CONCISE REPORT

A neuroimaging follow up study of a patient with juvenile central nervous system systemic lupus erythematosus

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Background: The course of central nervous system systemic lupus erythematosus (CNS-SLE) is largely unknown. New imaging techniques are available to assist in monitoring the disease course.
Objective: To report a case of juvenile CNS-SLE, in which magnetic resonance imaging (MRI) was used to assess disease activity.
Case report: A 10 year old female patient with SLE presented with convulsions; MRI and computed tomography (CT) of the cerebrum disclosed abnormalities. Despite adequate treatment, two years later she had a generalised convulsion, and MRI showed new lesions. MR spectroscopy (MRS) indicated neuronal loss, inflammation, and metabolically compromised tissue; magnetisation transfer imaging (MTI) showed an increase in whole brain lesion load. After exclusion of a malignancy, CNS-SLE was the most likely diagnosis, and cyclophosphamide pulses were administered. Initially, multiple sclerosis (MS)-like lesions regressed, but despite maximal immunosuppressive drugs, new lesions formed and disappeared. When immunosuppressive drugs had been stopped for six months MRI showed improved lesions and MTI histograms.
Discussion: In this case report, the anatomical substrate, metabolic aspect, neuroimaging, and clinical course of MS-like lesions in a child with CNS-SLE are described. The way in which radiological techniques can support clinical decision making in this young patient with progressive CNS-SLE is illustrated.

The pathogenesis of central nervous system involvement in patients with systemic lupus erythematosus (CNS-SLE) is currently investigated by animal models and by neuroimaging techniques. In aggregate, these techniques suggest a role for hypoperfusion, breakdown of the blood-brain barrier, and entrance of antineuronal antibodies into the brain, with changes in brain composition and loss of myelin.[1 2] Pathological studies that could verify or falsify these concepts are limited to case reports, and often lack a clear description of the clinical phenotype.[1] In clinical practice, CNS-SLE has always been regarded as diagnosis by exclusion[3]; treatment of patients in the acute stage of the disease, therefore, consists of a pragmatic approach. The clinical course of the disease, as well as the long term accumulation or reversibility of structural brain damage, remains largely unknown. Obviously, this has great impact on treatment decisions. Currently, advanced neuroimaging techniques are being investigated as tools for monitoring the disease.[1 4] To demonstrate the value of these techniques and contribute to the unravelling of this intriguing disease, we report on a patient with juvenile CNS-SLE, with documentation of the clinical course, pathology, and neuroimaging results.

CASE REPORT

A 10 year old white girl with normal psychomotor development presented with two convulsions. The relevant medical history included SLE, diagnosed at the age of 7, with a polyarthritis, mouth ulcers, positive antinuclear antibodies, thrombocytopenia, and granulopenia (according to the 1982 revised criteria of the American College of Rheumatology (ACR)[5]). In the years previously, several febrile episodes with thrombocytopenia, granulopenia, and arthralgia had occurred; an autoimmune haemolytic anaemia was treated with corticosteroids for six months. For the SLE, medical treatment had consisted of naproxen (Naprosyne) and hydroxychloroquine, and monthly intravenous infusions of gammaglobulins.

At the time of admission, neurological examination showed an increased intracranial pressure, noted as papillary oedema. Computed tomography (CT) and magnetic resonance imaging (MRI) disclosed a hypodense lesion in the white matter of the right occipital lobe with some mass effect and extension into the grey matter, which had been absent on a CT scan one year before. Symptoms were thought to be due to vasculitis, probably as a cerebral expression of the SLE; treatment with high dose corticosteroids, hydroxychloroquine, and naproxen was started, and the lesion was no longer visible on MRI after two months of treatment.

