Neuropsychiatric Systemic Lupus Erythematosus Manifestations Affecting the Quality of Life in Patients

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Abstract: Systemic lupus erythematosus (SLE) is a systemic autoimmune disease that can affect any organ. With SLE, one should always take into account the possibility of nervous system involvement. The aim of this study was to answer the question about the quality of life in patients with SLE with or without neuropsychiatric manifestations. We created a simple questionnaire, consisting of seven simple questions concerning physical and mental quality of life. In addition, socioeconomic status of patients was evaluated. The study group consisted of 59 patients with a mean age 51.9±16.6 years. 9 of them had neuropsychiatric manifestations. The quality of life survey conducted in patients with SLE groups according to the presence of neuropsychiatric manifestations. In SLE patients with neuropsychiatric manifestations sleep disorder, was most common. This deteriorated their quality of life in the mental sphere.

Keywords: Systemic lupus erythematosus, neuropsychiatric manifestations, quality of life.

INTRODUCTION

SLE is a chronic life-threatening systemic autoimmune disease. The diversity of symptoms and prognosis depend on the severity of the disease and damage of various organ systems including the central and peripheral nervous systems. Effective treatment plays an important role to the often unpredictable course of the disease [1-4]. Neuropsychiatric systemic lupus erythematosus (NPSLE) is associated with a poor prognosis. In 1999, the American College of Rheumatology (ACR) established case definitions for 19 specific neuropsychiatric syndromes, dividing them into two broad categories: central and peripheral [5] (Table **1**).

In December 2010, new guidelines for the management of SLE extending neuropsychiatric symptoms were published [6]. Based on the analysis of literature it can be estimated that the cumulative incidence of neuropsychiatric disorders in SLE is 30-40%, i.e. almost half less than before [6]. Previously it was believed that the form of neuropsychiatric SLE occurs in 14-75% of cases [7] . Neuropsychiatric disorders in 50-60 % of cases of the disease have occurred at the start or in the first year of its duration [6]. 40-50% of them were accompanied by generalized activity of the underlying disease [6]. It was recognized that such non-specific symptoms, such as headaches, mood and anxiety disorders, mild cognitive dysfunction, and not confirmed in an electroneurography examination polyneuropathy are common, but not indicative of SLE activity in the central nervous system (CNS). These symptoms were excluded from the group of reported neuropsychiatric symptoms, which decreased the total percentage of cases of neuropsychiatric SLE and increased the specificity of the symptoms included in the nomenclature of ACR. The following points: 4, 9, 10, 11 and 19 were removed.

The most commonly reported manifestations (cumulative incidence 5-15%) include cerebrovascular disease and seizures. In 1-5% of cases severe cognitive dysfunction, major depression, acute confusional state and peripheral nervous disorders have been observed; rare (<1%) is psychosis, myelitis, chorea, cranial neuropathies and aseptic meningitis [6].

CNS involvement in SLE is a challenge in diagnosis and therapeutic intervention. Despite years of research, previously unidentified biomarkers specific for the nervous system involvement in SLE and neuropsychiatric manifestations require a differential diagnosis with regard to infectious complications, metabolic and drug-induced.

The pathogenesis of neuropsychiatric manifestations in SLE is multifactorial and can involve various inflammatory cytokines, autoantibodies, and immune complexes resulting in vasculopathic, cytotoxic and autoantibody-mediated neuronal injury. The most common microscopic brain finding in SLE seems to be microvasculopathy. This is not specific, which may be due to complement activation and antiphospholipid antibodies [7]. The pathophysiologic role of autoantibodies, in particular anti-NR2 glutamate receptor antibodies may also play a role in cognitive dysfunction and psychiatric disease [7]. These

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Table 1: Specific Neuropsychiatric Syndromes of SLE

Central nervous system (CNS) of neuropsychiatric syndromes of SLE	Peripheral nervous system of neuropsychiatric syndromes of SLE
1. Aseptic meningitis	13. Acute inflammatory demyelinating polyradiculoneuropathy
2. Cerebrovascular disease	14. Autonimic disorder
3. Demyelinating syndrome	15. Mononeuropathy
4. Headache	16. Myastenia gravis
5. Movement disorder (chorea)	17. Cranial neuropathy
6. Myelopathy (transverse myelitis)	18. Plexopathy
7. Seizures	19. Polyneuropathy
8. Acute confusional state	
9. Anxiety disorder	
10. Mild cognitive dysfunction	
11. Mood disorder	
12. Psychosis	

antibodies are anti-DNA antibodies that cross-react with the NR2 glutamate receptor and mediate excitatory apoptotic cell death of neurons [7]. The anti-ribosomal P antibodies are involved in cognitive impairment, psychosis and depression [7]. Very important in pathogenesis of NPSLE are anticardiolipin antibodies and lupus anticoagulant. Also antibodies binding beta2-glycoprotein-1 and prothrombin can be detected.

