Review


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Abstract

Objectives. To identify the pathogenetic mechanisms of central nervous system (CNS) syndromes of systemic lupus erythematosus (SLE) as described in the literature.

Methods. Using PUBMED, we performed a systematic search of publications from 1980 onwards. Studies were eligible if they had been performed on patients or material from patients with CNS manifestations and definite SLE and when the CNS manifestations were not secondary. Criteria were formulated for the identification of pathogenetic mechanisms.

Results. The single most important cause of the CNS syndromes of SLE is ischaemia due to narrowing or occlusion of small vessels, arteries and veins. Antiphospholipid antibodies and premature atherosclerosis play roles in these processes, but they have not been delineated definitely. Intracranial and intraspinal haemorrhages are much less frequent than ischaemia and are presumably in part due directly to SLE. Vasculitis may cause ischaemia or haemorrhage in the CNS and is involved occasionally, as shown by imaging and histological findings. White matter damage is heterogeneous and ill-understood. It includes white matter degeneration and myelin vacuolation of the spinal cord, and reversible leucoencephalopathy due to oedema. Antibody-induced neuronal dysfunction in the CNS is a realistic hypothesis and may involve anti-ribosomal P antibodies and several other antibodies. Deficiency of psychological reactions forms a separate and entirely different category of mechanisms.

Conclusions. Causes have been identified or possible causes have been suggested for most of the CNS syndromes of SLE, thus offering rationales for different forms of prevention and therapy.

KEY WORDS: Systemic lupus erythematosus, Central nervous system-syndromes, Pathogenesis, Nomenclature.

The origin of the central nervous system (CNS) manifestations of systemic lupus erythematosus (SLE) used to be largely a mystery, but there has been some progress in our understanding. Inflammatory disorders are no longer considered to be the main cause of cerebral damage. It is now generally acknowledged that most changes in the cerebral vasculature are due to complex processes that are in part immunological and in part due to other factors. This insight has led to diversification of therapy, probably to the benefit of patients. It is less clear to what extent an immunological attack on the white matter or on neuronal cell bodies or synapses plays a role in the disease mechanisms and whether there is overlap with multiple sclerosis (MS). No one doubts that some of the mechanisms involved in so-called neuropsychiatric SLE are psychological. However, the border between the biological and psychological dimensions in the CNS manifestations is not always clear.

In a companion paper, based on a literature investigation, we established that SLE may induce 16 clinical CNS syndromes [1]. The purpose of the present investigation is to identify the pathogenetic mechanisms of these syndromes, as described in the literature, and to evaluate their significance.
Methods

Patients
The investigation concerned the mechanisms of SLE-induced CNS syndromes in children and adults of either sex [1]. Neonatal lupus was not included.

Definition of SLE-induced CNS syndromes
SLE was considered to be present if a patient had any four of the 11 criteria defined in 1982 by the American College of Rheumatology (ACR) or modified by the ACR in 1997 [2, 3]. A CNS syndrome was accepted as being inducible by SLE when it had been identified as such in a previous investigation [1], and when a secondary origin had been ruled out or was considered unlikely. A syndrome was considered as of secondary origin when (i) it was a side-effect of drugs used for SLE treatment, (ii) it was due to an immunocompromised status (e.g. intracranial infection), (iii) it was obviously due to hypofunction or dysfunction of other internal organs, or (iv) it was secondary to another CNS syndrome.

The search for literature
A PUBMED search was performed for studies in English, French or German concerning mechanisms of CNS manifestations of SLE published from 1980 onwards. Original articles, letters and reviews were accepted. We first asked for articles covering the combinations ‘SLE and CNS’ and ‘SLE and CNS diseases’. Subsequently, we asked for the combinations of SLE and specific mechanisms related to CNS syndromes. The total number of MeSH terms used was 42; these will be specified in the subheadings in the Results section. We studied abstracts of titles that seemed promising, and articles of interest were selected and analysed. The references in these articles were screened for other studies of interest. An article was of interest when it dealt with structural or functional changes in the CNS due to SLE, leading to neuropsychiatric symptoms; antibodies or other substances related to SLE causing symptoms; or psychological reactions to SLE responsible for neuropsychiatric symptoms. We also studied selected articles on related topics of other diseases, e.g. posterior reversible leukoencephalopathy, Devic’s syndrome, magnetic resonance imaging (MRI) of spinal cord lesions due to MS, etc.