Despite subsequent treatment with corticosteroids, hydroxychloroquine, azathioprine, and monthly intravenous immunoglobulins, at the age of 12 the girl presented again, with nausea, vomiting, double vision, and headache. A CT scan showed an isodense mass with a hypodense rim in the occipital region. When the medical condition deteriorated and the patient had a generalised convulsion with cyanosis and papillary oedema, an MRI of the brain showed two lesions near the genu and the splenium of the corpus callosum. Because these lesions had not been visible on the CT two years before and were compatible with malignant lymphoma, extensive diagnostic tests were performed to detect locations of a potential malignancy elsewhere in the body. None were found; all cultures were negative. Finally, a stereotactic biopsy from one of the cerebral lesions showed no sign of a specific (malignant) process but a reactive non-granulomatous inflammation (fig 1). Cerebral lesions progressed despite immunosuppressive therapy. Without any signs of exacerbations of SLE and no specific disturbances in cognitive functions as determined by neuropsychological examination, symptoms and signs were thought to be due to CNS-SLE with

Abbreviations: ACR, American College of Rheumatology; ASCT, autologous stem cell transplantation; CNS, central nervous system; CT, computed tomography; MRI, magnetic resonance imaging; MRS, magnetic resonance spectroscopy; MS, multiple sclerosis; MTI, magnetisation transfer imaging; SLE, systemic lupus erythematosus

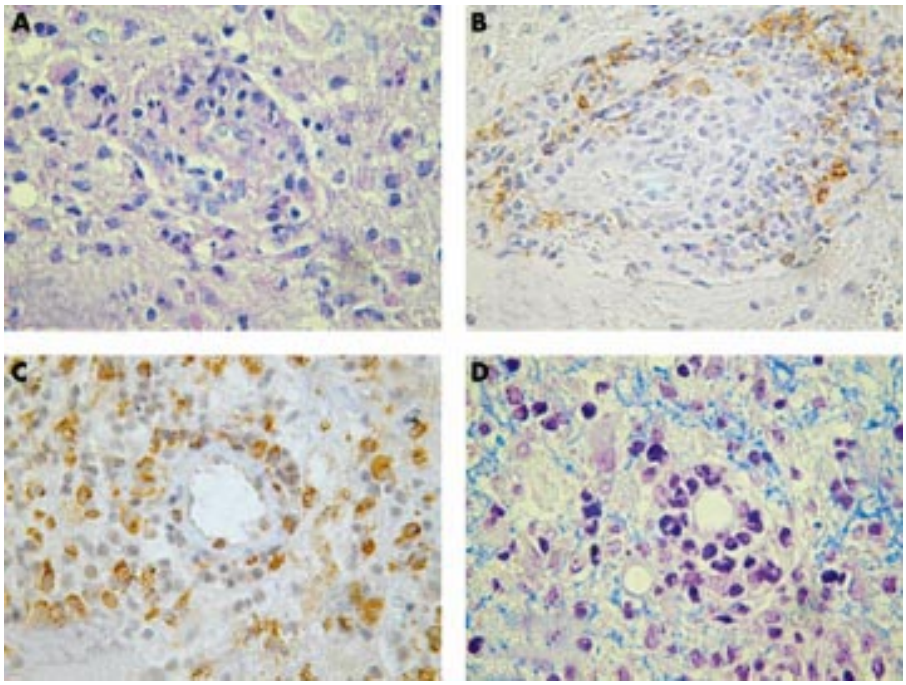

Figure 1 Histopathology of the brain tissue obtained by stereotactic surgery. (A) A mixed granulocytic and lymphocytic inflammatory reaction affecting the vessel walls is seen. The inflammatory response is non-specific. (Periodic acid-Schiff staining, ×400). (B) Among the population of mononuclear cells the B lymphocytes are immunopositive for the B cell-specific marker CD20 (×400). (C) Among the inflammatory cells many activated microglial cells are seen (immunohistochemistry for CD56; ×400). (D) The neuropilem shows oedema, but there are no signs of myelin-breakdown (Kluwer stain, ×400).