Other possible intrathecal markers for NPSLE include matrix metalloproteinase-9 (MMP-9), plasminogen activator inhibitor 1 (PAI-1) and mediators inflammation (IL- 6, 8,10, INF-alpha, TNF-alpha) [7].

Most common cause of focal symptoms is thrombosis, associated with the presence of antiphospholipid antibodies or endocarditis.

Generalized symptoms correlate with elevated antibody concentration and pro-inflammatory cytokines in the serum and cerebrospinal fluid.

Neuropsychiatric manifestations in SLE can be a complication of disease or used treatments (e.g. corticosteroids, non-steroidal anti-inflammatory drugs), or can be a symptom of a disease accompanying unrelated to SLE (high blood pressure, brain abscess, tumor).

The aim of this study was to assess the quality of life in patients with SLE with and without neuropsychiatric manifestations.

METHODS

SLE was diagnosed based on the fulfillment of four criteria for classification ACR of 1982, which was modified in 1997 and includes the criterion 10 (presence of immune disorders) or criterion 11 (abnormal titer of antinuclear antibodies) [8].

The questionnaires were very extensive [9-12]. We developed a questionnaire which consisted of seven simple questions about the sphere of psychosocial and physical quality of life of the patient. The latter area included physical exercise capacity and a general feeling of fatigue. The psychosocial area concerned: a sense of sadness/depression, the occurrence of stressful situations and sleep disorders. In addition, patients were asked to provide their socioeconomic status. Each question was rated in three categories, of which the lowest category represented the highest negative and positive (e.g., physical capacity: poor, moderate, good, feelings of sadness or stressful situations: often, moderately often, rarely/occasionally, socioeconomic status: low, average, good).

MATERIAL

The study group consisted of 59 patients with SLE, diagnosed based on ACR criteria of 1997 [8]. The patients had a middle-aged 51.9±16.6 years, and the age of the youngest was 18 and the oldest 86 years. 54 (91.5%) of the patients were women. The average (median) disease duration was 7 years and varied from one to 50 years.

The clinical symptoms of patients are shown in Table **2** according to frequency. The majority of patients from the study group (86%) had arthritis. Although there was a far lower incidence of photosensitivity (58%), malar rash (56%) and hematologic disorders (54%), they relate to more than half of the patients. Other symptoms were demonstrated in smaller number of patients.

Table 2: Clinical Symptoms of SLE Patients

Symptoms	SLE patients
Arthritis	51 (86%)
Photosensitivity	34 (58%)
Malar rach	33 (56%)
Hematologic dis order	32 (54%)
Renal dis order	21 (36%)
Pleurisy	13 (22%)
Neurologic dis order	9 (15,3%)
Oral ulcers	8 (14%)
Discoid rash	5 (8%)

RESULTS

In SLE patients, the diagnostic work-up (clinical, laboratory, neuropsychological, imaging tests) of neuropsychiatric manifestations should be similar to that of the general population with the same neuropsychiatric manifestations. 9 (15.3%) of the patients in the group presented NPSLE manifestations on the basis of the diagnostic work-up. The mean age was 49.3±10.5 years and the average (median) disease duration 4.5 years. 5 patients had cerebrovascular disease and 4 other seizures. The group of patients without NPSLE manifestations in both age and disease duration did not present statistically significant differences in comparison to the group of patients with NPSLE, although the results in the group without NPSLE manifestations were higher, and were 52.4±17.5 years and 7 years. We found no statistically significant differences between the occurrence of NPSLE manifestations and the sex of the patient. Clinical symptoms of SLE patients are presented in Table **2**.

The quality of life study conducted in patients with SLE groups according to the presence of NPSLE manifestations has not shown that it negatively affects the functioning of the patient, since there were no statistically significant differences between the groups in both the aspects of the sphere and in the area of psycho- physical condition. Ratings in both groups were very close. And so, in both groups, of the patients equally often referred to their physical capacity as weak or poor (44%), just as they characterized early fatigue as frequent or very frequent (54%) (Figure **1**).

