

CLINICAL, LABORATORY AND NEUROIMAGE FINDINGS IN JUVENILE SYSTEMIC LUPUS ERYTHEMATOSUS PRESENTING INVOLVEMENT OF THE NERVOUS SYSTEM

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ABSTRACT - Objective: To characterize neurological involvement in juvenile systemic lupus erythematosus. **Method:** The charts of all patients with the diagnosis of systemic lupus erythematosus before the age of 16 years, followed at the Rheumatology Unit of Pequeno Príncipe Hospital, from January 1992 to January 2006, were retrospectively reviewed, highlighting neuropsychiatric aspects. **Results:** Forty-seven patients were included. Neuropsychiatric syndromes were found 29 (61.7%): seizures (17 / 36.2%), intractable headache (7 / 14.9%), mood disorders (5 / 10.6%), cerebrovascular disease (4 / 8.5%), acute confusional state (3 / 6.4%), aseptic meningitis (3 / 6.4%), psychosis (3 / 6.4%), chorea (3 / 6.4%), Guillain-Barré syndrome (2 / 4.3%) and cranial neuropathy (1 / 2.1%). Morbidity indexes (SLEDAI and SLICC) were higher among patients with neuropsychiatric manifestations ($p < 0.05$). **Conclusion:** Neuropsychiatric syndromes are frequent, and add significant morbidity to juvenile systemic lupus erythematosus.

KEY WORDS: juvenile systemic lupus erythematosus, neuropsychiatric syndromes.

Achados clínicos, laboratoriais e de imagem no lupus eritematoso sistêmico juvenil com comprometimento do sistema nervoso

RESUMO - Objetivo: Caracterizar o comprometimento neurológico no lupus eritematoso sistêmico juvenil. **Método:** Os prontuários dos pacientes com o diagnóstico de lupus eritematoso sistêmico antes dos 16 anos de idade, em acompanhamento na Unidade de Reumatologia do Hospital Pequeno Príncipe, de janeiro de 1992 a janeiro de 2006, foram revisados retrospectivamente enfatizando aspectos neuropsiquiátricos. **Resultados:** Quarenta e sete pacientes foram incluídos. Síndromes neuropsiquiátricas foram encontradas em 29 (61,7%): crises convulsivas (17 / 36,2%), cefaléia intratável (7 / 14,9%), distúrbios do humor (5 / 10,6%), doença cerebrovascular (4 / 8,5%), estado confusional agudo (3 / 6,4%), meningite asséptica (3 / 6,4%), psicose (3 / 6,4%), coreia (3 / 6,4%), síndrome de Guillain-Barré (2 / 4,3%) e neuropatia craniana (1 / 2,1%). Índices de morbidade (SEDAI e SLICC) foram maiores em pacientes com manifestações neuropsiquiátricas ($p < 0,05$). **Conclusão:** Síndromes neuropsiquiátricas são um achado freqüente que acrescenta morbidade significativa ao lupus eritematoso sistêmico juvenil.

PALAVRAS-CHAVE: lupus eritematoso sistêmico juvenil, síndromes neuropsiquiátricas.

Systemic lupus erythematosus (SLE) usually presents itself in adulthood. Large SLE patient series estimate that 8-15% of the cases begin before the age of 16 years¹⁻⁵. Onset before 5 years of age is considered rare^{2,6}. The subset of SLE patients that initiate the disease before the age of 16 differs in both clinical manifestations and laboratory parameters from those with disease-onset after this age. Juvenile SLE (JSLE) generally has a more severe presentation and course than adult SLE^{2-5,7}. The female to male ratio

in adult SLE is considered to be around 10:1. Some authors report higher prevalence of male patients among JSLE^{3,5,8-10}. Lymphadenopathy and fever are more common presenting features in children^{2,8}. Nephropathy, both at onset and during the course of the disease, is more prevalent in JSLE¹⁻³. Cutaneous vasculitis⁴, discoid lupus skin lesions⁴, malar rash^{1,2}, alopecia³ and gastrointestinal involvement³ have been found to be more frequent in children, while arthritis⁴ was reported to be more prevalent in adult SLE.

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Neurological manifestations in general⁴, and particularly seizures^{3,4} and chorea², were found to be more frequent in JSLE. Autoantibody profiles also differ from adult to JSLE, anti-cardiolipin (IgG)², anti-DNA^{3,5}, anti-Sm⁵, and anti-RNP⁵ antibodies being more frequently positive in children.

