Review

Epilepsy in systemic lupus erythematosus

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ABSTRACT

Systemic lupus erythematosus (SLE) is an autoimmune systemic disease characterised by a broad spectrum of clinical manifestations that may also affect the central nervous system. Among the neurological symptoms, seizures were included in the criteria for the classification of SLE published by EULAR/ACR in 2019. Several studies have been undertaken to explore the role of SLE antibodies in the onset of seizures, however, their complex relation is still a matter of debate.

The most common seizure type reported is generalised tonic-clonic. EEG and MRI findings are usually non-specific; background slowing, brain atrophy and hyper-intense lesions on the white matter are the most common finding. Prognosis is overall favourable, with a good response to antiepileptic drugs and immunosuppressive therapy.

The purpose of this review is to summarise the most relevant literature contributions published over the years on the epidemiology, aetiopathogenesis, clinical aspects, diagnosis and treatment of seizures in the context of SLE.

Introduction

Systemic lupus erythematosus (SLE) is a chronic, autoimmune disease characterised by multiple organ involvement. The onset of the disease may occur at any age; however, it is most commonly diagnosed in women in the second to fourth decade of life (1). Neuropsychiatric SLE (NPSLE) is one of the most important manifestations of the disease and occurs in about half of the patients (2).

In 1999, the American College of Rheumatology (ACR) identified 19 different NPLSE syndromes in both adult and paediatric SLE populations (3). NPSLE has been reported to occur in 12–95% of SLE patients, and, among these, in 15–81% as the first manifestation of the disease (4, 5).

Epileptic seizures are among the most serious manifestations of SLE and are one of the classification criteria for NP-SLE. The prevalence ranges from 6% to 58% (6, 7), although a recent meta-analysis reported it to be around 7% (2). Seizures may occur at any time in the course of SLE, both as a consequence of the primary disease activity or secondary to metabolic dysfunction or toxic effects of the treatment (4, 8).

The purpose of this narrative review is to summarise and describe the clinical features, the pathogenesis and the diagnostic-therapeutic tools for epilepsy in SLE.

Pathogenesis

The aetiopathogenesis underlying NP-SLE is not clearly defined. Two potential mechanisms have been hypothesised: the first can act by damaging small and large vessels of the brain and is mediated by antibodies and immune complexes (9-12). The second mechanism refers to an autoimmune inflammation that increases the permeability of the blood-brain barrier and induces the formation of immune complexes and inflammatory mediators (11, 13). As with NPSLE, the underlying pathogenetic mechanism of epilepsy in SLE is still unclear; this mechanism appears to be multifactorial including vascular damage and the effect of autoantibodies and inflammatory mediators.

Vascular damage

Vascular damage is considered to be the main cause of epilepsy in SLE (14); furthermore, focal ischaemic damage and/or the presence of microinfarcts secondary to vascular occlusion due to thrombosis and haemorrhages are considered to be a possible causes of epilepsy (15-18). Moreover, the presence of strokes in patients with SLE seems to increase the risk of seizures (6, 19, 20). It was also reported that in SLE patients, chronic renal disease and

the consequent impaired production of erythropoietin could be relevant in the neovascularisation process; impaired neovascularisation and endothelial repair could be associated with microthrombotic events and seizure development. However, major thrombotic events are not associated with a shorter time-to-seizure occurrence (21).

Autoantibodies

The presence of autoantibodies plays an important role in the pathogenesis of SLE (Table I). Seizures in SLE could be the result of cortical vessel thrombosis induced by the procoagulant effect of some types of autoantibodies, such as the ones targeting phospholipid associated proteins (aPL) (22-25). Antibodies may access the central nervous system (CNS) through an interruption of the brain blood barrier or may be synthesised directly in the CNS. The brain blood barrier can be interrupted by small vessel vasculopathy, which, together with microinfarcts, constitutes the most common neuropathological finding in SLE (11, 13). At least 20 different autoantibodies (Abs) have been described. These include Abs that target brain-specific and systemic antigens (26).

aPL antibodies appear to be involved in focal neuropsychiatric manifestations (stroke or seizures) by promoting intravascular thrombosis (23, 11) or through an interaction between aPL and cellular elements of the CNS (27-29). Although aPL antibodies have been found to induce a prothrombotic state, they prolong coagulation with phospholipid-dependent mechanisms (30). Many studies evaluated the association of epilepsy with aPL (14, 23, 31, 32); however, the presence of these antibodies *per se* does not seem to be sufficient to determine the clinical manifestations (33). Furthermore, the available data are not enough to determine whether these antibodies are cause of or, alternatively, a secondary effect of epilepsy (33). Although a statistically significant association between the presence of aPL and seizures has been demonstrated, these data have not been confirmed. (5, 11, 31-35).

