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Rituximab therapy in anti-musk positive juvenile myasthenia gravis; A case report

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Abstract

Juvenile myasthenia gravis is a rare acquired disease of childhood. It is difficult to differentiate it from congenital myasthenic syndrome due to the negativity of the Acetylcholine receptor antibody. The Muscle Specific Kinase (MuSK) positive Myasthenia gravis is uncommon in children with a different disease courses and response to treatment. We report a 15 Y/O girl presented with prominent oculobulbar manifestation. She experienced multiple exacerbations when receiving corticosteroids, Acetylcholine esterase inhibitors and Azathioprine. Because of the positive anti-MuSK antibody in her follow-up, Rituximab started for her with the diagnosis of MuSK positive JMG. Her symptoms improved dramatically in response to lower dose of Rituximab (in comparison with previous studies) and remission was established. We found that children with MuSK-positive myasthenia respond well to Rituximab despite the failure of other immunosuppressant medications or acetylcholinesterase inhibitors.

Keywords: Juvenile myasthenia gravis; MuSK positive; Muscle Specific Kinase antibody; Rituximab.

Abbreviations: JMG: Juvenile Myasthenia Gravis; Musk: Muscle Specific Kinase Achrab: Acetylcholine Receptor Antibody; LRP4: Lipoprotein Receptor-Related Protein 4; Achei: Acetylcholinesterase Inhibitor.

Introduction

Myasthenia Gravis (MG) is a B cell-mediated autoimmune disease. Antibodies are directed against the postsynaptic membrane of the neuromuscular junction and lead to fluctuating muscle weakness and fatigability. Juvenile Myasthenia Gravis (JMG) is a rare acquired condition of patients younger than 19 years, representing 10% to 15% of all myasthenia gravis patients. In particular, children have a higher prevalence of isolated ocular symptoms, a higher probability of achieving remission, and a lower frequency of acetylcholine receptor antibodies. In young children, diagnosis can complicated to differentiate it from congeni-

tal myasthenic syndromes, which do not have an autoimmune basis [1,2].

Acetylcholine Receptor Antibody (AChRAb) is positive in up to 80% of the patients. Anti-Muscle-Specific Kinase (anti-MuSK) antibody is present at the neuromuscular junction of less than 5% of myasthenic cases. The latter is rare in children and is associated with a more severe forms of the disease, recurrent respiratory crisis ,and oculofacial symptoms [3,4].

In children, the anti-muscle-specific kinase-positive myasthenia reported rarely. We report a 15 Years old girl with features of Juvenile MG and positive for anti-MuSK antibody.

Case Presentation

A 15 Y/O girl, a known case of MG, came to our hospital with Respiratory distress, Diplopia and Nasal speech from 5 days prior to admission. Her symptoms began 6 months ago with left-side ptosis. Gradually progressive dysphagia, drooling, and respiratory distress added to her complaints and she was admitted with the diagnosis of MG in another hospital. Her symptoms completely improved after receiving 125 gr IVIG and she was discharged home with Pyridostigmine 60 mg TDS, Prednisolone 25 mg BD and Azathioprine 50 mg QID. From then on**,** she has been admitted several times with MG exacerbation.

In our center, she was awake and alert. Her speech was nasal. Without supplementary oxygen, she was mildly hypoxic with SPO_2 of 91%. She had rapid and shallow respiration and Decreased Neck force in flexion (4+/5). Lt side ptosis was present and there was a bilateral restriction of abduction and upward gaze. Facial strength was full and symmetric with tongue protrusion midline. Limbs' muscle force, tone and bulk, were all within normal limits. Deep tendon reflexes were 2+ in both upper and lower extremities, and bilateral plantar reflexes were down. The sensation was intact to light touch, vibration and joint position. There was no ataxia and her gait was normal. Her familial history was negative, and her pubertal age was 13 years old.

There was no gross pathology in thymus on the computed tomography scan. The CBC, estimated sedimentation rate, creatine kinase, serum chemistries and thyroid levels, were all in the normal range. Nasopharynx COVID PCR and PPD were negative and VZV IgG Ab was Positive. Acetylcholine Receptor Antibodies (AChRAb) and anti-Musk Antibodies (MuSKAb) tested with ELIZA. AChRAb was negative (0.1, N < 0.4 nmol/L) but she was positive for anti-MuSK Ab (>1/20).