Documentation of fundamental discrepancies between adult and JSLE motivate the analysis of pediatric patients as a separate subgroup. However, since JSLE comprises no more than 15% of all SLE patients, pediatric series are often too small to allow any conclusions to be drawn. In 1999, the American College of Rheumatology published the nomenclature and case definitions for neuropsychiatric lupus syndromes¹¹. Nevertheless, neuropsychiatric syndromes are still a controversial aspect of SLE. Neuropsychiatric manifestations in SLE are polymorphous and some authors suggest that a number of them are still not acknowledged by the 1999 nomenclature¹². It is also known that the involvement of the nervous system in SLE goes beyond the 19 standardized syndromes or any other neuropsychiatric sign or symptom reported, as asymptomatic patients submitted to neurophysiological examination, neuropsychological tests and neuroimage exams were shown to be neurologically compromised¹³⁻¹⁹.

We describe in detail 47 patients with JSLE, emphasizing neuropsychiatric manifestations.

METHOD

The charts of all patients with the diagnosis of SLE before the age of 16, followed at the Rheumatology Unit of Pequeno Príncipe Hospital from January 1992 to January 2006, were retrospectively reviewed. Cases of neonatal lupus were excluded. Fulfillment of at least 4 of the 1982 American Rheumatism Association criteria for SLE²⁰ was required for the diagnosis. Data concerning general patient information, clinical manifestations at onset and throughout disease course, laboratory parameters and clinical outcome were compiled. All cases reviewed were examined and accompanied by at least one of the authors. Leukopenia, lymphopenia and thrombocytopenia, when observed during treatment with cyclophosphamide, were considered as side effects of the medication and disregarded as SLE manifestations.

The search for neuropsychiatric manifestations was guided by the 1999 American College of Rheumatology's nomenclature and case definitions for neuropsychiatric lupus syndromes¹¹. This classification defines intractable headache as one that does not fulfill the criteria for migraine, tension headache, cluster headache or headache from intracranial hypertension and does not respond to usual pharmacologic treatment. Neuropsychiatric aspects, including standardized syndromes, minor symptoms (those not contemplated by the case definitions), neuro-

image and electroencephalogram (EEG), were highlighted. Seizures were classified according to the International League Against Epilepsy Criteria of 1981²¹. The SLE Disease Activity Index (SLEDAI)²², used to assess disease activity, was obtained at disease-onset and at the latest medical appointment. The Systemic Lupus International Collaborating Clinics Damage Index for SLE (SLICC)²³, used to assess disease morbidity or cumulative damage, was obtained 6 months after disease-onset and at the latest medical appointment. SLEDAI and SLICC scores were compared between patients with and without neuropsychiatric manifestations using the Mann-Whitney test. Mortality rates were compared between patients with and without neuropsychiatric manifestations using the chi-square test with Yates' correction. In both analysis, results were considered statistically significant if $p < 0.05$.

Continuous variables were presented as mean, standard deviation, median and interval. The use of median is advisable whenever the variation coefficient is greater than 0.3 and, in those cases, it was informed first in the text. Discrete variables were expressed as absolute frequencies and percentages. This research was approved by the Ethics Committee of Pequeno Príncipe Hospital.

RESULTS

Fifty-one medical charts were reviewed. Four patients were excluded: 3 had an initial diagnostic hypothesis of SLE that was not confirmed by clinical and laboratorial investigations and 1 had neonatal lupus. Forty-seven patients were diagnosed with SLE before the age of 16 at the Rheumatology Unit of Pequeno Príncipe Hospital from January 1992 to January 2006. Thirty-six (76.6%) were female. Concerning ethnicity, 73.8% were white and 26.2% were mulattos. Mean age at disease-onset was 11.4 ± 2.6 years, median 11.8 (5.3 / 15.2). Median delay of diagnosis was 2.0 months (0.0 / 73.0), mean 9.7 ± 18.9 . The median follow-up time was 27.2 months (1.9 / 151.4), mean 39.5 ± 39.1 . Ten patients were noted as poorly compliant and 9 abandoned follow-up.