Eligibility of publications and data extraction
We considered original publications and reviews to be eligible when they dealt with possible pathogenetic mechanisms of one or several of the CNS syndromes of SLE. These studies were used as the basis for conclusions. Results of other studies will be mentioned to confirm conclusions. In general, we shall not refer to studies of mixed case series composed of patients with definite SLE and lupus-like disease, and when we deviate from this rule this will be indicated. A secondary origin of a CNS syndrome was considered not present or not likely when it had been excluded on sufficient grounds by the authors or when grounds for a secondary origin were not present or not demonstrable. The data extracted from publications depended on the type of study (cohort study, case report, etc.) and concerned clinical features of syndromes and findings at imaging or other laboratory investigations.

Criteria for inclusion of a mechanism or a category of mechanisms
The four inclusion criteria are presented in the Box 1. For a mechanism or a category of mechanisms to be included, the presence of Criteria 1 and 4, 2 and 4, or 3 and 4 was required.

Results

Categories of pathogenetic mechanisms
(MeSH terms: SLE plus CNS diseases; CNS)
The pathogenetic mechanisms that were traced in the literature were ordered into five categories, each comprising one or several different processes (Table 1). We will evaluate the mechanism included in each of these categories, as far as deemed necessary, and provide reasons why they are likely or have been shown to be operative in SLE, or why they have to be excluded.

I. Ischaemia
The role of ischaemia in the causation of disorders of the CNS in patients with SLE is undisputed and is generally accepted as prominent. The changes caused by ischaemia may be in part irreversible and in part reversible, or they are entirely reversible. Reperfusion of an ischaemic area carries the risk of oedema and haemorrhage. Ischaemia is induced by a number of processes leading to transient or permanent narrowing or occlusion of vessels of different type and calibre. The factors mentioned in the literature as contributing to ischaemia in SLE are summarized in Table 2.

Table 1. Five categories of mechanisms underlying CNS manifestation in SLE mentioned in the literature

<table>
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Table 2. Factors contributing to CNS ischaemia in patients with SLE

<table>
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<th>No.</th>
<th>Factor</th>
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| 1.1 | Antiphospholipid antibodies (MeSH terms: SLE plus the following: CNS diseases; antibodies, antiphospholipid; lupus coagulation inhibitor; antibodies, anticardiolipin). Antiphospholipid antibodies (APL) are variously reported to be present in 20–55% or more of patients with SLE [4, 5]. The two classical components of the APL are antiphospholipid antibody (ACL) and lupus anticoagulant (LAC). In vivo, APL create a prothrombotic state [5], the reasons for which are as yet not entirely clear [5]. There is evidence for interplay between APL, thrombin generation and platelet activation [6]. In addition, APL appear to contribute to the development of atheroma (see I.3. Atherosclerosis). APL have been reported, sometimes in high numbers, in patients with different CNS manifestations of SLE, as illustrated by the following examples: chorea, four of six patients positive (one persistently, three variously positive and negative) [7]; epilepsy, 19 of 42 patients positive for ACL and seven of 16 patients positive for LAC [8, 9]; large cerebral artery occlusion, 17 of 30 patients positive for ACL and at least five of 30 patients positive for LAC [10]; myelopathy, 16 of 22 patients positive for ACL [11, 12]; a group of seven patients persistently positive for ACL performed less well in neurocognitive tests than three other groups of 5–24 patients variously positive or negative, or persistently negative [13]. The evidence for the association of APL with ischaemic stroke in SLE is as follows. (a) Cerebral infarcts in patients with SLE. ‘Cerebral infarction’ develops significantly more often in LAC-positive than in LAC-negative patients, as shown in a long-term, prospective study of 37 positive patients vs 37 age- and sex-matched negative patients. ‘Cerebral infarction’ is a late phenomenon in this study [14]. In another prospective investigation, no relationship was established between ‘cerebral vascular accidents’ (not including transient ischaemic attacks) and the presence of ACL. The number of patients in this latter study was considerable (500) and the follow-up time was short (mean, 8 months) [15]. (b) Thrombosis in patients with SLE. LAC and ACL are significantly related to arterial (myocardial and cerebral combined) and venous thrombosis in patients with SLE [4, 16]. In an investigation of 175 patients, LAC was the strongest risk factor both for arterial thrombosis [odds ratio (OR) 9.77, 95% confidence interval (CI) 1.74–31.15] [4] and venous thrombosis (OR 6.55, 95% CI 2.36–18.17) [4]. Screening of other APL components, e.g. anti-β2-glycoprotein I did not provide additional information [4, 16]. This conclusion is confirmed by results from a large data base, the Hopkins Lupus Cohort, which, however, also contains data from patients not complying with the ACR criteria for SLE [17, 18].

(c) Thrombosis in non-SLE patients. Although the results of most investigations are consistent with an increased risk of incident cerebral ischaemia in patients with APL, there are also deviant findings [for review, see reference 19]. Results from two large studies, one population-based, the other a cohort of male physicians, do not support the contention that immunoglobulin G (IgG) ACL is an independent risk factor for stroke [20, 21]. However, IgG ACL is significantly associated with future deep venous thrombosis [20] and myocardial infarction [22]. Results of other studies indicate that the titre rather than the presence of IgG ACL may be decisive for the association with thrombosis [23–26].