Her symptoms improved after receiving 100 gr IVIG (1 gr/kg/day per dose). Because of multiple exacerbations despite regular treatment with corticosteroid, Acetylcholinesterase Inhibitor (AChEI) and Azathioprine, we decided to start of Rituximab as the maintenance treatment according to anti MuSK Ab positive JMG. She received 500 mg Rituximab and was discharged home with Pyridostigmine 60 mg TDS, and Prednisolone 50 mg daily.

She received two more doses of Rituximab (500 mg) at six-month intervals and Prednisolon withdrawn gradually with no exacerbation. Medication was tolerated well and she did not report any adverse effects. After the third dose of injection, her serum was negative for Anti MusK antibody.

Discussion

Myasthenia Gravis (MG) caused by a defect of neuromuscular transmission due to antibodies that affect postsynaptic nicotinic AChR or other functionally related proteins like muscle-specific kinase, Lipoprotein Receptor-Related Protein 4 (LRP4) and Agrin in the neuromuscular junction and leads to fluctuating weakness.

Serum Antibodies against AchR found in 80-90% of patients with generalized MG, and 60% of ocular MG [5-7]. In those who are negative for AChR Ab, Hoch *et al.* First informed a serum Immunoglobulin G (IgG) antibody against the inner surface of the muscle membrane protein called the Muscle-Specific Kinase (MuSKAb) in less than 10% of patients [8]. It is suggested that retrograde signaling rather than complement activation is the primary mechanism of MuSK-associated myasthenic symptoms [9].

There are three types of myasthenia in children: Neonatal MG, a transient disease in infants born to myasthenic mother; Congenital Myasthenic Syndromes (CMS), which are multiple inherited disorders of neuromuscular transmission without autoimmune basis, and Juvenile MG (JMG), with pathogenesis similar to the adult-onset form of the disease [10,11], differentiating congenital myasthenic syndrome from Seronegative MG in young children would be challenging.

When MG presents before 19 years of age, it is named Juvenile Myasthenia Gravis (JMG). Despite the similarity in symptoms of JMG and adult-onset MG, there are many vital differences between features of JMG and adult onset disease [1].

The MuSK-positive MG is usually more common in the elderly, and it is a rare condition of Childhood and has marked female predominance. MuSK antibodies accompanied by the more severe form of the disease with prominent facial and bulbar weakness and frequent respiratory crises [1,7]. MuSK-positive JMG, has a poorer response to acetylcholinesterase inhibitors, experience more exacerbations or myasthenic crises, and require multimodal immunosuppressive therapy [12].

The most frequent clinical presentation of JMG is ptosis, accompanied by unilateral or asymmetric ophthalmoplegia, which may cause strabismus and persistent amblyopia. Most children also develop generalized muscle weakness of the bulbar and limb musculature, resulting in dysphonia, dysphagia (recurrent pneumonia due to choking), and proximal limb weakness [1,13].

Ocular myasthenia is the most common presentation of prepubertal JMG. A lower rate of generalization has been reported in case series in children. The progression may be even less frequent in prepubertal group [1,14]. There is an equal male: female ratio, higher rate of seronegativity, a better prognosis, and a higher rate of spontaneous remission in the prepubertal age group. The peri- or post-pubertal onset has more similarity with the adult-onset type [1,10,11,15].

In children, although thymoma is rare, imaging of the thymus (usually by CT scan) is necessary once the JMG has been diagnosed. Thymus hyperplasia is the most commonly reported pathology, although it is even less frequent in MuSK-positive MG [1,15,16].

MuSK positive pediatric Myasthenic patients have less response to AChEI and thymectomy. Rituximab, an anti CD20+ B cell chimeric monoclonal antibody, has shown efficacy in adults with MuSK antibody-associated myasthenia gravis and refractory to other conventional immunosuppressive treatment; however, there is little experience in children. Here we report a successful trial of Rituximab administration in MuSK-positive JMG with a lower dose compared with previous studies.

8-year follow-up Cohort study, suggested the clinical efficacy and safety of Rituximab injection in achieving disease remission and cortisone sparing in JMG patients with the induction dose of 1gr in 2 to 3 weeks apart [17]. Another literature review on the effective regimen of Rituximab injection for JMG, suggested the protocol that exists for lymphoma(one infusion (375 mg/m2) per week for four consecutive weeks) [18]. Although Rituximab is well tolerated with few reported adverse effects, we recommend a lower dose of Rituximab(500mg induction and every 6 months) in order to achieve clinical and laboratory remission.

Conclusion

Although Juvenile Myasthenia Gravis (JMG) is a relatively rare disorder, it is potentially life-threatening. Rituximab with a lower dose of the previous recommended regimen can be a proper medication in order to achieve disease remission, clinically and laboratory, particularly in the MuSK-positive group.

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