Clinical manifestations at onset and during JSLE evolution are summarized in Table 1. Neuropsychiatric lupus syndromes recognized by the American College of Rheumatology¹¹ diagnosed at disease-onset and during its evolution are presented in Table 2. Cognitive dysfunction was excluded, since proper neuropsychological tests were not performed. Median disease duration at presentation of the neuropsychiatric syndrome was 3.1 months (0.0 / 72.0), mean 12.0 ± 18.8 . Three (6.4%) of the 47 patients had two episodes of acute neuropsychiatric manifestation. The one patient with cranial neuropathy in our sample had recurrent peripheral facial palsy. Out of the 17 patients that presented with seizures, 9 (52.9%) were generalized clonic, 2 (11.8%) myoclonic, 3

Table 1. Clinical manifestations of JSLE.

Clinical manifestation	At disease-onset	During disease course
	No, n=47 (%)	No, n=47 (%)
Malar rash	15 (31.9)	38 (80.9)
Cutaneous vasculitis	8 (17.0)	16 (34.0)
Raynaud's phenomenon	0 (0.0)	8 (17.0)
Photosensitivity	4 (8.5)	27 (57.4)
Alopecia	8 (17.0)	25 (53.2)
Oral ulcerations	4 (8.5)	10 (21.3)
Arthritis	15 (31.9)	26 (55.3)
Myositis	0 (0.0)	2 (4.3)
Serositis	10 (21.3)	15 (31.9)
Pleuritis	8 (17.0)	11 (23.4)
Pericarditis	2 (4.3)	3 (6.4)
Peritonitis	2 (4.3)	5 (10.6)
Renal disorder	18 (38.3)	33 (70.2)
Hematological disorder	24 (51.1)	35 (74.5)
Anemia	13 (27.7)	20 (42.6)
Leukopenia	11 (23.4)	14 (29.8)
Lymphopenia	16 (34.0)	23 (48.9)
Thrombocytopenia	10 (21.3)	12 (25.5)
Pancytopenia	7 (14.9)	7 (14.9)
Fever	16 (34.0)	16 (34.0)
Weight loss	12 (25.5)	13 (27.7)
Lymphadenopathy	5 (10.6)	6 (12.8)

(17.6%) focal clonic and 1 (5.9%) focal tonic. Two (11.8%) patients had seizures during a hypertensive crisis. Three patients (17.6%) had one episode of status epilepticus, 1 (5.9%) generalized and 2 (11.8%) focal. One of our patients had various neuropsychiatric syndromes at disease onset (seizures, acute confusional state, aseptic meningitis and Guillain-Barré syndrome) and evolved with left transverse and sigmoid intracranial venous sinuses thrombosis in the presence of anti-cardiolipin IgG antibodies.

Occasional neuropsychiatric complaints, that do not fulfill any of the 19 case definitions, were observed in 26 patients (55.3%). Fifteen (31.9%) reported mild sporadic headache, 8 (17.0%) tremor, 5 (10.6%) irritability, 4 (8.5%) paresthesia of hands and feet and 2 (4.3%) vertigo. Considering both neuropsychiatric syndromes and minor neuropsychiatric symptoms, 41 (87.2%) of the 47 patients showed some level of neuropsychiatric involvement.

Neuroimage was performed in all 29 patients presenting with a neuropsychiatric syndrome, yielding abnormal results in 13 (44.8%). Thirteen patients (44.8%) were submitted to magnetic resonance imaging (MRI). Six (46.1%) exams yielded normal re-

Table 2. Neuropsychiatric lupus syndromes.

Neuropsychiatric Lupus syndromes	At disease-onset	During disease evolution
	No, n=47 (%)	No, n=47 (%)
Acute confusional state	2 (4.3)	3 (6.4)
Mood disorders	0 (0.0)	5 (10.6)
Cerebrovascular disease	1 (2.1)	4 (8.5)
Intractable headache	1 (2.1)	7 (14.9)
Aseptic meningitis	2 (4.3)	3 (6.4)
Psychosis	1 (2.1)	3 (6.4)
Seizures	7 (14.9)	17 (36.2)
Guillain-Barré syndrome	2 (4.3)	2 (4.3)
Cranial neuropathy	1 (2.1)	1 (2.1)
Movement disorder (chorea)	0 (0.0)	3 (6.4)

sults, 1 (7.7%) showed moderate ventricular ectasia, 1 (7.7%) moderate cerebral atrophy, 1 (7.7%) small parietal gliosis, 1 (7.7%) small left thalamic hyperintense lesion in T2-weighted images and 3 (23.1%) white matter lesions hyperintense in T2-weighted images (1 frontal, small and single, 1 frontoparietal small and multifocal and 1 fronto-temporo-parietal, extensive and asymmetrical). Patients who showed neuropsychiatric involvement from the year of 2002 onwards were investigated with MRI. Twenty (69.0%) were submitted to computerized axial tomography (CAT). Twelve (60.0%) exams yielded normal results, 5 (20.0%) showed moderate cerebral atrophy and 3 (15.0%) hypodense lesions suggestive of ischemic cerebrovascular infarcts (1 left temporoparietal region, 1 bilateral frontal and left occipital and 1 basal ganglia, thalamus, pons and mesencephalus).

