Original Article

Iran J Ped
June 2007, Vol 17 (No 2), Pp:135-139

Lupus Headaches in 55 Childhood-Onset SLE

Mohammad Hassan Moradinejad*[1], MD

1. Pediatric Rheumatologist, Tehran University of Medical Sciences, Tehran, IR Iran

Received: 23/07/06; Revised: 16/10/06; Accepted: 28/12/06

Abstract

Objective: Although headache is a common complaint among patients with lupus, no universally accepted explanation was available until the International Headaches Society adopted Lupus headache as a Nomenclature in its classification recently. Few studies indicate that lupus patients with positive anti-nuclear antibody (ANA) and positive antiphospholipid antibodies (aPL) experience more frequent headaches. The aim of this study was to determine the correlation between headache frequencies and ANA, anti-double strand DNA (anti-ds-DNA) and aPL positivity.

Material & Methods: In this prospective multicenter study were enrolled 55 children, 45 girls and 10 boys (F/M ratio:4.5), aged 3-16 years (mean 11.5 years), with neuropsychiatric lupus complaining of headache, that where followed-up for 5 years.. Whether lupus headache is a sign of progressive nature of the disease and how it should be treated is not clear yet. Those with active disease, hypertension, or tension headache were not included in this study.

Findings: We studied 55 children with definite lupus. Twenty three (43%) of our patients developed new or significantly worse, persistent headaches that sometimes were similar to migraine in the early course of their disease. However their headaches were not accompanied with disease flare up and the headaches were not found to be related to hypertension or use of other medications either. Accordingly, we came to a diagnosis of lupus headache for these patients. Among them 19/55 cases (35%) had a positive aPL and 53/55 cases (96%) had a positive ANA.

Conclusion: Lupus headaches are most likely multifactorial, and probably only a small proportion of them truly represent active lupus. The above data highlights probable correlation between aPL, ANA, an anti-ds-DNA and lupus headache. However, more research is required to find better treatments and to establish a definitive correlation among them.

Key Words: Lupus, Headache, Antiphospholipid antibody, Antinuclear Antibodies

*** Correspondence author.**
Address: Department of Rheumatology, Children's Medical Center, Dr Gharib Ave, Tehran, IR Iran
E-mail: moradine@tums.ac.ir

Introduction

Juvenile systemic lupus erythematosus (JSLE) is an episodic, multisystemic, autoimmune disease with high morbidity and mortality due to multiple organ involvement[1]. The minimum incidence of JSLE is 0.28 cases per 100,000 children per year, and prevalence of JSLE ranges between 12 and 40 cases per 100,000[2]. Severe headaches are reported in approximately 20% of cases of SLE. This form of headache is more common in males than in females (>2.5:1) and is most prevalent between the ages of 20 and 40 years [3,4]. These headaches have been termed "lupus headache" on the account of their relation to the disease[5], but their nature remains as unclear as their significance as an indicator of disease activity.

This research, examines headache manifestations of systemic lupus erythematosus (SLE) described in 55 patients with Juvenile SLE, and compares clinical records taken here with research undertaken elsewhere.

Although patients with lupus suffer headaches frequently, until recently there has been no universally accepted definition of this phenomenon, and there was a tendency to attribute headache symptoms to other causes unrelated to the SLE, such as conventional migraine or tension headache[6]. This changed when in 1999, the classification of headaches suggested by the International Headaches Society, for describing lupus headaches and was adopted by the American College of Rheumatology's (ACR) ad hoc Committee on Neuropsychiatric Lupus Nomenclature[7,8].

It is still unclear however, whether lupus headaches are a sign of active SLE, and best practices for treatment remain undetermined. This is partly due to the fact that the degree of lupus activity cannot be measured by a single laboratory test or by a limited set of findings in a physical examination[8]. Equally, when using the SLE disease activity index (SLEDAI) in children with lupus, the exact measurement of the headache appears not to be important for the determination of the disease activity[8, 9,10]. However, despite these challenges in capturing lupus headaches and correlating them to disease activity, the SLEDAI remains a good index to measure the JSLE activity in children[10]. The challenge here is to understand better the phenomenon of lupus headache itself.

