Case report

Disseminated lupus erythematosus - neurological manifestations in childhood:a case series of two patients

Abstract :

Neurolupus ischaracterized by a diverse spectrum of neurological manifestations, rangingfrommildsymptomssuch as headaches and mooddisturbances to severe complications like stroke and myelitis.

Neurologicalinvolvement in childhood lupus israrely the initial presentation. It can be central or peripheral, presentfrom the onset of the disease or appearsecondarilyduringits course. It isdirectlylinked to immunologicalinvolvement, or represents a complication of an intercurrent infection, hypertension, renalinvolvement, hemostaticabnormalities, or varioustreatments, particularlycorticosteroidtherapy, significantlycomplicatingdiagnosis.

Wepresenttwopediatric cases thatexemplify the diagnostic challenges and clinical implications associatedwith neurolupus.

Introduction:

Systemic lupus erythematosus (SLE) is an autoimmunedisordercharacterized by the production of antinuclearantibodies, particularly anti-native DNA antibodies. Itsetiologyremainsunknown, and itpresentswith a broadspectrum of clinical manifestations.

Neurolupus (NL) encompasses a diverse range of neuropsychiatric manifestations associatedwith SLE. These conditions exhibitheterogeneitybothclinically and therapeutically.

The objective of ourstudyis to delineate the criteria for attributingneurological and neuropsychiatric manifestations to SLE and to investigate effective management approaches.

Case presentations

Observation 1:

This is a 15-year-old girl with no familyhistory of autoimmunediseases, born to first-degreeconsanguineous parents who are in good health. The illnessbegan 1 monthbeforheradmiitiondto the hospitalwith memory problems, headaches, polyarthralgia, alopecia, and malar rash. The condition progressedwith abdominal distension, dyspnea, chest pain, fever, and general malaise. Clinicalexaminationrevealed a dyspneic, pale, febrilechildwith a heart rate of 120 bpm, muffledheartsounds, moderate ascites, pleural effusion, and lowerextremityedema.

Laboratory tests showedanemia, lymphopenia, thrombocytopenia, elevated C-reactiveprotein, increasederythrocytesedimentation rate, a positive direct Coombs test, hypoalbuminemia, hypocomplementemia, normal renalfunctionwithproteinuria. Chest X-ray revealedcardiomegaly and pleural effusion. Echocardiographyshowed a large pericardial effusion, dilatedinferior vena cava, and moderate to severe mitral regurgitation, confirming the diagnosis of cardiactamponade. Urgent pericardial drainage wasperformed. Cultures of the pericardialfluidwerenegative for bacteria and acid-fast bacilli. Cytologicalexamination of the fluiddid not show anyneoplasticcells. Immunological tests revealed the presence of anti-DNA, anti-nucleosome, and anti-histone antibodies. Anti-Smantibodieswerenegative. A renalbiopsyrevealed class IV lupus nephritiswith an activity index of 6

and a chronicity index of 2. Ophthalmologicalexaminationwas normal. A diagnosis of systemic lupus erythematosuswas made.

The patient wastreatedwithmethylprednisolonebolusesfollowed by oral prednisone with good clinicalresponse and completeresolution of the pericardial effusion. Threemonthslater, the patient presentedwith memory problems and slowedthinking. Brain MRI showed diffuse moderatewidening of the cortical sulci and demyelinatinglesions of the deep white matter, consistent with lupus. A repeatrenalbiopsyconfirmed class IV lupus nephritis, leading to the initiation of immunosuppressive therapywithmonthly cyclophosphamide boluses for 6 months, followed by oral azathioprine and hydroxychloroquine.

The patient has been underregular follow-up care with a one-yearretrospective.