Greater differences between these groups, although not statistically significant, were observed in the mental

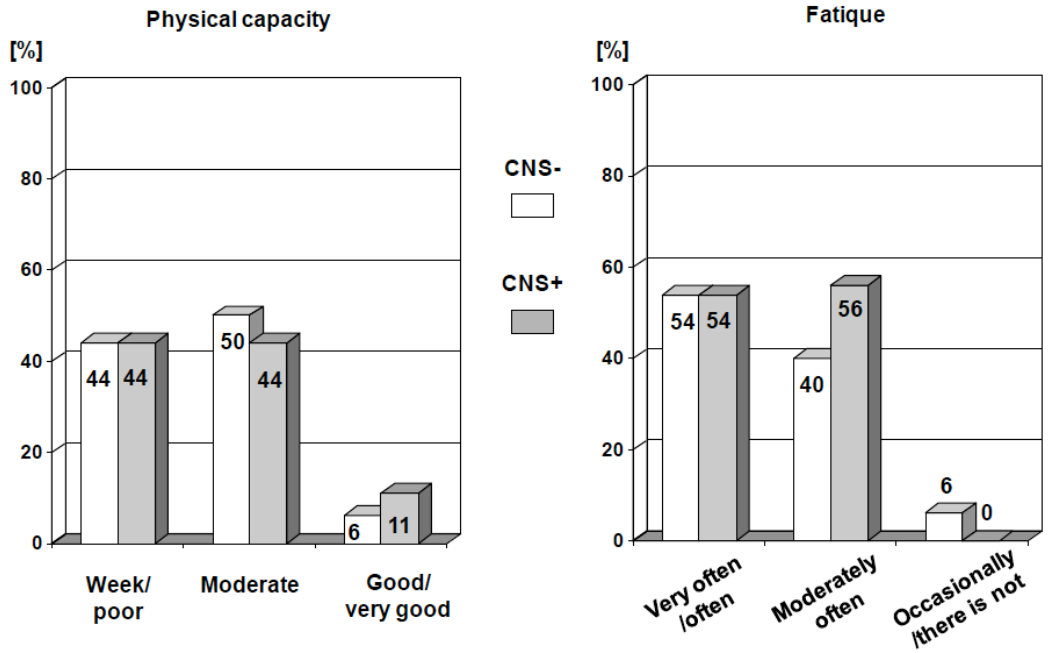

Figure 1: The sphere of physical quality of life in patients with SLE assessed physical performance and fatigue depending on the occurrence of NPSLE manifestations.

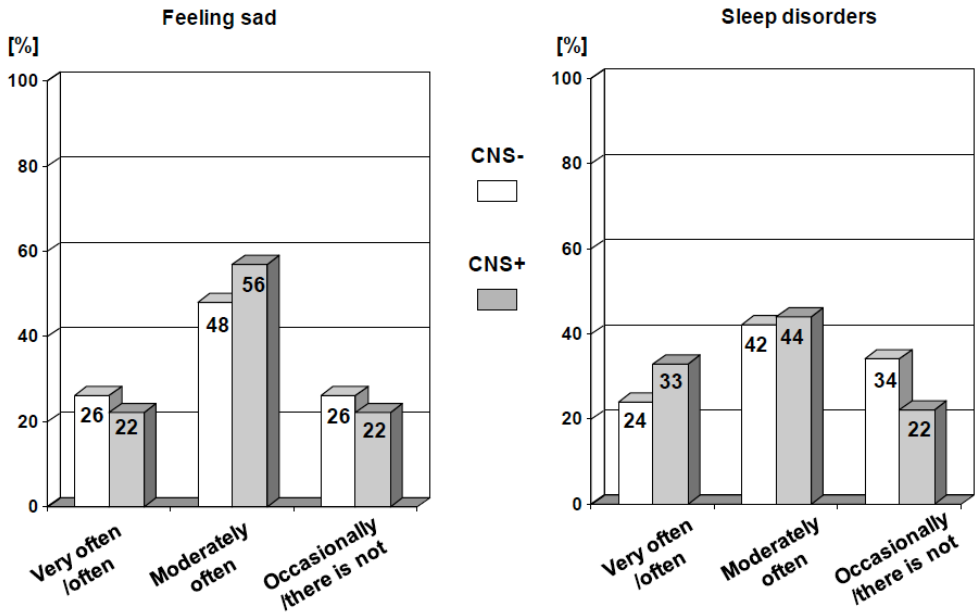

Figure 2: The sphere of mental quality of life in patients with SLE assessed feelings of sadness and sleep disorders, depending on the occurrence of NPSLE manifestations.

