NEUROPSICHIATRIC MANIFESTATIONS OF SYSTEMIC LUPUS ERYTHEMATOSUS: DIAGNOSIS AND TREATMENT APPROACH

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ABSTRACT

Neuropsychiatric involvement in systemic lupus erythematosus includes heterogeneous manifestations involving both the central and peripheral nervous system. A major issue in clinical evaluation is the attribution of neuropsychiatric symptoms to systemic lupus erithematosus. Antiphospholipid antibodies, immune complex, microangiopathy, early and accelerated arteriosclerosis are factors that have the main role in pathogenesis of neuropsychiatric manifestations of systemic lupus erithematosus. There are no neurological symptoms specific to systemic lupus erithematosus, but they can also occur very commonly in the general population. Lesions of nervous system can be focal or diffuse and may be due to systemic lupus erithematosus itself (primary lesions), but it also may be caused by other diseases or disbalances. Therapy of the neuropsychiatric manifestations depends on the nature of the pathological process (dominant inflammation or thrombosis). If it is result of an inflammatory neurotoxic process and in the presence of an increased activity of systemic lupus erithematosus, therapy includes glycocorticoids independently or in combination with immunosuppressives. Focal neuropsychiatric syndrome with antiphospholipid antibodies positivity should be treated with anticoagulant and/ or antiplatelet therapy. In addition, control of classical cardiovascular risk factors, stop smoking, and treatment with hydroxychloroquine is recommended.

Keywords: *Neuropsychiatric manifestations, systemic lupus erythematosus, diagnosis, treatment.*

INTRODUCTION

Systemic lupus erythematosus (SLE) is a chronic multisystem inflammatory autoimmune disease with a large spectrum of clinical presentations (1). Neuropsychiatric involvement in systemic lupus erythematosus (NPSLE) includes heterogeneous manifestations involving both the central and peripheral nervous system. A major issue in clinical evaluation is the attribution of NP symptoms to SLE. Due to the lack of a gold standard, it represents a clinical challenge that obligates the strict exclusion of any other potential cause. In clinical practice, an individual multidisciplinary diagnostic and therapeutic approach based on the suspected cause and severity of symptoms is recommended (2, 3).

PREVALENCE OF NPSLE

The prevalence of NPSLE is highly variable (range 4.3-91 %) and incidence (range 8-40 %), depending on patient selection method and on the nomenclature used to classify the event as NPSLE. It is noted that the incidence of neuropsychiatric disorders is significantly lower in patients with late onset of SLE (after the age of 50). (4, 5) The meta-analysis of large number of studies reported that NPSLE prevalence was 44.5 % in prospective studies versus 17.6 % in retrospective studies. (6) Disparities in frequency have been mainly attributed to differences within the definition used and stringency in attributing the events to SLE. Most of these studies included minor, nonspecific symptoms (e.g. mild depression or anxiety) that are investigator-dependent. After exclusion of these minor events and peripheral nervous system (PNS) syndromes, Kampylafka et al. reported an NPSLE prevalence of 4.3 % and an incidence rate of 7.8/100 person years. (7) NPSLE is a severe complication of SLE that is associated with a lower quality of life over time, with poor prognosis. (8) It has been reported a tenfold increase in mortality rate in NPSLE compared with the general population. (9)

PATHOGENESIS OF NPSLE

The pathogenetic mechanism of NPSLE has not been fully clarified. Antiphospholipid antibodies, immune complex, microangiopathy, early and accelerated arteriosclerosis are considered to have the main role. The European League Against Rheumatism (EULAR) defined the main risk factors for the emergence of neuropsychiatric manifestations of SLE: 1. high activity of the disease or a large degree of damage due to SLE, 2. previous neuropsychiatric disorder caused by SLE, 3. positive antiphospholipid antibodies (aPL) (10).

Many evidence show that blood-brain barrier dysfunction may be essential to the development of NPSLE, allowing the passive diffusion of auto-reactive antibodies and cytokines. This proces involves an abnormal reaction between the endothelium and the leukocyte that allows the passage of proteins and cells into the CNS (8, 11, 12). Endothelial cells, under the influence of proinflammatory cytokines, increase the expression of adhesive molecules, which allows the entry of lymphocytes into the CNS. In conditions of increased SLE activity, the level of intracellular adhesive molecules (ICAM-1) is also increased. The damage of the brain barrier increases the risk for corticosteroid induced psychiatric disorders in SLE too (8, 11).

