

Resistant Chorea Successfully Treated with Intravenous Immunoglobulin: A Case Report

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Abstract

Sydenham's chorea (SC) is common cause of acquired chorea in childhood. SC occurs mainly in children with untreated streptococcal infections. An effective list of therapeutic options has been used to treat this disorder: antiepileptic drugs (valproic acid, carbamazepine etc.), haloperidol, chlorpromazine, amphetamines, steroids, plasma exchange and intravenous immunoglobulins (IVIG). We report a 12-year-old girl with carditis and severely generalized chorea and successfully treated with IVIG. This case report shows that IVIG is an effective treatment for the chorea cases resistant to anticonvulsants, dopamine antagonists and steroids, although larger studies are needed to confirm this conclusion.

Keywords: Antiepileptic drugs, dopamine antagonist, intravenous immunoglobulins, Sydenham chorea

Introduction

Sydenham's chorea (SC) is the most common acquired chorea of childhood.^{1,2} SC occurs in about 10-15% of patients with acute rheumatic fever (ARF), in primarily ones with untreated streptococcal infections and usually presents as an isolated, frequently subtle, neurologic behavior disorder.² Treatment of SC is typically limited to supportive care and palliative medications. An impressive list of therapeutic options has been used to treat this disorder: dopamine receptor blockers (e.g. haloperidol, chlorpromazine), antiepileptic drugs [e.g. valproic acid (VPA), carbamazepine (CBZ)], and immune modulating therapy by means of prednisone, plasma exchange and

intravenous immunoglobulins (IVIG). Curative treatment is still in the experimental stage.^{3,4}

In this case, we describe a 12-years old girl, who presented with SC with severe disabilities in her daily life and we advocate the use of IVIG as a treatment option for SC.

Case Report

A 12-year-old girl, was admitted to our pediatric emergency department with complaint of intermittent swelling, redness, pain in the joints (migratory polyarthritits) for 2 weeks and, palpitations, involuntary movements and imbalance for several days.



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Her admittance vital parameters were as follows; blood pressure 120/60 mmHg, heart rate 104 beats/minute, respiratory rate 24 breaths/minute and temperature 37.9°C. She had intermittent, irregular, uncontrolled movements of the upper and lower extremities and to some extent also of the head and trunk. She exhibited darting tongue and milkmaid's grip with pronator sign and choreic hand. There were no further neurological abnormalities. Her cardiovascular examination presented a grade III-IV/VI° holosystolic regurgitant heart murmur on apical focus.

Complete blood cell count and the routine biochemical examination were normal; but erythrocyte sedimentation rate (ESR) was 23 mm/h, C-reactive protein (CRP) was 32.1 mg/L (N: <8 mg/L) and antistreptolysin O (ASO) titre was 371 Todd U/mL (N: 0-333 Todd U/mL). Rheumatoid factor, antinuclear antibody, anti-ds DNA antibody and anticardiolipin antibody were negative. Thyroid function test was also normal. In the throat culture no pathogens were isolated. PR interval was 0.16 second on electrocardiography and echocardiographic evaluation showed 3-4th degree mitral insufficiency, previous rheumatic heart disease (RHD; mitral valve echogenicity increased, mitral valve leaflet thickness: 6 mm). Brain magnetic resonance imaging (MRI) and electroencephalography were also normal.

The patient was hospitalized with the diagnosis ARF (migratory polyarthritis, active carditis and severe SC) and intramuscular benzathine penicillin G (1.2 milyon Unite), oral prednisolone (2 mg/kg/day, max 60 mg/day) and VPA therapy were started. On 10th day of hospitalization, patient's clinical status was worsened (she had incomprehensive speech with sucking and swallowing movements at rest, mood disorder with severe hypotonia, feeding, dressing and walking incapability); she also had periods of uncontrollable crying and extreme mood swings so we haloperidol added to VPA. Her clinical findings did not improve despite haloperidol and VPA treatment. Therefore, we started IVIG (0.5 g/kg/day for 4 days) on the 14th day of hospitalization. In addition, it was discontinued on the same day (before starting IVIG therapy) because of an extrapyramidal side effect related to haloperidol. We completed the steroid therapy to 6 weeks because of the active carditis. So we gave the IVIG in combination with steroids. After 48 hours of the last dose of IVIG, clinical findings including choreic movements and mood disorder were significantly improved. We continued VPA treatment for 3 more months. Her active carditis findings had improved in 1 month after discharge.