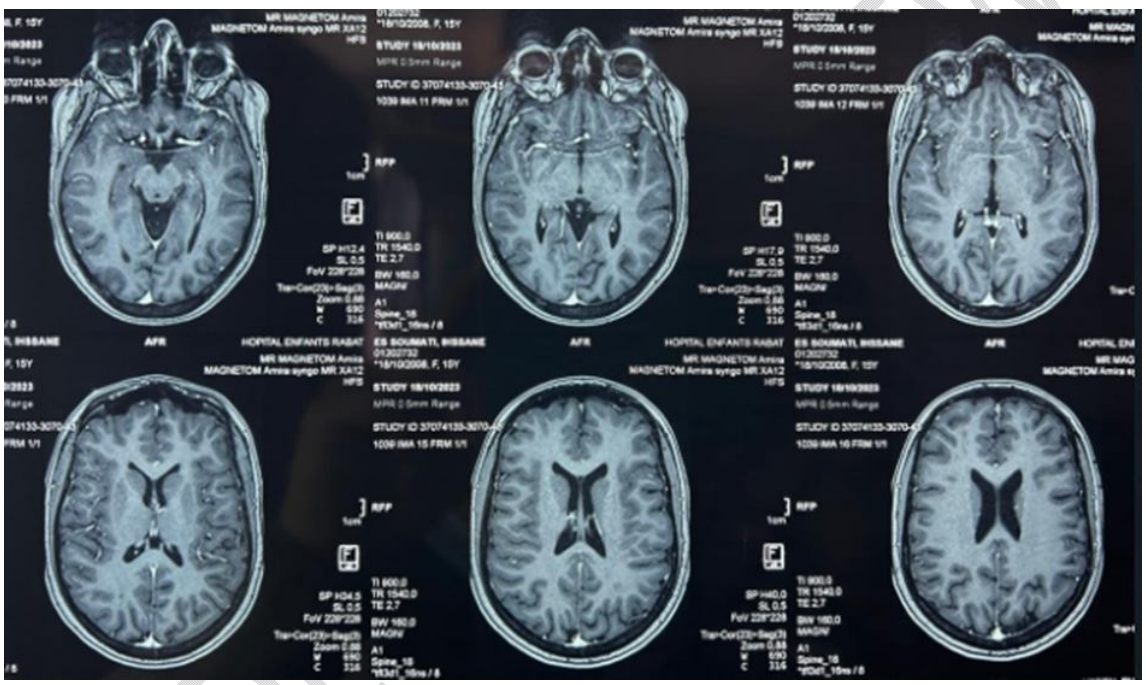

Figure 1: A transverse MRI scan of the brain, post-gadolinium injection, reveals diffuse moderatewidening of the cortical sulci and demyelinatinglesions in the deep white matter

Observation 2:

This is a 14-year-old childwith no familyhistory of autoimmunediseases, born to non-consanguineoushealthy parents. The illnessbegan 1 monthagowithasthenia, polyarthralgia, and abdominal pain in the context of a fever of 38.5°C, persistent, band-like headache, and general malaise. Clinicalexaminationrevealed an asthenic, pale, febrilechildwith a heartmurmur at the mitral area, a pinknailbed, and unremarkable skin, mucous membrane, and neurologicalexaminations. A CT scan showedleft pleural effusion, peritonealfluid in the right paracolicgutter, and bilateralaxillary and inguinal lymphadenopathy.

Laboratory tests showedpancytopeniawithanemia of 10 g/dL, normocyticnormochromic, withleukopenia at 1600 cells/mm³, thrombocytopenia at 70,000 cells/mm³, ferritin of 33511µg/l, elevatedliver enzymes, fibrinogen at 1 g/L, and lactate dehydrogenase (LDH) at 1562 U/L.". Bone marrowexaminationdid not show hemophagocytosis or blast cells. A diagnosis of macrophage

activation syndrome was made. The patient wastreatedwithmethylprednisolonebolusesfollowed by oral prednisone.

Subsequently, the patient developedlowerextremityedemawithproteinuria, a positive direct Coombs test, hypoalbuminemia, and normal renalfunctionwithhypocomplementemia.

