There is no doubt that SLE can be complicated by neurological manifestations, including epileptic seizures. What is sometimes not clear is the etiology of these manifestations because the disease is often characterised by a multisystem involvement and many conditions, including metabolic derangements, hypertension, vasculitis and the presence of autoantibodies can predispose to seizures. Because neurologic symptoms of SLE may have multiple causes, it is difficult to obtain precise prevalence figures for seizures. However, seizures are listed first on SLE activity indexes, which indicate their relevance. Indeed, a broad differential diagnosis must be considered in any lupus patient presenting with neurologic symptoms.

A careful evaluation should be done, including thorough searches for infection, metabolic derangements, coagulopathies, hypertensive encephalopathy and drug toxicities. It is important to distinguish isolated seizures from a true epileptic disorder, that is, a condition characterised by recurrent epileptic seizures.

When searching Medline with key words ‘lupus’ and ‘epilepsy’, we found 354 hits. However, only a minority were really dealing with the two disorders, and many articles were only on isolated case reports or small case series.

The coexistence of SLE and epilepsy has been studied by several groups. For example, the London group from St Thomas’ initially published two articles dealing with antiphospholipid antibodies (aPL) and CNS lupus, including epilepsy.1,2 In the first paper, the authors tried to determine whether, in a cohort of 221 patients with SLE, the occurrence of seizures was correlated with circulating aPL and concluded that epilepsy as a primary neuropsychiatric event was significantly associated with moderate-to-high titers of IgG anticardiolipin (aCL). In the second study, 96 of 340 unselected patients with SLE had CNS manifestations not attributed to any cause other than SLE, and 24 of them had epilepsy. Of the 53 patients who underwent a brain magnetic resonance imaging (MRI) study, 33 showed small high-density lesions suggestive of vasculopathy and 26 of them were positive for aPL. These two papers underlined one of the possible mechanisms for seizure occurrence in SLE, that is, ischemic changes aPL-mediated, and this has been confirmed by multiple additional studies (for review, see Cimaz, et al.3). Although this association is now well established, the presence of multiple comorbidities and the high baseline presence of aPL in SLE make comparisons between different studies difficult and incidence data even more difficult to extrapolate. Subsequently, Mikdashi, et al. found that 28 of 195 patients with SLE had epileptic seizures during the course of their disease, whereas recurrence of seizures, that is, epilepsy, was observed in 12 of them. Certain clinical features at baseline were independent predictors of seizures, whereas higher disease activity at baseline, concurrent multiple neuropsychiatric SLE manifestations and male gender were predictive of epilepsy.4 Again, the problems with this kind of study are that even if the seizures were defined as due to no other cause than SLE, this disease in itself can be the origin of seizures by a multitude of mechanisms, making interpretations very difficult. A similar study in a large cohort evaluated the frequency and risk factors of epileptic seizures in 519 patients with SLE. Again, isolated seizures were frequent, but their recurrence was rare because 60 patients with epileptic seizures were identified but only 7 had recurrent attacks (all with antiphospholipid antibody syndrome).5

Therefore, it appears that one of the major mechanisms for seizures and epilepsy in lupus is mediated by aPL. The pathogenetic bases for this are still poorly understood but include ischemic neuropsychenchymal insults and a direct immune interaction in the brain. In fact, known factors as thrombotic events explain only part of the increased occurrence of epilepsy in SLE, and the indirect or direct neuropsychopathogenic potential of aPL has been shown in animal studies and in vitro experiments.3 Conventional imaging modalities, such as MRI, may not detect small ischemic changes, and functional techniques, such as positron emission tomography, might be helpful in selected cases. In addition, aPL may not necessarily be linked to epilepsy. In a recent Finnish study in which the presence of autoantibodies was determined in a large cohort of almost 1000 patients with epilepsy,6 aCL was found in 4.5% but also in a similar percentage of a control group of 580...
healthy subjects. It is, therefore, possible that the mere presence of those antibodies may not be sufficient to induce clinical manifestations, but that additional factors, possibly SLE-linked, may be necessary. In this study, as well as in others, duration of epilepsy, frequency of seizures and poor control were associated with increased aPL positivity. This observation raises the question whether autoantibodies may be the effect, rather than the cause, of seizures because it is known that seizures can activate cytokine and autoantibody production. Another point worth mentioning is the possible interference with antiepileptic medications, some of which may induce the production of autoantibodies, sometimes complicating the understanding of the association between the two disorders. It is in fact known that in many cases of drug-induced lupus, the offending drug is an anticonvulsant.

Additional pathogenetic mechanisms must be considered, keeping in mind the multisystem nature of the disease and the conditions of the individual patient: a very thorough search needs, therefore, to be done before concluding that epilepsy is due to SLE per se. In this regard, one has also to consider that the concept of ‘autoimmune epilepsy’ has recently emerged and that epilepsy can also be associated with multiple autoantibodies, some of them directed against neural structures; therefore, more explanations for the association of the two disorders will possibly be discovered with the availability of new tests and new assays.