aspects (Figure **2**). The analysis showed that a feeling of sadness occurs in 26% of patients without and in 22% of patients with NPSLE manifestations. A greater percentage of the patients with NPSLE manifestations (22%) defined feeling sadness as frequent or very frequent. While 26% patients without NPSLE manifestations did the same. The largest differences were found in sleep disorders, as the group without NPSLE manifestations complain 12% less than the group with NPSLE manifestations (66% vs. 77.7%). Within the studied groups, 9% more patients with NPSLE manifestations identified this disorder as 'frequent or very frequent' – for the patients with NPSLE manifestations (33.3%) while for patients without NPSLE manifestations it was 24%. These differences, however, still did not reach statistical significance (Figure **2**).

Based on the survey it can be assumed that approximately in every 5-th patient, regardless of NPSLE manifestations, stress is a frequent companion of life (in the group without NPSLE manifestations 22%,

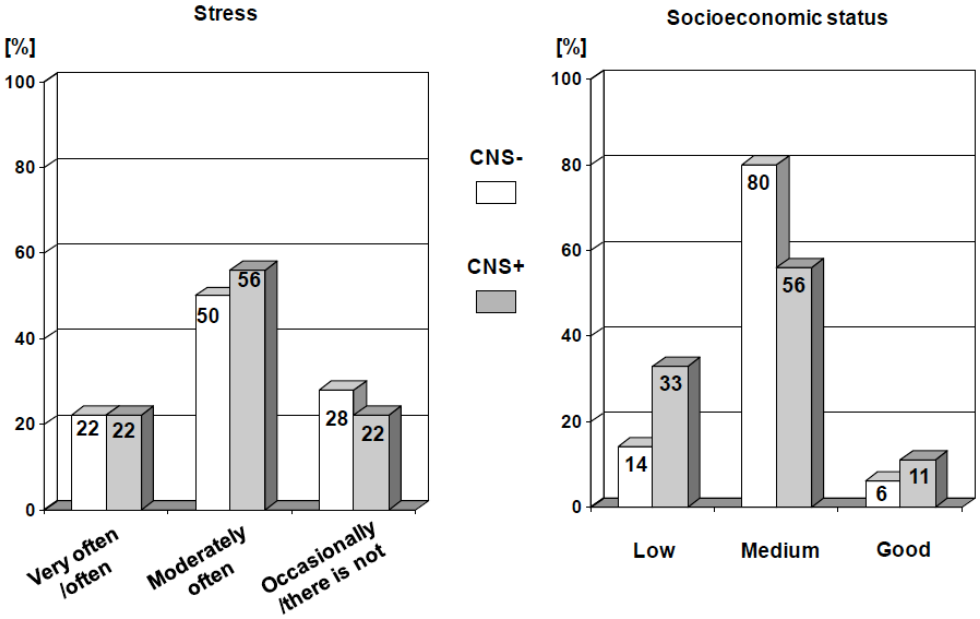

Figure 3: The sphere of psychosocial quality of life in patients with SLE evaluated the occurrence of stressful situations and socioeconomic status of patients according to the presence of NPSLE manifestations.

Table 3: Quality of Life in SLE Patients According to the Presence of Changes in the CNS

Parameters	No change in the CNS	With changes in the CNS	P
Physical capacity			
Week, poor	22 (44.0%)	4 (44.4%)	0.7344
Moderate	25 (50.0%)	4 (44.4%)	
Very good, good	3 (6.0%)	1 (11.1%)	
Fatigue			
Often, very often	27 (54.0%)	4 (54.0%)	0.6942
Moderately often	20 (40.0%)	5 (55.6%)	
There is not, occasionally	3 (6.0%)	0 (0%)	
Stress			
Often, very often	11 (22.0%)	2 (22.2%)	1.0000
Moderately often	25 (50.0%)	5 (55.6%)	
There is not, occasionally	14 (28.0%)	2 (22.2%)	
Feeling sad			
Often, very often	13 (26.0%)	2 (22.2%)	1.0000
Moderately often	24 (48.0%)	5 (55.6%)	
There is not, occasionally	13 (26.0%)	2 (22.2%)	
Sleep disorders			
Often , very often	12 (24.0%)	3 (33.3%)	0.8169
Moderately often	21 (42.0%)	4 (44.4%)	
There is not, occasionally	17 (34.0%)	2 (22.2%)	
Socioeconomic status			
Low	7 (14.0%)	3 (33.3%)	0.1879
Medium	40 (80.0%)	5 (55.6%)	
Good	3 (6.0%)	1 (11.1%)	

in the group with NPSLE manifestations (22.2%), as shown in Figure **3**.