Echocardiographyrevealed a slightlythickenedaortic valve withmildaorticregurgitation, grade I mitral regurgitation, and moderateleftventricular dilatation with good function. Antinuclearantibodies, anti-DNA antibodies, and anti-Smantibodieswerenegative. A renalbiopsyrevealed class IV lupus nephritis. The patient alsoreporteddecreasedvisualacuity, and an ophthalmologicalexaminationshowedisolatedperipapillarycotton-wool spots, consistent with lupus. Brain MRI (Figure 2) revealedbilateralfrontoparietal and cerebellarlesions, suggesting a demyelinating process, possibly multiple sclerosis-like, within the context of lupus.

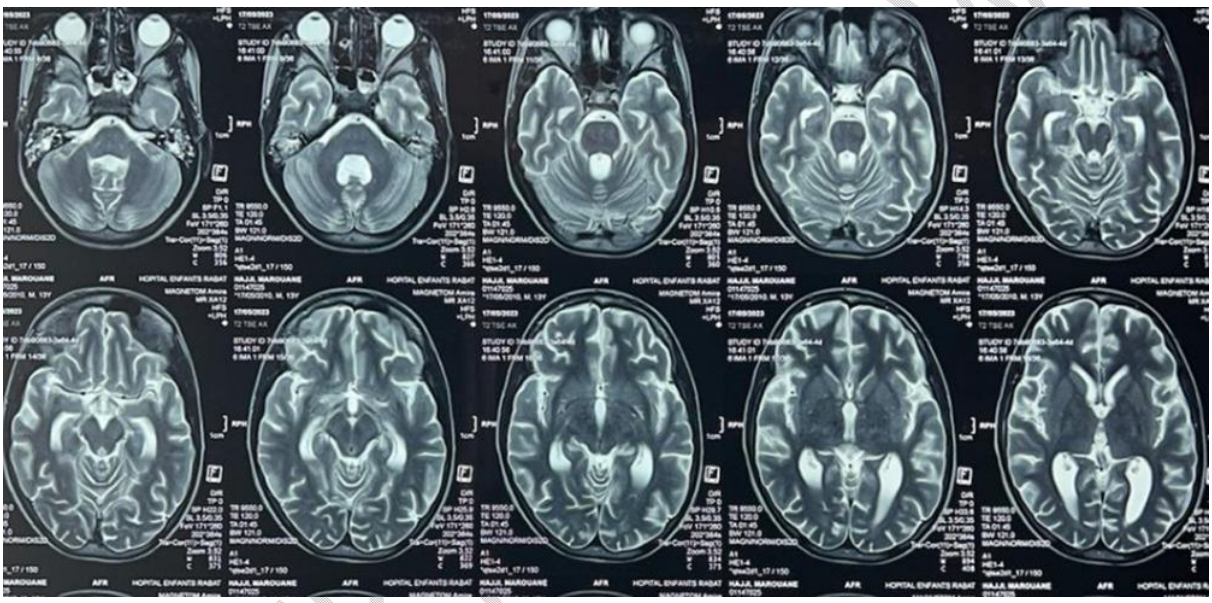

Figure 2: A transverse MRI scan of the brainrevealsbilateraldemyelinatinglesions in the frontal, parietal, and cerebellarregions.

Discussion:

The prevalence of SLE in childrenislow, approximately one case per 100,000 children (Platt et al., (1)). This disease has a strongfemalepredominance, with a sex ratio of 4.7 girls to 1 boy. Epidemiologicalstudies (Kornreich) show a bimodal age distribution at diagnosis:a first wavebefore 5 years (5%), a second between 5 and 10 years (35%), and a third, larger, between 11 and 15 years (60%) (2).

In 1999, the American College of Rheumatology (ACR) established a comprehensive classification of the neurological manifestations of systemic lupus erythematosus (SLE), groupedunder the term "neurolupus" or "neuropsychiatricsystemic lupus erythematosus" (NPSLE). Table 1 includes 12 central nervous system (CNS) and 7 peripheralnervous system (PNS) manifestations, providing a standardizedframework for describing and recognizing the variousneurological and psychiatric complications associatedwith SLE (3,4, 5).