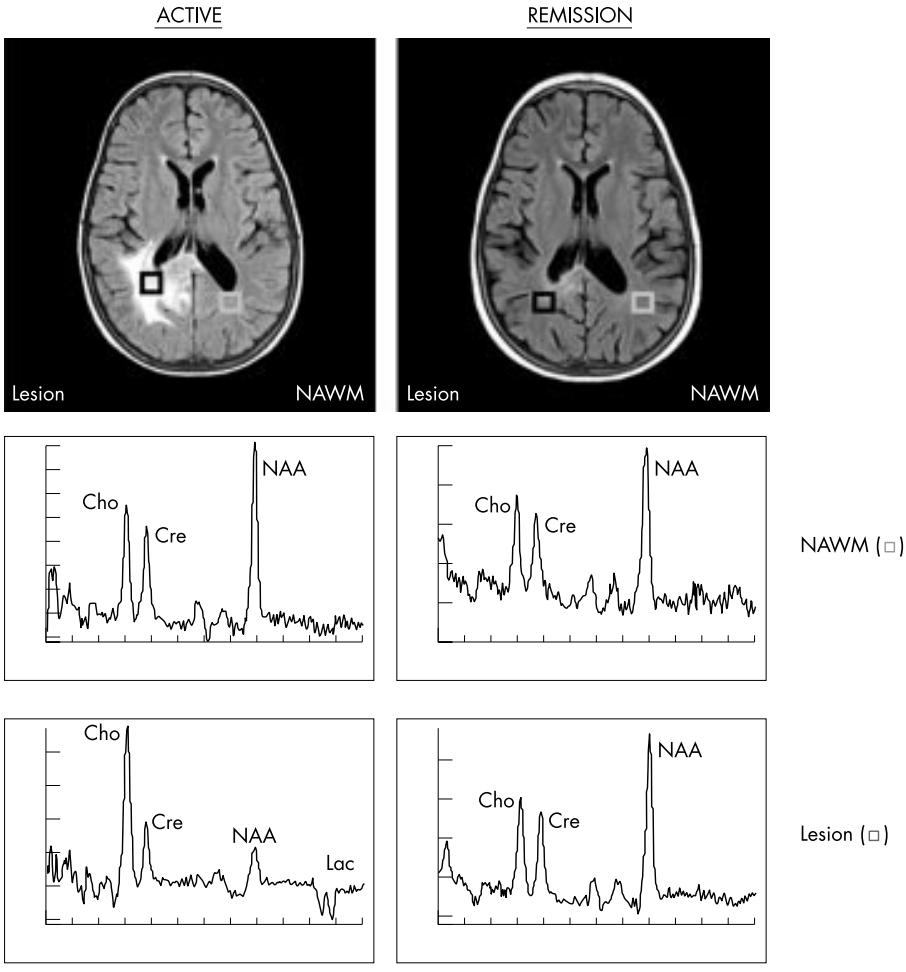

Figure 2 Fluid attenuated inversion recovery (FLAIR) images and MRS results of the occipitoparietal lesion and contralateral normal appearing white matter (NAWM), shortly after the generalised convulsion (active) and eight months later during clinical quiescent remission state (remission), when the patient was receiving pulses of cyclophosphamide. In the active state, the increased choline (Cho) and decreased *N*-acetyl-aspartate (NAA) peaks of the lesion indicate some degree of inflammation and neuronal damage. Also indicated are the creatine (Cre) peak and the double negative peak to the right side of the NAA peak, showing the presence of lactate (Lac), originating from metabolically compromised tissue. In remission, qualitative MR images show clear regression of the lesion, with normalisation of MRS metabolites (lactate no longer visible).

mass effect. Treatment with high dose corticosteroids and a single pulse of cyclophosphamide was started, and a follow up MRI two weeks later showed the same two lesions, but with less mass effect and oedema. Additionally, two advanced quantitative MR techniques were applied: magnetic resonance spectroscopy (MRS) and magnetisation transfer imaging (MTI). MRS permits monitoring of the biochemistry of the brain[6–8]; MTI is a quantitative MRI method used to measure

global lesion load in the whole brain in demyelinating disorders.[9–11] MRS was performed in regions of interest that were placed in the occipitoparietal lesion in the right hemisphere and in the contralateral normal appearing white matter (fig 2). At this time, MRS of the lesion pointed to neuronal cell loss, inflammation, and metabolically compromised tissue, in comparison with the contralateral healthy side (fig 2). Also, the results from MTI showed deviations to lower values, indicating some degree of demyelination. One month later, an MRI showed clear regression of the lesions and normalisation of spectroscopic metabolite ratios towards normal values.

