CASE REPORT

Successful treatment of Sydenham's chorea with intravenous immunoglobulin

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SUMMARY

We present a case of a 10-year-old girl diagnosed with Sydenham's chorea. Despite treatment with haloperidol and valproic acid for 2 weeks and antibiotics for 5 days, her symptoms continued to worsen. She became severely impaired in daily functioning, as she could barely speak or walk, experienced major feeding difficulties and required help with all daily activities. She was treated with intravenous immunoglobulin (IVIG). Within 4 days, her symptoms started to improve and after 1-month she had fully recovered. This case reminds us that Sydenham's chorea can result in major functional impairment. There is some evidence on the beneficial effect of IVIG in the treatment of Sydenham's chorea, as is evident in our case. Therefore, IVIG should be considered as a treatment option in patients with severe chorea.

BACKGROUND

Sydenham's chorea (SC) is one of the manifestations of acute rheumatic fever. It is characterised by chorea involving the face and extremities and can include psychiatric symptoms, hypotonia and muscle weakness.¹⁻³ Despite a declining incidence in high-income countries, SC remains the most common cause of childhood chorea,¹ occurring in approximately one-third of patients with acute rheumatic fever.⁴⁻⁶ Symptoms are most likely caused by anti-neuronal antibodies, which are formed after an infection with group A *Streptococcus*.⁷ The severity ranges from mild choreatic movements to severe functional impairment.²⁻⁸ SC is a self-limiting disease.⁴⁻⁹ However, symptoms can persist for months or years and relapses are not uncommon, making adequate treatment desirable.²⁻³⁻⁸

Treatment of SC consists of elimination of group A *Streptococcus*, prophylaxis to prevent recurrences and rheumatic heart disease, treatment of neuropsychiatric symptoms and supportive care.¹⁰ Various medications have been used to treat the chorea, such as dopamine receptor antagonists (eg, haloperidol), antiepileptics (eg, valproic acid or carbamazepine) and prednisone.²⁻³⁻⁸⁻¹⁰⁻¹¹ Studies examining these medications in patients with SC are small and often observational, objective outcome measurements are limited and study populations are heterogeneous.¹¹ Therefore, the best choice of treatment is uncertain.¹¹ Considering the suspected antibody-mediated pathogenesis of SC, intravenous immunoglobulin (IVIG) has also been proposed as a treatment option.¹⁰⁻¹¹ This case report describes a case of a patient with SC in whom treatment with IVIG was successful.

CASE PRESENTATION

A 10-year-old girl presented to the emergency department because of intermittent involuntary movements, loss of sensation in her left arm, slurred speech and an unstable gait since 3 days. The week before, she had experienced a runny nose without a sore throat or fever. She had no history of other illnesses, joint pain, skin rash or intoxication. She did not use any medication and her family history was negative for neurological or autoimmune conditions. At the emergency department, her symptoms seemed to be absent and neurological examination was completely normal. An MRI and electroencephalography of the brain were normal and she was sent home with a follow-up appointment. In the following week, the involuntary movements spread to her other extremities and face, which impaired her walking, speech and eating. Eleven days after the onset of her symptoms, she was admitted to the hospital for observation and further diagnostic testing with a presumed diagnosis of SC.

INVESTIGATIONS

MRI of the brain and electroencephalography showed no abnormalities. Laboratory investigations showed a normal complete blood cell count, erythrocyte sedimentation rate (ESR) of 19 mm/h, C reactive protein (CRP) of 1 mg/L, normal glucose and normal thyroid-stimulating hormone (TSH). Serology was negative for *Mycoplasma pneumoniae* and herpes simplex virus. Antinuclear antibody (ANA) and antineutrophil cytoplasmic antibody (ANCA) screening were negative. Antiphospholipid antibodies were negative. The antistreptolysin O (ASO) titre was 1560 IU/mL (reference value <200 IU/mL) and the anti-DNase B titre was 2970 U/mL (reference value <200 U/mL), indicating a recent streptococcal infection. Throat culture only revealed commensal bacteria. Echocardiography, to exclude rheumatic heart disease, showed minor mitral valve regurgitation. Ophthalmic evaluation revealed no Kayser-Fleischer rings, characteristic of copper accumulation in Wilson's disease, and plasma levels of ceruloplasmin were normal.

