, 90, 91]. All these traits render the diagnosis of SLE in the elderly population more challenging.

3.3.1 Differential Diagnosis of Late-Onset NPSLE

The differential diagnosis of SLE with neuropsychiatric manifestations is broad and includes any systemic illness that involves the central nervous system, peripheral nervous system or psychiatric condition. These include other rheumatic diseases such as giant cell arteritis or other vasculiditis, Sjögren's syndrome, sarcoidosis, late-onset rheumatoid arthritis; as well as various infections including endocarditis, tuberculosis, Lyme disease; malignancies, metabolic abnormalities such as diabetes mellitus, hypo/hyperthyroidism; and alcohol-related disorders and drug-induced side effects. Excluding other aetiologies and diseases that are more prevalent in the older population is essential prior to establishing a NPSLE diagnosis.

3.3.2 Drug-Induced NPSLE

The possibility of drug-induced lupus should always be considered in patients with late-onset SLE because of frequent co-morbidities and polypharmacy in this population [12, 92]. Drug-induced lupus is generally equally common in male and female individuals, and more common in older populations. Over 90 drugs associated with drug-induced lupus have been described. The highest risk drugs seem to be procainamide and hydralazine (15–20% and 7–13% risk of developing drug-induced lupus, respectively) [93]. Quinidine, isoniazid and sulfadiazine are considered moderate risk. Other drugs appear to be low or very low risk, including anti-tumour necrosis factor-α blockers. Drug-induced lupus is generally milder than SLE, and central nervous system involvement is typically rare. However, neurological involvement is not uncommon in quinidine-induced lupus with a frequency of up to 30% of patients [93]. Treatment includes drug discontinuation, with glucocorticoids reserved for severe symptoms or slow resolution [93, 94].

3.3.3 Clinical Manifestations of Late-Onset NPSLE

Neuropsychiatric conditions are common in the older population, including many of the ACR-defined NPSLE syndromes, often secondary to aetiologies other than SLE activity. For example, CVD is a common manifestation of atherosclerosis, hypertension and atrial fibrillation; polyneuropathy is a common manifestation of diabetes or vitamin B_{12} deficiency; acute confusional state, seizures, cognitive impairment and psychosis are frequent symptoms of dementia; and depression is very prevalent in the older population [95]. Therefore, an older patient with SLE and a non-specific NPSLE manifestation may be seen by psychogeriatric services where an NPSLE event may be overlooked. Hence, a high index of suspicion is needed in patients with a diagnosis of SLE and a possible NPSLE presentation [89]. The 1982 revised ACR SLE classification criteria [28] and their 1997 revision [84] include only two NPSLE manifestations: psychosis and seizures, and do not capture other NPSLE syndromes that may be more common in older patients. Newer classification criteria, the 2012 Systemic Lupus International Collaborating Clinics group criteria [96] and the 2019 ACR/European Alliance of Associations for Rheumatology classification criteria [85], include more NPSLE syndromes (mononeuritis multiplex, myelitis, peripheral or cranial neuropathy and acute confusional state to the former criteria, and delirium in the latter criteria), and will hopefully support more research and diagnosis of NPSLE in the older population, including late-onset SLE [85, 96].

Most studies on late-onset SLE do not elaborate on the specific NPSLE syndromes in this population. Some do mention seizures and psychosis (components of the 1982 and 1997 ACR classification criteria of SLE) as a common manifestation of NPSLE in the older patients [9, 10, 30, 31, 35, 97]. Nevertheless, case reports and series reveal additional NPSLE manifestations including cognitive impairment, movement disorders, cranial neuropathy, CVD, myelitis, acute confusional state, depression and peripheral neuropathy [9, 89, 98–100] responsive to corticosteroid and/or immunosuppressive therapy. Thus, any neuropsychiatric manifestation in a context of other systemic symptoms or signs suggestive of SLE should be investigated.

