

A novel therapeutic approach using the Zipper method to treat chorea in a pediatric-onset systemic lupus erythematosus patient

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Abstract

Pediatric-onset systemic lupus erythematosus is among the prototypic systemic autoimmune diseases seen in children. Although the neuropsychiatric involvement rate varies during the course of the disease, it is an important cause of morbidity and mortality. The clinical picture of neuropsychiatric SLE (NPSLE) is highly variable, and neurological features can precede systemic findings, leading to some diagnostic difficulties. NPSLE requires early and aggressive immunosuppressive therapy. Some patients can be resistant to immunosuppressive therapy. Chorea is a rare manifestation that occurs in 1.2%–2% of SLE patients and can result from an immunologically mediated mechanism, antiphospholipid autoantibodies or ischemia. Herein we present the first case of pediatric-onset SLE diagnosed with central nervous system involvement and treated with Zipper method. The Zipper method is a new immunomodulation treatment. The clinical findings of the patient, which were resistant to corticosteroids and cyclophosphamide, resolved by this novel treatment.

Keywords

Chorea, systemic lupus erythematosus, neuropsychiatric lupus, Zipper method

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Introduction

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease characterized by autoantibody production and immune complex formation, as well as multiple organ system involvement.¹ Pediatric-onset SLE is usually more severe than the adult-onset form, with a higher incidence of renal and central nervous system involvement.² SLE is the prototype of connective tissue diseases that can present with the complete spectrum of neurological and psychiatric dysfunction.³ Symptoms of neurological systems occur before SLE is diagnosed or during the course of the disease.^{4,5}

According to the American College of Rheumatology (ACR) Classification of neuropsychiatric (NPS) syndromes in SLE patients, central and peripheral nervous system symptoms are included.⁶ The most common NPS manifestations are headache, mood disorders, and cognitive dysfunction.⁷ Chorea is a relatively rare complication that is reported in 1.2%–2% of SLE patients.⁸ The pathogenesis of

chorea is in a dark region. The release of cytokines and chemokines—especially antiphospholipid antibodies via vascular mechanisms, blood brain barrier

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damage, and antibody neurotoxicity lead to common neurological symptoms.^{5,8-12} Additionally, these symptoms can occur due to multiorgan involvement and treatment complications.^{3,13} A strong association between chorea and antiphospholipid (aPL) antibodies has been reported in patients with SLE, lupus-like diseases, and primary antiphospholipid syndrome (APS).^{14,15}

Few pediatric cases were reported to present with chorea and subsequently be diagnosed as SLE.^{9,16} Most of the reported patients with chorea received immunosuppressive treatments, such as high-dose corticosteroids, cyclophosphamide (CYC), and combinations of the 2, or methotrexate.^{17,18} Herein we report on a 10-year-old boy with pediatric-onset SLE that presented with chorea and delirium. He was administered a novel treatment known as the Zipper method due to resistance to conventional therapy and rapidly progressing neurological involvement. As his anti-double-stranded DNA autoantibodies (anti-dsDNA) value, in particular, was very high, this treatment was chosen because it would quickly remove autoantibodies and inhibit complement activation.

The Zipper method is an immunomodulation treatment first used by Kesici et al.¹⁹ in 9 patients with Guillain-Barré syndrome (GBS), a complement-related autoimmune disease. The technique consists of consecutive meticulous plasma exchange and intravenous immunoglobulin (IVIG). This treatment might be a logical option in patients with immune-mediated diseases related to autoantibodies and complement activation.²⁰ It has not been used to treat other diseases in children. To the best of our knowledge this is the first report of a pediatric NPSLE patient treated with the Zipper method.

