Systemic lupus erythematosus (SLE) is a chronic multisystem autoimmune connective tissue disorder, which has variable clinical manifestations that range from mild to life-threatening. Young women between their late teens and early 40s have a much higher prevalence in developing SLE, with a female to male ratio of 9:1 [7]. In the United States (U.S.) for example, Lawrence et al. [8] reported that SLE appeared to be more common in black women than in other population groups. One U.S. retrospective study of patient medical records, by McCarty et al. [9] found that the disease was diagnosed 23 times more often in black women. Certain ethnic groups also appear to show a higher prevalence, such as people with Afro-Caribbean or African origin [10-13].

The worldwide prevalence of SLE ranges between 12 and 50 per 100,000. These figures vary and are related to location and to the patient’s ethnicity as well as better recognition of the disease today [14]. Factors such as sunlight, the contribution of infection, oestrogen hormones, stress and drugs may precipitate the disease and there is also a complex genetic basis [15]. It has been reported by Deapen et al. [16] that a genetic factor in the predisposition to the disease is reflected by 25% concordance in identical twins. Many of the recent genetic findings, [17, 18] seem reasonable from a mechanistic standpoint: they identify genes with important roles in the immune system; occasionally in conjunction with functional data of the alleles tested that also fit the paradigm of loss of self-tolerance. Inherited deficiencies of complement also plays a role, [19] with C1q, C1r, C1s C4, and C2 being the most important of the complement proteins, [20] however, no single cause for SLE has been identified. Recent data, [21] also suggested that a nearly ubiquitous virus Epstein-Barr virus (EBV) might also play a facilitating role [18-22].

A case-control study, by James et al. [23] demonstrated that EBV antibodies were present in 99%, and EBV DNA was present in 100% of the children and young adults who had SLE, which was significantly higher than those in the control group. Despite this, the association between active EBV infection and the precipitation of SLE remains unclear. Neuropsychiatric manifestations are increasingly recognised in patients with SLE. These include a wide variety of neurological and psychiatric features that account for considerable morbidity and mortality in these patients. They also involve both the central and peripheral nervous systems and range from subtle abnormalities of cognitive dysfunction and anxiety to obvious manifestations, such as stroke, seizures and psychosis. This article through systematic published literature, attempts to summarise the important neurological features of central nervous system disease of SLE.

Clinical Presentation

The widely recognised presentation of a young female presenting with inflammatory arthritis and a butterfly rash on the face (Fig 1) is relatively uncommon [2]. Non-specific symptoms of malaise, fatigue, arthralgia, oral ulcers, photosensitivity, lymphadenopathy, pleuritic chest pains, headaches, parasthesiae, symptoms of dry eyes and mouth, Raynaud’s phenomenon and mild hair loss are the more likely presentations [24].

The diagnosis of SLE of individual patients therefore requires certain clinical and laboratory data, [25] based on the widely accepted modified (1997) criteria suggested by the American College of Rheumatology (ACR) (although intended, and in fact more useful for research and therapeutic trial purposes) (Table 1) [24]. The means to early diagnosis is in the clinical evaluation of patients. It should include a complete ‘systems’ review with examination and subsequent investigations, guided by the extent of organ involvement [26]. For example, in primary care, a diagnosis of SLE or a related disorder is frequently apparent after clinical evaluation, urinalysis for blood and protein. Investigations such as a full blood count (FBC), which often shows an anaemia or a cytopenia, renal and liver function tests and acute phase reactants: a high erythrocyte sedimentation rate (ESR) with a normal C reactive protein (CRP) concentration are characteristic. A simple algorithm for the diagnosis of SLE is provided as an example (Fig 2) [27-29].