Conclusions. There is an association of APL with arterial and venous thrombosis in patients with SLE [argument (b), above]. LAC is a stronger risk factor than Ig ACL [argument (b)]. An association between APL and ischaemic stroke in patients with SLE is likely [arguments (a) and (b)]. The presence of APL complies with Criteria 2 and 4 and is accepted as a mechanism contributing to cerebral ischaemia.

I.2: Other antibodies against anticoagulants in patients with SLE (MeSH terms: SLE plus the following: CNS diseases; blood coagulation disorders; protein C; protein S). Protein S levels tend to be decreased in patients with SLE. Antibodies to protein S were found in six of 27 SLE patients without APL. A relationship with cerebral artery thrombosis and ischaemic stroke was not established [27].

Conclusions. The presence of antibodies to protein S does not (yet?) comply with the criteria for inclusion as a mechanism.

I.3: Premature atherosclerosis (MeSH terms: SLE plus the following: CNS diseases; arteriosclerosis; lipids). The risk factors for premature atherosclerosis in SLE are summarized in Table 3 [see references 28–40]. The evidence that SLE is involved in premature atherosclerosis of extracranial or intracranial arteries can be summarized as follows.

(a) An investigation of 498 women with SLE revealed a high rate of coronary heart disease. In the 35–44 yr age category, the rate of myocardial infarction was 50 times that of women without SLE [31].

Table 3. Risk factors for premature atherosclerosis in SLE

<table>
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<tr>
<th>Risk Factor</th>
<th>Description</th>
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<tr>
<td>Chronic inflammatory processes and immunological factors, including antiphospholipid antibodies [30, 37, 38]</td>
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<td>Dyslipoproteinaemia [36, 39]</td>
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<td>Renal disease [40]</td>
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<tr>
<td>Treatment with corticosteroids [28]</td>
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<tr>
<td>Other risk factors for atherosclerosis in the general population [28]</td>
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(b) In 175 women with SLE, an independent and strong association was found of SLE with coronary events, with focal carotid plaques and increase in the intima–media wall thickness of the carotid artery [32]. Stroke was due to cerebral infarcts in 28 of 34 patients in three large retrospective case series comprising 591 patients with SLE [33–35].

(c) Patients with SLE—even those in an inactive stage without renal disease who have not been treated with corticosteroids for the last 6 months—have a characteristic combination of high plasma levels of triglycerides and very low density lipoprotein and a low level of high-density lipoprotein [36, 39].

(d) Chylomicron metabolism in 10 selected patients with inactive SLE, without renal disease, who were not treated with corticosteroids, was compared with that in healthy age- and sex-matched controls and was found to be abnormal because of insufficient lipolysis, putatively due to reduced lipoprotein lipase activity [36].

Conclusions. There is good evidence of premature carotid artery atherosclerosis in SLE [arguments (a) and (b)]. SLE induces a state of dyslipoproteinemia and is thus likely to contribute to premature atherosclerosis [arguments (c) and (d)]. Premature atherosclerosis complies with inclusion Criteria 1, 2 and 4 and is accepted as a mechanism.

I.4: Small-vessel angioptihapy (MeSH terms: SLE plus the following: CNS diseases; CNS; pathology; brain; cognition disorders; MRI). (a) Authors of five studies describing post-mortem investigations of the brains of 88 patients agree that small-vessel angiopathy is the predominant structural abnormality [41–45]. Changes in the walls of affected vessels are described as proliferation of intimal cells, increase in fibrous tissue, and mucoid hyperplasia or hyalinization. The lumen of small vessels may become occluded by fibrin thrombi, organized thrombi or fibrous webs. Small vessels may be surrounded by microglia clusters, small infarcts, haemorrhages or ‘white matter necrosis’. There are also perivascular inflammatory infiltrates [41, 44]. All of these changes may occur throughout the pia–arachnoid and the nervous tissue.

(b) On MRI, T2-weighted images of the brain reveal in many patients small punctate lesions of increased signal intensity, localized mainly in the periventricular and subcortical white matter. In two studies, these were seen in 21 of 40 patients with prior CNS manifestations and in 19 of 50 patients without CNS manifestations [46, 47; for review, see reference 48]. It is suggested that they represent small infarcts with loss of nerve fibres and local gliosis [49, 50].

(c) The pathogenesis of these vascular changes is not clear [51]. Results of a meticulous histopathological investigation of four patients point to more prominent small-vessel angiopathy in patients with APL than in those without APL [45].