Primary neuropsychiatric disorders in SLE are due to direct neuronal damage. Patogenetic mechanisms are: autoantibodies against receptors for N-methyl-d-aspartate glutamate (anti-NR2), accelerated arteriosclerosis and antiphospholipid antibodies leading to prothrombotic condition (13). Although some mechanisms are common to focal and diffuse syndromes, there is a clear relationship between the presence of vasculopathy and antiphospholipid antibodies (aPL) and focal NPSLE (cerebrovascular disease, seizure, chorea, myelopathy), and between inflammatory mediators and diffuse NPSLE (14). Antiphospholipid antibodies can induce blood-brain barrier dysfunction, through their interaction with endothelial cells and induce neurotoxicity (12). There are immune mechanisms mediated by inflammation, anti-neuronal antibodies (P antibodies), cytokines, increased permeability of the blood-brain barrier and intrathecal formation of immune complexes, in most diffuse neurological syndromes (such as psychosis or acute confusion) (14).

Autopsy findings in patients with NPSLE show a very wide range of CNS changes: multifocal infarcts, cerebral cortex atrophy, major infarction, haemorrhage, vasculitis, ischemic demyelination and multiple demyelinization fields, as in systemic sclerosis. The most common histological findings are cerebral microinfarcts, while vasculitis occurres very rarely (15).

DIAGNOSTIC APPROACH OF NPSLE

There are very different data about the incidence and prevalence of NPSLE. One of the reasons for such great differences is the fact that none of the neurological symptoms is specific to SLE, but can also occur very commonly in the general population (depression, headache). Modifying the criteria for NPSLE, in order to exclude mild or more subjective manifestations, led to an increase in the specificity of the criteria from the previous 46% (Table 1.a.), up to the current 93% (Table 1b.) (16).

In addition to primary CNS lesions which are caused by the disease itself, CNS damage can be secondary, for example, in patients with uremic syndrome, electrolyte disbalance, hypertensive encephalopathy, hypoxia, infections, or medication (psychosis induced by glicocorticoid therapy, dizziness and headache caused by antimalarials, aseptic meningitis caused by ibuprofen or azathioprine).

Table 1. Neuropsychiatric disorders in SLE as defined by the American College of Rheumatology (ACR) 1999 and their modification 2001.

a. American College rheumatology (ACR) defined syndromes (1999)	
Central nervous system	*Peripheral nervous system*
Epilepsy	Cranial neuropathy
Psychosis	Polineuropathy (confirmed by EMNG)
Cerebrovascular disease	Mononeuropathy
Headache	Gillan-Barre syndrome
Demelinization	Vegetative disorders
Motility disorder	Plexopathy
Aseptic meningitis	Myasthenia gravis
Acute confused state	
Anxiety disorder	
Cognitive dysfunction	
Mood disorder	
Myelopathy	
b. Modified Objective Criteria (2001)	
Epilepsy	Cranial neuropathy
Psychosis	Polineuropathy (confirmed by EMNG)
Cerebrovascular disease	Mononeuropathy
Demelinization	Gillan-Barre syndrome
Motility disorder	Vegetative disorders
Aseptic meningitis	Plexopathy
Acute confused state	Myasthenia gravis
Cognitive dysfunction (moderate and severe)	
Depression (severe)	

Assessment by physicians, whether neuropsychiatric syndromes are a direct consequence of active SLE, or are a consequence of therapy or complications of long-lasting illness, is very important for deciding on further treatment. There are no clinical tests that can help us evaluate whether neuropsychiatric manifestations are directly related to active SLE. Factors that can help include: general activity of SLE, previous history of neuropsychiatric changes, the presence of antiphospholipid antibodies.

Different attribution models have been proposed to distinguish NP events, depending on whether or not they are due to SLE. The minor and most common neuropsychiatric events (headache, mild depression, anxiety, minor cognitive complaints, and electromyographynegative polyneuropathy) used as exclusion events in the most relevant attribution models. These minor events became known as the "Ainiala criteria" (16-19).