Case report

A 10-year-old male was admitted in our pediatric rheumatology clinic with involuntary movements of his right arm and leg, which started one week earlier. He was dysarthric, unable to walk without support, and had difficulty performing daily activities. He had a 3-month history of intermittent fever and oral ulcers. There was no history of photosensitivity, rash, hair loss, Raynaud's phenomenon, headache, loss of consciousness, seizure, substance use, or any illness. He had a negative family history of rheumatic and neurological diseases. Upon physical examination there were intermittent and irregular aimless choreic movements in his right arm and leg. Cranial nerve evaluation was inconclusive because the patient was apathic. Deep tendon reflexes were normal. There were no signs of cerebellar involvement or meningeal irritation. No pathological feature was detected via other system

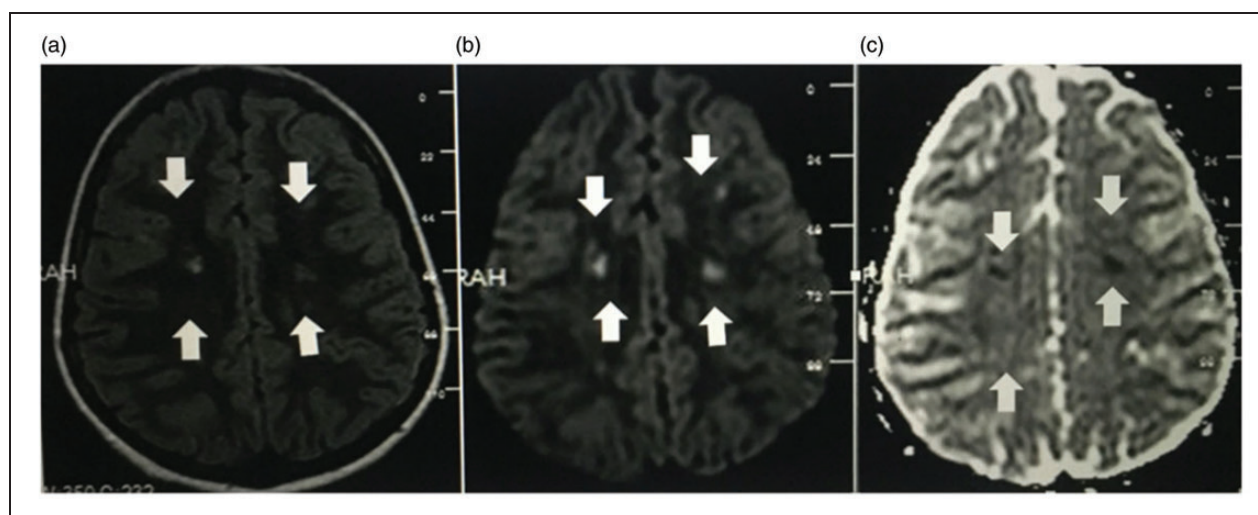
examinations. Initial complete blood count and biochemistry tests were normal except for low platelet count (Platelet: 121,000/ μ L) and mildly elevated serum creatinine (Cr: 0.85 mg/dl). C-reactive protein was normal but the erythrocyte sedimentation rate was 63 mm/hour. There was no proteinuria in urine test. Antistreptolysin O (ASO) titre was 249 IU/mL (<200 IU/mL). The coagulation profile and thyroid function tests were normal. The patient's direct coombs' test was positive. The serum complement levels were studied and both C3 and C4 were below the normal limits (C3: 0.334 g/L, normal: 0.83–1.77 g/L and C4: <0.0673 g/L, normal: 0.12–0.4 g/L). Antiphospholipid workup showed positive lupus anticoagulant, negative anti-cardiolipin IgM and IgG, and negative anti-b2 glycoprotein IgM and IgG antibodies. The mixing test failed to correct lupus anticoagulant and the second lupus anticoagulant value was within normal limits. N-methyl-D-aspartate (NMDA) antibodies were also negative. Laboratory values and immunologic parameters at presentation, and after corticosteroid, CYC, and the Zipper method are given in Table 1.

He had first-degree mitral regurgitation based on echocardiography, but no mitral prolapse. Bone marrow evaluation and cerebrospinal fluid (CSF) examination were normal. CSF oligoclonal band and viral examination were negative. Abdominal ultrasonography showed hepatosplenomegaly. Transaminase values were normal. Electroencephalography (EEG) was normal and there was mild elongation of bilateral VEP sequences during a fever-free period. Cranial magnetic resonance imaging (MRI) showed millimetric pathological signal changes in the bilateral periventricular-subcortical white matter indicative of diffusion restriction compatible with infarct areas (Figure 1(a) to (c)). Cranial magnetic resonance (MR) angiography showed irregularities in the right internal carotid artery cavernous segment, as well as thinning and irregularities in the left internal carotid artery clinoid, supraclinoid and communicating segments. The left anterior communicating artery was hypoplastic (Figure 2). There were focal hyperintensity areas at the head of the caudate nucleus and diffusion restriction areas compatible with the infarct areas (Figure 3). MR venography was normal and there was no evidence of thrombosis.

