Neuropsychiatric involvement in juvenile systemic lupus erythematosus

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Neuropsychiatric involvement is an important cause of morbidity and mortality in systemic lupus erythematosus (SLE) and it has been reported to occur in 22-95% of the childhood SLE patients. The aim of this study was to evaluate the neuropsychiatric involvement in our juvenile SLE patients.

This was a cross-sectional assessment of patients to investigate the relationship between the involvement of the nervous system and the clinical factors, including autoantibodies, renal involvement and disease activity. We used Symptom Checklist-90-R (SCL-90-R), designed to measure the psychopathological symptoms. As controls, we used 20 healthy adolescents and 20 patients with chronic diseases without any neuropsychiatric manifestations.

Overall, 55% (n=11) of the patients displayed neurological symptoms and/or signs. However, central nervous system (CNS) imaging showed pathological findings only in four of these patients. Patients with headache only had normal CNS imaging. Nine patients had moderate to severe depression. When SLE patients were compared to healthy controls and to adolescents with chronic diseases, they were found to be significantly more depressed.

In conclusion, pediatric rheumatologists should be aware of the frequency of neuropsychiatric disturbances in SLE. The neuropsychiatric disorders do not always correlate with disease activity and these children need professional psychological evaluation.

Key words: systemic lupus erythematosus, neuropsychiatric lupus, anti-cardiolipin antibodies.

Neuropsychiatric involvement in systemic lupus erythematosus (SLE) is an important cause of morbidity and mortality and it has been reported to occur in 22-95% of the childhood SLE patients[1-3]. The clinical spectrum may include neurologic manifestations such as seizures and demyelinating syndromes, or it may be of psychological nature like mood disorders, psychoses and cognitive abnormalities. There is no definitive test for the accurate diagnosis of neuropsychiatric SLE (NPSLE), and in addition to neurologic and rheumatologic examinations, brain imaging and neuropsychological assessments often become necessary.

In the literature, there have been few reports of neuropsychiatric evaluation in pediatric SLE patients[4,5]; hence, in this study we aimed to thoroughly report the neuropsychiatric involvement in our SLE patients. Moreover, we have substantiated the study by quantifying the psychiatric status of our patients and by further investigating any correlations between the psychiatric status and the disease parameters.

Material and Methods

All adolescent SLE patients who were admitted to the Department of Pediatric Nephrology and Rheumatology at Hacettepe University Medical School between September 2006 and March 2007 were recruited. Some of the patients were newly diagnosed in this period whereas others were on follow-up. This study consisted of 20 children (18 females, 2 males). All patients underwent a substantial neurological examination by a pediatric neurologist and a psychological work-up. Review of systems included a history of neurological complaints including headache, poor school performance, hearing loss, forgetfulness, and visual disturbances. During laboratory evaluations, complete blood count, urine analysis, C-reactive protein, erythrocyte sedimentation rate, anti-nuclear antibody, anti-ds DNA, lupus anticoagulants, and anti-cardiolipin antibodies were tested.

The disease was classified according to the American College of Rheumatology (ACR) Classification Criteria for SLE[6], and the disease activity was assessed by Systemic Lupus Erythematosus Disease Activity Index (SLEDAI).

Cranial magnetic resonance imaging (MRI) was performed in 14 patients who had positive findings in their medical history or neurological examination. Patients who had convulsions during their follow-up were also assessed by electroencephalography.

Symptom Distress Check List (SCL-90-R) questionnaire was used to quantify depression and anxiety. SCL-90 is a scale developed by the Johns Hopkins University, Psychometric Research Unit, for determining the level of psychological mood disorders and severity[7]. This checklist has been validated in Turkey and has been used previously[8,9]. It includes 90 questions in 10 parts. The level of anxiety and depression of the patients was assessed by the two sub-scales of the SCL-90-R. The scores ranged between 0-4 and those who had scores greater than 2 were classified to have severe anxiety or depression.

A group of 20 normal adolescents (aged 16-18 years) and 20 adolescent patients with chronic diseases [bronchial asthma[7], chronic hepatitis[6], and chronic renal failure[7]] served as controls and diseased controls for comparison of the anxiety-depression scores.

All data were analyzed using SPSS 15.0 (SPSS Inc., Chicago, IL, USA) for Windows. Values were expressed as mean (or median) ± standard deviation and percentages. Multiple group analyses were done by Kruskal Wallis and Bonferroni tests. Fisher's exact test and Pearson's chi-square statistics were used for discrete variables, while Mann-Whitney U test was used for continuous variables. The relationships between variables were assessed by Pearson's correlation analyses. Statistical significance was set at $p<0.05$.