EEG was performed in 26 (89.7%) of the patients presenting with a neuropsychiatric syndrome. It was considered normal in 12 (46.2%). Eleven exams (42.35%) revealed disorganization of background activity. In 6 exams (23.1%) epileptic paroxysms were registered, 3 (11.5%) focal and 3 (11.5%) generalized.

Considering immunological parameters, anti-nuclear antibodies were tested in all 47 patients, positive in 32 (65.3%). Anti-DNA antibodies were tested in 46 patients, positive in 12 (26.0%). LE cells were tested in only 17 patients, positive in 10 (58.8%). C3 levels were low in 9 (22.5%) out of the 40 patients tested. From of the 25 patients tested, Anti-Sm was positive in 5 (20.0%), Anti-Ro in 3 (12.0%) and Anti-La in 1 (4.0%). Anti-cardiolipin antibodies were tested in 30 patients, 13 (43.3%) of whom had positive IgG and 8 (26.7%) positive IgM antibodies. Lupus an-

ticoagulant was tested in 16 patients, positive in 3 (18.8%). Three (6.4%) patients did not have any positive auto-antibodies.

SLEDAI scores obtained at disease-onset and SLICC scores obtained 6 months after disease-onset and at the latest medical consultation were higher among patients with neuropsychiatric manifestations ($p < 0.05$). SLEDAI scores at the latest medical consultation were not statistically different between patients with and without neuropsychiatric manifestations ($p = 0.306$).

Six (12.8%) of the 47 patients died. Five of them (83.3%) belonged to the group with neuropsychiatric manifestations. Mortality rates were not statistically different between patients with and without neuropsychiatric manifestations ($p = 0.882$). All six patients that died had renal involvement. The circumstances leading to death were of infectious nature in four (66.7%), and complications of renal failure in two (33.3%).

DISCUSSION

The female to male ratio observed in our patient sample was 3.3:1, which is in agreement with the previous observation that JSLE has a higher male prevalence than adult SLE^{3,5,8-10,24}.

Race distribution was probably influenced by local ethnical background, where white and miscegenation among white, black and Native Americans predominate. None of our 47 patients was either black or Asian. A 1999 American study of 39 JSLE cases in Florida reports 41% white, 33% black and 26% Hispanic²⁵. The largest pediatric series of SLE, a French multicenter study, reports 46% white, 31% black, 20% North African and 3% Asian²⁶. The high prevalence of Hispanic and North African descent in these series also reflects a local bias which is inherent in any population study.

The average age at disease onset was 11.4 ± 2.6 years, which is in concurrence with pediatric series that indicate that mean age at JSLE presentation varies from 11.0 to 11.5 years^{2,24,26,27}. Our youngest patient was 5.3 years at disease presentation. Even though onset before the age of 5 is rare^{2,6}, a case of SLE beginning at 1.5 years has been reported²⁶.

Among our patients, the median delay of diagnosis was 2.0 months, that agrees with a previous report of 2.8 months²⁶.

In our series, the most frequent clinical manifestations at JSLE onset were malar rash and arthritis in 31.9%, fever in 34.0%, renal involvement in 38.3%

and hematological disorder in 51.1%. Previous pediatric series reported malar rash in 39-55%^{1,2,26}, arthritis in 61-65%^{2,25}, fever in 41-58%^{2,26}, renal involvement in 20-67%^{1,2,4,25,26} and hematological disorder in 24-72%^{25,26}.

Renal disorder was present in 70.2% of our patients throughout the course of the disease. Rates as high as 50% have been formerly described². The high prevalence of nephropathy confirms disease severity in children, since renal involvement is known to be directly correlated to disease gravity^{9,28,29}.