The patient was diagnosed as SLE according to the revised criteria of the American College of Rheumatology (ACR) for classification of SLE.²¹ According to the European League Against Rheumatism (EULAR) NPSLE treatment recommendations published in 2010 corticosteroid treatment was administered initially and CYC was subsequently given as an additional immunosuppressive because it was a

Table 1. Laboratory values and immunological parameters of the patient.

	First admission	After pulse steroid and cyclophosphamide	After Zipper method
Haemoglobin (gr/dl)	11	10.9	9.7
White blood cell (mm ³)	7230	26820	6030
Platelet (mm ³)	121000	90000	202000
Sedimentation (mm/hour)	63	44	18
C reactive protein(mg/dL)	19.9	<3.14	<3.14
Blood urea nitrogen (mg/dL)	24	32	19
Creatinine (mg/dL)	0.85	0.63	0.55
ALT (U/L)	16	6	22
AST (U/L)	30	11	19
Complement 3 (0,83–1,77 g/L)	0.334	0.348	1.16
Complement 4 (0,12–0,4 g/L)	<0.0673	<0.0673	0.198
Prothrombin time(sn)	13.2	11.6	11.5
aPTT(sn)	22	18.9	20.7
Direct Coombs	Positive	Positive	Negative
Urine test	Normal	Normal	Normal
ANA(negatif <1/80) (ELISA)	>1/640	>1/640	>1/320
Anti ds DNA(<12IU/ml) (mikroelisa)	>300	>300	29.4
Anti-Sm(immunblotting)	Negative	Negative	Negative
Lupus anticoagulant (<1.2)	1.44	1.0	0.9
Anti fosfolipid IgM	Negative	Negative	Negative
Anti fosfolipid IgG	Negative	Negative	Negative
Anticardiolipin IgM	Negative	Negative	Negative
Anticardiolipin IgG	Negative	Negative	Negative
Anti beta-2 glikoprotein I IgM	Negative	Negative	Negative
Anti beta 2 glikoprotein I IgG	Negative	Negative	Negative

**Figure 1.** Millimetric pathological signal changes in the bilateral periventricular-subcortical white matter indicative of diffusion restriction compatible with infarct areas.

serious case unresponsive to corticosteroid.²² Treatment was started with methylprednisolone 30 mg/kg/day (for 5 days and then reduced to 2 mg/kg/day), hydroxychloroquine 5 mg/kg/day and haloperidol 1 mg/day. During follow-up the patient's

temperature decreased after the first corticosteroid dose and did not increase again. His choreic movements did not improve, he was unresponsive to verbal stimuli. His orientation and cooperation were impaired. CYC was started as a second

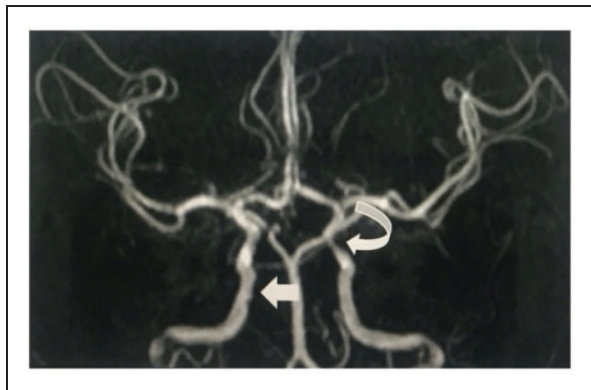


Figure 2. Irregularities in the right internal carotid artery cavernous segment, as well as thinning and irregularities in the left internal carotid artery clinoid, supraclinoid and communicating segments.