Studies have shown that headache does not occur significantly more often in patients with SLE than in the general population (11, 20, 21). However, it is very important that the onset of headache, in an appropriate clinical context, is examined for the possibility of developing cerebral or subarachnoid haemorrhage, aseptic meningitis, or sinus thrombosis. If there are no risk factors (temperature, infection, antiphospholipid antibodies, anticoagulant therapy, immunosuppressive therapy, focal neurological signs, mental status disorders, meningism, and increased general activity of SLE), headache in patients with SLE does not require more extensive examination than what would be done in the general population that does not suffer from SLE. One of the non-specific symptoms is depression. It is very common in the general population and there is no way to differentiate it from depression within the NPSLE (21).

Demyelinization of CNS and transverse myelitis occur in about 5% of patients with SLE and usually associated with positive antiphospholipid antibodies (20, 21). Demyelinization of the CNS can be difficult to differentiate from multiple sclerosis in differential diagnosis. SLE and multiple sclerosis rarely occur together. So if there are no clear criteria for SLE, it is considered as the case of multiple sclerosis. Transverse myelitis is characterized by the appearance of paraplegia or quadriplegia, depending on which level of the spinal cord the

pathological process occurs. It can progress to a higher level with time (20, 21).

Peripheral nervous system disorders include the most common polyneuropathy, and less frequently monoeuropathy, acute demyelinizating polyradiculoneuropathy, myasthenia gravis, plexopathy and muscular weakness and atrophy. Sensomotor peripheral neuropathy is the most common form of peripheral nervous system involvement in SLE (21).

Acute psychosis occurs very rarely in SLE (about 2%) and is presented by the occurrence of delusions (incorrect beliefs that are maintained by using objective evidence, contrary to and in spite of cultural norms) or hallucinations (perceptions that occur in the absence of external stimulus) (20, 21). Corticosteroids induced psychiatric disorder occurs in about 10% of patients who are at high doses of prednisolone (≥1 mg / kg) and are more likely to experience mood disorders (93%) rather than psychosis(21). In clinical practice, it is important to exclude psychosis induced by high doses of corticosteroids or psychoactive drugs.

Cognitive dysfunction involves disturbance at the level of memory, learning, processing of information and expression. Cognitive dysfunction in NPSLE is manifested by disturbance of attention, visual memory, verbal memory, executive functions and psychomotor speed. Most SLE patients have mild to moderate levels of cognitive dysfunction. Severe degree of cognitive dysfunction occurs in a small number of NPSLE patients (2-3%). Special neuropsychological tests are used in cognitive dysfunction diagnosis (11, 20, 21).

When evaluating SLE patients with new neuropsychiatric symptoms, the same diagnostic algorithms should be applied as in all other patients with the same symptomatology. When suspected of infection, examination of a cerebrospinal fluid should be done. In patients with epileptic seizures, it is necessary to do electroencephalography. The occurrence of confusion and psychosis requires examination of the metabolic status and history of drug use. Neuropathies require the examination of vitamin B12 status. Magnetic resonance with angiography is used most often to exclude structural changes.

Magnetic resonance imaging (MRI) has become the gold standard tool for NPSLE assessment, replacing computed tomography (CT) in the evaluation of brain pathology among these patients. The average sensitivity of MRI in active NPSLE is 57% (22, 23). The MRI changes described in NPSLE patients range from small focal lesions in white matter, defined as white matter hyperintensities, to severe large lesions. Abnormal findings may be divided in three groups, according to their pathophysiology and imaging features: small-vessel disease, large-vessel disease, and inflammatory-like lesios

(24) Small vessel disease (30%- 75% of MRI findings in NPSLE), includes white matter hyperintensities, cortical brain atrophy, lacunes, small subcortical infarcts, and microbleeds. Among them white matter hyperintensities being the most commonly documented in SLE patients. The majority of small vessel lesions are often considered non-specific, as they may be related to age, hypertension, disease duration, low complement, aPL antibodies, and the presence of NPSLE manifestations, mainly cognitive dysfunction, seizures, and cerebrovascular disease.