In fact, the incidence of headache in patients with JSLE has not been found to be clearly higher than in the general population. However, a unique trait of these headaches has been observed in some studies, which noted that lupus patients who tested positive for anti-phospholipid antibodies (aPL) were at a higher risk of experiencing lupus headaches. This study finds a correlation between positive testing for aPL and lupus headaches as well[10,11,12]. We also observe that patients with JSLE showed significantly higher levels of aPL (particularly anticardiolipin antibodies).

Material & Methods

This prospective multi center study enrolled 55 children with lupus that were followed up for 5 years in Iran. All the cases of JSLE that were admitted in the pediatric rheumatology department of the Children's Medical Center Hospital, between 1998 and 2003 were included in this study. The diagnosis of juvenile lupus erythematosus was made on the basis of clinical findings and confirmed by histopathologic examination and/or by immunofluorescence studies. Furthermore, the diagnosis of JSLE was made only when at least 4 of the criteria established by the American Rheumatism Association (ARA) were present. Those with active disease, hypertension, and/or tension headache were not included in this study. These limiting criteria helped us diagnose lupus headache in 23 of our 55 patients, by the terms of the American College of Rheumatology's (ACR) ad hoc Committee on Neuropsychiatric Lupus Nomenclature[7, 8].

In 23 out of 55 children with lupus diagnosis, lupus headaches occurred early in the course of their disease. Following data was recorded: sex, age of onset, age at the time of diagnosis, family history of headaches and

SLE, clinical characteristics, location and number of lesions. The patients were followed up 1 to 5 months after the onset of juvenile lupus erythematosus.

Findings

We reviewed 55 children with definite lupus. Age of onset and mean age was 3-16 and 11.5 years, respectively. Sex distribution: 45 girls, and 10 boys for a female to male ratio of 4.5:1. Twenty three (43%) of our patients developed new or significantly worse, persistent headaches that sometimes were similar to migraines in the early course of their disease. However, their headaches were not accompanied with disease flare-up and were not found to be related to hypertension or to the use of other medications. Twenty-one patients (38%) had CNS manifestations. Of these, seven had them before the initiation of high-dose steroid therapy, while in the other 14 patients these CNS manifestations appeared after high-dose steroid treatment.

In this group, 19 of 55 cases (35%) tested positive for aPL and 53 of 55 cases (96%) tested positive for ANA. Patients with JSLE showed significantly higher levels of aPL (particularly anticardiolipin antibodies). Neurological abnormalities were detected in 20% of the 55 JSLE patients by MRI (including cerebral atrophy, infarcts).

In the first instance, when the lupus headache was not accompanied by more serious complications, we administered symptomatic therapy: anticonvulsants in 45/55, anti-depressants in 35/55, and immuno-suppressive drugs: Corticosteroids in 55/55, Azatioprine in 45/55, Cyclophosphamide in 55/55 cases, as well as anti-coagulation: aspirin, in 35/55, Heparin or Warfarin in 12/55 cases.

Discussion

Lupus headache must be differentiated from other neurological manifestations of SLE in the host[3, 4, 13]. A review of the 55 CNS syndromes clinically associated with JSLE helped us in isolating lupus headache from other manifestations. Accordingly, in our group of 55 patients, we diagnosed a sure case of lupus headache in only 23 of the children. Among the other patients we found “Confusion” in 20, “Difficulty in concentration” in 10, and “Seizures or strokes” in 25. This distribution is consistent with previous reports, which attribute headache pain in SLE patients to a variety of neuropathological causes[4, 13, 14].

Other studies, have found behavioral disturbances occurring within the first year of the disease to be among the most common symptoms of cerebral pathology. In this study we noted “Confusion” in 20/55 patients, and “Difficulty in concentration” in 10/55.

