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EDITORIAL

Conventional and intravenous immunoglobulin therapy in paediatric antiphospholipid antibodies-related chorea

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Chorea is one of the non-thrombotic neurological complications associated with antiphospholipid antibodies (aPL) and it is the most common motor disorder associated with autoimmune disease both in adult and paediatric populations.[1–3] It is characterized by involuntary, aimless, rapid, non-stereotyped movements involving mainly face and limb muscles; psychiatric symptoms such as emotional lability or obsessive-compulsive behaviour could also be present.[4]

Chorea may occur in the context of central nervous system infections (herpes simplex virus, varicella zoster virus, mycoplasma) and other diseases of different aetiologies (neurodegenerative, metabolic, genetic, vascular, endocrinological and toxic).[5]

Sydenham's chorea (SC) caused by streptococcal infection is the most prevalent form of acquired chorea in children between the ages of 5 and 15 years,[4] though chorea may also be a neurological complication of systemic lupus erythematosus (SLE) and is strongly correlated with aPL positivity.[1,6]

Chorea has been described in association with primary antiphospholipid syndrome (APS, Hughes' syndrome) in a number of patients, many of whom were children.[2,3] In recent years APS has been increasingly recognized in various underlying paediatric autoimmune and non-autoimmune diseases.[7] The diagnostic criteria of paediatric APS are the same as in adult patients, excluding recurrent fetal losses,[2] and do not take into account patients presenting aPL-related non-thrombotic clinical manifestations that are common in the paediatric population, especially in underlying autoimmune disease.[8]

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It is known that non-thrombotic complications, in children as well as adults, can precede the onset of APS, before the occurrence of thrombosis.[9] In the Ped-APS Registry,[2] of the 19% of children presenting with associated non-thrombotic clinical manifestation at the time of the initial thrombotic events, 7% had migraine, 4% chorea, 3% epilepsy and 1% mood disorder. aPL may produce neurological signs indirectly causing brain endothelial dysfunction[10] or directly damaging the white matter and structures binding to the neuronal cell surface of the basal ganglia, that are the cerebral structures responsible for the movement disorder.[11]

In most cases chorea is a benign, self-limiting condition lasting six to seven months and, when it is disabling and protracted, symptomatic treatment is useful.[4] In the literature several studies are related to the management of adult and paediatric SC, a neurological complication of acute rheumatic fever (ARF).

However, the common treatment both in adults and children is based firstly on the use of symptomatic therapy that can improve the neurochemical imbalance within the basal ganglia, between the neurotransmitters dopamine and gamma-aminobutyric acid (GABA), that can lead to motor disorder.[12] Dopamine receptor antagonists mainly used in children include haloperidol, risperidone and primozide (the last one used in children 12 years or older). Haloperidol is the first-line therapy used in children at a dose of 0.025 mg/kg/day in divided doses up to a maximum of 0.15 mg/kg/day. The treatment should last no more than four to eight weeks to avoid the risk of tardive dyskinesia and Parkinsonism.[12] Risperidone is also used in young patients affected by a severe type of chorea.[13] In adult patients other atypical neuroleptics and xenazine could represent effective alternatives, but there have been no controlled studies in children.[14] Valproic acid (20–25 mg/kg/day in two doses for 12 weeks) was considered effective and safe in the treatment of chorea, especially in severe cases when

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haloperidol treatment has failed.[13] Genel et al. compared the efficacy of carbamazepine (15 mg/kg/day) with valproic acid (20–25 mg/kg/day) in 24 children affected by SC, showing no significant difference between the groups in term of clinical improvement, time to remission and recurrence rates.[15]

The presence of antibodies against neuronal cell surface in patients affected by SC or other chorea-related autoimmune diseases, including aPL-related chorea, suggests the possibility of using immunomodulant treatment in these cases.[3,10] In the literature many studies reported the efficacy and the beneficial use of corticosteroid and intravenous immunoglobulin (IVIG) treatment in autoimmune paediatric diseases.