Central nervous system disease

History

Central nervous system (CNS) involvement in SLE was first described by Kaposi in 1872 [2]. Osler in 1903 was the first to report a recurrent focal cerebral ischaemia in SLE [3]. Libman and Sacks [4] described endocarditis in SLE in 1924. The association of the lupus anticoagulant (LA) and thrombosis in patients with SLE was described by Bowie et al. [5] in 1963, and in 1968 Johnson and Richardson reported neuropathological findings in 24 cases of SLE [6]. In 1988, Devinsky et al. [7] reported on an autopsy study of 50 SLE patients; 10 of whom had embolic cerebral infarcts, five caused by Libman-Sacks endocarditis and four from other cardiac sources.

Neurological features

CNS disease is highly diverse and remains a challenge in terms of pathogenesis, assessment and treatment and it is now better to consider CNS disease in terms of separate syndromes. It is a serious but potentially treatable illness,
which still presents very difficult diagnostic challenges. The ACR defines 19 different syndromes in its classification for the neurological complications of SLE (Table 2), as opposed to previous incomplete terms such as central nervous system lupus, neurolupus or lupus cerebritis [34].

CNS involvement is reported to occur in 14-70% of SLE patients [39]. The most common neurological manifestations of SLE are the organic encephalopathies, which comprises of all the potential variations of acute confusion, lethargy, or coma; chronic dementias; depression, mania, or other affective disturbances; or psychosis.

**Headache**

Of the more frequently encountered CNS complications, headaches are extremely common. Fernandez-Nebro et al. [32] and Raskin et al. [33] stated that up to 40% of individuals experience severe disabling headaches at least once per year. There are, however three controlled studies in the literature on chronic or episodic headache [41] that cannot be tracked back to other SLE syndromes [31, 32]. The results are rather conflicting, however, and do not allow for a definitive conclusion. For example, a link between migraine and SLE activity and ‘flare – ups’ has definitely not been established [34, 35].

If future research confirms that migraine is indeed induced by SLE, the neurological burden would still be overestimated by including migraine without restriction in the list of SLE neurological criteria. Early studies showed that headaches might respond to corticosteroid treatment and this proved to be more effective than the conventional anti-migraine therapy used in controlling headaches in SLE patients [36, 37].

A clear distinction between CNS manifestations due to SLE and those due to antiphospholipid (Hughes) syndrome (APS) has been indicated [38]. An association of migraine headache with antiphospholipid antibodies (APAs) has once again been implicated, as shown by Provenzale et al. [40]. However, more recent studies have found no such link [39].

**Seizures**

Seizures are the next most frequent neurological complication and are known to occur in 14-25% of patients (compared with 0.5-1% in the general population) [42]. Seizures may result from cerebral vasculitis, cardiac embolism, opportunistic infection, drug intoxication, or associated metabolic derangements. They are more likely to be associated with APS than with cerebral vasculitis, which is extremely rare in clinical practice [43]. Electrolyte disturbance and medicinal effects should be excluded, especially those resulting from antidepressants, stimulant medications to treat fatigue, or withdrawal from sedatives or alcohol. The primary neurological presentation of SLE is more common than originally thought (10/41 patients) and included both seizures (4 cases) and movement disorders including Parkinsonism and chorea (4 cases) [44].

Higher overall frequencies of seizures (42%); an early manifestation in 27%, and in 10% seizures were the first SLE symptom seen. Epileptic seizures are among the most common CNS manifestations in SLE.

In separate studies, Sibley et al. [45], Steinlin et al. [46] and Briciotti et al. [47] demonstrated that generalized tonic-clonic seizures (formerly known as grand mal seizures), simple and complex partial seizures, reflex seizures and status epilepticus all occur [48].

It is presumed that most seizures in patients with SLE would be elicited by vascular abnormalities in the brain, or would be either due to CNS infections or secondary to other signs, but this cannot always be demonstrated.

In a large retrospective study, in 18 out of 266 patients, seizures were not attributable to any cause other than SLE [49].