(d) Cerebral small-vessel vasculopathy has been suggested to underlie the cognitive disorder of SLE patients who are otherwise without neuropsychiatric diseases [52]. In support of this hypothesis, cerebral small-vessel disease due to hypertension and ageing leads to predominantly subcortical dementia [53, 54]. In one patient with SLE, biopsy investigation pointed to small-vessel angiopathy as contributing to leukoencephalopathy [55].

Conclusions. Cerebral small vessel angiopathy is the predominant histopathological abnormality in SLE [argument (a)]. It is suggested to cause cognitive disorder in many patients [argument (d)]. It complies with Criteria 1 and 4 and is accepted for inclusion as a mechanism.

I.5: Thrombosis (MeSH terms: SLE plus the following: intracranial thrombosis; cerebral artery diseases; thrombosis, carotid artery; sinus thrombosis intracranial; pseudotumour cerebri). (a) The incidence of ischaemic stroke in patients with SLE is increased [33, 34, 35; for review, see reference 1] and has been demonstrated in some cases to be due to occlusion of large arteries [10]. Premature atherosclerosis may be assumed to be involved in this occlusion and is in part due directly to SLE (see I.3: Premature atherosclerosis). Another process contributing to occlusion is the increased activation of the haemostatic system. Thromboxane biosynthesis is enhanced in patients with SLE, pointing to platelet activation, and the plasma level of a marker of thrombin generation (prothrombin fragments F1 + 2) is increased [6]. APL may further atherosclerosis and may play a role in the increased activation of haemostasis [6, 37].

(b) Short case series and single case reports have been published on cerebral venous thrombosis (CVT) in adults and children with SLE [56–63; for review, see reference 1]. The presence of APL increases the risk of venous thrombosis in patients with SLE [4, 16] and is suggested to increase the chance of CVT [64, 65]. The association of two such rare disorders as CVT and SLE, even in young adults and children, is a strong argument for the induction of one by the other.

Conclusions. Thrombosis of cerebral arteries and veins is likely to be induced at least in part directly by SLE and complies with the criteria 1 and 4. It is acceptable for inclusion as a mechanism.

1.6: Emboli (MeSH terms: SLE plus intracranial embolism). Cerebral emboli may potentially derive from valvular or endocardial vegetations or from plaques in the carotid artery or other large arteries [32, 41, 66].

(a) In a prospective study of 69 SLE patients that covered almost 5 yr and in which approximately 60% of the patients had valvular disease, five patients developed ischaemic strokes. They all had cardiovalvar abnormalities [66].

(b) In case reports, embolization of cardiac origin was demonstrated histologically [67, 68].

(c) Pathologists agree that some cerebral ischaemic infarcts should be attributed to emboli [41, 42].

(d) The incidence of transient ischaemic attacks is increased in SLE [for review, see reference 1]. Some
transient ischaemic attacks (TIAs) may be embolic in origin.

Conclusions. Embolism is likely to be the cause of cerebral ischaemia in at least some cases in view of arguments (a) and (b). This contention is supported by arguments (c) and (d). Cerebral embolism complies with Criteria 1 and 4 and is accepted as a mechanism.

I.7: Dissection (MeSH terms: SLE plus the following: CNS disease; cerebral artery diseases; dissection). Dissection of arterial walls may result in arterial occlusion, aneurysmatic widening or haemorrhage. Trauma is probably the most frequent cause of dissection of extracranial arteries; atherosclerosis and vasculitis are risk factors [69]. Figures about the incidence of non-traumatic dissection in the population are not available. Dissection of the aorta was first described in SLE patients, and dissection of extracranial arteries has also been reported in three patients [10, 70] and possibly one other case [71]. It is currently possible to visualize dissection by non-invasive imaging techniques (magnetic resonance angiography or CT angiography), which will facilitate evaluation of its role in cerebral artery occlusion in SLE in the near future.

Conclusions. The possibility should be entertained that dissection contributes significantly to the occurrence of cerebral ischaemic infarcts in SLE. Inclusion of dissection as a mechanism awaits more reports.

I.8: Vasculitis (MeSH terms: SLE plus vasculitis, central nervous system). Although cerebral vasculitis is generally considered to be rare in patients with SLE, there is no denying that it occurs. Post-mortem investigation of brain pathology has shown vasculitis in at least one of 24 cases [41] and changes interpreted as healed vasculitis in the pia–arachnoid in one of 10 cases [43]. Studies of single cases have established cerebral vasculitis by biopsy or post-mortem investigations, in some cases with very convincing illustrations showing the histological findings [72–77]. In other case reports, cerebral vasculitis was established by arteriography [78, 79]. Cerebral vasculitis in SLE may be widespread [78] but in some cases it is restricted to one region [73, 74] or part of one vessel [41]. Localized forms of vasculitis have been reported in patients with aneurysmatic bleeding [77]. Some vasculitides concern small cerebral vessels and others predominantly large arteries [73, 78].