Unfortunately, every third patient in the group with NPSLE manifestations determines their socioeconomic status as low (33.3 %) (Figure **3**). This variant occurs much less frequently in the group without NPSLE manifestations, since only in 14% of patients. Although in both groups the most common answer was granted in the medium category, the group without NPSLE manifestations mentioned it in 80% of their answers, whereas the group with NPSLE manifestations chose it 55.6%.

DISCUSSION

In our study, SLE patients with or without neuropsychiatric manifestations often referred to their physical capacity as weak or poor (44%), and to early fatigue as frequent or very frequent (54%). Greater differences were observed between these groups in the psychological aspects. The largest differences were found in sleep disorders, the group with occasional sleep disorder without NPSLE manifestations complain 12% less than the group with NPSLE manifestations. Unfortunately, every third patient with neuropsychiatric manifestations defined their socioeconomic status as low. This variant occurs much less frequently in the group without neuropsychiatric manifestations, since only in 14% of these patients.

A 3-year prospective study, which included 1206 SLE patients from different countries, assessed the incidence, nature of neuropsychiatric manifestations and their relationship to various factors [13]. Symptoms are divided into two categories related and unrelated to SLE. During follow-up, 40.3% of patients experienced one neuropsychiatric manifestation, while 17% experienced a number of neuropsychiatric

manifestations, of which 13-23,6% were related to SLE. They excluded neuropsychiatric manifestations to other causes most frequently occurred than SLE, such as infectious or drug-induced adverse effects. Overall, the whole group of patients had the most frequent headaches, mood disorders, cognitive dysfunction, seizures, anxiety disorders, cerebrovascular disease, psychosis, polyneuropathy and mononeuropathy. Among the symptoms associated with SLE more than 90% related to the CNS, and almost 80% were dispersed. Neuropsychiatric manifestations were usually reported on the first visit, after which they confirmed the increase of their incidences. The prognosis of lupus neuropsychiatric manifestations is good in case of regression of neuropsychiatric symptoms. The prognosis is also good if the symptom appear at the onset of SLE. Older age at diagnosis of SLE, longer disease duration and a higher result of SLEDAI scale at the time of the onset of symptoms were associated with a lower chance of improvement in patients. Neuropsychiatric manifestations significantly affected the deterioration of the quality of life in patients with SLE [13].

Pathomechanism changes in the CNS of SLE patients with lupus neuropsychiatric manifestations are not fully understood. Post mortem histopathologic studies in people with SLE have demonstrated an array of pathologies including multifocal microinfarcts, gross infarcts, hemorrhage, cortical atrophy, ischemic demyelination and patchy multiple sclerosis-like demyelination. Sibbitt *et al.* [14] compared the results of imaging the CNS by magnetic resonance imaging (MRI) with the post mortem brain study in 14 patients who died due to complications of NPSLE. The average age of patients was 37 years, more than 90% were women, 71% of patients had a history of seizures, in 64% coexisted lupus nephritis, antiphospholipid antibodies also was detected in 64% of patients. In all patients MRI detected small focal lesions in the white matter, in 64% moderate or significant cortical atrophy, in 57% moderate or significant ventrical dilation, in 50% acute cerebral edema and/or acute leukoencephalopathy, in 43% diffuse white matter, in 36% gliosis scar following ischemic stroke or hematoma to form cysts or without formation of cysts, in 29% ischemic stroke, in 21% acute intracranial hemorrhage. In most cases, a big change found in the autopsy respond to changing patterns of variation found in MRI. Microscopic examination showed that 57% of patients had acute or chronic vascular or parenchymal damage, 50% parenchymal edema, 43% gliosis hyperplasia, 36% diffuse loss of neurons and axons, 29% microinfarcts, microemboli, remodeling of blood vessels, 14% acute hemorrhage, 7% extensive calcification of vessels.

The authors demonstrated that the major cause of changes in NPSLE are thromboembolism and hypercoagulability, often associated with the presence of antiphospholipid antibodies, and the presence of endocarditis Libman-Sacks. Changes in heart valve in patients with endocarditis Libman-Sacks are a source of thromboembolic material in NPSLE. Deposition of immune complexes in vessels in NPSLEus occur only in 3-5 % of cases [14].

Muscal *et al.* [15] demonstrated that children with SLE often have cognitive function and changes in imaging of the CNS in the form of brain atrophy and cerebellar and hyperintense lesions in the white matter.