One of the most studied aPLs by far is the anti-cardiolipin (aCL) antibody. The association between aCL antibodies and seizures is reported in a large number of studies (14, 23, 31, 36-40), and several authors suggested a correlation between their presence and diffuse microscopic brain damage (41-43).

Anti-β2-glycoprotein I (anti-β2-GPI) has been proposed as an anti-phospholipid antibody for thrombotic events (44). In addition to aCL antibodies, a correlation between Anti-β2-GPI and seizures in the course of SLE has been proposed (17, 45, 46).

Anti-Smith (Sm) antibodies are SLE-specific autoantibodies found in approximately 10–30% of SLE patients and are rarely present in the sera of patients with other rheumatic diseases (48).

According to recent studies, the presence of anti-SmD1 antibodies is independently associated with a higher risk of epilepsy (35, 48). Regardless, given the low positive rate of anti-Sm antibodies in SLE, these antibodies do not seem to be applicable for clinical use; anyway a recent study suggest the usefulness of anti-SmD1 as predictive marker for some SLE-related manifestations, including epilepsy (48).

Anti-aquaporin 4 antibodies (AQP4) are antibodies directed against a water-channel protein, aquaporin 4, which may cause astrocyte toxicity, particularly in the optic nerve; these antibodies are present in 70–90% of patients with neuromyelitis optica (4).

Table I. Antibodies in NPSLE.

Antibody	% in SLE	Effects
aPL Anti-β2-GPI aCL Lupus anticoagulant	10-44	Prothrombotic effects Accelerate atherosclerosis Involvement in diffuse NPSLE
Anti MAP 2	rare	Pathogenesis is unknown Their presence in CSF correlates with neurological symptoms
Anti-Sm	10-30	Higher risk of epilepsy
Anti-ribosomal P	Up to 46	Bind to the limbic system, implicated in mood Induce TNF production Associated with many NPSLE, mainly psychosis
Anti NMDA-R	Unknown	Cross reacts with a subset of anti-dsDNA leading to neuronal death Frequently associated with NPSLE
Anti AQP4	3	Astrocyte toxicity Involved in neuromyelitis optica
Anti-endothelial cell (AECAs)	>60	- Induce expression of adhesion molecules in endothelial cells - Induce endothelial secretion of cytokines

Antineuronal antibodies (NAbs) represent a group of autoantibodies that react to neuronal components. Some studies assessed the presence of these antibodies in the cerebrospinal fluid of patients with NPSLE, including NAbs against a) voltage-gated potassium channel (VGKC)-complex antigens, b) contactin-associated protein-like 2 (CASPR-2), c) leucine-rich glioma inactivated 1 (LGI1), d) glutamic acid decarboxylase (GAD65), e) N-methyl-d-aspartate receptor (NMDA-R), f) alpha-amino-3-hydroxy-5-methyl-4-isoxazoleproprionic acid receptor (AMPA-R) and h) type B gamma aminobutyric acid receptors (GABAB-R). These antibodies have been linked to epilepsy with an acute or subacute onset and were included in the recommendations to identify autoimmune epilepsy in children (49). The detection of one or more NAbs in serum or cerebrospinal fluid of children with a new onset epilepsy of unknown cause may be useful for the diagnosis (49).

Pro-inflammatory cytokines

Several studies analysed the role of inflammation in the pathogenesis of NPSLE. Pro-inflammatory cytokines and their receptors are present in different areas of the CNS and appear to play a role in the pathogenesis of NPSLE, even if the molecular mechanisms are still un-

clear (50). Several studies have proven the intrathecal production of cytokines including INF γ, IL-10, IL-6, IL-8, CXCL10, CCL2 (4, 51, 53-54). Among these cytokines, IL6 was reported to have the strongest association with NP-SLE. Consequently, due to this strong association, IL6 may be used as an important diagnostic tool in NPSLE (4).

However, given the multitude of clinical manifestations related to NPSLE, it is very difficult to identify a reliable association between a single inflammatory biomarker and neuropsychiatric events.