Conclusions. Cerebral vasculitis complies with Criteria 1 and 4 and is accepted as a mechanism.

I.9: Vessel spasm (MeSH terms: SLE plus the following: disease, Raynaud; migraine). Exposing patients with SLE and Raynaud phenomenon to a cold stressor test provokes defects in cerebral blood diffusion or an increase in such defects in some of them. This does not happen in patients without Raynaud’s phenomenon [80]. No clinical syndrome has so far been associated with cerebral vessel spasm.

Conclusions. Spasm of cerebral arteries complies with Criterion 1 but not Criterion 4 and cannot be accepted as a mechanism.

II. Haemorrhage (MeSH terms: SLE plus the following: haemorrhage, cerebral; subarachnoid haemorrhage; subdural haematoma; epidural haematoma)

(a) Findings in case series [33–35], reports of single cases and post-mortem investigations support an increased incidence in SLE of various types of intracranial and intraspinal haemorrhages, including intracerebral, subarachnoid, subdural and epidural haemorrhages [see reference 1, sections, 15, 16: Stroke and transient ischaemic attacks and 17, 18: Subdural and epidural haematomas].

(b) This increased incidence has been surmised to be related to several causes: hypertension, hypercholesterolaemia, prolonged corticosteroid medication and changes induced by SLE [34, 35, 81]. Thrombocytopenia may also play a role [34, 35, 81].

(c) In some patients with SLE, subarachnoid haemorrhages remain unexplained, but they are often shown to be due to rupture of a saccular aneurysm or, rarely, a fusiform aneurysm [35, 77, 82]. Interestingly, most reports of cerebral aneurysms in SLE are from Japanese centres. A retrospective investigation revealed that subarachnoid haemorrhage had been diagnosed in 10 of 258 patients. SLE was the only risk factor in five patients. Angiography in eight patients revealed aneurysms in four [82]. According to another Japanese study, 23 SLE patients with cerebral aneurysms had been published by August 1990 [83]. More patients have been described since then [84]. Saccular aneurysms are not congenital but develop [85]. In patients with SLE, aneurysms occur not only in intracranial arteries but also in other arteries [86, 87].

Conclusions. The incidence of various types of intracranial or spinal haemorrhage is increased in SLE [argument (a)]. The mechanisms underlying the haemorrhages have not been elucidated sufficiently [argument (b)]. The incidence of subarachnoid haemorrhages due to ruptured saccular aneurysms is likely to be increased in Japan [argument (c)].

III. White matter damage

Table 4 summarizes the types of white matter damage in SLE that are mentioned in the literature. The lesions differ in size, distribution and histology.

Table 4. Different forms of white matter damage

<table>
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<tr>
<td>1</td>
<td>Small punctate MRI lesions predominantly in the periventricular and subcortical white matter. Histology: small infarcts with loss of axons and myelin and with gliosis</td>
</tr>
<tr>
<td>2</td>
<td>Demyelinating plaques in brain and brainstem</td>
</tr>
<tr>
<td>3</td>
<td>Lesions of the optic nerves, and lesions of the spinal cord extending over two vertebrae or more, as in Devic’s syndrome. Histology: vacuolar myelin degeneration, axonal loss, white matter necrosis</td>
</tr>
<tr>
<td>4</td>
<td>Extensive white matter lesions (leucoencephalopathy) as revealed by MRI or CT, in brain and brainstem, reversible in at least some cases, due to oedema or confluent small lesions</td>
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</tbody>
</table>
III.1: Small punctate white matter lesions. These are considered to be due to small infarcts and vessel angiopathy (see I.4: Small-vessel angiopathy).

Conclusions. Small punctate white matter lesions comply with Criteria 1 and 4 and are accepted as a mechanism.

III.2: Plaques of demyelination in brain and brainstem (MeSH terms: SLE plus demyelinating diseases; MRI). The arguments for this type of demyelination are clinical and histological.

(a) Clinical. The reversible and relapsing course of some CNS syndromes in patients with SLE [88, 89] resembles the course of relapsing MS, which is primarily a demyelinating disease. Reversibility of clinical signs is, however, not pathognomonic for inflammatory demyelination, as demonstrated by TIAs and recovery after stroke.

(b) Imaging. Focal changes in the white matter of the brain visualized by MRI are generally held to be due to ischaemic infarcts and oedema, as appears from an analysis of 27 patients [90], spectroscopic imaging [91] and a recent review [48].