Another under-recognised cause of epileptic seizures in SLE is the posterior reversible encephalopathy syndrome, or reversible posterior leukoencephalopathy, a condition characterised by altered mental status, headache, visual changes and seizures in association with imaging findings indicating a predominantly posterior leukoencephalopathy. Although its pathophysiology is not well understood, it is believed that vasogenic edema plays a major role. In the setting of systemic hypertension, autoregulation of cerebral blood flow may fail, with cerebral hyperperfusion and disruption of the blood brain barrier, which in turn results in vasogenic edema and haemorrhages. Anticonvulsants may be necessary for immediate control of seizures but are not usually required in the long term. In patients with active SLE, corticosteroids and cyclophosphamide have been the most frequently used treatments.

In SLE, the risk of disease is influenced by complex genetic and environmental contributions: for example, alleles including HLA-DRB1, IRF5 and STAT4 are established susceptibility genes. More recently, new genetic loci for SLE have been described: a promoter-region allele associated with reduced expression of B lymphoid tyrosine kinase and increased expression of C8orf13 (chromosome 8p23.1), and variants on chromosome 16p11.22, near the genes encoding integrin α M (ITGAM or CD11b) and integrin α X (ITGAX). A genetic predisposition for specific system involvements is also possible, which may be relevant to idiopathic epilepsy, as possibly related to lupus per se. Indeed, in a recent study, Bautista, et al. used a covariate-based linkage analysis to detect a potential genetic locus on chromosome 15 influencing the development of seizures in individuals with SLE. The authors hypothesised that the phenotypic heterogeneity seen in SLE may reflect an underlying genetic heterogeneity and studied a large number of multiplex SLE families for seizures susceptibility with the genotyping of microsatellite markers. A potential susceptibility locus on chromosome 15 was detected. Seizures that were associated with known risk factors such as drugs or metabolic derangements (e.g., uremia, ketoacidosis or electrolyte imbalances) were excluded. In line with what was previously discussed in this series, there was no difference in aPL positivity in patients with and without seizures. Finally, the authors state that some individuals may have had seizures unrelated to SLE diagnosis. This finding seems to strengthen, rather than weaken their findings because if lupus and epilepsy coexist just by chance, the possibility of a genetic predisposition of the two disorders would be even more important with respect to when other factors play a role. Being just two clinical diagnoses and per se both heterogenous entities, the choice of cause and effect between them, or even of a random association, can sometimes be very difficult.

Seizures are rarely the presenting symptom of SLE; they often appear later in the course of the disease, typically during flares of systemic or central nervous system lupus. Seizures contribute to poor outcome when they occur in children, and in a study, they doubled the rate of mortality when found with nephritis in adults.

Both focal and generalised seizures occur in SLE. In one series of 91 patients with SLE, 22% had experienced generalised seizures and only 5% had focal attacks. Generalised seizures can either represent the only manifestation of brain involvement in CNS lupus or may represent an expression of hypertensive metabolic encephalopathy. Focal seizures have been variously attributed to cerebrovascular complications, abscess or meningitis, whereas status epilepticus has been reported especially as a preterminal event.

In patients with seizures, brain MRI should be rapidly performed to search for intracranial haemorrhage, ischemia or other brain lesions. However, although about 75% of patients with active disease
will show some sort of MRI abnormality, there seem not to be a distinctive pattern that is associated with seizure occurrence. The same applies to EEG investigations as epileptiform abnormalities are often observed in patients with SLE without seizures and missing in those with seizures.14

Epileptic seizures in SLE may result from a combination of immune, vascular, metabolic and inflammatory mechanisms. Generalised seizures are associated with increased titers of antineuronal antibodies, elevated levels of IgG and oligoclonal bands and cytokine production.14 Antibodies against brain reactive antibodies, synaptosomes and gangliosides20,21 are also increased in patients with seizures. aCL antibodies from patients with SLE reduce γ-aminobutyric acid (GABA)-mediated chloride currents in snail neurons.22 This finding might provide one explanation for a mechanism of seizure precipitation in SLE. Cerebral ischemic changes can be the pathological substrate for seizures either at the post-acute stage when the infarct occurs (acute symptomatic seizures) or at a later stage even months or years afterwards (remote symptomatic seizures).14

Treatment with antiepileptic drugs (AEDs) is not necessarily needed if a precipitant factor for seizures can be identified and treated. However, if frequent seizures occur, short-term AED treatment can be necessary until the lupus flare is controlled. Although drug-induced lupus has been reported with the use of various AEDs, it is unlikely that treating a patient with SLE with an AED will exacerbate the underlying disorder.14

In summary, SLE can be complicated by epileptic seizures in a sizeable proportion of cases. Sometimes seizures recur, fulfilling the definition of epilepsy. However, many are the possible causes, many of which are still to be discovered. Among the most common, aPL play a definitely major etiologic role even if the precise mechanisms have yet to be fully clarified. Genetic studies will hopefully shed more light on the factors underlying the co-occurrence of epilepsy and lupus.

References


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