In conclusion, the mechanism underlying the pathogenesis of epileptic seizures, during SLE is still inconclusive. There is evidence that seizures originate from vascular damage within the white matter; on the other hand, systemic inflammation and the immune-mediated processes, underlying the pathology, seem to play an equally important role.

Clinical features

NPSLE encompasses a variety of clinical manifestations ranging from subtle cognitive dysfunction to psychosis, seizures and strokes (4). Epileptic seizures occur in 6% to 58% (6, 7) of patients with SLE at any time over the course of the disease (55, 56).

Epilepsy may be one of the earliest manifestations of CNS involvement and may occur several years prior to generalised SLE, understandably leading to the erroneous diagnosis of isolated epilepsy (57). It may also appear after the onset of SLE (22); however, epilepsy onset is generally early in the disease course, with a median interval from the time of SLE diagnosis to onset of first seizure of 0.14 (-0.50 to 7.57) years (11). The appearance of seizures may also be related to a flare of the disease or to an inadequate dosage of immunosuppressive drugs (58).

Hopia *et al*. observed that 16 (44%) of 36 patients with epilepsy had seizure onsets before SLE diagnosis and only 8 (22%) presented seizures at SLE diagnosis (18). In a cross-sectional study, 18 patients (43.9%) presented NPSLE symptoms at the time of diagnosis, 10 (24.4%) during the first year afterwards and 13 (31.7%) more than one year after the diagnosis; seizures were reported in 9.5% of patients in the whole cohort (59).

Different seizure types have been described in SLE: patients may experience generalised tonic-clonic, simple partial, complex partial seizures and status epilepticus (60-67)). Generalised tonic-clonic seizures (67–88%) are the most frequently reported (61), followed by partial seizures (5, 6, 58, 62, 63). Although uncommon, other possible manifestations reported are myoclonic seizures (24), Mesial Temporal Lobe Epilepsy (64) and facio-brachial dystonic seizures (65).

Sometimes, SLE onset manifests as status epilepticus or a complex partial status epilepticus in the absence of a history of epilepsy; in these cases, diagnosis may be difficult, given the absence of its typical clinical features (20, 66, 67).

Various factors may be associated with epilepsy occurrence: gender, ethnicity, age, disease activity level, extra-CNS involvement and medications. Some studies showed that epilepsy in SLE is associated with the female gender (6, 34), early disease onset and younger age (21, 34). The latter is also associated with a shorter time-to-seizure occurrence (21, 23, 68). Furthermore, a correlation between African ethnicity and early onset epileptic manifestations has been demonstrated (21, 34).

Disease activity levels throughout the course of SLE also play an important role in time-to-seizure occurrence. Accordingly with previous studies (21, 34), Kampylafka *et al*. confirmed that epileptic seizures were more frequent in patients with higher disease activity scores (69).

Regarding the relationship between epilepsy and extra-CNS involvement, many studies have shown a link to renal damage. In the Kampylafka series, glomerulonephritis was present more often in patients with epilepsy and occurred concurrently with the onset of epileptic seizures (69). This observation is in line with a previous study showing that epilepsy was a frequent manifestation in patients with lupus nephritis (70); however, no correlation with a specific type of glomerulonephritis has been proven (69). In contrast, musculoskeletal and skin involvement has been associated with a longer time-to-seizure occurrence (21).

A final point of interest is the observation of an inverse relationship between seizures and anti-malarial therapy, suggesting a possible protective effect of these drugs (21, 34). The precocious use of hydroxychloroquine may reduce the risk of seizures, especially in patients who do not use immunosuppressive agents (34). Although definitive data have not been found, this appears to be due to the interaction between the two classes of drugs (34). The exact mechanism of the protective effect of hydroxychloroquine is still unknown, but it may result from a combination of the anti-inflammatory, antithrombotic and antiplatelet properties of antimalarial drugs (21). In contrast, the use of corticosteroids is associated with increased risk of seizures (34).

Most seizures are isolated, but recurrence may happen in 12% to 43% of cases, especially during the first year of the disease (6, 23). In the majority of cases, recurrent seizures replicate the same seizure type that occurred during the first episode (58); however, risk factors for the recurrence are not well defined. In Mikdashi *et al*. series, the only factor associated with seizure recurrence was stroke (6), while Gonzales-Duarte *et al*. have shown that stroke, the onset of seizures in the first year after the diagnosis of SLE and the presence of antiphospholipid syndrome were all significantly associated with recurrence (58).

