Successful rituximab therapy for pediatric antiphospholipid-related chorea: a case report and review of the literature

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Title: Successful rituximab therapy for pediatric antiphospholipid-related chorea: a case report and review of the literature

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Abstract

Chorea is considered a non-thrombotic manifestation of the antiphospholipid syndrome, often preceding thrombotic events in children. It can be present in up to 5% of pediatric patients with antiphospholipid syndrome. Immunomodulatory treatment regimens seem to be successful in these patients, emphasizing the underlying immunological etiology. Corticosteroids are considered first line treatment, but chorea tends to be therapy-resistant and guidelines about second-line therapy in children are solely based on small case studies. We present a case of a therapy-resistant chorea, successfully treated with rituximab. Furthermore, we give an overview of the existing literature concerning rituximab for the
Treatment of chorea in children. Our findings indicate that rituximab can be considered a safe option to treat APS-related chorea in children.

**Keywords**

Chorea, antiphospholipid syndrome, rituximab, child
Introduction

Chorea is defined as involuntary, non-repetitive and jerky movements that are variable in speed. The dancelike appearance resulted in the term chorea, which finds its origin in the Greek word for dance or ‘χορός’. Voluntary acts typically amplify the choreatic movements and therefore fine motor skills are often compromised. Chorea can coexist with athetosis and/or (hemi)ballism, and are often difficult to distinguish from each other. Athetosis is described as a choreatic movement with a slower rate, often originating from the distal upper extremities. Ballism on the other hand, is a forceful, flinging movement that arises mostly from proximal muscles, generating a larger amplitude.\(^1\,^2\) Chorea results from dysfunction of neural networks connecting basal ganglia, thalamus and frontal cortex, and are due to impairment of inhibitory gamma-aminobutyric acid output. Etiology of chorea is extremely diverse, and is preferentially classified as acquired, inherited or idiopathic, although age and rapidity of onset are used to differentiate etiology.\(^1\) In children, Sydenham chorea, due to a group A streptococcal infection, is the most important cause of chorea, accounting for more than 50% of cases.\(^3\)

Antiphospholipid syndrome (APS) is defined by vascular thrombosis or pregnancy morbidity combined with persistently positive antiphospholipid antibodies (aPL): lupus anticoagulant (LA), anticardiolipin antibodies IgG and IgM (aCL) and anti-beta-2-glycoprotein-I antibodies IgG and IgM (anti-β2GPI). In the pediatric population, this definition is of limited use, as in children non-thrombotic clinical manifestations such as thrombocytopenia, hemolytic anemia and neurological disorders, including chorea, can precede thrombosis.\(^4\,^6\) Currently, the Task Force on APS Classification is working on the development of new diagnostic criteria.\(^6\) APS can be primary, or secondary, associated with other disorders, of which systemic lupus
erythematous is the most important one in children. Prevention of (secondary) thrombosis and immunomodulation are the cornerstones of APS treatment.

Rituximab is a chimeric monoclonal antibody against CD20-positive B-cells and is widely used in pediatric medicine, for the treatment of non-Hodgkin lymphoma and nephrotic syndrome. In rheumatology, rituximab is used as second-line treatment in adult patients with systemic Lupus erythematous (SLE) and catastrophic APS. In children, its use in rheumatology is scarce and mainly recommended for SLE patients with life-threatening or refractory symptoms.

This case report describes an 11-year-old girl presenting with a new-onset, progressive chorea. To the best of our knowledge, this is only the second case of successfully managed antiphospholipid-related chorea with rituximab administration. We give an overview of the existing literature concerning rituximab for the treatment of chorea in children.