3.3.3.1 CVD Stroke is common in the older population with a lifetime risk of approximately 25% [101]. There are two types of strokes: ischaemic and haemorrhagic, and both are increased in frequency in SLE, with an incidence rate between 3 and 20%, especially in the first 5 years of disease, with an increased relative risk of up to 8 [102]. The contributing factors to the occurrence of stroke in SLE are hypercoagulable state, cerebral vasculopathy, atherosclerosis, thrombosis and emboli of Libman–Sacks endocarditis as well as traditional cardiovascular disease risk factors (e.g. systemic arterial hypertension, hyperlipidemia, diabetes and smoking) [103]. Antiphospholipid syndrome (APLS) is an autoimmune multisystem disorder characterised by arterial, venous or small-vessel thromboembolic events and/or pregnancy morbidity in the presence of antiphospholipid antibodies (including anticardiolipin, lupus anticoagulant or anti-beta 2-glycoprotein). Antiphospholipid syndrome accompanies approximately 30% of patients with SLE and the combination of these two conditions can amplify the risk of APLS-mediated CVDs [104].

The evaluation for SLE is not part of the usual diagnostic work-up in older patients experiencing a stroke or transient ischaemic attack. An older individual presenting with a cerebrovascular accident and any other clinical symptoms or signs suggestive of SLE or APLS prompts further investigation as described above. The presence of livedo reticularis,

in particular, raises the possibility of Sneddon's syndrome, characterised by the development of an ischaemic CVD (frequently with leucoaraiosis and/or small lacunar infarcts) coupled with livedo reticularis. Sneddon's syndrome can be associated with autoimmune diseases particularly APLS/SLE in almost half of cases [105]. In patients with SLE, exclusion of common causes of stroke (ischaemic and haemorrhagic) and secondary causes of stroke (metabolic or endocrine disturbances, infections and adverse drug reactions) is essential before attributing stroke to SLE activity [103]. In the absence of other symptoms or signs suggestive of SLE, the probability that stroke represents a sole manifestation of SLE in older adults, even in the presence of positive serologies (e.g., ANA or antiphospholipid antibodies [lupus anticoagulant or anti-cardiolipin]) is extremely low. The attribution of stroke in an older individual to either SLE activity or atherosclerosis can be challenging but carries significant implications on treatment. A SLE-related stroke requires the use of specific SLE drugs (anti-malarial agents, glucocorticoids and immunosuppressants), while an APLS-related stroke necessitates anticoagulation, and the management of atherosclerotic-related stroke in patients with SLE follows the same recommendations for general older adults. In patients with persistently positive moderate-to-high titres of antiphospholipid antibodies, long-term oral anticoagulation therapy is not indicated if the diagnosis of primary APLS or secondary APLS (associated with SLE) is not confirmed. Tight control of modifiable risk factors through physical activity, diet and treatment of co-morbidities (such as hypertension, diabetes, dyslipidemia, obesity and smoking) is key to reducing atherosclerotic-related cerebrovascular accidents in SLE. For atherosclerotic-related cerebrovascular accidents, low-dose aspirin should be initiated as recommended in the general population [103].

3.3.3.2 Cognitive Impairment Major neurocognitive disorder (dementia) and mild neurocognitive disorder (mild cognitive impairment) are common in older adults, with prevalence estimates in the USA of about 18% [106] and 14% [107], respectively. Dementia is defined in the *Diagnostic and Statistical Manual of Mental Disorders*, *Fifth Edition* as a significant cognitive decline based on a subjective report or report of a knowledgeable informant, associated with objective cognitive impairment on standardised testing and impairment in everyday functioning [20]. The most common type of dementia is Alzheimer's disease, although there are many potential dementia aetiologies, such as vascular dementia, Lewy body dementia, alcohol-related dementia and others [20]. Mild cognitive impairment is defined as subjective cognitive impairment accompanied by evidence of cognitive impairment on objective testing, but without a substantial impairment in everyday functioning [20]. Systemic lupus erythematosus across the lifespan is associated with cognitive impairment [61] and has been found to be associated with a higher risk of dementia in a meta-analysis that included 81,631 patients with dementia in three cohort studies (relative risk: 1.50 [95% confidence interval 1.37–1.64]) [108]. Specifically, SLE has been associated with an increased risk of vascular dementia [109]. The mechanism underlying the increased risk of dementia in patients with SLE has yet to be established but is likely multifactorial. Potential contributors include CVD and stroke or microangiopathy related to a hypercoagulable state, presence of autoantibodies directed toward brain tissue (e.g. anti-*N*-methyl-D-aspartate antibodies) and associated inflammation and excitotoxicity, as well as increased levels of tau and beta-amyloid protein (reflective of the pathological process underlying Alzheimer's disease) in the central nervous system [109, 110]. Of note, cerebrovascular disease, including stroke, increases the risk for both vascular dementia and Alzheimer's disease [111]. Thus, in addition to disease-modifying lupus medications, older adults with lupus should be counselled about optimising brain health, including via adequate control and monitoring of cerebrovascular risk factors (blood glucose, blood pressure, smoking, atrial fibrillation, high cholesterol) [112], engaging in regular physical exercise, consuming a balanced diet, avoiding high-risk alcohol consumption and staying socially and intellectually active [113].