(c) Histology. Small oval or round areas of myelin vacuolation with some degree of axonal damage, or areas of white matter necrosis with myelin vacuolation at the border of the lesion, have been reported in three patients with SLE, aged 13, 21 and 42 yr [44, 92, 93]. In two of them the areas were clearly localized around veins. The changes were observed throughout the white matter of the brain, basal ganglia and brainstem and the white matter of the spinal cord. Patients presented with subacute encephalopathy, myelopathy or both. These lesions were suggested to be due to acute demyelinating encephalomyelitis (ADEM) complicating SLE [92, 93]. ADEM is rare and affects mostly children. In a patient with incompletely defined SLE, multiple oval lesions with necrosis or myelin vacuolation were observed predominantly in the periphery of the white matter of the spinal cord and were considered to be related to obstruction of small vessels penetrating from the pia-arachnoid into the cord [94].

Conclusions. Disseminated (perivenous) myelin vacuolation or necrosis of the CNS has been reported in only a few cases and may be an associated CNS autoimmune disease or an SLE-induced mechanism. For the present, it is considered to comply with inclusion Criteria 1 and 4 and is accepted as a mechanism.

III.3: White matter lesions in optic neuropathy and transverse myelitis (MeSH terms: SLE plus the following: optic nerve diseases; optic neuritis; spinal cord diseases; myelitis transverse; neuromyelitis optica). Optic neuropathy or myelopathy each occur in approximately 1% of patients with SLE. Myelopathy is probably somewhat more frequent than optic neuropathy [see reference 1, section 28, 29: Optic neuropathy and myelopathy]. The two syndromes occur in a substantial minority of patients who are affected consecutively or simultaneously (Devic’s syndrome or the ‘optic–spinal’ form of MS), as shown in a review of 105 cases [95]. Devic’s syndrome is considered by some authors to be an autoimmune disease in its own right. The myelopathy of Devic’s syndrome extends over two or more vertebrae and is characterized histologically by necrosis and cavitation. The course of Devic’s syndrome is monophasic, relapsing or chronic [96–99].

The MRI of SLE optic neuropathy is not well known. A variable degree of swelling and increased signal intensity on T2-weighted images has been described in patients with undefined SLE [100]. The histopathology has not been examined sufficiently [101].

The most common MRI findings in SLE myelopathy are T1 and T2 signal abnormalities and widening of the cord [102]. MRI lesions are longer than those in most cases of MS [103] and similar to those in Devic’s syndrome. They may extend over the entire length of the spinal cord [102, 104]. Since 1980, pathological examination of SLE myelopathy has been performed in one case of definite SLE [44] and in two other patients for whom the criteria for the diagnosis SLE criteria were not given [94]. The histological changes in the SLE patient and in one of the patients with undefined SLE comprised oval areas of myelin vacuolization or necrosis, mainly in the periphery of the white matter of the cord. The lesions of the second patient with undefined SLE resembled those seen in a case of SLE described before 1980 [41]. Myelopathy had been present in this latter case for months [41]. At post-mortem investigation, ‘white matter degeneration’ involving myelin and axons was present from the cervical to the sacral segments and over the whole circumference of the cord, most severely in the periphery. Myelin vacuolation was seen at the margins of the lesions, bordering normal white matter [41].

Spinal cord compression develops in patients with spinal subdural or epidural haematoma (for review, see reference 1, section 17, 18: Subdural and epidural haematomas).

Conclusions. There are still many unanswered questions regarding the nature of SLE-induced optic neuropathy and myelopathy. White matter degeneration in the optic nerve and spinal cord complies with Criteria 1 and 4 and is accepted for inclusion as a mechanism.

III.4: Leucoencephalopathy (MeSH terms: SLE plus leucoencephalopathy). As shown in case reports, leucoencephalopathy may develop in the brain and brainstem of SLE patients within days, weeks or a longer period [55, 105–109]. The lesions may be largely or partly reversible and in such cases are suggested to be due to oedema. In most patients, a definite cause has not been identified. Leucoencephalopathy has, however, been described in a patient with pseudotumour cerebri syndrome [108].

It is of interest that a reversible type of leucoencephalopathy may develop as a hypertension emergency and in association with drug treatment (cyclosporin, tacrolimus, interferon α, FK 506, erythropoietin) or thrombotic thrombocytopenic purpura and other disorders [110, 111]. These lesions predominate in most cases in posterior parts of the brain, the occipital lobes and the parietal or temporal lobes, spreading from
there to other parts. In a large majority of patients they
give rise to an encephalopathic syndrome with cerebral
loss of vision and other neurological signs [posterior
leucoencephalopathy syndrome (PLS)]. PLS has been
diagnosed in two patients with lupus nephritis (SLE
criteria not given) [110]. Several patients with undefined
SLE have been described who had visual complaints and
reversible white matter lesions predominating in the
occipital poles [112].