Large vessel disease is less frequent than small vessel lesions (10%-15% of NPSLE MRI findings). It causes medium to large size vessel infarcts (single or multiple), involving both the grey and white matter (22). Inflammatory-like lesions are rather less common, accounting to for 5%-10% of NPSLE (24).

The lack of sensitivity of conventional MRI has led to the exploration of other techniques. These techniques include quantitative MRI, such as: magnetic resonance spectroscopy, magnetization transfer imaging, diffusion tensor imaging, and diffusionweighted imaging, or fluorodeoxyglucose positron emission tomography (FDG-PET) and single photon emission CT (SPECT). Nonetheless, these techniques, have low specificity, and did not show a high degree of validity in the differential diagnosis, which limits their use in clinical practice (25).

TREATMENT APPROACH IN NPSLE

Therapy NPSLE depends on the nature of the pathological process (dominant inflammation or thrombosis). In some cases, both lesion mechanisms are present at the same time. In cases where neuropsychiatric manifestations arise as a result of an inflammatory neurotoxic process (aseptic meningitis, optic neuritis, transversal myelitis, peripheral neuropathy, epilepsy, psychosis, acute confusional state) and in the presence of an increased generalized activity of SLE, therapy includes glycocorticoids independently or in combination with immunosuppressive drugs (azathioprine, cyclophosphamide) (23, 25). In the most severe forms of NPSLE, refractory to standard immunosuppressives, intravenous immunoglobulins, plasma replacement and rituximab might be effective. (23, 25).

In the LUMINA cohort hydroxychloroquine and moderate prednisolone dose delayed the first NPSLE manifestation, regardless of the type of event (27). The SALUD study showed that aspirin improved cognitive function in older patients with risk factors. In other studies, the odds of having cognitive impairment was significantly lower for patients taking hydroxychloroquine (28). When the neuropsychiatric event is acute and diffuse, it is presumably mainly inflammatory and almost always associated with generalized SLE activity. In this scenario, SLE global activity should be controlled at the same time as NPSLE is assessed, and if NPSLE is severe (acute confusional state, seizures, encephalitis) it should be treated with immunosuppressive drugs. Steroids have been used in several different doses (prednisolone 0.5- 1 mg/kg/day or bolus of intravenous methylprednisolone 3-5 days of 500 mg to 1 g/day (29). Cyclophosphamide can be used in two regimens. The low-dose EuroLupus regimen

intravenous 500 mg every other week for six cycles and the USA National Institutes of Health regimen of 1 g/monthly for 6 months (30, 31).

In maintenance treatment after induction therapy with cyclophosphamide or high-dose steroids, in severe NPSLE, azathioprine or mycophenolate mofetil can be used.(28, 32, 33) A recent revision reported the positive effects of rituximab (with high rates of response) and belimumab in severe NPSLE.(33). In severe refractory cases, intravenous immunoglobulins and plasmapheresis have been successfully used as bridge therapy, mainly when infection is not completely ruled out, in pregnant patients, or when there are life-threatening symptoms (15, 23, 26).

SLE patient with focal neuropsychiatric syndrome (ischemic and cerebral venous thrombotic events) and aPL positivity should be treated with anticoagulant therapy (15, 23, 26). In addition, control of classical cardiovascular risk factors, stop smoking, and in cases with positive antiphospholipid antibodies treatment with hydroxychloroquine is recommended. Other focal syndromes (seizures, ischemic optic neuropathy and chorea associated with antiphospholipid syndrome, as well as in myelopathy refractory to immunosuppressives) as also patterns of microvascular disease, might benefit from antiplatelet drugs or anticoagulation. If there are other clinical or laboratorial signs of inflammation, additional immunosuppression should be considered (15, 23, 26). Anticoagulant therapies have an advantage over antiplatelet for the purpose of secondary prevention of a cerebrovascular accident (CNS infarction or transient ischemic event) in patients with an antiphospholipid syndrome. In contrast, antiplatelet therapy is used for the primary prevention of cerebrovascular injury in patients with high titar of antiphospholipid antibodies.