Case report

An eleven-year-old girl with no significant medical history presented with progressive involuntary movements of all four limbs, head and mouth. These movements suddenly started one week before presentation, as small movements of mouth and tongue, affecting her speech. Intermittently she complained of diplopia. She had no fever, but did suffer from a cold three weeks prior to presentation. She did not take any medication or drugs in the weeks before presentation. Her parents originated from Nigeria, were not consanguineous and had no relevant medical history. Physical examination showed asymmetric choreatic movements of neck, face, upper and lower limbs, which were more pronounced in the upper
limbs. The predominantly hemiballistic movements disturbed normal gait and coordination. She was not able to walk independently in a safe way and a dysarthric speech was observed. Clinical tests for evaluation of chorea, more specifically spooning, milkmaid’s grip, darting tongue and touchdown sign, were all positive. Physical examination did not show any other abnormalities. Clinical evolution can be seen in table 1 and in the online video.

As Sydenham chorea is one of the most prevalent causes of acquired chorea, empiric treatment with amoxicillin and methylprednisolone was started. However, diagnostic work-up showed a negative bacterial throat culture, repeatedly negative antistreptolysin O titres, a normal electrocardiography and echocardiogram. Total blood count, C-reactive protein, sedimentation, thyroid, liver and kidney function were all normal. Initial brain magnetic resonance imaging (MRI) was normal, but was disturbed by motion artefacts. Despite this treatment, progression of chorea continued and work-up was extended. Cerebrospinal fluid analysis, including bacterial PCRs and cultures, was within normal ranges. Wilson disease was excluded and urinary organic acid analysis was normal. LA was normal but aCL IgG and IgM, as well as anti-β2GPI IgG and IgM were highly abnormal (table 2). These findings were compatible with an antiphospholipid-related chorea. Therefore acetylsalicylate and haloperidol were started, respectively for prevention of thrombosis and symptomatic treatment. Hydroxychloroquine was started as adjunctive immunomodulator. Since symptoms were still slowly progressive, therapy and differential diagnosis were reconsidered. MR angiography, performed after administration of benzodiazepines, did not show any sign of vasculitis. Tissue transglutaminase-IgA, allowing to exclude celiac disease, total complement, immunoglobulins and lymphocyte subsets were all normal. Serology for human immunodeficiency virus, hepatitis B and C, Borrelia and syphilis were normal as well. Echography of the abdomen, chest radiography and interferon-gamma-release assay were
reassuring, limiting the possibility of tuberculosis or lymphoma. Symptomatic treatment was switched from haloperidol to carbamazepine, due to lack of effect and possible long-term side-effects. Thrombotic prophylaxis was intensified to subcutaneous low-molecular-weight heparin (LMWH) and high-dose acetylsalicylic acid. Because of lack of improvement with methylprednisolone, the presumed late-effect of hydroxychloroquine and the quite disabling character of the chorea, adjunctive therapy with either intravenous immunoglobulins (IVIG), plasmapheresis or rituximab was considered. After thorough consideration, rituximab was administered, due to its considerable better safety profile and easier administration compared to plasmapheresis. Moreover, IVIG was poorly available due to the COVID-19 pandemic, and is not reimbursed in Belgium for this indication. Rituximab was given in a dose of 375 mg/m² weekly for 4 weeks, according to existing guidelines for administration in children with SLE.

Three days after the first administration, our patient started to improve, with clearer speech, less intensive hemiballistic movements of the left arm and better coordination. Whether this early clinical effect was due to the rituximab, the low-dose carbamazepine or the natural course of the disease, is not entirely clear, but she continued to improve during the following doses of rituximab. Hydroxychloroquine was stopped and corticosteroids were tapered over 8 weeks. Subcutaneous LMWH and acetylsalicylic acid were switched to rivaroxaban, allowing a long-term anti-thrombotic prophylaxis with a minimum of follow-up. Lab results after the first dose of rituximab showed an expected suppression of B-cells, and 2 months after presentation, only beta-2-glycoprotein IgG stayed elevated, but also normalised after 5 months. Presently, our patient is asymptomatic and functions normally. She is receiving monthly IVIG due to a hypogammaglobulinemia, as a consequence of the rituximab administration. Carbamazepine was successfully tapered one year after presentation. Anti-thrombotic prophylaxis is advised lifelong.
**Literature review**

A search through PubMed and Web of Science was performed in August 2021 with the following search terms; [chorea AND rituximab] and [antiphospholipid AND rituximab AND (pediatric OR child)]. All retrieved articles were analysed and the references of clinically relevant papers were scanned for identification of additional manuscripts. This query yielded only two other reports of rituximab use for chorea. Scanning through Google Scholar provided one other report of rituximab administration for APL-related chorea. Table 3 shows the characteristics of these patients retrieved from the literature as well as our own case.