Results

The mean age of the patients, mean age at diagnosis and mean disease duration (years) were 17.35±3.24 (18-23), 11.90±2.19 (8-16), and 5.50±3.69 (1-13), respectively. The demographic and clinical features of the patients are summarized in Table I. Mean SLEDAI scores at the time of diagnosis and at the last visit were 26.56±14.85 and 8.82±7.74, respectively. While seven patients (35%) had neurological signs and symptoms at the initial presentation, during their follow-up, the frequency of neurological signs and symptoms increased to 55%. Neurological examination revealed positive findings in 25% of the patients. Anti-cardiolipin and anti-phospholipid antibodies were present in 40% and 20% of the patients, respectively. Renal involvement was present in 50% of the patients. During the six months of follow-up, none developed further neurological features or deterioration.

Moderate to severe depression was detected in nine (45%) patients. Severe anxiety was defined in four (20%) patients, who also had severe depression. No significant correlation was found between depression status and the presence of anti-cardiolipin antibodies ($p=0.670$).

The frequency of neurological involvement at initial presentation was 2 (18.2%) among 11 mildly depressed cases and 5 (55.6%) among 9 severely depressed cases. However, the relation between the presence of initial neurological involvement and depression levels did not reach statistical significance ($p=0.16$). The anxiety scores of mild and severely depressed groups showed significant difference ($p=0.003$). Anxiety and depression

Table I. Demographic and Clinical Features of the SLE Patients

Patient No.	Age (year)	Sex	Disease duration (year)	Neurological findings at onset	Current neurological symptoms	Current neurological findings	MRI findings	Renal involvement	Severe depression	Severe anxiety
1	14	F	4	None	Hand tremor	Hand tremor	Abnormal	–	–	–
2	16	F	7	L hemiparesis	L hemiparesis	L hemiparesis	NA	+	+	–
3	17	F	1	None	Forgetfulness, headache, phonophobia	None	Normal	+	+	–
4	19	F	7	Hearing loss, decreased visual acuity	Forgetfulness, headache	R hemihypoesthesia	Normal	+	+	+
5	19	F	7	None	None	None	NA	–	–	–
6	19	F	10	None	None	None	NA	–	–	–
7	16	F	8	None	None	None	NA	+	–	–
8	15	F	1	None	None	None	Normal	+	–	–
9	13	F	1	Encephalopathy	None	None	Abnormal	–	–	–
10	16	F	5	None	Headache	None	Normal	+	+	–
11	16	F	2	None	None	Hand tremor	Normal	–	–	–
12	22	F	10	None	Headache	None	Normal	–	–	–
13	12	F	1	Vertigo, diplopia	Headache	None	Abnormal	–	+	+
14	18	F	5	None	Headache	None	Normal	+	–	–
15	16	F	6	Seizure	None	None	Normal	+	+	–
16	22	F	8	None	Headache	None	Abnormal	+	+	–
17	23	M	10	Seizure	None	None	Normal	–	–	–
18	22	F	13	None	None	None	NA	–	+	+
19	13	M	3	Seizure	Headache	None	Normal	–	+	+
20	19	F	1	None	None	None	NA	+	–	–

SLE: Systemic lupus erythematosus. NA: Not available. L: Left. R: Right.

scores were found to be positively correlated ($r=0.80$, $p<0.001$). Patients with mild and severe depression were found to be statistically similar with regard to age, sex, anti-cardiolipin antibodies, renal involvement, SLEDAI, disease duration, and neurological signs or symptoms. Nine patients (45%) had a decline in school performance. Of those, 6 (66.7%) had severe depression and 3 (27.3%) had mild depression.

When SLE patients were compared to healthy and diseased controls, they were found to be significantly more depressed ($p=0.013$) (Fig. 1). There were no significant differences among the groups concerning anxiety.

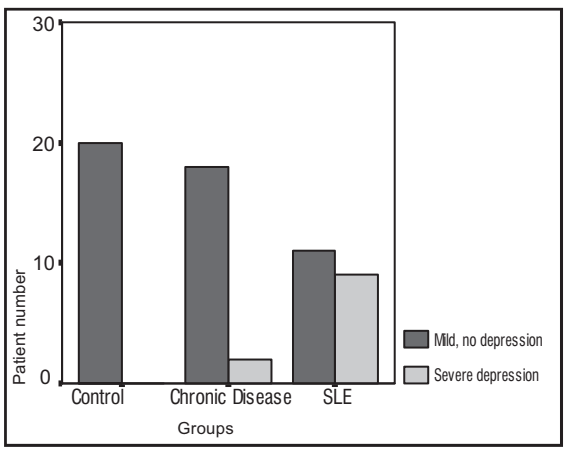

Fig. 1. The distribution of severe depression among healthy controls, adolescents with chronic disease and SLE patients.