Central Nervous System Manifestations	PeripheralNervous System Manifestations
1. Headaches 2. Mooddisorders (depression) 3. Anxietydisorders 4. Psychosis 5. Cognitive dysfunction 6. Epilepsy 7. Cerebrovascular manifestations 8. Myelopathy 9. Demyelinating syndrome 10. Acute confusional state 11. Abnormalmovements 12. Asepticmeningitis	1. Cranial nerve involvement 2. Polyneuropathy 3. Dysautonomia 4. Mononeuropathy 5. Myasthenia gravis 6. Guillain-Barré syndrome 7. Plexopathy

Table 1 : ACR classification of neuropsychiatric manifestations in systemic lupus erythematosus (3).

Unterman et al. reported a 56% prevalence of neuropsychiatric manifestations in theirmeta-analysis. Headacheswere the mostcommon (28%), followed by mooddisorders (21%), cognitive impairments (20%), seizures (10%), stroke (8%), and anxiety (6%) (4).

Parihk et al.'sstudy of 108 childrenwith lupus foundthat 25% experiencedneurological manifestations. Theseoccurredbeforediagnosisin 4%, at diagnosisin 15%, and afterdiagnosisin 26%. All patients hadheadaches, 56% hadbehavioral changes (depression, confusion), 25% had chorea, and 19% reportedvisualloss (6).

Both patients experienced persistent headaches. The girl had cognitive impairments and depression at diagnosis, whereas the boy developeddecreasedvisualacuity over time.

- ✓ **Brain MRI :**

is the gold standard for evaluating central nervous system involvement in lupus, includingcerebral, spinal cord, vascular, and inflammatorylesions. T2 hyperintensities are commonlyfound in the periventricular and subcortical white matter, particularly in the frontal and parietal lobes (7,8). FLAIR sequencesenhance the detection of these T2 hyperintensities, especially in periventricular and subcortical regions.

Although white matterhyperintensities are frequentlyobserved in patients withneuropsychiatric manifestations, the cause-and-effectrelationshipis not alwaysestablished. Studies have shownthat certain morphological and signal characteristics of hyperintensities (number, size, association withotherlesions, intensity, contours) couldberiskfactors for the development of neuropsychiatricsymptoms, but theseresultsremain to beconfirmed by largerstudies (9).

Hyperintensities in the gray matter (cortex and basal ganglia) suggest a direct neuronal damage by antineuronalautoantibodies (4).

Lacunarinfarcts are foundin 21% to 60% of patients with neurolupus (10).

Our patients' MRI findings are consistent withpreviousstudies.

- ✓ **Cerebrospinalfluidanalysis :**

is crucial to exclude viral or bacterialmeningitis ormeningoencephalitis in immunosuppressedchildrenwith lupus (11), althoughaseptic lupus meningitisshouldbeconsidered.

- ✓ **Magnetic ResonanceSpectroscopy (MRS) :**

By identifying and quantifying the amounts of differentmolecules in the brain, this technique revealsabnormalities invisible to conventional MRI exams. The analysisfocuses on biomarkerssuch as N-acetylaspartate (NAA), total choline (includingitsdifferent components), myo-inositol, and creatine. Creatine, present at a relatively constant level in glial and neuronal cells, serves as an internalreference to normalize the concentrations of othermetabolites and allow for inter-individualcomparisons (8).

Brooks et al. demonstratedthat the reduction of NAA wasassociatedwith neuronal loss, thusconfirmingitsrole as a marker of neuronal integrity in the context of neurolupus (12).

The decrease in NAA isreversible in some cases, indicating a possible recovery of neurons. Nevertheless, it can alsobe the sign of future neuronal degradation, detectable by MRI (10,13). While the release of choline, resultingfromdemyelinationprocesses, is an indirect marker of membrane alteration. Although not specific to the severity of the lesion, the elevation of choline levelsiscorrelatedwith an increase in gliosis, vasculitis, and tissue edema, suggestingongoingpathologicalactivity (12).