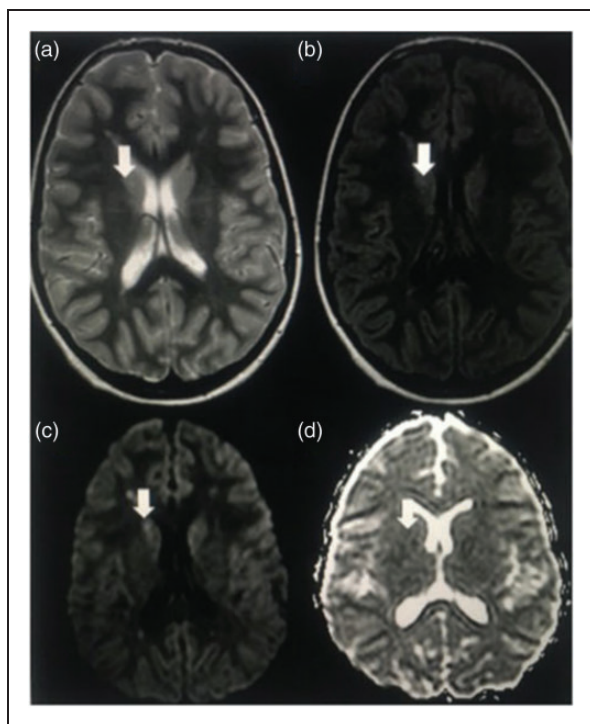


Figure 3. Focal hyperintensity areas at the head of the caudate nucleus and diffusion restriction areas compatible with the infarct areas.

immunosuppressive in accordance with the EULAR recommendations as the patient's neurological symptoms did not improve and thrombocytopenia continued.²³ CYC 1 g/m² was administered, on day 7 of hospitalization, 2 days after the last pulse corticosteroid dose. No side effects due to pulse corticosteroid and CYC treatments were observed. Anticoagulant treatment was not administered. It was thought that the suspicious infarct areas were due to primary disease

involvement and antiphospholipid antibodies were also negative. There was no improvement in the clinical signs of central nervous system involvement, 2 days after CYC was administered. His aphasia persisted, he was confused, he had a blank facial expression, and he did not respond to questions with his eyes or verbally. The patient was transferred to the intensive care unit (ICU) in order to begin the Zipper method due to the rapid deterioration of central nervous system findings, unresponsiveness to conventional therapy and the high level of autoantibodies.

The Zipper method

The Zipper method is a novel treatment protocol first used by Kesici et al.¹⁹ in 9 intubated GBS patients (mean age: 10.9 years) with a rapid disease course and poor prognosis. The treatment consists of IVIG administration following plasma exchange and continues with plasma exchange again after 24 hour for 5 cycles. All patients benefited from the treatment and were discharged from hospital with full recovery. Except for urticarial rash in 1 of the patients, serious side effects were not observed.

The mechanism of action of plasma exchange is clearance of harmful antibodies in circulation. IVIG neutralizes autoantibodies via inhibiting complement activation and membrane attack complexes. If IVIG is administered after plasma exchange is completed, the patient's natural immunoglobulins are depleted during the most active period of disease. If plasma exchange is performed after IVIG treatment is completed, the effect of IVIG is reduced, but the Zipper method is different. This technique starts with plasma exchange. At first, one and a half volume of patient plasma is removed by 5% albumin as replacement solution. After plasma exchange the plasma is cleared of autoantibodies, and the autoantibody transition starts from the tissue to the plasma as a rebound. After the plasma exchange session, IVIG 0.4 g/kg is administered. As antibody removal from the tissue is completed in 24 hour, the next plasma exchange session starts 24 hour after IVIG with a volume change. IVIG infusions are given following each plasma exchange session. IVIG given immediately after plasma exchange neutralizes the antibodies, blocks the Fc receptors by inhibiting the activation of complement and prevents the formation of a new membrane attack.²⁴ The plasma exchange-IVIG cycle is repeated 5 times.¹⁹ In the presented patient the Zipper treatment was completed as 5 cycles over the course of 9 days.