Stroke accounts for approximately 20% of neurologic events in SLE and is often secondary to the incidence of anti-phospholipid antibodies or cardiogenic embolism[8,9,10,15]. In our study for example, 25 of 55 patients suffered seizures or strokes, 19/55 cases (35%) were aPL positive, and 53/55 cases (96%) F-ANA positive.

Further complicating matter is the fact that, as noted by Brunner et al, “people with lupus, experience headaches which are unrelated to their lupus, i.e., sinus headache, tension headache and migraine”[7, 8]. Still, many different presentations of CNS lupus can occur with abnormal neuroimaging including atrophy, infarct, and discrete gray matter lesions. Brain CT scans, although they are more widely available than MRI scans, are also nonspecific and have proven to be less reliable than MRI as an investigative tool for CNS. In our series CT scans detected abnormalities in 25/55 cases. MRI may also show extensive bilateral white matter abnormalities suggestive of edema in the cerebral hemispheres.

Moreover, not only are PET and SPEC more expensive procedures, they are unavailable at this time in Iran. In our group of 55 JSLE patients, abnormal MRI findings occurred in 43% of the patients. Among them, 16% had cerebral atrophy, and 58% showed fixed foci of T1 and T2, 26% had both

patterns. These test results can help to distinguish between lupus headache and more advanced CNS damage caused by SLE [16]. In our cases, conventional EEG revealed abnormality in 33 of 55 patients; radionuclide brain scans showed abnormalities in 22/55. CSF findings can be useful in this regard as well, but often they are non-specific.

Abialmouna et al for example, record "a modest protein elevation and pleocytosis in the cerebrospinal fluid of 25-60% of patients with CNS lupus." In our study we conducted CSF examination in all of our 55 patients. This procedure excluded infection as a cause of neuro-pathological symptoms, as smear and culture were both negative in all cases. WBC and RBC counts were all normal, though we did note high protein (>3gr) and low sugar (<50mg), Anti-ds-DNA positive (+>4.5) in CSF in 18/23, and low complement in CSF in 12/23.

It should further be noted that auto antibodies, while useful in the diagnosis of lupus itself, have not consistently been demonstrated to correlate with CNS involvement of the disease. Antineuronal antibodies, however, have been reported to correlate with CNS disease. The presence of anticardiolipin antibodies and the lupus anticoagulant have also been suggested as risk factors for CNS involvement in SLE[10,11,12]. Lupus headaches in particular, are more common in patients with anti-phospholipid antibody syndrome (aPL)[17,18]. In our group of 55 patients, 45 of them showed elevated levels of Anti-ds-DNA in blood tests, and 25 showed high positive levels of Anti-ds-DNA in CSF examination. Antineural antibodies were also found to be elevated in the blood in 10 of 55 patients. Low Complement was also noted in 43/55 patients' blood and in CSF of 12/23 of the patients. Further examination of blood showed elevated F-ANA (>1:160) in 52 of 55 patients, and higher aPL and IgG in 23/55 cases.

Treatment for CNS lupus involves high-dose steroids and cytotoxic agents such as cyclophosphamide, as is usually the case in patients with renal glomerular disease or other significant organ system involvement[19].

Our procedure for treating lupus headache reflected two concerns: first, whether the lupus headache was the primary concern, or whether it was the presenting symptom of a secondary and more dangerous complication; and second, that in some cases the lupus headache was a multifactorial phenomenon requiring simultaneous treatment of several pathologies.

Conclusion

Although this study has observed some degree of correlation between lupus headaches and positive testing for aPL, and despite noting a much higher degree of correlation between these headaches and the presence of antinuclear antibodies (ANA), at this stage it is impossible to conclude that lupus headaches are not multifactorial. Furthermore, due to the general lack of correlation between lupus headaches and disease flare-up, in most cases they are unlikely to indicate active lupus. However, the high incidence of lupus headaches among JSLE patients asserts the need for more research to discover effective treatments and to develop tests to identify sufferers of lupus headaches so as to intervene before more permanent damage from JSLE results. Whether lupus headache is indicative of the progression of the disease is not clear yet, nor is it clear how it should be treated.