Stroke and recurrent transient ischaemic attacks (TIAs) are among the CNS diagnoses seen in 3-15% of cases; although these figures vary according to the literature [44, 45]. Yearly strokes were calculated for example, using data from 91 patients with SLE observed for 599 patient-years. It was found that the stroke rate dropped from 6.6% in year 1 to 0.6% during years 6-10 [46].

The International Classification of Diseases (ICD-9) code for SLE, estimated with SLE in one Japanese centre, covering a 20 year period, revealed that 10 of

<table>
<thead>
<tr>
<th>SLE criterion</th>
<th>Definition or examples</th>
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<tbody>
<tr>
<td>Serositis</td>
<td>Plauritis – pleuritic pain, Pleuraleffusion Pericarditis – ECG changes, pericardial rub, pericardial effusion</td>
</tr>
<tr>
<td>Oral ulcers</td>
<td>Often painless sores</td>
</tr>
<tr>
<td>Arthritis</td>
<td>Nonerosive – two or more peripheral joints affected</td>
</tr>
<tr>
<td>Photosensitivity</td>
<td>Skin rash as a result of unusual reaction to sunlight</td>
</tr>
<tr>
<td>Blood</td>
<td>Haematological disorder; Haemolytic anaemia Leucopenia Lymphopenia Thrombocytopenia</td>
</tr>
<tr>
<td>Renal disorder</td>
<td>Proteinuria (with 3+ or more protein noted in urinalysis specimen or 0.5 g of protein/day); Cellular casts in urine</td>
</tr>
<tr>
<td>Antinuclear antibody</td>
<td>Antibodies to nuclear consituents</td>
</tr>
<tr>
<td>Immunological disorder</td>
<td>Anti-DNA antibodies Anti–Sm antibodies Antiphospholipid antibodies</td>
</tr>
<tr>
<td>Neurological disorder</td>
<td>Seizures Psychosis</td>
</tr>
<tr>
<td>Malar rash</td>
<td>Fixed erythema over the malar eminences</td>
</tr>
<tr>
<td>Discoid rash</td>
<td>Erythematous raised patches may scar</td>
</tr>
</tbody>
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ECG = electrocardiogram

A mnemonic to remember the eleven symptoms is ‘SOAP BRAIN MD’.

Table 1: ACR Classification Criteria for SLE [26]

The diagnosis of SLE requires the presence of four or more of the following eleven criteria simultaneously or in succession (also see algorithm in Fig 2).
### Table 2: The neurological complications of SLE [30]

**Central nervous system**

**Neurological**
- Aseptic meningitis
- Cerebrovascular disease
- Multifocal subacute lesions
- Headache (including migraine and idiopathic intracranial hypertension)
- Movement disorders (particularly chorea)
- Myelopathy
- Seizure disorder

**Psychiatric**
- Acute confusional state
- Anxiety disorder
- Cognitive function
- Mood disorder
- Psychosis

**Peripheral nervous system**

- Acute inflammatory demyelinating polyradiculopathy
  - (Guillain – Barre syndrome)
- Autonomic disorder
- Cranial neuropathy
- Mononeuropathy, single or multiplex
- Myasthenia gravis
- Plexopathy
- Polineuropathy

### Figure 2. An algorithm for the diagnosis of SLE. (ANA = antinuclear antibody; ACR = American College of Rheumatology; anti-dsDNA = antibody to double stranded DNA antigen; antiSm = antibody to Sm nuclear antigen).

Information from references: [25-29]
258 patients had at some time experienced a (clinically defined) subarachnoid haemorrhage. Figures in the literature on TIAs in SLE indicate that the overall incidence is raised [84, 46, 57].

**Aseptic meningitis**

Acute, chronic or recurrent aseptic meningitis is a rare manifestation of SLE. The term is often used for a meningeal syndrome of non-infectious origin with some degree of nuchal rigidity (neck stiffness) and with increased white cells (pleocytosis) in the cerebrospinal fluid (CSF) [85, 58]. Pathologically, meningeal inflammation is found in almost one-fifth of patients [58]. SLE should be considered in any patient who initially presents with a meningeal picture and in whom organisms have not been identified, especially if the meningitis is recurrent. Aseptic meningitis has been reported in patients with stroke or ‘ischaemic brain lesions’; vasculitis was not demonstrated, but was not ruled out [80, 61].