DIFFERENTIAL DIAGNOSIS

SC is the most common cause of childhood chorea,¹ but there is an extensive differential diagnosis, including infections, autoimmunity, endocrine disorders, intoxications, intracerebral (vascular) lesions and inherited diseases.¹²⁻¹³ Infectious causes include central nervous system infections with herpes simplex virus, varicella-zoster virus, mycoplasma and, rarely, infections with HIV or spirochetes.¹²⁻¹³ On the basis of the negative serology and normal

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blood cell count, ESR and CRP, an infectious cause was less likely in our patient. Several autoimmune diseases (such as systemic lupus erythematosus, central nervous system vasculitis and the antiphospholipid syndrome) can cause childhood chorea.^{12 13} However, our patient had no additional symptoms, negative ANA and ANCA screening and negative antiphospholipid antibodies. Genetic diseases (such as phenylketonuria, mitochondrial diseases, Wilson's disease or Huntington's disease) were highly unlikely because of a negative family history, the age of our patient, normal ophthalmic examination and normal blood tests. Hyperthyroidism was ruled out by a normal serum TSH. There was no history of intoxication or any sign of cerebral ischaemia or localised disease on MRI. On the basis of the clinical presentation in combination with elevated ASO and anti-DNase B titres, our patient was diagnosed with SC.

TREATMENT

After she was diagnosed with SC, our patient was treated with amoxicillin 500 mg three times a day for 5 days (37.5 mg/kg/day), followed by feneticillin 250 mg two times a day (12.5 mg/kg/day) for 5 years to prevent recurrent streptococcal infections and thereby prevent rheumatic heart disease. To reduce chorea symptoms, valproic acid 12.5 mg/kg/day was prescribed. She was admitted for 4 days. On discharge, haloperidol 0.3 mg two times a day (0.015 mg/kg/day) was added, because there had been no diminution of the choreatic movements.

After her discharge, the symptoms gradually worsened over the following 10 days. Eventually, she suffered from continuous choreatic movements, which severely impaired her daily functioning. She could barely speak or walk, experienced major feeding difficulties and lost 3 kg body weight. To quantify chorea severity, several rating scales have been proposed.¹⁴ Recently, Walker *et al*¹⁴ developed the Red×Clinical Rating Scale, which is easy to use by untrained physicians. At the time of her most severe chorea, our patient scored 28 of the maximum of 30 points (video 1, online only).

She was readmitted 11 days after her initial discharge and received IVIG (2 g/kg). The haloperidol was stopped because of insufficient effect. The valproic acid was optimised to 25 mg/kg/day. Supportive care consisted of enteral feeding, physiotherapy and speech therapy to allow communication and safe swallowing.

Video 1 Patient experiencing Sydenham's chorea before treatment with intravenous immunoglobulin (see online for video).

OUTCOME AND FOLLOW-UP

In summary, at first presentation our patient had a history of mild chorea symptoms. Eight days later, she was admitted to the paediatric ward because of increasing symptoms. She was treated with amoxicillin and valproic acid. Three days later, she was discharged and haloperidol was added. Eleven days after her discharge, she was readmitted because of severe disabling chorea and treated with IVIG, while haloperidol was stopped.

Four days after administration of IVIG, the chorea started to improve. Within 10 days, our patient was able to sit up and walk short distances. At this point, her chorea severity was 15 on the Red×Clinical Rating Scale.¹⁴ After a hospital admission of 11 days, she was admitted to a rehabilitation centre, where her symptoms continued to improve. Four weeks after IVIG administration, she had fully recovered and was discharged from the rehabilitation centre. The following week, she stopped using the valproic acid, which she had used for 7 weeks in total.

One year after her initial presentation, she developed mild difficulties moving her left arm and leg. Occasionally, her speech was slurred. Also, there were some involuntary movements of her left hand. All symptoms were mild, with a maximum score of 4 on the Red×Clinical Rating Scale.¹⁴ Throat culture showed no potentially pathogenic microorganisms. She was treated with amoxicillin 500 mg four times a day (35 mg/kg/day), for 5 days. The symptoms disappeared after 8 weeks without any additional treatment. Repeat echocardiogram after 1.5 years showed minor mitral valve regurgitation, similar to the initial echocardiogram. This will be followed up.

DISCUSSION

The exact effect of IVIG in the treatment of SC remains unclear, but it is suspected that immunoglobulin inactivates anti-neuronal antibodies that are formed in SC.^{10 11} To the best of our knowledge, there are only three relevant previous reports on the use of IVIG in patients with SC.^{15–17}

In a trial by Walker *et al*,¹⁵ 20 children were randomised into two groups, either receiving only haloperidol (0.025–0.05 mg/kg/day) or a combination of haloperidol and IVIG (1 g/kg on 2 consecutive days). Chorea severity was quantified by a self-designed rating scale, based on several previously reported rating scales.^{16 18 19} The scale consisted of 16 items. If the symptom was present, it would score 1 point, regardless of the intensity of that specific symptom. The chorea severity was significantly lower at 1 month (p value 0.006), 3 months (p value 0.011) and 6 months (p value 0.034) after diagnosis in children receiving IVIG in addition to haloperidol.