References

1. Tan EM, Cohen AS, Fries JF, et al. The 1982 revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum. 1982;25(11):1271-7.
2. Hochberg MC. Updating the American College of Rheumatology Revised Criteria for the Classification of Systemic Lupus erythematosus. Arthritis Rheum. 1997; 40(9):1725.
3. Quintero-Del-Rio AI, Van Miller. Neurologic symptoms in children with

systemic lupus erythematosus. J Child Neurol. 2000;15(12):803-7.
4. Yancey CL, Doughty RA, Athreya BH. Central nervous system involvement in childhood systemic lupus erythematosus. Arthritis Rheum. 1981;24(11):1389-95.
5. Sibley JT, Olszynski WP, Decoteau WE, et al. The incidence and prognosis of central nervous system disease in systemic lupus erythematosus. J Rheumatol. 1992;19(1): 47-52.
6. Barron KS, Silverman ED, Gonzales J, et al. Clinical, serologic, and immunogenetic studies in childhood-onset systemic lupus erythematosus. Arthritis Rheum. 1993; 36(3): 348-54.
7. Headache Classification Committee of the International Headache Society: Classification and diagnostic criteria for headache disorders, cranial neuralgias and facial pain. Cephalalgia. 1988;8(Suppl 7): 1-96.
8. Brunner HI, Feldman BM, Bombardier C, et al. Sensitivity of the Systemic Lupus Erythematosus Disease Activity Index, British Isles Lupus Assessment Group Index, and Systemic Lupus Activity Measure in the evaluation of clinical change in childhood-onset systemic lupus erythematosus. Arthritis Rheum. 1999; 42(7): 1354-60.
9. Bombardier C, Gladman DD, Urowitz MB, et al. Derivation of the SLEDAI. A disease activity index for lupus patients. The Committee on Prognosis Studies in SLE. Arthritis Rheum. 1992;35(6):630-40.
10. McNeil HP, Chesterman CN, Krilis SA. Immunology and clinical importance of antiphospholipid antibodies. Adv Immunol. 1991;49:193-280.
11. Lee T, Von Scheven E, Sandborg C. Systemic lupus erythematosus and antiphospholipid syndrome in children and adolescents. Curr Opin Rheumatol. 2001; 13(5):415-21.
12. Barron KS, Silverman ED, Gonzales J, et al. Clinical, serologic, and immunogenetic studies in childhood-onset systemic lupus erythematosus. Arthritis Rheum. 1993; 36(3):348-54
13. Gladman DD, Urowitz MB, Goldsmith CH, et al. The reliability of the Systemic Lupus International Collaborating Clinics/ American College of Rheumatology Damage Index in patients with systemic lupus erythematosus. Arthritis Rheum. 1997;40(5):809-13.
14. Sfikakis PP, Mitsikostas DD, Manoussakis MN, et al. Headache in systemic lupus erythematosus: a controlled study. Br J Rheumatol. 1998;37(3):300-3.
15. McHugh NJ, Moye DAH, James IE, et al. Lupus anticoagulant: clinical significance in anticardiolipin positive patients with systemic lupus erythematosus. Ann Rheum Dis 1991;50(8):548-52.
16. Stimmler MM, Coletti PM, Quismorio FP. Magnetic resonance imaging of the brain in neuropsychiatric systemic lupus erythematosus. Semin Arthritis Rheum. 1993; 22(5):335-349.
17. Hanson VG, Horowitz M, Rosenbluth D, et al. Systemic lupus erythematosus patients with central nervous system involvement show antibodies to a 50-kD neuronal membrane protein. J Exp Med. 1992; 176(2): 565-73.
18. Kaell AT, Shetty M, Lee BC, et al. The diversity of neurologic events in systemic lupus erythematosus: prospective clinical and computed tomographic classification of 82 events in 71 patients. Arch Neurol. 1986;43(3):273-276.
19. Wysenbeek AJ, Leibovici L, Zoldan J. Acute central nervous system complications after pulse steroid therapy in patients with systemic lupus erythematosus. J Rheumatol 1990;17(12):1695-6.