Diagnosis

When evaluating an SLE patient with epilepsy, it is crucial to determine whether or not the seizure represents a manifestation of SLE or a complication of treatment (11); coincidental diseases such as vasculitis, ischaemia, injury, infection, metabolic abnormality and systemic disease should be excluded (71).

Electroencephalography (EEG) abnormalities are common in SLE (60 to 70% (61)) but non-specific (72); in particular, there are no characteristic focal or diffuse abnormalities correlated to seizure type, and abnormalities may also vary with the activity of the disease (7, 73). Despite a statistically signifi-

cant correlation between epilepsy and aPL activity (74), a typical EEG pattern in patients with positive serologic profiles has yet to be found (14). EEG may show diffuse or focal slowing [frequencies less than 8 Hz (7)], spikes or sharp wave discharges (75). The most common abnormality is generalised slowing of the background activity (19). Typical epileptiform discharges such as spikes, polyspikes and waves are correlated with a higher risk of seizure recurrence (72); however, epileptiform abnormalities were found in patients with SLE without seizures and were absent in some patients with seizures (12). If epileptiform activity is reported in EEG, its characteristics and location may be helpful to determine the most appropriate treatment (7).

EEG findings are infrequent in patients who have experienced a single event; if present, these patients tend to have a higher risk of recurrence (23, 61).

Every patient with SLE seizure should perform a brain magnetic resonance imaging (MRI) to rule out intracranial bleeding, ischaemia or any other lesion (12). Brain MRI abnormalities are common, especially in patients with recurrent seizures (23), however, some lesions that appear during SLE flares can recover afterwards (7).

Abnormalities involve both grey and white matter, ranging from T2 white or grey matter hyperintensities, to diffuse or focal brain atrophies, infarcts, haemorrhages, ventricular dilatations, lacunes and inflammatory lesions (22). Grey matter lesions may progress to diffuse brain atrophy, which is a common finding, possibly linked to cognitive decline (61) and to EEG diffuse slowing (7). Brain atrophy may also represent a risk factor for the onset of seizures (71). Focal atrophy usually involves the hippocampus and may be related to the activity and duration of the disease, the long-term use of corticosteroids or the number of neurologic events experienced by the patient over the long term (75).

Changes in white matter may be observed on Fluid Attenuated Inversion Recovery (FLAIR) sequences and are probably related to either an active disease or a remote vasculopathy or inflammatory disease (76). In this setting, MRI is the best tool to localise these regions and to study their evolution over time. Ischaemic strokes have been reported to be the most common findings (58); small high-intensity lesions are also reported (12). Predictive factors for worsening of the white matter lesions include previous CNS involvement, elevated title of aPL antibodies (75) and total corticosteroid dose administered.

Recently, more advanced techniques are able to detect structural and functional abnormalities at the level of biochemical processes, which may be related to SLE's neuropsychiatric manifestations and cognitive dysfunction, and may anticipate the appearance of macroscopic anatomical lesions and parenchymal atrophy (77).

Single-photon emission computed tomography (SPECT) was proved to be useful to diagnose early cognitive dysfunction and to aid in the interpretation of uncertain findings (78); this technique is able to show hypo-perfuse areas of the brain, which have sometimes been correlated with EEG and MRI abnormalities in SLE patients affected by seizures (79).

Similarly, functional MRI (fMRI) and dynamic susceptibility contrast-enhanced perfusion MRI (DSC-MRI) are able to describe early brain function impairment in relation to parenchymal perfusion modifications (77, 80).

Other innovative techniques such as magnetic resonance spectroscopy (MRS), magnetic transfer imaging (MTI) and diffusion Tensor MRI (DTI) are considered useful for evaluating brain tissue injuries, although they are still not applicable in daily clinical (78); however, these tools may facilitate longitudinal human research studies without the use of ionising radiation with the advantage of superior spatial resolution (81).