Neuropsychiatric lupus syndromes occurred at disease onset in 27.7% and during disease evolution in 61.7% of our patients. Prior series have reported comparative rates of 0-28%^{2,25,27,30-32} and 22-75%^{2,17,27,30-32} respectively. Methodological challenges in confronting series are due to the variability in the criteria used to define the neuropsychiatric syndromes and in the cut-off age of JSLE, which ranges from 14^{2,33} to 16^{3,5,26,34} and to 18⁴ years. Mean disease duration at presentation of the neuropsychiatric syndrome ranges from 1³¹ to 10.2³⁰ months in available reports. In our series, patients manifested neuropsychiatric syndromes with an average of 12.0 months of JSLE.

The most common neuropsychiatric manifestation in our patients was seizures, both at disease onset (14.9%) and during JSLE evolution (36.2%). Corresponding rates of 4-21%^{26,31,35} and 11-61%^{27,30-32,35} respectively have been observed. Seizures are more frequently found in JSLE^{3,4} and are the main clinical manifestation of neurological involvement in this subgroup of SLE patients^{27,31}. To the best of our knowledge, seizure semiology has not been described in detail in pediatric SLE series. A large Brazilian study³⁶ including 519 adult SLE patients, observed 19 patients with epileptic seizures at disease onset, 63% generalized tonic-clonic and 37% complex partial. Forty-one patients developed seizures during the course of the disease, all of them had generalized tonic-clonic seizures. Two cases of fatal status epilepticus were reported. In our series, 3 of the 17 (17.6%) patients with seizures had one episode of status epilepticus, 1 (5.9%) generalized and 2 (11.8%) focal. Recent adult case reports emphasize the importance of considering the differential diagnosis of complex partial status epilepticus in SLE patients presenting with confusion, acute behavioral changes or psychotic symptoms^{37,38}. Myoclonic seizures were observed in one of our patients. This is an infrequent finding that has been formerly described

in a case report³⁹. Two of our patients had seizures during hypertensive crisis. Both were considered to have primary central nervous system involvement by SLE, given that in one case the epileptic seizure was accompanied by a cerebrovascular ischemic lesion, and in the other seizures recurred despite normalization of blood pressure levels. This distinction is of great relevance, since seizures caused by metabolic and electrolytic disturbances or hypertension (provoked seizures), while isolated neurological signs, should not be considered as neurological SLE compromise.

The following most common neuropsychiatric syndromes among our patients were intractable headache (14.9%), mood disorders (10.6%) and cerebrovascular disease (8.5%). Pediatric series report prevalences of 7-10%^{26,31}, 5%²⁵ and 2-3.5%^{26,31} respectively at disease presentation. These rates rise to 10-20% for headache and 6.6-12% for stroke during the course of the disease^{27,30,35}.

Chorea was found in 6.4% of our patients. Although it is considered a rare SLE manifestation in adults², it is more frequent in JSLE² and has been observed in 0.6-2.3% at disease onset^{26,31} and in 1-6% during disease course^{30,32,35}.

One of our patients presented with recurrent facial palsy leading to the diagnosis of SLE. Cranial neuropathies are uncommon in JSLE and more so is facial neuropathy. An isolated case has been reported in a 16 year-old girl⁴⁰.

Intracranial venous sinus thrombosis is not considered by the American Academy of Rheumatology as a neuropsychiatric syndrome of SLE. However, it has direct neurological implications and, as in our study, isolated cases have been reported in JSLE associated with the presence of anti-phospholipid antibody^{41,42}.

Subjective neuropsychiatric complaints are relatively common among patients without the diagnosis of a neuropsychiatric lupus syndrome and correlate with cognitive impairment⁴³. Symptoms of depression and anxiety may, in some instances, show a relationship with disease activity⁴⁴. Considering previous observations, where even asymptomatic patients may show abnormalities in neuroimage, neuropsychological and neurophysiological tests¹³⁻¹⁹, we suggest that all patients presenting with minor neuropsychiatric symptoms be investigated with according subsidiary exams in order to clarify the presence or lack of neuropsychiatric involvement.

Among our patients with nervous system involvement, 46.1% had normal MRI and 60.0% normal CT. Comparative pediatric series report rates of 35-78%^{30,45} and 19-80%^{27,45} respectively. Jennings et al.⁴⁶, analyzing MRI in SLE patients with neurological compromise, found that 34% had normal exams, 25% had ischemic lesions and 60% had hyperintense white matter signals on T2-weighted images. The author comments that it is, at times, difficult to distinguish between ischemic and inflammatory lesions on MRI grounds. Cerebral and corpus callosum atrophy in adult SLE patients has been assessed by Appenzeller et al.⁴⁷. In their study of 115 SLE patients and 44 healthy controls, the authors established that cerebral and corpus callosum volumes were significantly smaller in SLE patients and that this finding was unrelated to total corticosteroid dose but positively correlated with disease duration, presence of neurological involvement and cognitive deficit.