In NPSLE patients with symptoms of psychosis, antipsychotics and / or antidepressants are indicated. Cognitive behavioral treatment has very positive effects on symptoms of depression. In psychiatric manifestations of SLE, combined therapy with glycocorticoids and immunosuppressants (induction therapy with cyclophophamide initially, and later in the maintenance phase of remission with azathioprine) in most cases leads to significant improvement of symptoms (60-80% of patients). However, there is a possibility of a relapse occurring and ranges up to 50%. In patients with psychiatric disorders refractory to therapy, rituximab can lead to significant improvement. Most psychiatric episodes are resolved within 2-4 weeks, while 20% of patients develop a chronic psychotic disorder (11, 15, 26).

In patients with seizures anticonvulsive drugs are recommended. If seizures reflect increased SLE activity and the exacerbation of the inflammatory process, glycocorticoids and immunosuppressants are recommended. The pulses of methylprednisolone and cyclophosphamide have shown good effects in cases of refractory seizures in the context of increased SLE activity (15).

Myelopathy in SLE is usually manifested as transverse myelitis, but in some cases it can be caused by an ischemic or thrombotic event. In patients with myelitis, combined therapy with methylprednisolone and pulses of cyclophosphamide can be very effective, especially at the onset of the disease. (15) After introduction of aggressive antiinflammatory therapy in a timely manner, the neurological improvement, as well as the improvement on magnetic resonance occurs within a few days to 3 weeks. Relapse of myelitis is common especially during the reduction of the dose of glycocorticoids and occurs in 50-60% of patients. In patients with ischemic myelopathy and antiphospholipid antibodes, anticoaglutination therapy might be usefull. Therapeutic plasma replacement may be a therapeutic option in severe cases of myelitis. In patients with a late diagnosis of SLE myelopathy and delay in initial therapy for more than 2 weeks, severe neurological deficits occur, followed by extensive lesions on the spinal cord magnetic resonance (15, 26).

Cranial neuropathy in NPSLE usually involves the third, fourth, sixth and eighth cranial nerves, and rarely the fifth and seventh. Pulse doses of methylprednisolone and cycofosfamide are recommended. Optical neuritis within the NPSLE is usually associated with a greater lack of vision. Immunosuppressive tearapy is also indicated, while anticoagulant therapy may have effects in patients with positive antiphospholipid antibodies refractory to immunosuppressives. (15, 26) In peripheral nervous system disorders monotherapy with glycocorticoids or in combination therapy with immunosuppressive drugs gives good results in 60-75% of patients. Intravenous immunoglobulins, plasma replacement therapy and rituximab can be used in severe cases (15, 23, 26).

Treatment of cognitive dysfunction in NPSLE involves treatment of causes of anxiety and depression worsening, as well as control of cardiovascular risk factors. Psychoeducational group treatments have shown improvement in the domain of memory and ability for daily activities. Patients with cognitive dysfunction and increased activity of SLE generally benefit from glycocorticoid and immuno-suppressives, and those with antiphospholipid syndrome of anticoagulant therapy (15, 26).

Analysis of implementation EULAR's preventive measures for the treatment of NPSLE, pointed that glycocorticoids and immunosuppressive therapy are often used not only in cases where there are clear indications (inflammation-aseptic meningitis, myelitis, cerebral vasculitis, cranial and peripheral neuropathies and psychosis), but also in thromboembolic cerebrovascular events, with no clear indications for their use (34).

CONCLUSION

Neuropsychiatric symptoms constitute an uncommon and poorly understood event in SLE patients, and pose a diagnostic and therapeutic challenge to the physician. Assessment by physicians, whether neuropsychiatric syndromes are a direct consequence of active SLE, or are a

consequence of therapy or complications of long-lasting illness, is very important treatment decision. Factors that are directly related to active SLE include: general activity of SLE, previous history of neuropsychiatric changes, the presence of high titar of antiphospholipid antibodies. Therapy NPSLE depends on the nature of the pathological process (dominant inflammation or thrombosis). If NPSLE is result of an inflammatory neurotoxic process and in the presence of an increased activity of SLE, therapy includes glycocorticoids independently or in combination with immunosuppressives. Focal neuropsychiatric syndrome with antiphospholipid antibodies positivity should be treated with anticoagulant and/ or antiplatelet therapy. In addition, control of classical car diovascular risk factors, stop smoking, and treatment with hydroxychloroquine is recommended.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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