MRS displays metabolic brain alterations by studying the movements of proton groups at different frequencies of the magnetic field, making it capable of diagnosing NPSLE in the absence of white and grey matter alterations. Low levels of N-acetylaspartate (NAA) and IgG aPL are two metabolic compounds proposed to be involved with NPSLE, though not specific to the disease, due to their links to injured tissue and micro infarcts. Decreases in NAA levels were found in patients with generalised seizures and other NPSLE manifestations not associated with evidence of thrombosis, suggesting that other causes of injury might be involved (82); however, its relationship with SLE and epilepsy was not explored, so its utility on that matter is still uncertain.

MTI refers to an application of MRI that offers the potential of a window on tissue structure and structural components that are normally not resolvable with MRI (83). In particular, Steens *et al*. (84) conducted a study where an association between aCLs and brain damage was detected by MTI in NPSLE patients. Among the NSLE patients enrolled in the study, 6 patients with seizures (4 with primary generalised tonic-clonic seizures, 2 with absence seizures) were included. Punctate areas of increased signal were detected in 2 patients with primary generalised tonic-clonic epilpesy, both of which were the only positives in the group either for immunoglobulins (both IgM and IgG) against aCLs or for Lupus anticoagulant; They were both negative for anti-dsDNA and anti-ENA. Interestingly, none of the patients of the study had abnormalities on conventional MRI, suggesting a possibly relevant role of subtle brain lesions in the pathogenesis of epilepsy in SLE. In conclusion, MTI was suggested to be a good method for distinguishing active NPSLE from other differentials and for monitoring treatment trials in NPSLE (71).

Diffusion Tensor Imaging (DTI) provides assessments of white matter microstructural changes using measures of fractional anisotropy in normal appearing areas on conventional MRI. Mackay *et al*. (85) described how changes in the microstructure of several brain regions and in network connectivity have been found with this technique, which is similar to what was assessed by the functional methods discussed above; however, none of the studies have been performed on patients with epilepsy; therefore, we are still in need of significant insight concerning possible mechanisms underlying this clinical manifestation and the clinical uses of these tools.

Table II. Clinical, laboratory and imaging features suggestive of autoimmune epilepsy.

- Recurrent and/or uncontrolled seizures (occurring every three months or less)
- Acute or subacute onset
- Onset with status epilepticus without a history of epilepsy
- Multiple types of seizure
- Resistance to antiepileptic drugs
- Personal or family history of autoimmunity
- Finding autoantibodies in serum and/or cerebrospinal fluid
- Evidence of CNS inflammation
- Viral prodrome
- MRI changes consistent with autoimmune encephalitis

Differential diagnosis

An accurate differential diagnosis of epilepsy and the definition of an autoimmune etiology are essential, because the type and efficacy of treatment depends on the specific epileptic disorder. Furthermore, early immunotherapy may slow, halt, or even reverse the epileptogenic process in these patients (65, 86-90).

Clinical features suggestive of autoimmune epilepsy, including SLE-related epilepsy, are listed in Table II. They include recurrent and/or uncontrolled seizures (occurring every three months or less) in patients with personal or family history of autoimmune disease, acute or subacute onset that is often preceded by viral prodrome, multiple types of seizure or status epilepticus at the onset in absence of a history of epilepsy, resistance to antiepileptic drugs and response to immunotherapy. Moreover, there may be an autoimmune cause for epilepsy when specific autoantibodies, inflammatory changes in cerebrospinal fluid or on MRI are present.

To improve the recognition and diagnosis of patients with suspected autoimmune epilepsy, Zuliani *et al*. proposed guidelines for the identification of autoimmune mediated epilepsy (91). However, the physician's ability to correlate patient's clinical features with laboratory and instrumental data remains essential for a correct evaluation of epilepsy for autoimmune diseases such as SLE-related epilepsy.

Treatment

Several studies assessed the benefits of immunosuppressive therapy in SLE patients with CNS involvement (61). When seizures are considered to be secondary to an acute inflammatory event or to a flare of the disease, EULAR recommends the use of glucocorticoids (GCs) alone or in combination with immunosuppressant drugs (92).

GCs and cyclophosphamide

The biological effects of GCs assist in the regulation of the immune response and inflammation. This class of drugs often represents one of the most effective treatments for the acute phase of several autoimmune diseases including SLE, since it has the fastest anti-inflammatory effect compared to the other immunosuppressive therapies available. It is widely used to control mild–severe flares of SLE (93) or SLE with serious organ involvement (80).