Prevalence of abnormal EEG findings in JSLE with neuropsychiatric manifestations has been reported in 45-71% of the patients^{14,27,30}, which is in agreement with our 53.8% rate. EEG analysis in adult SLE patients has suggested that, in those with neurological involvement, the left hemisphere, namely the left temporal region, is selectively involved^{48,49}.

Higher SLEDAI scores at disease-onset and higher SLICC scores 6 months after disease-onset and at the latest medical consultation, observed among the subset of patients with neuropsychiatric syndromes, suggest a correlation between central nervous system involvement in SLE and acute gravity at disease presentation as well as short and long-term morbidity, respectively. Overall prognosis of JSLE patients with neuropsychiatric involvement is reported by some authors to be good^{31,35}, while others report neuropsychiatric sequelae in 40-56%^{14,27}. Ravelli et al.⁵⁰, in a 387 patient multicenter cohort study designed to assess cumulative organ damage in JSLE, found the occurrence of a neuropsychiatric syndrome at disease-onset, among other variables, to be associated with disease damage. The report of the initial series of 128 adult patients from the San Antonio Lupus Study of Neuropsychiatric Disease, indicated that neuropsychiatric syndromes largely contributed to SLEDAI and SLICC scores, denoting that nervous system involvement is a major contributor to acute and chronic morbidity⁵¹. A Japanese study comprising 100 adult SLE patients without clinical expression of neurological involvement showed that 23% of the patients had asymptomatic brain lesions on MRI and, in this subgroup, higher SLEDAI scores were

observed, signaling that nervous system involvement, even when asymptomatic, correlates with disease activity¹⁹.

Mortality rates of JSLE vary from 4 to 10%^{14,27,30,31}, which is lower than the 12.8% found at our series. The high prevalence of renal involvement in our sample (70.2%) and in the group of lethal evolution (100%) implicates in disease severity. This may be due to a bias generated by the presence of a large Nephrology Unit at our hospital. As observed in our series, the most frequent cause of death reported is infection³⁰.

We conclude that neuropsychiatric syndromes are a common manifestation of JSLE, both at disease-onset and during its course. Present data point toward a greater morbidity in this subgroup of JSLE patients, prompting physicians to regard neuropsychiatric syndromes, alongside renal involvement, as a marker of JSLE severity.