Cardoso et al. first reported on the use of immunosuppressive treatment with steroids in SC patients resistant to conventional therapy, suggesting that corticosteroid treatment is well tolerated and effective.[16] Another randomized, double-blind study evaluated 22 children affected by SC treated with prednisone (2 mg/kg/day) for four weeks. In the following eight to 12 weeks these patients showed a significant reduction in chorea movements compared with a 15-patient placebo group.[17] Teixera et al. first reported on the use of intravenous methylprednisolone treatment, followed by oral prednisone.[18] Fusco et al. showed in a four-year observational study the beneficial use of intravenous methylprednisolone (25 mg/kg) in 10 patients with a paralytic form of SC for five days, followed by oral deflazacort therapy (0.9 mg/kg/day).[19] Although deflazacort therapy appears to have less negative impact on growth rate and on metabolic sequelae than prednisone treatment, several potential severe side effects can occur, especially in young people (Cushing's syndrome, hypertension, effect on growth and weight). Also Dale et al. reported on the use of methylprednisolone and oral prednisolone in young patients presenting with chorea associated with SLE and aPL, or aPL only. In patients resistant to corticosteroid treatment, azathioprine, cyclophosphamide, plasma exchange and rituximab are also used.[3]

In recent years IVIG therapy has been successfully used in young patients with severe forms of chorea who failed to respond to conventional therapy[20] or have developed severe side effects (parkinsonism and dystonia).

In the management of movement disorders associated with aPL positivity, several different therapeutic strategies have been proposed, mainly in adult patients.[21–23] In the literature there are no clinical studies on the use of IVIG in children with aPL-related chorea. On the other hand, there are data on the use of IVIG treatment in SC.

van Immerzeel et al. reported on two children with SC successfully treated by IVIG (0.4 g/kg/day for five days).[20] Garvey et al. compared plasma exchange and IVIG with prednisone in eight children affected by SC (IVIG was used at a dose of 1 g/kg/day for two days). The authors found no statistically significant differences between the three groups, but clinical improvement was more rapid and robust in the IVIG and plasma exchange groups than in the prednisone ones.[24]

Walker et al. compared 10 children affected by SC treated with standard management alone to 10 children who received IVIG, demonstrating an improved outcome in clinical rating scales and brain single-photon emission computed tomography in the group treated with IVIG.[25]

In the literature the correlation between aPL-related chorea and ARF is well known mainly in adult patients, suggesting a possible overlap in humoral and cellular autoimmunity.[26,27] These are two diseases linked by a similar pathogenic mechanism in which the same therapeutic approach can be considered.

Recently we reported for the first time clinical details of two children presenting with aPL-related chorea during streptococcal and varicella infection.[28] Both cases underwent cranial and medulla magnetic resonance imaging (MRI) with negative results and a detailed immunological assessment that excluded SLE and other autoimmune diseases. In the first case only antinuclear antibodies (ANA) were found to be positive and lupus anticoagulant was positive several months after the acute phase with transient positivity in the following assessments. In the second case anti-β2 glycoprotein IgM and ANA were found to be positive. Both children failed to respond to conventional therapy (haloperidol, valproic acid, oral corticosteroids), and dramatically improved within one month after the first IVIG treatment with a complete resolution of the chorea one month after the second IVIG treatment. There were no side effects and both girls have a good tolerance.

Although the mechanism by which the IVIG acts isn't known, a possible involvement of B cell lymphocytes can inactivate antineuronal antibodies in patients affected by SC and in other autoimmune diseases with chorea[3] by an anti-idiotype network, as demonstrated in other autoimmune diseases.[29]

These data suggest that IVIG treatment is beneficial and useful in paediatric aPL-related chorea, and it should be considered as a treatment option in children who do not respond to conventional

treatment. Moreover, IVIG could be important not only for the clinical effect but also to prevent prothrombotic disease in APS. However, we encourage other case reports and prospective studies on children to allow a better evaluation in large series and to better understand the mechanism of efficacy of IVIG in neurological aPL manifestations.

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Conflict of interest statement

The authors have no conflicts of interest to declare.

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