The patient has still been followed up without medication for 6 months without any problems.

Discussion

Acute rheumatic fever is still one of the most important causes of acquired heart disease all over the world and especially in developing countries. The diagnosis of this disease is made using the Jones criteria, revised by the American Heart Association in 2015. The revised Jones criteria were evaluated in 2 main categories according to

the annual incidence of ARF as low risk (ARF incidence ≤ 2 per 100.000 school-aged children or all-age RHD prevalence of ≤ 1 per 1000 population per year) and moderate-high risk groups.⁵ In the most recent wide-based study from Turkey, the annual incidence was reported to be 8.84/100.000 in the moderate risk group.⁶ The revised Jones criteria include major and minor criteria. The major criteria consisting of carditis, arthritis (polyarthritis only in low-risk population and monoarthritis or polyarthritis in moderate- and high-risk populations), chorea, erythema marginatum and subcutaneous nodules. The minor criteria consisting of arthralgia, fever ($\geq 38^{\circ}\text{C}$), ESR ≥ 30 mm/h and/or CRP ≥ 3.0 mg/dL, prolonged PR interval (after accounting for age variability (unless carditis is a major criterion). According to these criteria, the diagnosis of ARF was made in patients with recurrent ARF who had 2 major or 1 major and 2 minor or 3 minor criteria in addition to evidence of previous group A β -hemolytic streptococcal (GABHS) infection.⁵ In our case had a high ASO value and had previous RHD and active carditis findings in her echocardiography. In addition, the major criteria were migratory polyarthritis and chorea, and the minor criteria were levels of ESR and CRP elevation. We diagnosed ARF in our case who met 3 major and 1 minor criteria according to the revised Jones criteria.

SC is an antineuronal antibody-mediated neuropsychiatric disorder caused by a poststreptococcal, autoimmune condition affecting control of movement, mood, behaviour and is a major diagnostic criteria of ARF.⁷ The age of onset of SC is 5-15 years old and it is more common in girls. SC is usually one of the late manifestations of ARF compared to the other major criteria of revised Jones criteria (arthritis and carditis). Chorea usually occurs weeks or months after GABHS pharyngitis. Generally, chorea in SC is generalized; however, hemichorea occurs in about 25% of patients. Although symptoms of SC is a benign and self-limiting disease, in rare cases the associated severe hypotonia as to be completely disabling, a variant known as severe chorea or chorea paralytica. Neuropsychiatric symptoms, including emotional lability, personality changes, obsessive compulsive behaviors, irritability, anxiety, and anorexia, are common and mostly predate the appearance of SC.⁸ In a recent article from Italy, reported 171 children with SC under the age of 18. They declared 66% had generalized chorea, 34% had hemichorea, and 51% had neuropsychiatric findings.⁹ In the differential diagnosis of SC included that drug intoxication, tic disorder, choreoathetoid cerebral palsy, encephalitis, intracranial tumor, hyperthyroidism, antiphospholipid antibody syndrome, autoimmune (systemic lupus erythematosus-SLE, systemic vasculitis) and metabolic diseases (e.g. Huntington disease, Wilson's disease).⁵ In our case, there was no history of intoxication, hypoxic delivery or hyperbilirubinemia requiring exchange transfusion at the newborn. In addition, diagnoses of encephalitis, antiphospholipid antibody syndrome, SLE, hyperthyroidism, intracranial mass, Wilson's disease and Huntington's disease were excluded due to physical examination, laboratory findings and normal brain MRI. Also, this case had severe generalized chorea that

caused complete disability and neuropsychiatric findings. We diagnosed ARF in our case who met 3 major and 1 minor criteria according to the revised Jones criteria.

