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Opsoclonus Myoclonus Syndrome: Response to Plasmapheresis

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An 18-month-old with idiopathic opsoclonus-myoclonus, refractory to therapy with ACTH, corticosteroids, and clonazepam received plasmapheresis along with oral corticosteroids and azathioprine. The subject improved dramatically following this treatment. Anticerebellar antibodies were detected from the plasma in this patient and in a 2½-year-old girl with cerebellar ataxia secondary to an adrenal ganglioneuroma.

Key words: *Opsoclonus myoclonus syndrome, Plasmapheresis, Antineuronal antibodies.*

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Opsoclonus-myoclonus syndrome (OMS) is a rare neurological disorder characterized by progressive opsoclonus (irregular, rapid, horizontal and vertical eye movements), myoclonus, cerebellar dysfunction and severe hypotonia. Evidence for an autoimmune mechanism includes the presence of serum autoantibodies to several neural antigens and improvement of symptoms with immunosuppressive therapy.

Plasmapheresis has been described as a modality of treatment in idiopathic OMS(1). We report the beneficial effects of plasmapheresis in, to the best of our knowledge, in the youngest patient of OMS in the world literature. We also found the presence of antineuronal antibodies in 2 subjects with OMS, which indicate its autoimmune etiology.

Case Report

An 18-month-old male boy born of non consanguineous marriage was brought with complaints of instability of gait, chaotic eye movements and severe irritability, since one year of age, following an attack of fever. He was asymptomatic till then, with normal

developmental milestones. There was no significant prenatal, natal, or postnatal insult. There was no family history of similar illness.

He was diagnosed as having post-viral cerebellar ataxia in the local hospital, and was treated with dexamethasone and clonazepam. The ataxia improved initially, but relapsed when corticosteroids were tapered. Brain MRI, EEG, 24 hr urinary catecholamines, abdominal ultrasound, and peripheral smear were normal. On examination he was highly irritable, and had chaotic eye movements, titubation, severe truncal ataxia and bilateral intention tremor. The sleep was interrupted due to frequent myoclonic jerks of the limbs, and there was loss of ability to communicate even non-verbally. A provisional diagnosis of idiopathic opsoclonus myoclonus syndrome was made, and he was investigated to rule out an occult neuroblastoma. Chest X-ray, CT scan of the chest and abdomen, bone marrow study and urinary catecholamine level were normal. He was started on ACTH injections at a dose of 20 U daily subcutaneously with gradual increase to 40 U daily. There was significant improvement within 10 days, and ACTH was slowly tapered off over a period of 1 month. At this time the child was able to walk with support but still had severe bilateral intention tremor of the hands. Therapy with intravenous immunoglobulin (IVIG) was not possible due to the cost involved. The medical team, in consultation with the family, decided to initiate a trial of plasmapheresis with concomitant immunosuppression.

A plasmafilter (GAMBRO) was utilized with 40 ml/kg/day of plasma exchange with fresh frozen plasma as replacement fluid. Plasmapheresis was performed on days 1, 3, 5, and then twice weekly for two more weeks. He developed severe anemia with hemolysis after the last plasmapheresis, and received a fresh blood transfusion. Within 2 weeks after

initiation of pheresis he showed signs of improvement. By two months he made a near-total recovery. The patient also received concomitant treatment with prednisolone and azathioprine. Prednisolone was given for 6 months at a dose of 1 mg/kg/day, and then tapered gradually to 0.5 mg/kg as a single dose on alternate days for two years. Azathioprine (1 mg/kg/day) was given orally for a year.

Serum samples showed weak reactivity against 40 KD autoantibodies probably due to prior ACTH therapy and plasmapheresis.

The subject is now 5-year-old and off all medications since 12 months. His gross motor ability is normal for age, but his fine motor ability is below average though his handwriting is legible. The expressive and receptive language skills by Washington's scale are found to be appropriate for 4 years. He has normal social skills.

Another 2½-year-old girl child presented with cerebellar ataxia and opsoclonus of one yr duration, and on evaluation had a 1.8 × 2 cm tumor in the left adrenal gland. The serum, tested before removal of the tumour, showed reactivity against 150 KD, 54 KD and 62 KD autoantigens. Immunohistochemistry identified the tumor as a ganglioneuroma and hence no chemotherapy or plasmapheresis was given. The child gradually recovered and is asymptomatic since the last one year.

