Case Report

J Ped. Nephrology 2015;3(2):75-78
http://journals.sbmu.ac.ir/jpn

A Case of Refractory Systemic Lupus Erythematosus with Acute Psychosis

How to Cite This Article: Naseri M, Sarvari Gh, Maleknejad M, Moshari J. A Case of Refractory Systemic Lupus Erythematosus with Acute Psychosis. J Ped. Nephrology 2015;3(2):75-78.

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Received: Feb-2015
Revised: Feb-2015
Accepted: Mar-2015

A case of refractory systemic lupus erythematosus was admitted with repeated tonic colonic seizures, intractable vomiting, diarrhea, and headache. Neurologic examinations, lumbar puncture analysis, and electroencephalogram were normal but magnetic resonance imaging of the brain showed dilated ventricles and sulci. Despite standard induction therapy, the patient gradually entered a confusional state, disorientation that changed to abnormalities in verbal and working memory, and finally no verbal communication for several days and avoided eating food and taking oral drugs. The patient achieved partial remission of the disease (improved symptoms of psychosis and renal function despite a high titter of anti-double strand DNA and positive anti-nuclear antibodies) with plasmapheresis, intravenous immunoglobulin, and anti-psychotic medication. Our case is interesting because he was refractory not only to standard treatments, but also he did not respond to therapeutic options that are used in refractory systemic lupus erythematosus and presented with psychosis that is an unusual clinical presentation in SLE .

Keywords: Lupus Erythematosus, Systemic; Lupus Vasculitis, Central Nervous System; Psychotic Disorders; Child.

Running Title: Refractory SLE with Acute Psychosis

Introduction

Cases of systemic lupus erythematosus (SLE) refractory to standard treatments are uncommon [1]. Neuropsychiatric SLE (NPSLE) which may present as stroke, transient ischemic attack, cognitive dysfunction, acute confusion, seizure disorder, and psychosis is a common complication of SLE [2]. However clinically severe neuropsychiatric involvement is rare (7.8/100 person years) [3], and acute psychosis has been rarely reported [4]. For refractory NPSLE, intravenous immunoglobulin, plasmapheresis, and rituximab have been recommended [5]. In this case report, we present a child with refractory SLE and severe neuropsychiatric complications including psychosis, acute confusion, and repeated seizures.

Case Report

An 8-year-old boy was admitted to the nephrology department with malar rash, abnormal urinary sediments (proteinuria and microscopic hematuria), a protein/creatinine ratio of 2/1, normal blood pressure, with no edema and normal renal function tests. He complained of intermittent fever during the last 2 years. Preliminary investigations were done and revealed mild anemia (Hb=9 gr/dl) and thrombocytopenia [platelet count was 75000 cell/micro litter (cell/µL)], low serum c3 and c4 levels, positive anti- nuclear antibodies (ANA) and anti-double strand DNA. Kidney biopsy was

performed that revealed focal lupus nephritis without any crescent formation, an activity index of 4/24 and a chronicity index of 0/12.

High dose oral prednisolone (2mg/kg/day) was recommended one week prior to hospitalization, so the patient had a normal body temperature at admission. Induction therapy started with intravenous methylprednisolone 25 mg/kg/day for six consecutive days; then, intravenous cyclophosphamide 500 mg/m2 as single dose was administered. The patient was discharged after 3 weeks with oral prednisolone 2 mg/kg daily, mycophenolate mofetil (MMF) 1200mg/m2 daily, and enalapril 0.2mg/kg/day.

Ten days later, he was admitted again with buccal ulcers, thrombocytopenia, and repeated vomiting. The patient again received 5 doses of intravenous methylprednisolone, and azathioprine 2.5 mg/kg daily replaced MMF because of severe gastrointestinal symptoms. Five months later, he was again admitted with anemia (Hb=8.8 gr/dl) and thrombocytopenia. The patients' platelet count was 79000 cell/µ and white blood cell (WBC) count was 3600 cell/µL with 55.9% polymorphonuclear (PMN) cells. The patient also had abnormal urinary sediment including 3 positive samples of proteinuria and microscopic hematuria. Serum c3 and c4 levels were within normal ranges whereas ANA was positive (1.2 IU/ml). During the past 5 months, azathioprine was unfortunately discontinued and the patient received prednisolone 25 mg every other day. Induction therapy with intravenous methylprednisolone for six consecutive days was started; the patient received the third dose of intravenous cyclophosphamide, and then he was maintained on oral prednisolone, MMF, and hydroxychloroqiune sulphate 5mg/kg daily.