Cyclophosphamide was initially developed as an anti-neoplastic drug thanks to its ability to induce cellular apoptosis via the formation of irreversible crosslinks within DNA. Subsequently, the same mechanism of action was found to be useful in autoimmune diseases in order to eliminate autoimmune effector cells (T-cell, B-cells and NK cells) (94).

CNS manifestations in SLE usually require high doses of GCs administered intravenously or orally (72). Intravenous methylprednisolone or cyclophosphamide have shown efficacy in refractory seizures in the context of generalised Lupus activity, with a significant decrease in the number of events and a drastic improvement of EEG (96). However, the only randomised trial reporting the effects of immunosuppressant drugs in NPSLE found that steroids were more effective when combined with cyclophosphamide (95).

Antimalarial agents

Antimalarial agents (AM) were firstly used as antibiotic drugs for treatment and prevention of malarial infections. Later, new applications in different fields of medicine were discovered; indeed, they represent a useful maintenance therapy in SLE to prevent disease flares and their manifestations, including seizures recurrence (21). This beneficial effect is related to the capacity of AMs to reduce T-cell and B-cell hyperactivity as well as pro-inflammatory cytokine gene expression (97).

Hydroxychloroquine was demonstrated to prevent worsening of brain lesions found on MRI (98). The propitious effect of this medication on NPSLE may be related to its anti-inflammatory, antithrombotic and antiplatelet properties (21), which are all linked to vascular damage likely related to the disease's pathophysiology. In patients with persistently positive, moderate-to-high titles of aPL (92) and when abnormalities possibly related to vascular damage are found, the start of a prophylactic, antiplatelet or anticoagulation treatment is justified (99); however, further studies are required to confirm the link between aPL and epilepsy in SLE, validating the use of anticoagulant or antiplatelet medications in combination with antiepileptic drugs (AEDs) (100).

Intravenous immunoglobulins (IVIg) and plasmapheresis

IVIgs constitute a mixture of natural antibodies of the IgG subclass derived from the blood of healthy donors; the positive effect seen in the immune system is due to the suppression of autoreactive B lymphocytes and the neutralisation of pathogenic autoantibodies produced by these cells. Similarly, plasmapheresis is an extracorporeal blood purification technique that consists of the removal of large molecular weight substances from the plasma, followed by replacement with either freshly frozen or stored plasma in order to remove any component that may cause the perpetuation of the immune-mediated damage (93).

Plasmapheresis followed by IVIg was proposed by Kampylafka as first line treatment for epileptic patients with aPL antibodies (101). The Assessment Subcommittee of the American Academy of Neurology suggested that plasmapheresis may have a role in patients experiencing a more severe illness,

Table III. Data on the use of AEDs in SLE.

Reference	n	Seizure type/ epilepsy	Therapy administered	Outcome
Fields *et al*. 1990	3	Generalised seizures (cerebritis)	GCs	Complete recovery, no recurrence
Hussain *et al*. 1999	11	9 Generalised seizures	1 GCs, Cy	No recurrence
			1 GCs, Cy, VPA	Recurrence
			1 GCs, VPA	Recurrence, cognitive deficits
			3 GCs, Cy	No recurrence, cognitive deficits
			1 GCs	Die for massive intracranial bleeding
			1 GCs	Recurrence
			1 GCs	No recurrence
		1 Focal seizure	GCs	No recurrence, cognitive deficits
		1 Generalised and focal seizure	GCs, Cy	No recurrence
Boupas *et al*. 1991	2	Unknown	Cy	Complete recovery, no recurrence
Brinciotti *et al*. 1993	1	Partial epilepsy with reflex seizure	Cy	No recurrence
Mecarelli *et al*. 1999	1	Generalised seizure	GCs, Cy, Plasmapheresis, BZD, CBZ	No recurrence
Kwong *et al*. 2000	2	Generalised seizures	GCs, Phenobarbital, Phenytoine, BZD	No recurrence
			GCs, Cy, IVIgs, BZD, phenobarbital,	No recurrence
Appellanzer 2004	5	1 Complex partial epilepsy	None (surgery)	No recurrence
		1 Complex partial epilepsy	Phenobarbital	Recurrence
		1 Simple and complex partial and secondary generalised seizure	Surgery + CBZ	No recurrence
		1 Complex partial seizure	CBZ	No recurrence
		1 Generalised tonic-clonic seizure	CBZ	Lost to follow-up
Gonzales-Duarte 2008	64	Unknown	Monotherapy in 56 patients (Phenytoin/ CBZ/ VPA / LEV/ Diazepam) Polytherapy in 18 patients	50% of the patients had at least 1 episode
Toyota *et al*. 2012	7	Mesial Temporal lobe epilepsy	VPA + CBZ	1 Not followed
			VPA + BZD	1 seizure free
				1 seizure reduction after surgery
			BZD	1 seizure free
			VPA	1 persistent seizures
				1 not followed
			VPA + LEV	1 seizure free
Kampylafka *et al*. 2016	9	Generalised tonic-clonic seizures (3 status epilepticus)	3 GCs 8 GCs+Cy 4 IVIg 1 Plasmapheresis 3 Rituximab + AEDs (all patients)	Unknown
Hopia *et al*. 2019	36	33 Focal seizures 1 Generalised seizure 2 unclassified	5 CBZ 3 LEV 3 Phenytoine 3 Lamotrigine 1 VPA 1 Phenytoin+ VPA 1 VPA + Lamotrigine 1 VPA+ LEV 1 CBZ + LEV 1 LEV + BZD 1 Lacosamide+ Pregabalin+ LEV 1 LEV+ Phenobarbital + Phenytoin + Topiramate [¥]	Unknown