3.3.4 Serological Manifestations of Late-Onset NPSLE

Serological findings of SLE may change with ageing as well. Although studies are inconsistent, many report a lower incidence of positive anti-Sm, anti-U1-ribonucleoprotein, dsDNA antibodies or reduced C3 in late-onset SLE, which may reflect the difference in disease activity and renal involvement [9, 27, 30]. Anti-dsDNA and anti-Sm antibodies, though not sensitive, are specific for SLE, making the presence of these antibodies very useful for distinguishing patients with SLE from patients with other systemic autoimmune and non-autoimmune diseases [114, 115]. Rheumatoid factor positivity is more frequent, probably owing to the higher prevalence of rheumatoid factor in the healthy older population [116, 117]. Frequency of ANA positivity is increased in the older healthy population as well [117], and a threshold of ANA titres > 1:160 was suggested in the older age group instead of the classical threshold titre of > 1:80 [12]. Studies on the serologic pattern in late-onset NPSLE are absent; however, case reports do emphasise positive anti-dsDNA antibodies with low serum complements in the vast majority of cases [89, 98–100].

4 Management

4.1 Principles of NPSLE Management

Neuropsychiatric lupus treatment presents a therapeutic challenge [118]. The general approach for treatment depends on the underlying pathophysiological mechanism, whether it is presumed to be inflammatory or ischaemic, although the clinical distinction between the two processes is sometimes not feasible, or the two processes may coexist in the same patient [55].

Glucocorticoids continue to be the cornerstone agents for NPSLE syndromes with underlying inflammatory mechanisms that are attributed to SLE activity (such as aseptic meningitis, optic neuritis, transverse myelitis, peripheral neuropathy, refractory seizures, psychosis and acute confusional state). Glucocorticoids are used in the induction phase of treatment, usually in moderate-to-large doses (40–60 mg/day) [119, 120] but some manifestations (such as myelitis and generalised seizures) require pulse therapy with methylprednisolone (500–1000 mg/day) [121].

The use of immunosuppressive agents such as cyclophosphamide, mycophenolate mofetil and azathioprine is suggested by some studies for the treatment of NPSLE [122, 123]; however, randomised trials for new drugs for NPSLE are lacking. Rituximab (anti-CD20 monoclonal antibody) is used in NPSLE refractory to standard therapy [13, 55, 123–126].

Moderate-to-large doses of prednisone (40–60 mg/day) are often used to treat NPSLE regardless of the patient's age [119, 120]. However, patients should be monitored closely for potential adverse events of prednisone, including induced diabetes, hypertension, steroid-induced psychosis and others. Adverse events should be managed accordingly and, depending on their severity, the dose of prednisone can be tapered faster, albeit with close monitoring because of a risk of NPSLE relapse. Often adults aged 18 years and older will require the use of an immunosuppressant to treat NPSLE such as azathioprine, mycophenolate mofetil or cyclophosphamide. The safety profile from lupus nephritis trials favours azathioprine and mycophenolate mofetil over cyclophosphamide, a finding that is also applicable is older adults [127]. Anifrolumab, a type I interferon receptor antagonist, has recently been approved for moderate-to-severe SLE. Phase IIb and phase III trials had showed positive results in patients with moderate-to-severe SLE, especially in patients who had a strong type I interferon signature at baseline [128, 129]. Although patients with active severe NPSLE were excluded from those studies, type I interferon inhibition might have a future role in the treatment of NPSLE, most likely in patients with a strong type I interferon signature. Antiplatelet/antithrombotic therapy is recommended when the underlying pathophysiological mechanism is ischaemic in the context of persistently positive moderate-to-high titres of antiphospholipid antibodies [13, 55, 120, 126].