The most common of major manifestation in ARF is carditis (clinical and subclinical carditis). In a national ARF study from Turkey, they had been reported incidence of clinical carditis, subclinical carditis, polyarthritis, aseptic monoarthritis, polyarthralgia and SC had 53.5%, 29.1%, 52.8%, 10.3%, 18.6% and 7.9%, respectively.⁶ Also, the patients with SC frequently have clinical or subclinical carditis. Orsini et al. reported carditis in 81% (subclinical in 65%),⁹ and Gürses et al. in 93% of children with SC.⁶ In our case had active carditis, SC and migratory polyarthritis. She also had RHD on her echocardiography. Possibly she had a previous episode of ARF. Therefore, we have seen these 3 major criteria together.

The mainstay treatment of SC includes dopamine receptor blockers (eg, haloperidol, chlorpromazine) and certain antiepileptic medications like VPA and CBZ. VPA is recommended as the first-line agent in the treatment of SC,^{3,10} especially in severe cases of SC where trials with haloperidol and diazepam have failed.¹¹ CBZ is used in some institutions to treat SC. A comparative study from Turkey compared the effectiveness of VPA with CBZ on SC patients and revealed no significant difference between the groups with respect to time of clinical improvement and time to complete remission, duration of therapy and the recurrence rates.¹²

Because SC is an immune-mediated disease, it has been hypothesized that steroids in an immunomodulatory dose may ameliorate the symptoms of SC that are refractory to neuroleptic and antiepileptic drugs. Indeed, immune modulating therapy, like corticosteroids or immunoglobulin infusion, was found to improve SC.^{4,7,13-15} Several studies (case reports or retrospective cohorts) demonstrated that prednisone had improved the course of the disease.⁴ However, many of these reports noted a rapid relapse of symptoms or the development of important side effects. We completed the steroid therapy to 6 weeks because of the active carditis. So we gave the IVIG in combination with steroids.

Van Immerzeel et al reported a successful outcome of two patients treated with IVIG 400 mg/kg/day for 5 days.¹³ Garvey et al reported the comparison of plasma exchange and IVIG with prednisone. The results were not statistically significant but clinical improvement appeared to be more rapid and robust in the plasma exchange and IVIG groups.⁴

A novel randomized study made by Walker et al. compared the outcomes of 10 children treated with standard management alone with 10 who received additional IVIG.⁷ The outcomes were assessed using a clinical rating scale, brain singlephoton emission computed tomography, and the duration of symptomatic treatment. All three outcome measurement tools found to be improved in the IVIG group.

Although there are different treatment options in SC, there is no internationally accepted consensus for its treatment.¹⁶ Boersma et al.¹⁵ also administered their treatment similar to our case. Since our patient had

severe chorea, we initially given VPA, after added haloperidol. On the 14th day of hospitalization, we discontinued it because of an extrapyramidal side effect related to haloperidol. We started additional IVIG therapy to on-going 2 mg/kg/day prednisolone therapy after the fail of 14-day VPA therapy and 4-day haloperidol therapy to our patient and observed clinical improvement (chorea and carditis) 48 hours after the last dose of IVIG. We continued VPA treatment for 3 more months. Her active carditis findings had improved in 1 month after discharge. Our findings are correlated with the results of previous studies.

Conclusion

Sydenham's chorea is a infrequent presentation of ARF. Inadequate treatment of SC may result in severe functional disability. SC should be considered in the differential diagnosis in children aged 5-15 years with movement disorder. It has been reported that immunotherapy (especially IVIG and plasmapheresis) is beneficial in cases with severe chorea. Therefore, we conclude that IVIG therapy may help for improvement in severe SC and carditis patients whom didn't respond to classical medications such as VPA, dopamine receptor blockers and steroid.

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