One month after receiving the third dose of intravenous cyclophosphamide, complete blood count (CBC) showed pancytopenia (Hb=9.6 gr/dl, platelet count=101000 cell/µL, and WBC count= 2900 cell/µL with PMN=73.8%). The reticulocyte count was 3.5%, and indirect and direct combs tests were negative. Because of leukopenia, intravenous cyclophosphamide was discontinued and bone marrow aspiration was performed. A decreased number of the precursors of megakaryocytic and erythroid cells, maturation arrest of myeloid cells in the myelocyte stages, and a myeloid to erythroid ratio of 5/1 were the main findings. In addition, less than 5% of myeloid cells were blast cells.

Ten months after the onset of the disease, he again was admitted with repeated tonic colonic seizures, transient unconsciousness, intractable vomiting, diarrhea, and headache. Normal neurologic examinations, mild hypertension (Bp=120/80 mmHg) with no edema and normal urine output (>500 CC/1.73 m2) were the main findings. Serum electrolyte levels were normal, but renal function tests revealed mild renal dysfunction (serum BUN =30mg/dl and serum creatinine =1.2 mg/dl).

Urine analysis and stool examinations were normal. The serum c3 level was in the normal range but the c4 level was high, whereas the titter of anti-DS DNA (IgG) was high (>150 IU/ml) and ANA was positive (3.2 IU/ml). Analysis and culture of the cerebrospinal fluid were normal. When the patient was on phenobarbital sodium valporate, electroencephalography was done that was unremarkable. Magnetic resonance imaging (MRI) of the brain showed dilated ventricles and sulci (Figure 1).

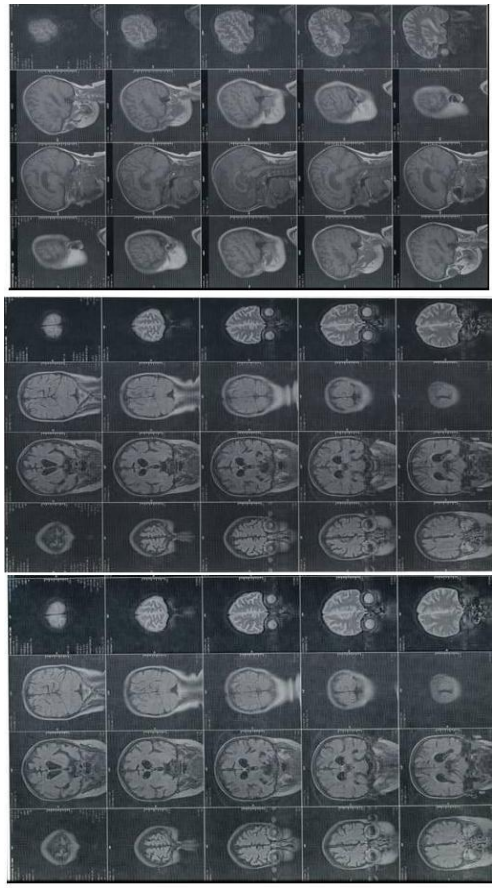

Fig 1. Magnetic resonance imaging. (MRI) of the brain MR imaging of the brain was performed on a 1.5 Tesla superconducting magnet using Axial T2 &FLAIR, Sagittal TI&72 & Coronal T2 weighted sequences without Gd. The ventricles and sulci are generally dilated (pseudo brain atrophy due to steroid therapy)

The patient gradually entered a confusional state characterized by confusion, apathy, disorientation that changed to abnormalities in verbal memory, and finally no verbal communication for several days and avoided eating food and taking oral drugs. The patient was inducted with intravenous methylprednisolone for 6 consecutive days followed by intravenous cyclophosphamide. Then, plasmapheresis started every other day for six sessions and intravenous immunoglobulin (IVIG) 0.5 gr/kg for 4 consecutive days was added as induction therapy. Then, the patient was maintained on oral prednisolone while MMF was replaced with azathioprine. Haloperidol 0.25 mg twice daily was added to control symptoms of psychosis. One week later, the symptoms of psychosis gradually started to improve, and verbal aphasia completely resolved and the patient started to eat and take oral drugs at the time of discharge. At discharge, ANA and anti-DS DNA were checked again but the titters did not change (ANA=3.2 IU/ml and anti-DS DNA>150 IU/ml). Table I presents the results of laboratory tests on the last admission.