4.2 Management of Late-Onset NPSLE

Medications for patients with late-onset SLE do not differ in most studies; however, some observational studies report lower use of cyclophosphamide and others report lower doses of glucocorticoids and of cyclophosphamide [9, 29, 35]. Direct information on the treatment of NPSLE in late-onset SLE is lacking, except for several case reports that used lower doses of glucocorticoids, sometimes as a sole treatment without the addition of immunosuppressants [89, 98–100].

Glucocorticoids, immunosuppressive drugs and biologic agents have numerous side effects. Glucocorticoids may cause severe infections, osteoporosis, myopathy, hypertension, fluid retention, arteriosclerosis, arrhythmias, cataracts and hyperglycaemia, which are more frequent in older, comorbid and polymedicated patients. Glucocorticoids are also associated with cognitive impairment and delirium in some patients [119, 130], conditions that again occur more frequently in older adults. Immunosuppressive drugs and biologic agents may expose patients to severe infection risk and the potential development of neoplasia. This risk may be increased in older adults who are often predisposed by their age to the development of these conditions. In a series of 31 patients with late-onset SLE, 40% of patients had glucocorticoid complications, leading the authors to suggest that therapy in late-onset SLE should be more conservative [91]. Interestingly, in another series, a significantly higher prevalence of cyclophosphamide-induced complications in patients with late-onset SLE was reported even though the mean cumulative dose of cyclophosphamide was lower [29]. The decision of the extent of therapy for an NPSLE manifestation in an older patient should be tailored and individualised according to the patient's severity of NPSLE involvement, comorbidities and functional status [9]. In addition to the use of glucocorticoids and immunosuppressants, symptomatic treatment of different NPSLE events is crucial. For instance, in psychosis, the use of antipsychotic medication is required for symptom control, especially given that prednisone is not fully effective before 4–6 weeks of treatment. Similarly, in the case of seizure events attributed to SLE, it is important to use anti-seizure medications along with glucocorticoids.

A special effort should be made to assess and manage pre-existing conditions including diabetes, uncontrolled hypertension, heart failure and peripheral oedema, cataracts or glaucoma, peptic ulcer disease, presence of infection and low bone density or osteoporosis prior to commencing glucocorticoids and immunosuppressive therapy [131]. Patients

Table 2 Aging-related pharmacological changes and their potential association with neuropsychiatric symptoms in systemic lupus erythematosus