There are reports of aseptic meningitis following non-steroidal anti-inflammatory drugs (even after only a single tablet) in SLE and mixed connective tissue disease.

Jolles et al. [83] stated that up to 60% of patients with SLE are estimated to have CNS symptoms associated with inflammation at some time during their illness, and that this could predispose them to drug-induced aseptic meningitis (DIAM). Maignen et al. [84] suggested that various drugs (non-steroidal anti-inflammatory agents such as ibuprofen and sulindac, antibiotics such as cotrimoxazole, trimethoprim, ciprofloxacin and miscellaneous drugs such as carbamazepine, human immune globulin and muromonab CD3) can be associated with development of DIAM and those patients with SLE and/or connective tissue disorders are at a higher risk. Ibuprofen, for example, has been reported on a number of occasions as a cause of aseptic meningitis, especially in patients with SLE [84, 60].

The exact mechanism for the reaction to these agents is not fully understood, but it is speculated that APAs possibly have a role. Meningeal symptoms occur a few hours after drug intake and resolve without sequelae within one or two days after the drug is withdrawn.

Chorea, although rare, is often quoted as the classical neurological feature of SLE [85]. There are conflicting reports, as suggested by Janvas et al. [86] and Cervera et al. [87, 88] in regard to its incidence, ranging from 1-4%. It can develop at any time, but is more likely to appear during an acute flare, which has led some investigators to suggest that it could be used as a marker of disease activity, where there is a reported recurrence rate of up to 25%. It has also been associated with stroke [89] and with idiopathic intracranial hypertension and dural sinus thrombosis in children [90]. It is not yet clear, however, whether it is due to a vascular insult or to antibody-induced neuronal dysfunction [71, 72].

Psychiatric disturbances range from mood and personality disorders to psychosis, the latter being defined as a psychotic disorder, according to the criteria of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) [93]. No unique clinical picture is seen, but three relatively distinct patterns can be discerned: ‘pure’ behavioural or psychiatric illness without clouding of consciousness, subacute encephalopathy/encephalitis, and dementia. Affective disorders, particularly anxiety and depression are the most common (e.g. in 103 of 414 outpatients from two studies and 19 of 43 hospitalised patients from another study), though not in similar proportions in the studies [74, 76].

It has, however, not been shown that these disorders occur more frequently in patients with SLE [77] than in those with rheumatoid arthritis or other chronic diseases [78-80]. The association with psychotic episodes – ‘lupus psychosis’ – is more reliable [81], although its distinction from corticosteroid induced psychosis can be difficult. In a large and often quoted retrospective study, 11 of 266 patients developed psychosis during a mean follow-up period of at least 90 months [42]. Delusions, visual and auditory hallucinations, catatonia and conversion disorders are all well recognised [82].

Dementia is a commonly accepted complication, although little detailed published information is available. According to DSM-IV, ‘cognitive disorder’ can be compensated for at least partially; the diagnosis therefore requires neuropsychological assessment [74]. The percentage of patients with SLE suffering from cognitive disorder varies among studies. For example, an overall incidence of cognitive changes in SLE of 55% has been suggested [83, 84]. In four studies, these figures varied from 21-35%; [85-88] and from 43-67% in two other studies [89, 90]. All these variations are due in part to different cut-offs that were chosen for normality by these different authors.

Furthermore some authors [91, 92] contend that the degree of cognitive disorder fluctuates over time, but this is disputed by others [93]. Two possible causes of cognitive disorder have been suggested: small vessel vasculopathy and an antibody mediated effect on neuronal functioning [94, 95]. Disturbances of the cranial [96-98] and peripheral nerves – single and multiplex [99, 100], sensorimotor [101-103], and autonomic lesions [102, 104-106], myasthenia gravis [107, 108], and Guillain-Barré syndrome [109-111], have all been reported in SLE, albeit with limited study.