However, theseabnormalities can befound in otherneurodegenerativediseasessuch as Alzheimer's and multiple sclerosis (12,13).

- ✓ **Brain single-photon emissioncomputedtomography (SPECT) :**

"Brain SPECT, by assessingcerebral perfusion, demonstratesincreasedsensitivity in detectingbrainlesionsrelated to lupus, particularly in deepbrainregions. Focal hypoperfusions are frequentlyobserved, even in the absence of lesions visible on MRI, and are oftenassociatedwithdiseaseactivity. The clinicalresolution of theseabnormalitiessuggests a close linkwithpathologicalactivity (13,14).

Neurolupus treatment:

The therapeutic management of neurolupus iscomplex and based on an individualizedapproach. Mild or nonspecific manifestations benefitfrom standard symptomatictreatment. Severeinflammatory and autoimmune manifestations require immunosuppression, the choice and duration of which are determined by the severity of the disease and the therapeuticresponse. Corticosteroids and immunosuppressants are first-line treatments, althoughscientificliterature data islimited.

- ✓ **Corticosteroidtherapy :**

is the first-line treatment for inflammatoryneurological manifestations of lupus. The EULAR recommendationsspecify the administration modalities and dosages according to the differentclinical manifestations. Bolus corticosteroids (at a dose of 7.5 to 15 mg/kg for 3 consecutivedaysfollowed by oral administration at a dose of 1 mg/kg) are particularlyindicated in severeforms and spinal cordinvolvement. The combination of corticosteroids and immunosuppressantsmaybeconsidered in refractory cases or in cases of significantsystemicactivity (16,17).

- ✓ **Cyclophosphamide :**

In a 2005 study by Barile-Fabris et al., twotreatments for neurolupus werecompared:monthlythentrimonthly cyclophosphamide for a year, and monthlymethylprednisoloneboluses for four months, followed by everytwo and thenthreemonths. All patients initiallyreceivedmethylprednisolone. Whilebothtreatmentsimprovedsymptomsinitially, cyclophosphamide was more effective in maintainingthisimprovement long-term. Patients on methylprednisolonehad more frequent relapses as bolus frequencydecreased (18).

Dosingis not standardized. By analogywithrenalinvolvement, a dose of 500 to 700 mg/m² (with a maximum of 1200 mg) every four weeks for six months can beconsidered, adjusting the dose according to the patient. Maintenance therapy is then essential to prevent relapses withalternatingsteroids (10-20 mg of prednisolone everyotherday) and substituting azathioprine (2 mg/kg/day) for methotrexate (initial dose of 7.5 mg/week, increased or decreased by 2.5 mg/weekdepending on response or sideeffects; maximum 20 mg/week) can beinstituted for an additional minimum of 10 months, depending on the response, followed by a gradualwithdrawal (17).

Mycophenolate and cyclosporine can be as effective as methotrexate and azathioprine. Case reports and smallstudiessuggestintravenousimmunoglobulins and thalidomide maybebeneficial for some patients (19).

- ✓ **Rituximab**:

EULAR experts consider rituximab as a second-line therapeutic option for patients sufferingfromconfusional states, psychoses, or myeliteswho do not respond to conventionaltreatments (17).

Our patients receivedmethylprednisolonebolusesfollowed by oral administration, thenintravenous cyclophosphamide bolusesmonthly for 6 months, followed by azathioprine, with good clinical and biologicalevolution.

Conclusion:

Systemic lupus erythematosus (SLE) islesscommon in childrenthan in adults and has a more severeprognosis in boys. The diagnosis of neurolupus remainscomplex due to itsclinicalpolymorphism, but it must beestablishedbased on a set of chronological, clinical, and paraclinical arguments, given the diversity of itspathophysiologicalmechanisms.

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