Discussion

Opsomyoclonus, myoclonic encephalopathy of Kinsbourne or "dancing eyes-dancing feet" syndrome is a devastating and debilitating disease with an unfavourable outcome. The pathophysiology of OMS has been speculated to involve IgG and IgM autoantibodies directed against neural antigens in cerebellar Purkinje cells, cerebral cortical neurons and axons. The auto-

antibodies in OMS are distinct and therefore suggest a causal relationship(1). The immune mechanism may be a Type II or IV hypersensitivity. However, it is not commercially viable to do routine autoantibody testing in OMS, due to the large variety of potential autoantibodies that may be found in OMS with Neuroblastoma(2).

The overall incidence of OMS in children with neuroblastoma is approximately 3%. Approximately 90% patients with neuroblastoma and OMS show long term survival, whereas only 55% of all children with NB survive their disease. The tumor of children with OMS are almost exclusively neuroblastoma, ganglioneuromas or rarely hepatoblastoma. The neuroblastoma associated with OMS is a small, well differentiated tumor with favourable histological subtype expressing low number of *n-myc* copies. Amplification of *n-myc* in neuroblastoma is known to correlate with advanced stage or rapid progression of disease. *N-myc* is never found in benign ganglioneuromas. The other agents known to cause symptoms of OMS include poisoning due to thallium, strychnine, organophosphates, toluene and drugs like amtryptiline, lithium, phenytoin.

Viruses such as Epstein-Barr virus, St. Louis encephalitis, Coxsackie B3 and mumps have been identified with postviral OMS. Post viral OMS is considered to be secondary to "molecular mimicry" wherein immune cells primed against the viral peptides attack neural cells expressing similar antigens(3). Anti-neurofilament antibodies of 210 KD (IgG) were found in sera from children with OMS and the disappearance of the antibody during ACTH treatment suggests clinical relevance(3-5). The mechanism of brain injury in OMS may be by direct attack by antigen specific T cells, non-specific lymphocytes such as natural killer cells or

cytokines released by activated cells or autoantibodies.

Currently, there is no well accepted treatment for OMS. Generally treatment has consisted of immunosuppression to reduce the formation of antibodies and towards removal of antibodies. ACTH and corticosteroids both lead to rapid improvement of the neurological symptoms, but most patients have frequent relapses following tapering or withdrawal of the drug(6). ACTH seems to act as a direct immunosuppressive and appears to inhibit the antibody response to T-cell dependent antigens. Corticosteroids decrease lymphocyte differentiation and proliferation, inhibit phagocytosis, and suppress production of interleukins(7). There are small case reports of treatment with IVIG, plasmapheresis and immunoadsorption in OMS patients(3,8,9). IVIG has shown promising results but needs to be administered in high dose for prolonged periods. IVIG downregulates interleukin 2 production by T-cells. Tumors, if associated, should be removed.

There is only a single case report in the world literature of therapeutic plasmapheresis for idiopathic OMS in a 6-year-old child(1). There is anecdotal evidence of cases in adults, but our patient was the youngest child ever to have undergone plasmapheresis for OMS.

Immunoadsorption offers the advantage of avoidance of colloid infusion following plasmapheresis. However the protein A column that are available bind only to IgG. Pheresis is more immunosuppressive by non-selectively removing other plasma proteins, which is an advantage in OMS where both IgG and IgM antibodies are incriminated.

The justification for concomitant use of oral immunosuppressive medications was based on prior evidence that the suppression of antibody production and prevention of

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antibody rebound effect were helpful in the outcome of this disease(10,11).Our patient tolerated these medications well and had no adverse effects other than transient cushingoid features. The dramatic clinical improvement in our patient within 2 weeks of initiation of plasmapheresis strongly supports the notion that it was the pheresis that was of benefit. He was able to walk without support following pheresis, which he had never been able to do with ACTH or corticosteroids. Earlier he relapsed whenever the steroid dosage was tapered, but this time the improvement was maintained even after discontinuing pheresis and after tapering the dose of corticosteroids. He has not had any relapse of OMS since 3 years post-pheresis.

We propose that plasmapheresis with concomitant oral immunosuppression should be considered as a potentially effective treatment for idiopathic OMS in a child who is refractory to conventional treatment with ACTH, corticosteroids and IVIG, because delay in treatment might lead to continued brain damage.

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