**Discussion**

Chorea can be present in up to 5% of pediatric patients with APS. Different hypotheses exist on the pathophysiology of chorea in association with aPL. Historically chorea was contributed to the occlusion of lenticulo-striatal arteries and subsequent ischemia of the basal ganglia, but lack of neuroimaging abnormalities has subverted this hypothesis. Moreover, as immunomodulatory treatment regimens seem to be more successful in these patients than anticoagulation, a non-thrombotic immunological pathogenesis is more presumable than an isolated thrombotic cause. Probably there is a direct effect of aPL on neuronal tissue, interfering with excitatory pathways through glutamate receptor overactivation, possibly resulting in chorea. Considering these mechanisms, the positive effect of rituximab could be explained by B-cell depletion, leading to a decreased antibody production as seen in different patients, as well as in ours. But the effect of rituximab seems to be more extensive than a solely reduction of B-cells, as it is probably altering autoreactive lymphocyte response. Rituximab normally is reserved for children with refractory or life-threatening symptoms of autoimmune diseases, as already suggested in pediatric rheumatology guidelines. In children
with chorea linked to autoimmune diseases, the use of rituximab in clinical practice is limited, but its mechanism of action, makes it an interesting treatment option. Our case emphasizes the safe and successful administration of rituximab, with complete resolution of chorea within weeks. Of course, prospective studies need to investigate in which circumstances rituximab can have an added value in treating not only chorea, but also other complications of autoimmune diseases. A limitation to this case report is the lack of a second elevated aPL titre up until now. This could be explained by the longstanding effect of B-cell depletion following the four-week course of rituximab. The absence of an elevated aPL theoretically makes a classification of primary APS impossible, however, lack of other causes of chorea and high titres of all four aPL antibodies, allows us to retain the original diagnosis.

To conclude, chorea in children has a broad differential diagnosis and an extensive work-up is obligatory. Treatment of chorea should not only be symptomatic but also guided by the underlying etiology. As chorea is a rare but important neurological complication of APS and other autoimmune diseases in children, early immunomodulatory treatment needs to be taken into account. Rituximab can be considered a safe option if corticosteroids fail, allowing an early and successful resolution.

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References


Appendix: Tables

Table 1: Clinical evolution and treatment of chorea

Table 1: Clinical evolution and treatment of chorea. N.A.: not applicable. aCL: anticardiolipin antibodies IgG and IgM; anti-β2GPI: anti-beta-2-glycoprotein-I antibodies IgG and IgM; LMWH: low molecular weight heparin.
**Table 2: evolution of autoantibodies**

Table 2: Evolution in autoantibodies. N.P.: not performed; U/mL: units per milliliter; g/L: gram per liter; µL: microliter; Ig: immunoglobulins; ANA: antinuclear antibodies; ANCA: Antineutrophil cytoplasmic antibody; C3: complement C3; C4: complement C4.
Table 3: Characteristics of patients treated with rituximab for chorea

Table 3: Characteristics of patients treated with rituximab for chorea. F: female; aCL: anticardiolipin antibodies IgG and IgM; anti-NMDAR: anti-N-methyl-D-aspartate receptor; anti-β2GPI: anti-beta-2-glycoprotein-I antibodies IgG and IgM; aPLs: antiphospholipid antibodies; LA: lupus anticoagulant.
Video file

Video 1: clinical evolution of chorea before and after rituximab administration.

Descriptive legend: the video file consists of a series of clinical neurologic examinations, showing improvement after rituximab administration. The timeline is indicated by the text shown at the beginning of each fragment.