Discussion

Our patient was a case of refractory SLE with neuropsychiatric, hematologic and renal involvements. The patient presented with headache, repeated seizures, acute confusional state, psychosis, evidence of acute renal failure, and hematologic findings which worsened despite standard induction immunosuppressive therapies. Renal function tests and symptoms of psychosis dramatically improved after adding plasmapheresis and haloperidol, whereas no improvement was achieved in pancytopenia and the patient required pack cell and platelet transfusion and administration of granulocyte colony stimulating factor (G-CSF). Kampylafka et al. found acute psychosis in 4.3% of the SLE patients [3]. Two groups of criteria are used for making a final diagnosis of NPSLE; the first group criteria consist of seizure, psychosis, cerebrovascular events, cranial nerves lesions, and quantitative alterations of consciousness, and the second group includes cognitive dysfunction, lupus headache, peripheral neuropathy, MRI, EEG and electroneuromyogram (ENMG) changes, positive anti-ribosomal P antibodies (aRPA), positive antiphospholipid antibodies (aPL).(6) The presence of at least one criterion from the first group and two criteria from the second groups is sufficient for making a final diagnosis of NPSLE.No single laboratory test is available to confirm a diagnosis of NPSLE [7]. Abdel-Nasser et al. [8] found a positive correlation between the presence of aRPA with psychiatric manifestations of SLE, particularly mood disorders for which aRPA is specific, but not sensitive. They believe that absence of aRP in patients with SLE may help to exclude lupus psychosis. We did not check this test in our case since it was not available.

Neuropsychiatric manifestations have been reported in 20–95% of pediatric onset SLE [9-13]. According to a study by Singh et al [14], although neuropsychiatric manifestations are common in childhood SLE (51%), SLE psychosis is not common (9.4%). As our case, neuroimaging studies in their participants showed diffuse cerebral atrophy in 5 cases that was associated with ventriculomegaly in 3 patients. In contrast to our case, their patients responded to standard treatments; hence, they did not require plasmapheresis.

Our patient is interesting because he was a case of SLE that was refractory not only to standard treatments, but also he did not respond to therapeutic options that are used in refractory SLE such as IVIG infusion and plasmapheresis. We succeeded to achieve partial remission of the disease (remission of renal and neuropsychiatric symptoms) without serologic remission in our patient. Rituximab was not used since our patient had intermittent neutropenia and a history of 2 episodes of severe bacterial (pseudomonas sepsis) and viral (cytomegalovirus meningitis) infection during standard immunosuppressive treatments.

Conflict of Interest

None declared

Financial Support

None declared

Acknowledgement

The authors would like to appreciate Dr. Ashrafzadeh (pediatric neurologist), Dr. Sasan (pediatric infectious diseases subspecialist), Dr. Hebrani (pediatric psychologist), and Dr. Badiee (pediatrics hematologist) for their help in the management of the patients.

Table I. Laboratory findings of the patient on the last admission

Laboratory test	Day 1 of admission	One week after admission [1]	Day 10 of admission [2]	Day 14 of admission [3]	Day 17 of admission [4]
Serum Creatinine	1.2 mg/dl	4.2 mg/dl	3.2 mg/dl	1.9 mg/dl	0.7 mg/dl
Serum Hb [5]	8.1 gr/dl	6.5 gr/dl [6]	7.2 gr/dl	6.9 gr/dl [7]	10.6 gr/dl
Platelet count	88000 Cell/mm3	78000 Cell/mm3	66000 Cell/mm3	31000 Cell/mm3	20000 Cell/mm3
WBC [8] count and differential count of PMN [9]	3800 cell/µL;66%	4900 cell/µL ;78%	1400 cell/µL ;94%	1000 cell/µL ;92%	600 cell/µL ;90%

1) End of induction with intravenous methylprednisolone and cyclophosphamide
2) Beginning of plasmaphresis 3) after 2 sessions of plasmaphresis
4) after 4 sessions of plasmaphresis 5) Hemoglobin 6) patient received pack cell 10 cc/kg and serum Hb reached to 11.1 gr/dl
7) Patient received pack cell 10 cc/kg and serum Hb reached to 10.6 gr/dl 8) White blood cells 9) polymorph nuclear cells

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