Garvey *et al*¹⁶ randomised 18 children into three groups: 4 were treated with IVIG (1 g/kg on 2 consecutive days), 6 with prednisone (1 mg/kg/day during 10 days, followed by a taper) and 8 with plasma exchange (5 or 6 procedures with 45 mL/kg of plasma volume exchanged per procedure). They also used a self-designed scale to assess chorea severity. Symptoms were scored on frequency, intensity and amplitude. Also, the ability to perform daily activities was incorporated in their rating scale. The chorea severity 1 month after treatment was lower in the group of children treated with IVIG, compared to children treated with plasma exchange or prednisone. However, these differences were not statistically significant, possibly due to the small groups.

A major quality of the two clinical trials is their randomised design.^{15 16} These studies also have several limitations, however. First, the patient and the investigator were not blinded for the treatment and there was no placebo used in the control groups. Second, other conditions (such as hospitalisation) were not the

same in the intervention group as in the control group. Third, since IVIG is an experimental treatment, it is most likely that the patients described in these trials form a selected group of patients with severe symptoms. This leads to poor generalisability of the results to the entire group of children with SC. Also, the optimal timing and dosage of IVIG for patients with SC has not been investigated.

In addition to these trials, van Immerzeel *et al*¹⁷ presented two children who completely recovered from their chorea within 1-week after IVIG administration (400 mg/kg/day for 5 days).

In our case, it is most likely that the treatment with IVIG led to the improvement of symptoms (instead of the natural disease course), since the chorea symptoms were still progressing before treatment with IVIG and started to lessen shortly thereafter.

Full recovery was achieved 1 month after IVIG administration, which is relatively long compared to the cases described by van Immerzeel *et al*.¹⁷ It is important to emphasise that our patient had a very severe presentation of SC.

To conclude, SC can result in major functional impairment for which adequate treatment is needed. Treating SC with IVIG could be beneficial. However, the amount and quality of evidence are limited. Therefore, we recommend considering IVIG as a treatment option on an individual basis in case of severe functional impairment.

Patient's perspective

- ▶ Powerlessness, anger and grief. The first period of her disease and the hospital admission were very difficult for our daughter. She turned from a healthy 10-year-old girl into a helpless child who could not even eat anymore. After the treatment with intravenous immunoglobulin (IVIG), she slowly started to improve. It is still difficult for her to talk about this period. Once in a while she speaks about it, but she mainly mentions that she felt angry and sad. She was not able to do anything and she felt like nobody understood her.
- ▶ For us as her parents, the first period of her disease was very difficult as well. We saw the symptoms increase in our normally healthy daughter and wondered where this would stop. We feared that she might have a brain tumour, because the first investigations were aimed at her head. After the diagnosis of Sydenham's chorea, she received medication and we took her home. She could not sit up or walk without assistance. One of us constantly had to be with her. Everything revolved around her and sadly her younger sister often did not get enough attention. The nights were tough, because she also suffered from severe uncontrolled movements at night. She was covered in bruises. The symptoms worsened and we could no longer communicate with her or feed her. She often choked on her food. She had to be readmitted to the hospital. This caused a lot of distress, because she did not want to leave her own environment. She was treated with IVIG and got a nasogastric tube. We were all very sad and the next 2 weeks were full of uncertainties. At first, there was almost no progress and we felt discouraged. After a few days, we noticed small improvements, or didn't we? We were so afraid to be disappointed that we hardly dared to believe we saw these improvements. When she was clearly getting better, we were very relieved. After she was admitted to the rehabilitation centre, she got much better quickly. One month after the treatment with IVIG, she returned home, safe and sound.

Learning points

- ▶ Sydenham's chorea can result in major functional impairment for which adequate supportive care and symptomatic treatment is needed.
- ▶ Various medications are currently used to reduce chorea, but due to lack of solid evidence there is no international consensus on the preferred choice of treatment.
- ▶ There is some evidence for a beneficial effect of intravenous immunoglobulin in the treatment of children with Sydenham's chorea. Therefore, it should be considered as a treatment option in case of severe functional impairment.

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Contributors NAB wrote the article; JH was in charge of the patient from an infectious disease perspective. JH and HS took care of the patient and helped write the article from their own specialism. TK advised on the care of the patient and supervised the case report.

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