Based on clinical presentation, course, and neuroimaging results, the most likely diagnosis at that time was a demyelinating multiple sclerosis (MS)-like syndrome in SLE, according to the ACR criteria of "multiple discrete areas of damage within the central nervous system occurring at different times and occasions".[12] Despite continuing treatment with low dose corticosteroids, azathioprine, and intravenous immunoglobulins, three months later the three lesions described earlier increased in volume again, and their size was similar to the period before the cyclophosphamide pulse. Therefore, a treatment regimen consisting of monthly pulses of cyclophosphamide (750 mg/m^2) and prednisone in a dose of 60 mg with monthly tapering of 10 mg was started. Although during these cyclophosphamide pulses MRI initially showed a decrease of the lesion volume and normalisation of MTI and MRS measures, after the completion of six pulses a follow up MRI showed a new large lesion in the right thalamic region, without evident clinical symptoms and with MTI and MRS values within the normal range. Cyclophosphamide (750 mg/m^2) course was lowered to three monthly intervals. After two months, the thalamic lesion had disappeared on MRI and no new lesions were detected.

In the meantime the patient had a laparoscopic splenectomy for an autoimmune thrombocytopenia. Although her clinical condition remained well, and detailed neurological and neuropsychological examinations did not show specific cognitive deviations or deterioration as a result of organic cerebral dysfunctioning, a follow up MRI three months later showed a new lesion in the left frontal cortex. Now, it was concluded that the disease was progressive under maximal adequate immunosuppressive therapy, and the following treatment was proposed. After harvesting of the bone marrow, a preparative regimen of 200 mg/kg cyclophosphamide would be given, followed by stem cell rescue. During the preparation interval before harvesting of the bone marrow, follow up MRI four months later showed no increase of the recent lesion and therefore treatment was postponed.

When treatment had been stopped for six months an MRI showed clear regression of the large frontal lesion, no new lesions, and improvement of whole brain MTI histograms. Given the absence of clinical symptoms, both for the SLE itself and for the neurological complications at that moment, the autologous stem cell transplantation (ASCT) was postponed, and the patient was followed up carefully, clinically as well as neuroradiologically. However, four months later, MRI showed that the lesion in the left frontal cortex had progressed, with subjective complaints of possible memory loss. Because the lesion was small and the symptoms minimal, no specific treatment was started. MRI was repeated six months later, again showing a small new lesion in the frontal cortex of this now 14 year old girl.

DISCUSSION

CNS lupus may present as discrete lesions on MRI, considered to be the result of damage to the white matter. The nature, clinical course, and response to high dose immunosuppressive therapy of these lesions in a child with SLE have to our knowledge never been described before. In this case of CNS-SLE, the anatomical substrate, metabolic aspects, neuroimaging, and clinical course of the MS-like lesions were monitored closely.

The cerebral lesions in this patient were responsive to immunosuppressive treatment, but reoccurred several times at different locations. Because the disease was progressive with maximal treatment, even higher immunosuppressive treatment with stem cell rescue was considered.[13] Involvement of the central nervous system in SLE is associated with early death, and good results have been reported with ASCT in patients with SLE.[14–16] However, with ASCT planned, the "flare" aspect of CNS lupus, with waxing and waning of the disease, became even more clear in this patient. Taking into account the fact that mortality due to transplantation in SLE is as high as 10–15%,[14] and the "relapsing-remitting" nature of the flares without lasting damage, would have led us to reconsider the proposed ASCT. On the other hand, if the disease progression would have led to irreversible damage while the patient received maximal treatment, ASCT would seem to be justified. In this clinical and therapeutic dilemma, we chose to use frequent conventional MRI and advanced quantitative neuroimaging techniques like MTI and MRS to monitor the disease.