REFERENCES

- Cervera R, Khamashta MA, Font J, et al. Systemic lupus erythematosus: clinical and immunologic patterns of disease expression in a cohort of 1,000 patients. The European Working Party on Systemic Lupus Erythematosus. *Medicine* 1993;72:113-124.
- Font J, Cervera R, Espinosa G, et al. Systemic lupus erythematosus (SLE) in childhood: analysis of clinical and immunological findings in 34 patients and comparison with SLE characteristics in adults. *Ann Rheum Dis* 1998;57:456-459.
- Costallat LT, Coimbra AM. Systemic lupus erythematosus: clinical and laboratory aspects related to age at disease onset. *Clin Exp Rheumatol* 1994;12:603-607.
- Carreno L, Lopez-Longo FJ, Monteagudo I, et al. Immunological and clinical differences between juvenile and adult onset of systemic lupus erythematosus. *Lupus* 1999;8:287-292.
- Tucker LB, Menon S, Schaller JG, Isenberg DA. Adult and childhood-onset systemic lupus erythematosus: a comparison of onset, clinical features, serology, and outcome. *Br J Rheumatol* 1995;34:866-872.
- Dubois EL, Tuffanelli DL. Clinical manifestations of systemic lupus erythematosus: computer analysis of 520 cases. *JAMA* 1964;190:104-111.
- Meislin AG, Rothfield N. Systemic lupus erythematosus in childhood: analysis of 42 cases, with comparative data on 200 adult cases followed concurrently. *Pediatrics* 1968;42:37-49.
- McCombs RP, Patterson JF. Factors influencing the course and prognosis of systemic lupus erythematosus. *N Engl J Med* 1959;260:1195-1204.
- King KK, Kornreich HK, Bernstein BH, Singsen BH, Hanson V. The clinical spectrum of systemic lupus erythematosus in childhood. *Arthritis Rheum* 1977;20(Suppl):S287-S294.
- Cassidy JT, Sullivan DB, Petty RE, Ragsdale C. Lupus nephritis and encephalopathy: prognosis in 58 children. *Arthritis Rheum* 1977;20(Suppl):S315-S322.
- ACR Ad Hoc Committee on Neuropsychiatric Lupus Nomenclature. The American College of Rheumatology nomenclature and case definitions for neuropsychiatric lupus syndromes. *Arthritis Rheum* 1999;42:599-608.
- Hanly JG. ACR classification criteria for systemic lupus erythematosus: limitations and revisions to neuropsychiatric variables. *Lupus* 2004;13:861-864.
- Khedr EM, Khedr T, Farweez HM, Abdella G, El Beih EA. Multimodal electroneurophysiological studies of systemic lupus erythematosus. *Neuropsychobiology* 2001;43:204-212.
- Loh WF, Hussain IM, Soffiah A, Lim YN. Neurological manifestations of children with systemic lupus erythematosus. *Med J Malaysia* 2000;55:459-463.
- Weiner SM, Otte A, Uhl M, Brink I, Schumacher M, Peter HH. Neuropsychiatric involvement in systemic lupus erythematosus: Part 2. Diagnostic and therapy. *Med Klin* 2003;98:79-90.
- Gladman DD, Urowitz MB, Slonim D, et al. Evaluation of predictive factors for neurocognitive dysfunction in patients with inactive systemic lupus erythematosus. *J Rheumatol* 2000;27:2367-2371.
- Mortilla M, Ermini M, Nistri M, Dal Pozzo G, Falcini F. Brain study using magnetic resonance imaging and proton MR spectroscopy in pediatric onset systemic lupus erythematosus. *Clin Exp Rheumatol* 2003;21:129-135.
- Leritz E, Brandt J, Minor M, Reis-Jensen F, Petri M. "Subcortical" cognitive impairment in patients with systemic lupus erythematosus. *J Int Neuropsychol Soc* 2000;6:821-825.
- Nomura K, Yamano S, Ikeda Y, et al. Asymptomatic cerebrovascular lesions detected by magnetic resonance imaging in patients with systemic lupus erythematosus lacking a history of neuropsychiatric events. *Intern Med* 1999;38:785-795.
- Tan EM, Cohen AS, Fries JF, et al. The 1982 revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum* 1982;25:1271-1277.
- Commission on Classification and Terminology of the International League Against Epilepsy. Proposal for revised clinical and electroencephalographic classification of epileptic seizures. *Epilepsy* 1981;22:498-501.
- Gladman DD, Ibanez D, Urowitz MB. Systemic lupus erythematosus disease activity index 2000. *J Rheumatol* 2002;29:288-291.
- Gladman D, Ginzler E, Goldsmith C, et al. The development and initial validation of the Systemic Lupus International Collaborating Clinics/American College of Rheumatology damage index for systemic lupus erythematosus. *Arthritis Rheum* 1996;39:363-369.
- Bandeira M, Buratti S, Bartoli M, et al. Relationship between damage accrual, disease flares and cumulative drug therapies in juvenile-onset systemic lupus erythematosus. *Lupus* 2006;15:515-520.
- Iqbal S, Sher MR, Good RA, Cawkwell GD. Diversity in presenting manifestations of systemic lupus erythematosus in children. *J Pediatr* 1999;135:500-505.
- Bader-Meunier B, Armengaud JB, Haddad E, et al. Initial presentation of childhood-onset systemic lupus erythematosus: a French multicenter study. *J Pediatr* 2005;146:648-653.
- Haji Muhammad Ismail Hussain I, Loh WF, Soffiah A. Childhood cerebral lupus in an Oriental population. *Brain Dev* 1999;21:229-235.
- Tejani A, Nicastrì AD, Chen CK, Fikrig S, Gurumurthy K. Lupus nephritis in black and Hispanic children. *Am J Dis Child* 1983;137:481-483.
- Rosenberg AM. Systemic lupus erythematosus in children. *Springer Semin Immunopathol* 1994;16:261-279.
- Olfat MO, Al-Mayouf SM, Muzaffer MA. Pattern of neuropsychiatric manifestations and outcome in juvenile systemic lupus erythematosus. *Clin Rheumatol* 2004;23:395-399.
- Quintero-Del-Rio AI, Van Miller. Neurologic symptoms in children with systemic lupus erythematosus. *J Child Neurol* 2000;15:803-807.
- Schmutzler KMRS, Vilanova LCP, Lima JGC, Hilário MO, Naspitiz CK. Juvenile systemic lupus erythematosus: neurological involvement. *Arq Neuropsiquiatr* 1997;55:606-609.
- el-Garf A, Salah S. Juvenile systemic lupus erythematosus among Egyptian children. *J Rheumatol* 1990;17:1168-1170.
- Costallat LT, Coimbra AM. Systemic lupus erythematosus: clinical and laboratory aspects related to age at disease onset. *Clin Exp Rheumatol* 1994;12:603-607.
- Steinlin MI, Blaser SI, Gilday DL, et al. Neurologic manifestations of pediatric systemic lupus erythematosus. *Pediatr Neurol* 1995;13:191-197.
- Appenzeller S, Cendes F, Costallat LT. Epileptic seizures in systemic lupus erythematosus. *Neurology* 2004;63:1808-1812.
- Tsuji M, Tanaka H, Yamakawa M, Sagawa R, Azuma H. A case of systemic lupus erythematosus with complex partial status epilepticus. *Epileptic Disord* 2005;7:249-251.
- Fernandez-Torre JL, Sanchez JM, Gonzalez C, Fernandez-Guinea O. Complex partial status epilepticus of extratemporal origin in a patient with systemic lupus erythematosus. *Seizure* 2003;12:245-248.
- Mecarelli O, Feo MR, Accornero N, Paffetti A. Systemic lupus erythematosus and myoclonic epileptic manifestations. *Ital J Neurol Sci* 1999;20:129-132.
- Blaustein DA, Blaustein SA. Antinuclear antibody negative systemic lupus erythematosus presenting as bilateral facial paralysis. *J Rheumatol* 1998;25:798-800.
- Roldan-Molina R, Roman J, Escudero A, et al. Unusual and aggressive thrombotic onset in two children with antiphospholipid-antibody syndrome and systemic lupus erythematosus. *Joint Bone Spine* 2004;71:327-330.