Conclusions. Leucoencephalopathy other than PLS is
considered to comply with Criteria 1 and 4 and is
admitted for inclusion as a mechanism.

IV: Neuronal dysfunction due to antibodies (Table 5)
(MeSH terms: SLE plus the following: antibodies;
cytokines)

Autoantibodies against neuronal membrane receptors
may hinder neurotransmission in the CNS and cause
neurological signs. An investigation of a specific form
of paraneoplastic cerebellar ataxia provided strong
arguments for this hypothesis [113]. Antibodies against
neuronal nuclear or cytoplasmic antigens are held by
some authors not to be neuropathogenetic themselves
but to reflect T-lymphocyte activation [114].

The evidence for a role of antibodies in the patho-
genesis of neuronal dysfunction in SLE is at present
circumstantial, both from the clinical and from the
laboratory point of view. SLE psychosis, defined in
DSM IV as a ‘disorder due to a general medical con-
tdition’ [1, 115], is not related to any known structural
changes and recovers without residual abnormalities.
Such a course might be explained by antibody-induced
reversible neuronal dysfunction. A relationship with
neuronal antibodies and cognitive disorder would be
conceivable [116]. The neuropathological changes in
patients with chorea are in some cases diffuse and not
easily explainable by focal vascular abnormalities
[117]. An antibody-mediated syndrome would be an
alternative. A role for antibodies has also been sug-
gested in the pathogenesis of inappropriate secretion of
antiadrenergic hormone in SLE [118, 119].

Though many authors have found antineuronal
antibodies in patients with SLE, there is as yet no
robust evidence for a causal relationship of a specific
antibody with any CNS syndrome. The strongest evi-
dence for a relationship, as far as clinical significance is
concerned, is for three ribosomal phosphoproteins
(antiribosomal P antibodies) [121]. They are frequent
in patients with lupus psychosis and increase during the
active phase of this disorder. However, they are not
present in all patients with lupus psychosis and are not
specific for lupus psychosis or CNS disease [121, 126].

Cytokines and complement are involved in immuno-
logical processes in the CNS but how they interact
and contribute to CNS disease and whether they are
associated with specific CNS syndromes is not yet
clear [127].

Conclusions. Neuronal dysfunction due to antibodies
in SLE-induced CNS disease seems an attractive idea
and may explain many CNS syndromes. However, there
is still insufficient evidence. It can therefore not yet be
accepted as a mechanism for clinical syndromes in SLE.

V: Deficient psychological reactions (MeSH terms:
SLE plus the following: coping skill; depression; mood
disorder; anxiety disorders)

The term ‘coping’ refers to strategies used by individuals
to manage stressful life situations [128, 129]. Physical
illnesses may act as a stressful life situation and may
precede the onset of depression or elicit anxiety when
coping is deficient (insufficient or abnormal) [128, 130,
131]. The liability to develop clinical depression in
response to stressful life situations is determined in part
by an inherited vulnerability. The results of a study of
46 patients with undefined SLE suggests that the coping
strategies used were not disease-specific [132].

Conclusions. Coping ability and hereditary predis-
position are likely to be involved in psychopathological
reactions in patients with SLE, as in other chronic
diseases. They comply with Criteria 3 and 4 and are
acceptable as disease mechanisms in SLE.

Discussion

Current knowledge holds ischaemia to be the main cause
of CNS manifestations in SLE. The mechanisms lead-
ing to ischaemia are diverse and involve abnormalities of
coagulation; thickening of vessel walls due to different
causes; the development of focal atherosclerotic plaques
in large arteries; and, in some cases, inflammatory
processes. In a few patients, CNS syndromes are due
to intracranial and intraspinal haemorrhages but the
factors that lead to the rupture of vessel walls have not
yet been analysed sufficiently. Lesions in the cerebral
white matter are in general ischaemic in origin and in
a few cases they are due to reversible oedema. The
white matter changes in the optic nerves and spinal
cord are poorly understood. Antibody-mediated neur-
onal dysfunction is still under investigation. Deficiency
of psychological reactions is likely to play an important
role and belongs to another dimension.