The current case report is an illustration of the dynamic nature of lesions caused by CNS-SLE. Intriguingly, some of the lesions also disappeared without MRI evidence of scarring brain tissue. The waxing and waning nature of this disease illustrates the complexity of treatment decisions. Because treatment decisions are made for the purpose of relieving current symptoms or improving prognosis, the therapeutic decisions in patients with CNS-SLE are extremely difficult given the lack of knowledge on prognosis. Therefore, we propose that, besides careful internal and neurological examinations, sophisticated radiological techniques such as MRS and qualitative MRI can be helpful in making therapeutic decisions.

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REFERENCES

1 **Huizinga TW**, Steens SC, van Buchem MA. Imaging modalities in central nervous system systemic lupus erythematosus. Curr Opin Rheumatol 2001;13:383–8.
2 **DeGiorgio LA**, Konstantinov KN, Lee SC, Hardin JA, Volpe BT, Diamond B. A subset of lupus anti-DNA antibodies cross-reacts with the NR2 glutamate receptor in systemic lupus erythematosus. Nat Med 2001;7:1189–93.
3 **Rood MJ**, Breedveld FC, Huizinga TW. The accuracy of diagnosing neuropsychiatric systemic lupus erythematosus in a series of 49 hospitalized patients. Clin Exp Rheumatol 1999;17:55–61.
4 **Sibbitt WL**, Sibbitt RR, Brooks WM. Neuroimaging in neuropsychiatric systemic lupus erythematosus. Arthritis Rheum 1999;42:2026–38.
5 **Tan EM**, Cohen AS, Fries JF, Masi AT, McShane DJ, Rothfield NF, *et al.* The 1982 revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum 1982;25:1271–7.
6 **Sibbitt WL**, Haseler LJ, Griffey RR, Friedman SD, Brooks WM. Neurometabolism of active neuropsychiatric lupus determined with proton MR spectroscopy. AJNR Am J Neuroradiol 1997;18:1271–7.

7 **Axford JS**, Howe FA, Heron C, Griffiths JR. Sensitivity of quantitative (1)H magnetic resonance spectroscopy of the brain in detecting early neuronal damage in systemic lupus erythematosus. Ann Rheum Dis 2001;60:106–11.
8 **Chinn RJ**, Wilkinson ID, Hall-Craggs MA, Paley MN, Shortall E, Carter S, *et al*. Magnetic resonance imaging of the brain and cerebral proton spectroscopy in patients with systemic lupus erythematosus. Arthritis Rheum 1997;40:36–46.
9 **van Buchem MA**, Tofts PS. Magnetization transfer imaging. Neuroimaging Clin N Am 2000;10:771–88.
10 **Bosma GP**, Rood MJ, Zwinderman AH, Huizinga TW, van Buchem MA. Evidence of central nervous system damage in patients with neuropsychiatric systemic lupus erythematosus, demonstrated by magnetization transfer imaging. Arthritis Rheum 2000;43:48–54.
11 **Bosma GP**, Rood MJ, Huizinga TW, de Jong BA, Bollen EL, van Buchem MA. Detection of cerebral involvement in patients with active neuropsychiatric systemic lupus erythematosus by the use of volumetric magnetization transfer imaging. Arthritis Rheum 2000;43:2428–36.
12 **ACR**. The American College of Rheumatology nomenclature and case definitions for neuropsychiatric lupus syndromes. Arthritis Rheum 1999;42:599–608.
13 **Bloom BJ**. New drug therapies for the pediatric rheumatic diseases. Curr Opin Rheumatol 2001;13:410–14.
14 **Furst DE**. Stem cell transplantation for autoimmune disease: progress and problems. Curr Opin Rheumatol 2002;14:220–4.
15 **Tyndall A**, Passweg J, Gratwohl A. Haemopoietic stem cell transplantation in the treatment of severe autoimmune diseases 2000. Ann Rheum Dis 2001;60:702–7.
16 **Wulffraat NM**, Sanders EA, Kamphuis SS, Rijkers GT, Kuis W, Lilien M, *et al*. Prolonged remission without treatment after autologous stem cell transplantation for refractory childhood systemic lupus erythematosus. Arthritis Rheum 2001;44:728–31.