42. Yuen SY, Lau KF, Steinberg AW, Grattan-Smith PJ, Hodson EM. Intracranial venous thrombosis and pulmonary embolism with antiphospholipid syndrome in systemic lupus erythematosus. *J Paediatr Child Health* 2001;37:405-408.
43. Denburg SD, Stewart KE, Hart LE, Denburg JA. How "soft" are soft neurological signs? The relationship of subjective neuropsychiatric complaints to cognitive function in systemic lupus erythematosus. *J Rheumatol* 2003;30:1006-1010.
44. Navarrete MG, Brey RL. Neuropsychiatric systemic lupus erythematosus. *Curr Treat Options Neurol* 2000;2:473-485.
45. Turkel SB, Miller JH, Reiff A. Case series: neuropsychiatric symptoms with pediatric systemic lupus erythematosus. *J Am Acad Child Adolesc Psychiatry* 2001;40:482-485.
46. Jennings JE, Sundgren PC, Attwood J, McCune J, Maly P. Value of MRI of the brain in patients with systemic lupus erythematosus and neurologic disturbance. *Neuroradiology* 2004;46:15-21.
47. Appenzeller S, Rondina JM, Li LM, Costallat LT, Cendes F. Cerebral and corpus callosum atrophy in systemic lupus erythematosus. *Arthritis Rheum* 2005;52:2783-2789.
48. Glanz BI, Laoprasert P, Schur PH, Robertson-Thompson A, Khoshbin S. Lateralized EEG findings in patients with neuropsychiatric manifestations of systemic lupus erythematosus. *Clin Electroencephalogr* 2001;32:14-19.
49. Glanz BI, Schur PH, Khoshbin S. EEG abnormalities in systemic lupus erythematosus. *Clin Electroencephalogr* 1998;29:128-131.
50. Ravelli A, Duarte-Salazar C, Buratti S, et al. Assessment of damage in juvenile-onset systemic lupus erythematosus: a multicenter cohort study. *Arthritis Rheum* 2003;49:501-507.
51. Brey RL, Holliday SL, Saklad AR, et al. Neuropsychiatric syndromes in lupus: prevalence using standardized definitions. *Neurology* 2002;58:1214-1220.