n: number of patients affected by seizures in the cohorts
GCs: glucocorticoids; Cy: cyclophosphamide; VPA: valproate; BZD: benzodiazepines; CBZ: carbamazepine; LEV: levetiracetam.
[¥] AEDs administered during the retrospective study. n=14 were not currently receiving any drug during the observation.

refractory to standard treatment; however, its use has to be established on a case-by-case basis (102, 103).

Antiepileptic therapy

SLE patients with seizures are generally responsive to AEDs (104-108). Data reported in literature about the use of AEDs in SLE patients are summarised in Table III.

The general approach to seizures is the same as for non-SLE patients, which involves tailoring an individualised strategy that weighs the risk of recurrence with the adverse effects. The choice of the AED reflects the general rules followed in epilepsy. Generalised epilepsies respond to valproic acid or lamotrigine (104); phenytoin or barbiturates may be considered as alternatives (22). If focal or partial epileptiform activity is present on EEG, carbamazepine or phenytoin are typically used. In patients refractory to the current regime, the addition of a second AED or surgical management might be mandatory (7). Clobazam and levetiracetam are useful alternatives for treating Mesial Temporal Lobe Epilepsy with SLE and during pregnancy (109).

The duration of treatment varies according to the patient's clinical features (104). In 76% of cases, seizures attributed to SLE resolve spontaneously without medication (110); moreover, only 1.3% of patients experiencing a seizure will develop further recurrent unprovoked events in the future (23). Accordingly, EULAR recommends delaying the start of an AED regimen in patients with single or rare seizures in the absence of red flags, such as MRI lesions related to seizures, epileptic abnormalities on EEG prior brain injury or risk of recurrence. Recurrence is estimated considering the features of the onset (i.e. partial complex seizure), the presence of focal neurological signs, the occurrence of two or more unprovoked events within 24 hours, the presence of epileptiform discharges on EEG and/or the presence of lesions likely caused by seizures on a MRI (61, 92).

After the beginning of antiepileptic therapy, epileptic patients can develop drug resistance in about 30% of cases. Consequently, polytherapy should be considered but only after the failure of at least two previous monotherapies (111). Considering the great number of AEDs available, the number of possible associations is very high; antiepileptic polytherapy should always be tailored to each patient according to the epilepsy type in order to identify the best AED combination that maximises efficacy and minimises possible adverse effects.

In general, the selection of AEDs based on their different mechanisms of action can augment global effectiveness. Moreover, polytherapy can increase the undesirable drug-drug interactions that must be considered by the physicians.

Conclusions

Epilepsy is a common manifestation in patients with SLE; symptoms are often variable and non-specific and can represent the onset of the disease. In addition, the pathogenesis is probably multifactorial, and an autoimmune mechanism has been proposed, considering the presence of anti-neuronal antibodies and the inflammatory changes in cerebrospinal fluid or on MRI.

The general approach to epilepsy is the same as for non-SLE patients, which involves an individualised strategy that weighs the risk of recurrence with the adverse effects. AEDs are generally efficacious and the overall prognosis is favourable; however, in intractable cases, the combination of immunotherapy may improve seizure outcome.

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