Overall, 55% (n=11) of the patients in this cohort displayed neurological symptoms and/or signs. However, MRI showed pathological findings only in four of these patients. Table II summarizes the MRI findings of these patients. All findings were interpreted not to be important and no follow-up was suggested.

All patients received steroids, 10 patients received cyclophosphamide, 9 received either azathioprine or mycophenolate mofetil and 1 received hydroxychloroquine. Plasmapheresis was performed for severe systemic disease in one patient.

Discussion

Neuropsychiatric involvement is an indicator of disease severity and activity and it is an important determinant of quality of life in patients with SLE. The rates for the presence of neurological involvement in SLE vary within a wide range owing to various factors[10,11]. Psychiatric manifestations occur in 20%–56% of juvenile SLE. Seizures, psychiatric disorders and headache are the most commonly reported manifestations[12,13].

Generalized or focal seizures have been reported in 6–51% of SLE patients and may be related to active disease, cicatricial lesions, or acute inflammation of various causes[14,15]. Neurological involvement was present in 55% of our patients. Although convulsion has been reported as the leading feature in most series, it was present in only 15% of the patients in our series. However, convulsion was not necessarily a poor prognostic factor in our patients. Seizures occurred as a single attack and recurrent attacks did not occur in our study group[16,17].

The patients with neurological signs had some important findings in imaging. The girl who presented with vertigo and high anti-cardiolipins showed multiple infarcts on central nervous system (CNS) imaging; this was interpreted to be due to the presence of these antibodies as well as the microangiopathy. In fact, she developed widespread purpura over her skin simultaneously. The skin biopsy showed microangiopathic changes and remission was achieved with immunosuppressive therapy and plasmapheresis. Herewith, we also propose that the favorable prognosis of neurological involvement in our patients could be attributed to the intense immunosuppressive regimens they received.

Psychiatric manifestations are common in patients with NPSLE but a number of studies revealed no difference in the rate of depression between patients with SLE and other rheumatic diseases[18,19]. The rate of

Table II. MRI Findings of the Patients

Patient no.	MRI findings
1	Mild cerebellar tonsillar ectopia, Rathke cleft cyst
9	Hemorrhagic pituitary microadenoma
13	Multiple infarcts
16	Small white matter lesions consistent with acute ischemia

NPSLE-related psychiatric syndromes varies partly because of the lack of standardized definitions[20]. We used SCL-90-R, designed to measure psychopathological symptoms, in our patients. In patients with rheumatic diseases, SCL-90-R has been a well-documented psychological screening instrument[20], and it has also been validated in the Turkish population[8,9]. A surprisingly high percentage of children with SLE had mood disorders that were not noticed by their families or the physician. A chronic disease in adolescence usually exerts negative effects on the lives of children. One would expect this to be more pronounced in patients with a long disease duration and severe disease activity[21,22]. However, in this study, albeit a small cohort, significant depression did not correlate with SLEDAI and disease duration. Furthermore, SLE patients had more depression when compared to other adolescents with chronic diseases. This may suggest that depression in SLE is not just a functional consequence and that the mood disorder in these patients may be more "organic" in nature than expected. The fact that patients with significant depression had more neurological symptoms and/or signs also supports this hypothesis.

Systemic lupus erythematosus patients are often admitted with headaches, which may be related to the underlying disease itself, increased intracranial hypertension or nonspecific. Headaches can occur as a component of active SLE, but are probably unrelated to SLE in most cases[23,24]. Forty percent of patients complained of headache during the last visit as a neurological symptom; however, none had pathology on CNS imaging. A headache without accompanying positive neuro-exam is probably not of clinical significance in these patients. Therefore, we suggest that patients with no neurological symptoms and those with a normal neuro-exam do not need neuroimaging for screening purposes.

School performance questionnaire showed that two-thirds of those with significant depression had poor school performance. This reflects how the quality of life of these patients is affected. Similarly, in patients who had milder scores for depression, school performance was better.

In conclusion, pediatric rheumatologists should be aware of the frequency of neuropsychiatric disturbances in SLE. Although this is only a pilot study, it suggests that the neuropsychiatric disorders do not always correlate with disease activity and these children need professional psychological evaluation. We also suggest that immunosuppressive treatment that is applied for renal involvement in the majority of the cases may have a beneficial role also in the outcome of neurological problems. Further studies are awaited to construct evidence-based guidelines for the treatment of neuropsychiatric involvement in SLE patients.

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