Pharmacological category	Aging-related changes	Examples of neuropsychiatric effects of pharmacological changes
Absorption	Reduced active transport in the small intestine can lead to lower absorption of some drugs and vitamins/minerals May be altered by disease states and medications that affect gastric acid secretion, gastric emptying, splanchnic blood flow and small intestine absorption	Supplemental vitamin B_{12} and iron absorption lower because ofdue to reduced active transport. Vitamin B_{12} deficiency is associated with a variety of neuropsychiatric symptoms (cognitive impairment, depression). Low iron can cause fatigue and depressive symptoms Dietary vitamin B_{12} absorption may be also be less efficient in older adults and those taking medications that reduce gastric acid secretion.
Distribution	Change in body composition (relative reduction in total body water and lean body mass, relative increase in body fat) results in higher serum levels of drugs that are water -soluble and prolonged half-life for drugs that are lipid- soluble Blood protein and protein binding levels are decreased in older adults	Digoxin is water- soluble and often requires lower dosing in older adults. Toxicity is associated with delirium Diazepam is highly lipid- soluble and its half-life may be increased in older adults. Diazepam and all benzodiazepines are associated with an increased risk of cognitive impairment and delirium in older adults Highly protein-bound drugs such as valproic acid (toxicity associated with confusion/delirium) may have higher free concentrations because ofdue to lower protein binding in older adults and in people with chronic kidney disease.
Metabolism	Ageing is generally associated with a reduction in first-pass metabolism due to a reduced liver mass and blood flow. Cytochrome P450 enzyme activity is generally preserved, but can be reduced in conditions such as liver and kidney disease and in frail older adults	Calcineurin inhibitors (tacrolimus and cyclosporine) are extensively metaboliszed by the liver. Older adults are more susceptible to the neurotoxic effects of these medications (psychosis, encephalopathy), likely owingdue to a variety of factors including changes in hepatic metabolism
Clearance	Reduced renal function, particularly glomerular filtration rate, affects excretion of many drugs Changes in liver size and blood flow affects clearance of drugs that are extensively metabolized by the liver	Most opioids are renally excreted, and accumulation can result in significant adverse effects, including sedation, cognitive impairment and delirium.
Pharmacodynamics	There are numerous pharmacodynamic changes associated with aging. Older adults are generally more sensitive to all psychoactive medications for a variety of reasons that are not completely understood, but likely include alterations to brain receptors (e.g., dopamine and acetylcholine), as well as other aging-related brain changes (e.g., cerebrovascular disease).	Older adults are more sensitive to the neuropsychiatric adverse effects of corticosteroids (cognitive impairment, delirium, depression, mania, psychosis, insomnia) Older adults are more likely to experience cognitive impairment and delirium from anticholinergic medications (e.g., diphenhydramine, dimenhydrinate, tricyclic antidepressants, oxybutynin)

should receive appropriate immunisations, adequate vitamin D and calcium supplementation, and side effects should be monitored closely [131–133].

The identification and treatment of non-SLE-related factors are important in all cases, even in those patients in whom SLE is the main contributing factor. Comorbid factors such as infection, metabolic abnormalities and cardiovascular risk factors, which are more prevalent in the older population, should be considered. General management includes the correction of exacerbating factors and symptomatic therapy when applicable [13, 17, 55].

In general, older adults have altered pharmacokinetic and pharmacodynamic profiles, including reduced renal and hepatic clearance and increased volume of distribution of lipid-soluble drugs, (resulting in longer half-lives), as well as increased sensitivity to some drug classes [134]. Ageing-related pharmacological changes and their potential association with neuropsychiatric symptoms in SLE are described in Table 2. Further, many older adults are exposed to polypharmacy, increasing the potential for medication interactions, and increasing the likelihood of medication non-adherence, particularly for older adults with cognitive impairment. Finally, all medications should be reviewed, and those potentially contributing to NPSLE syndromes, such as anticholinergics, benzodiazepines or opioids in the setting of cognitive impairment, should be adjusted if clinically feasible. Strategies such as involvement of a multidisciplinary team, including pharmacy, nursing, occupational therapy, and geriatric medicine or psychiatry, may help to optimise care of older adults with NPSLE.

5 Outcome

Many studies have shown that the severity of SLE declines with ageing and that less severe disease with a more benign course is encountered in late-onset SLE compared with younger adults [9, 11, 12, 33, 91, 135], yet most studies emphasise a poorer prognosis [11, 12, 29, 39, 135, 136] with higher damage accrual and mortality rate. This differences probably reflect the higher frequency of comorbidities and higher organ damage, due to ageing and longer exposure to classical vascular risk factors [11, 12, 29]. Accordingly, the cause of death in patients with late-onset SLE is usually not related directly to SLE activity but to infections, cardiovascular disorders, malignancies or drug-induced complications [6, 33, 137]. To our knowledge, no study has investigated the prognosis and outcome of late-onset NPSLE in particular.

6 Conclusions

Neuropsychiatric systemic lupus erythematosus in older individuals is an under-studied and potentially under diagnosed condition. Although relatively uncommon, it poses a diagnostic and therapeutic challenges and is likely to increase in prevalence with our ageing population. Observational studies are needed to characterise the presentation and course of NPSLE in older adults, specifically, and clinical trials are required to enhance our knowledge in the management and outcome of NPSLE generally. These clinical trials should take a lifespan approach, including older adults in the design and analysis of the study.

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