**Antiphospholipid syndrome (Hughes syndrome)**

The ‘antiphospholipid syndrome’ (APS) was first described in patients with SLE (secondary APS), but may occur in the absence of any other disorder (primary APS). In other words, the ramifications of this syndrome extend beyond SLE, to all disciplines of medicine. An emerging notion is the distinction between CNS manifestations due to SLE and those caused by APS [112]. Some components of APS have been recognised since the 1950s, but the complete syndrome was not fully described until 1983 [113]. Since then the classification criteria have been updated to include manifestations not previously classifiable [114]. Classification criteria for catastrophic APS have been validated, and a worldwide register set up to record clinical data for these rare patients in order to analyse treatment and outcomes [115]. A description of the clinical features of 1000 patients with this syndrome remains the largest of such series [116]. It is defined as the association of antiphospholipid antibodies (APAs) with arterial or venous thrombosis, recurrent foetal loss, thrombocytopenia or neurological disorders such as stroke and TIAs, transverse myelopathy, chorea and migrainous headache.

Primary APS, however rarely progresses to SLE. One study carried out on 128 patients over a 9 year period showed that only 8% developed SLE; where a positive antiglobulin test was used as a clinically significant predictor of progression [117]. The spectrum of clinical features of APS continues to broaden with descriptions of renal artery stenosis [118], metatarsal fractures [119], avascular necrosis [120], and abnormalities of vascular function [121]. Accelerated atheroma has become a major focus of research in individuals that have APS, with investigations showing cross-reactivity of antiphospholipids with oxidized LDL and early signs of arterial disease in these particular patients [121, 122].

George and Shoenfield [123] have termed APS as the ‘crossroads of autoimmunity and atherosclerosis’. The controversies of treatment of APS remain, mainly in terms of the amount of anticoagulation required to prevent recurrent thrombosis. Two prospective studies by Crowther et al. [124] and Finazzi et al. [125] indicated that a high-intensity regime of anticoagulation, with international normalized ratios (INRs) above 3.0, were no better than conventional therapy with INRs of 2.0-3.0 in the prevention of recurrent thrombosis. This contradicted previous retrospective data.
A further study by Levine et al. [134] added impetus to this research by suggesting that positive baseline antiphospholipids in stroke patients failed to predict future cerebro-vascular occlusive accidents. It also stated that routine screening for antiphospholipids was not warranted. The study has subsequently been criticised as flawed, in that it was not designed to address the issue of screening and that only one baseline measurement was used. Most doctors therefore, still regard antiphospholipid testing as being essential, especially in young stroke victims.

**Conclusion**

SLE was once considered a rare disease with a universally fatal outcome. The past twenty years, however, have shown that this disorder is more common than originally thought and that it is treatable, with the majority of patients now having almost normal life spans. One must be aware, however, that a patient who is diagnosed with SLE at 20 years of age still has a 1 in 6 chance of dying by 35 years of age, mostly from the disease itself and/or related infections. Reducing the cardiovascular risk, which still claims substantial loss of life, is also of major importance.

The neurological features of central nervous system disease of SLE are slowly beginning to be unravelled, although there are still many questions that need to be answered. Delay in diagnosis, especially in patients with low-grade disease, remains problematic. The remaining challenges are in improving the quality of life for these particular patients by improving the symptoms of SLE. For example we will need to develop biomarkers and neuroimaging tests for SLE – associated neuropsychiatric disease that have the ability to identify the underlying pathological mechanism and guide therapeutic decisions [135], which will hopefully result in more effective treatment for this potentially life-threatening illness.

**References**

antiphospholipid syndrome. Clinical, radiologic and immunologic characteristics of 50 patients from our clinics and the recent literature. Medicine; 76:203-212.