After the Zipper method

On second day of the Zipper method the patient began to speak and get out of bed and walk. At the end of fifth day his speech was clearly understood and he could walk comfortably. After zipper therapy, the patient's platelet values returned to normal and neurological findings improved. After 1 week of follow-up his chorea resolved completely. The patient left the ICU and was taken to the service after the treatment. Haloperidol was reduced and discontinued after 1 month. The patient remained on corticosteroid 2 mg/kg/day and hydroxychloroquine 5 mg/kg/day. The discharge plan included monthly CYC treatment for 6 months. As of the time this report was prepared the patient was in his third month of treatment without neurological sequelae or choreic movements. His gait and speech were normal. Additional cranial imaging was not performed because he was in the early follow-up period.

To the best of our knowledge the presented patient is the first pediatric case to present with chorea as the initial clinical neuropsychiatric sign related to SLE that improved significantly without any side effects in response to the Zipper method. Pulse corticosteroid and CYC did not improve the confusional state in the patient. The Zipper method provided dramatic favours. In response to the Zipper method the presented patient's choreic movements began to decline beginning on the second day, and the patient started to speak again and leave the ICU able to walk.

Discussion

The differential diagnosis of chorea includes cerebrovascular events, drug intoxication, hyperthyroidism, Huntington's disease, Sydenham's chorea, and such rheumatologic diseases as SLE.²⁵ In SLE patients chorea can occur due to immunologic-mediated mechanisms or ischemia and mostly to aPL-mediated-up to 92% of cases.^{26,27} The cause of chorea in SLE patients with negative aPL antibodies is not precisely known. Direct activation of the basal ganglia circuits and ischemia affecting the basal ganglia channels connecting the thalamus and cerebral cortex play a role in the pathogenesis of aPL-mediated SLE chorea.^{28,29} Some ischemic events might be associated with thrombosis mediated by anti-cardiolipin (aCL) antibodies.⁹ The presented patient is a rare case of pediatric-onset SLE-related chorea with no aPL antibodies. In the present patient we think that among the mechanisms that led to chorea were antibodies causing inflammatory vasculopathy in the cerebral vessels or neuronal dysfunction caused by immune complex deposition. A large study that included 50 chorea patients with

SLE, lupus-like disease, or antiphospholipid syndrome (APS) reported that 45% of the patients had hemichorea, whereas 34% had recurrent attacks of chorea.⁹ In the presented patient chorea and central nervous system involvement developed without accompanying APS.

Cerebrospinal fluid features and MRI findings are non-specific in NPSLE patients, but are useful for excluding other causes of neuropsychiatric symptoms.³⁰ The most common cranial MRI abnormal findings in patients with SLE are white-matter hyperintensity (8%-75% of patients predominantly in the frontoparietal region) and cerebral atrophy (9%-67%).³¹ Similarly, the presented patient had millimetric pathological white matter changes and vascular wall irregularities. MR angiography findings indicated that the MRI findings represented suspicious vasculitic involvement areas, but no obvious stenosis, occlusion, or aneurysmatic dilatation was noted.

Anti-dsDNA antibodies are the most common SLE-specific antibodies. A subset of these antibodies—anti-DNA/NMDA antibodies—cross-react with NMDA.^{8,32,33} It has been shown that both murine and human anti-DNA/NMDA antibodies preferably bind to the active NMDA receptor and cause excessive calcium flow, overstimulation, neuronal dysfunction, and cell death. This specific anti-DNA/NMDA antibody is observed in 30%–40% of anti-dsDNA (+) patients.⁸ In the presented patient NMDA antibodies were negative, eliminating the diagnosis of anti-NMDA receptor encephalitis.

