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RESEARCH ARTICLE OPEN ACCESS

JUVENILE MYASTHENIA GRAVIS: MUSK POSITIVE: WITH 3 CARDINAL SIGNS

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ABSTRACT

Anti muscle specific tyrosine kinase (Musk) antibody is the most common antibody identified in seronegative myasthenia gravis (SNMG). Juvenile onset musk myasthenia has different clinical course as demonstrated in our case with spontaneous remission followed by resurgence of symptoms with ocular complaints. Musk myasthenia characteristically presents with bulbar and respiratory muscle involvement with a high rate of myasthenic crisis. Early identification is necessary to decrease the incidence of myasthenic crisis. We report a atypical case of musk myasthenia gravis with 3 cardinal signs which responded completely to immunosuppressants.

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INTRODUCTION

80% of myasthenia gravis (MG) are acetylcholine receptor antibody positive with rest 20% contributed by antibody negative myasthenia gravis known as seronegative myasthenia gravis (SNMG)(1). Muscle specific tyrosine kinase (MuSK) antibody was discovered by Hoch in 2001 contributing to approximately 70% of SNMG (2). Seronegative myasthenia gravis is no longer considered seronegative as newer antibodies are getting discovered like LRP4 (Low density Lipoprotein Receptor Related Protein 4) and Agrin (3), (4), (5). Musk myasthenia gravis is distinct from Ach- R myasthenia in clinical presentation as well as in its pathogenesis. 3 different clinical presentations were described by Guptill and Sanders as: 1) Patients with predominant bulbar and respiratory involvement, 2) Patients with presentation similar to Ach R antibody positive myasthenia gravis, and 3) Patients with isolated head drop (6). LRP4 and Musk form a tetramer which is responsible for Agrin induced clustering of AchR. This pathogenesis is blocked by Anti Musk antibodies (7). IgG4 antibodies are found in Musk MG as against IgG1 and IgG3 antibodies found in Ach Ab MG which causes complement activation (8). This pathogenesis makes different treatment strategies for Musk MG which responds to steroids and other immunosuppressive treatment more as compared to acetylcholinesterase inhibitor (9). Musk MG is a life-threatening condition with diagnosis relying mainly on the antibody levels as electrophysiology is mainly negative (10). Here we present a case report of juvenile musk MG patient who presented first with the ocular symptoms followed by bulbar involvement with 3 cardinal signs of the disease (11).

CASE REPORT

19 years old male came with complaints of bilateral drooping of eyelids at the age of 4 years, which resolved spontaneously within 1 month. Then at the age of 11 years he had similar complaints of drooping of eyelids which was more severe this time and with diurnal variation as he used to extend his neck for seeing objects in the evening. Approximately 1-month later patient had complaints of nasal voice as noted by friends. Subsequently 4 to 5 months later he developed episodes of nasal regurgitation which were more for liquid and semisolid meals. All these symptoms used to exacerbate in the evening with improvement after rest. He denied diplopia, shortness of breath and limb weakness. Examination revealed spontaneous and fluctuating bilateral ptosis. He had normal extra ocular movements without obvious dysconjugate gaze. He had no facial or jaw weakness; as well as no evidence of weakness in neck, trunk and limb muscles. Reflexes and sensory examination was normal. Also forced complete eye closure was not possible suggestive of orbicularis oculi muscle weakness unmasking the Barre sign. (FIGURE 1) Oral examination revealed grooved tongue with 2 additional to central grooves; (FIGURE 2) suggestive of trisulcated tongue. There were no tongue fasciculations. Deviation of uvula to right side revealing curtain sign was seen. (FIGURE 3) Electroneuromiography was within normal limits with no evidence of decremental response. So was the neostigmine test. Even so the patient was suspected to be myasthenia gravis and started on pyridostigmine with no significant improvement. MRI brain as well as CECT chest was normal. Thyroid, ESR, ANA and creatine kinase levels were normal. His AChR antibody titre was normal. MusK Ab titre was 10.4 U/ml. (positive>0.4). He was subsequently started on

steroids 1 mg/kg dose followed by significant improvement. In the next 6 months he did not have any nasal regurgitation episodes as well as voice improved. He was later started on immunosuppressant (azathioprine). In the following 6 months; the 3 semiological cardinal signs persisted with symptomatic improvement.