Table 6 combines the results of the present literature
investigation with those of our previous investigation
of CNS syndromes in SLE [1]. A modified version of the

Table 5. Antibodies and neuronal dysfunction

<table>
<thead>
<tr>
<th>Antibodies</th>
<th>Target</th>
<th>Putative syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antineuronal antibodies</td>
<td>50 kDa synaptic membrane protein [120]</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>52 kDa neuronal protein [116]</td>
<td>Cognitive disorder?</td>
</tr>
<tr>
<td>Antiribosomal P antibodies</td>
<td>Ribosomal P0, P1, P2 proteins [121]</td>
<td>Psychosis, depression [121]</td>
</tr>
<tr>
<td>Antineurofilament antibodies</td>
<td>205 and 160 kDa [122]</td>
<td>–</td>
</tr>
<tr>
<td>APL</td>
<td>β2-glycoprotein I [123], Myelin [124]</td>
<td>Cognitive disorder [13, 125]</td>
</tr>
<tr>
<td></td>
<td>Indirect, by effects on coagulation and vessel walls</td>
<td></td>
</tr>
</tbody>
</table>
The ACR nomenclature system is shown in the left column. The right column presents possible pathogenetic mechanisms, as reviewed in these two investigations. The advances that have been made in our knowledge of the pathogenetic mechanisms of SLE-induced CNS manifestations have therapeutic consequences. Narrowing of vessels and atherosclerotic plaques develop gradually and are not easily reversible. Interventions for the purpose of primary prevention have been proposed and require evaluation, e.g. prophylactic aspirin and lowering the concentration of serum lipids. Ischaemic infarcts and haemorrhages occur suddenly and in some cases may be open to intervention, such as the thrombolysis of occluded large intracranial arteries and the clipping or coiling of aneurysms. Anticoagulation may be indicated for cerebral sinus thrombosis. In the case of occlusion of arteries, secondary prevention is needed. The efficacy of all these forms of treatment in SLE patients requires investigation and confirmation.

Prevention and new forms of (symptomatic) treatment are not only of interest for TIAs and stroke. Strategies to prevent vascular changes may be relevant to the cognitive functioning of patients. Preparing patients for the uncertainties of their disease may help to prevent psychological reactions. For other CNS syndromes, more insight is needed into their pathogenesis before the same approach is applicable, e.g. the prevention of cerebral oedema in SLE. Though the prevention and treatment of CNS syndromes do not cure SLE, they may improve the patient's well-being and survival.

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References

Table 6. Pathogenetic mechanisms of central nervous system syndromes induced by SLE

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Aseptic meningitis</td>
<td>Vascularitis; other still unknown causes? [1]</td>
</tr>
</tbody>
</table>
| 2 Cerebrovascular disease | Ischaemic infarct: APL, atherosclerosis, thrombosis of arteries or veins, emboli, vasculitis;
| 2.1 Stroke | Haemorrhage: intracerebral or subarachnoid. Due to vessel wall changes, e.g. aneurysms and other changes, and thrombocytopenia. |
| 2.2 TIAs | Emboli from atherosclerotic plaques and cardiac vegetations, or haemodynamic mechanisms |
| 3 Myelopathy and optic neuropathy | White matter necrosis |
| 3.1 Devic’s syndrome | Myelin vacuolation or white matter necrosis; vasculitis(?), subdural or epidural haematomas [1] |
| 3.2 Myelopathy only | Myelin vacuolation or other unknown mechanism |
| 4 Tumour cerebri syndrome | Idiopathic intracranial hypertension [1]; cerebral sinus thrombosis; subdural or epidural haematoma [1] |
| 5 Movement disorders | Vascular insult or neuronal antibodies |
| 5.1 Chorea | Unknown |
| 5.2 Parkinsonism | Neuronal antibodies? [1] |
| 5.3 Chronic cerebellar ataxia | |
| 6 Epileptic seizures | |
| 6.1 Generalized convulsive seizures | Unknown; temporal lobe dysfunction? [1] |
| 6.2 Partial or complex partial seizures | As 6.1 or secondary to other SLE-induced abnormalities, presumably mostly cerebrovascular |
| 6.3 Partial seizures with secondary generalization | As 6.1 or secondary, as above |
| 6.4 Reflex seizures | As 6.1 or secondary, as above |
| 7 Delirium (encephalopathy) | Leucoencephalopathy due to small vessel disease (?); oedema due to venous flow obstruction; SIADH a causing brain oedema; (perivenous) white matter lesions; vasculitis [see also reference 1] |
| 8 Cognitive dysfunction | |
| 8.1 Cognitive disorder, fluctuating | Small vessel angiopathy? Antineuronal antibodies? |
| 8.2 Dementia | Multiple ischaemic infarcts or leucoencephalopathy |
| 9 Psychosis | Antiribosomal P antibodies; antineuronal antibodies? |
| 10 Anxiety disorder | Coping difficulty, hereditary vulnerability |
| 11 Depression | Coping difficulty; hereditary vulnerability; other unknown factors of biological origin |

The CNS syndromes in the table are classified according to the modified ACR nomenclature system [1].

aSyndrome of inappropriate secretion of antidiuretic hormone.