In cases of NPSLE; infections, metabolic abnormalities, hypertension, drug side effects and psychosocial dysfunction should be ruled out before initiating treatment.³² Glucocorticoids are the main therapy. CYC can be used in moderate to severe patients and those that don't respond to other treatments within 3-5 days and to reduce the corticosteroid dose.^{34,35} There are a limited number of controlled studies on the effectiveness of CYC in NPSLE patients. Fanouriakis et al.³⁶ administered monthly pulse CYC treatment to 50 SLE patients with a mean age of 45 years that had signs of NPSLE, reporting partial or complete response in 84% of the NPSLE cases and that 10% had stable disease, whereas the remaining 6% had no improvement or exacerbation. They concluded that CYC yields an effective and sufficient response in resistant NPSLE patients during long-term follow-up. A controlled study observed that adding IV CYC to methylprednisolone was more effective in a cohort of 32 patients with NPSLE.³⁷

In very serious or life-threatening SLE cases that do not respond to other conventional treatments, plasma exchange, IVIG, and rituximab have been used.^{38,39} IVIG is associated with a decrease in the SLE activity

score and an increase in the complementary factor 3 (C3) level, but there are only a few studies that included NPSLE patients.⁴⁰ In a study conducted with 9 NPSLE patients, IVIG was observed to be effective and safe in NPSLE patients with mood swings and cognitive impairment.⁴¹ IVIG has mild and temporary adverse effects, most commonly headache, nausea, fatigue, palpitations and shortness of breath; serious side effects are thromboembolic events.⁴¹

Since plasmapheresis is useful for removing free antibodies, complementary components and immune complexes, it can be used in patients with severe symptoms that are unresponsive to treatment and high auto-antibodies and in those unresponsive to corticosteroid and CYC therapy.³⁴ Neuwelt et al.⁴² retrospectively identified 26 SLE patients that received plasmapheresis alone or in combination with CYC; improvement was noted in 74% of the patients. Wright et al.⁴³ reported the short-term efficacy of therapeutic plasma exchange as an adjunct to standard immunosuppression during the acute phase of the disease in 22 pediatric-onset SLE patients with renal, pulmonary and CNS symptoms. According to the French Hemapheresis Society, the most common side effect of plasmapheresis is hypocalcemia.⁴⁴ Catheter infections and thromboses at the intervention sites, hypotension, hypervolemia, transient fluid oedema and pulmonary oedema and deep vein thrombosis are other side effects that can be seen.^{42,43} Antiplatelet or anticoagulation therapy is administered if there is thrombosis and related clinical symptoms in antiphospholipid positive patients.^{22,45,46} In those with movement disorders symptomatic treatments, such as dopamine antagonists, anti-anxiolytics and anticonvulsants are usually effective.^{22,35}

In the largest SLE chorea case series by Cervera et al.⁹ that was published in 1997, it was reported that among patients aged 23 ± 12 years responded well to corticosteroids, haloperidol, antiaggregant drugs, anticoagulants or a combination of these treatments. The presented patient did not have improvement of neurological findings despite corticosteroids and CYC administered as the first-line immunosuppressive drug; as such, he was then treated with the Zipper method. Kesici et al.¹⁹ treated 9 GBS patients with a mean age of 10.9 years (range: 6–16 years) using the Zipper method; all 9 patients benefited from the treatment and recovered without any neurologically sequelae. The presented patient is the first pediatric case presenting with chorea as the first clinical neuropsychiatric symptom related to SLE to greatly improve without any side effects in response to the Zipper method. The limitation of the present case is its short duration of follow-up.

The Zipper method had never been previously used in pediatric patients, except for those with GBS.

Although IVIG and plasmapheresis have been used in resistant pediatric-onset SLE patients, to date no other patients administered the Zipper method have been reported. In pediatric-onset SLE patients with central nervous system involvement that are resistant to corticosteroid and CYC treatment and have a high level of autoantibodies the Zipper method should be considered, as in the presented case it was effective beginning with the first day of treatment.

Conclusion

Chorea is a rare manifestation of SLE that can be the initial and only manifestation of SLE. Other etiological causes of chorea should be excluded while performing diagnosis. SLE should be considered in the differential diagnosis of any child with unexplained new-onset hemichorea. Whereas corticosteroids and CYC are commonly used to treat neuropsychiatric involvement of SLE, plasmapheresis and IVIG are used in rare resistant cases. The present findings show that the Zipper method can be considered a promising immunomodulation strategy, but additional randomized controlled trials are required to unequivocally prove its efficacy.

The case was approved by the local ethics committee and written informed consent was obtained from the parents of the patient for his treatment and case publication.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Ethical approval

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