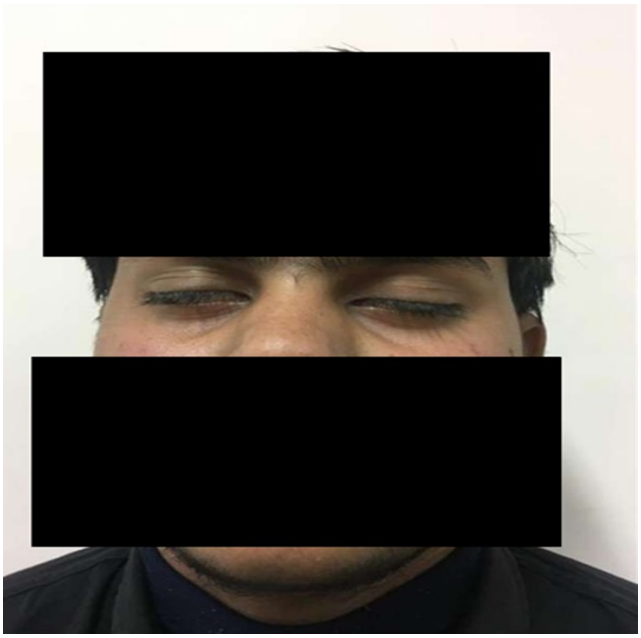

Figure 1. Barre sign: Incomplete forced complete eye closure suggestive of orbicularis oculi muscle weakness

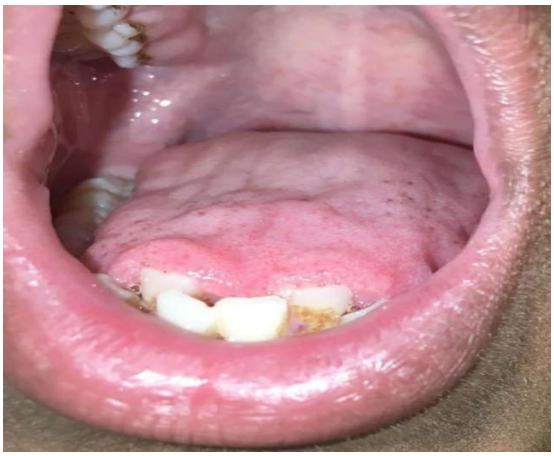

Figure 2. Trisulcated tongue: Oral examination showing grooved tongue with 2 groves additional to central groove

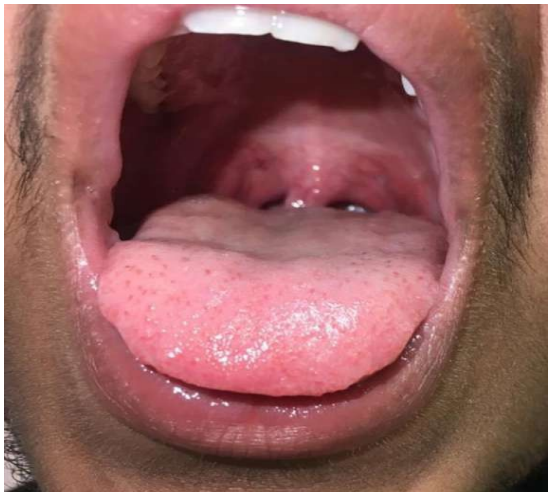

Figure 3. Curtain sign: Deviation of uvula to right side revealing

DISCUSSION

MUSK MG is clinically distinct from AchR MG. The distinct clinical feature of MuSK MG is bulbar weakness. Some cases present with ocular manifestations like AchR MG; like in our case which started with ocular symptoms at 4 years of age; although resolved spontaneously which is not seen in adult patients. NMJs are damaged irreversibly in the age-related manner in the MuSK Ab MG. Spontaneous improvement in MuSK MG is associated with developmental changes of NMJs. Anlar et al demonstrated a case of spontaneous improvement at 6 years of age (12). Electrophysiological testing is difficult in MuSK MG. EMG is also misleading as sometimes showing small polyphasic units suggestive of myopathy as against other times showing active and hyperexcitable features such as fibrillations and fasciculations suggestive of neurogenic disorder (13). Also, single fibre EMG is negative in as much as half MuSK MG in reports; so, this is also not a reliable investigation (14). Neostigmine test is also not reliable. So, diagnosis relies mainly on the antibody levels. Antibody levels falls after successful treatment (15). Also, with supportive evidence from 3 semiological cardinal signs as in our case points to musk positive myasthenia. Farrugia et al demonstrated the bulbar and facial muscle weakness and wasting with fatty replacement on MRI in MusK MG patients as against Ach AB patients (16). Musk antibodies per se lead to muscle thinning. Barre sign, curtain sign and trisulcated sign together are characteristically associated with Musk MG and support the diagnosis. Barre sign is incomplete closure of eyelids even after forceful effort due to weakness of orbicularis oculi. Trisulcated sign is presence of 3 grooves over tongue due to tongue atrophy. Curtain sign is deviation of soft palate and uvula. As the musk MG has higher chances of myasthenic crisis; so early diagnosis and management is lifesaving. With limited parameters to diagnose musk MG; 3 semiological signs can be useful for pointing diagnosis to the same.

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