Diagnosis of NPSLE requires the exclusion of other causes such as the underlying disease, especially infection of CNS, metabolic and hormonal disorders, and adverse effects of drugs. In order to exclude patients with febrile infection it is recommended to test cerebrospinal fluid. In the case of seizures electroencephalography is recommended. Patients with cognitive impairment should undergo neuropsychological testing.

A typical treatment of neuropsychiatric disorders in SLE patients is the application of high doses of glucocorticoids and cyclophosphamide or azathioprine, cyclosporine, or mycophenolate mofetil. Mycophenolate mofetil in a dose of 2-3 g per day is a new therapeutic option.

CONCLUSION

In the patients with SLE with CNS involvement are more common sleep disorder, which affects the deterioration of their quality of life in the mental sphere.

REFERENCES

[1] Smolen JS. Therapy of systemic lupus erythematosus: a look into the future. Arthritis Res 2002; 4(Suppl 3): S25. http://dx.doi.org/10.1186/ar579

[2] Ginzler EM, Moldovan I. Systemic lupus erythematosus trials: successes and issues. Curr Opin Rheumatol 2004; 16: 499. http://dx.doi.org/10.1097/01.bor.0000133659.14482.59

[3] Goldblatt F, Isenberg DA. New therapies for systemic lupus erythematosus. Clin Expo Immunol 2005; 140: 205. http://dx.doi.org/10.1111/j.1365-2249.2005.02795.x

[4] Wallace DJ. Improving the prognosis of SLE without prescribing lupus drugs and the primary care paradox. Lupus 2008; 17: 91. http://dx.doi.org/10.1177/0961203307086267

[5] The American College of Rheumatology nomenclature and case definitions for neuropsychiatric lupus syndromes. Arthritis Rheum 1999; 42: 599-608. http://dx.doi.org/10.1002/1529-0131(199904)42:4<599::AID-ANR2>3.0.CO;2-F

[6] Bertsias GK, Ioannidis JP, Aringer MI, *et al*. EULAR recommendations for the management of systemic lupus erythematosus with neuropsychiatric manifestations: report of a task force of the EULAR standing committee for clinical affairs. Ann Rheum Dis 2010; 69: 2074-82. http://dx.doi.org/10.1136/ard.2010.130476

[7] Papescu A, Kao AH. Neuropsychiatric systemic lupus erythematosus. Curr Neuropharmac 2011; 9: 449-457. http://dx.doi.org/10.2174/157015911796557984

[8] Hochberg MC. Updating The American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum 1997; 42: 1725. http://dx.doi.org/10.1002/art.1780400928

[9] Scott DL, Garrood T. Quality of life measures: use and abuse. Baillieres Best Pract Res Clin Rheumatol 2000; 14: 663-87. http://dx.doi.org/10.1053/berh.2000.0106

[10] Fries JF, Spitz P, Kraines RG, *et al*. Measurement of patients outcome in arthritis. Arthritis Rheum 1980; 23: 137-145. http://dx.doi.org/10.1002/art.1780230202

[11] Meenan RF, Gertman PM, Mason JH. Measuring health status in arthritis. The arthritis impact measurement scales. Arthritis Rheum 1980; 23: 146-52. http://dx.doi.org/10.1002/art.1780230203

[12] Ware JE Jr, Sherbourne CD. The MOS 36-item short-form health survey (SF-36).I. Conceptrual framework and item selection. Med Care 1992; 30: 473-83. http://dx.doi.org/10.1097/00005650-199206000-00002

[13] Hanly JG, Urowitz MB, Su L, *et al*. Systemic Lupus International Collaborating Clinics (SLICC). Prospective analysis of neuropsychiatric events in an international disease inception cohort of patients with systemic lupus erythematosus. Ann Rheum Dis 2010; 69: 529-35. http://dx.doi.org/10.1136/ard.2008.106351

[14] Sibbitt WL Jr, Brooks WM, Kornfeld M, *et al*. Magnetic resonance imaging and brain histopathology in neuropsychiatric systemic lupus erythematosus. Semin Arthritis Rheum 2010; 40: 32-52. http://dx.doi.org/10.1016/j.semarthrit.2009.08.005

[15] Muscal E, Bloom DR, Hunter JV, *et al*. Frequency of neuro-psychiatric dysfunction in anti- SSA/SSB exposed children with and without neonatal lupus. Lupus 2010; 19: 300-6. http://dx.doi.org/10.1177/0961203309354542

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