Post-varicella myasthenia gravis

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ABSTRACT

Myasthenia gravis is an autoimmune disease of neuromuscular junctions. We report a three-year-old boy with post-varicella myasthenia gravis. This patient, to the best of our knowledge, is the youngest in age and second reported case of the condition. The patient presented with drooping of both eyelids which increased as the day progressed, two weeks after varicella infection. Repetitive nerve stimulation tests showed decremental response in action potential, and the child responded dramatically to test doses of neostigmine. A diagnosis of post-varicella myasthenia gravis was made and the patient was started on oral pyridostigmine. He is doing well at follow-up and there is no recurrence of symptoms to date.

Keywords: myasthenia gravis, post-varicella myasthenia gravis, repetitive nerve stimulation test, varicella infection

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INTRODUCTION

Myasthenia gravis is an uncommon disorder affecting neuromuscular junctions, characterised by easy fatigability of the muscles. It is known to have an autoimmune aetiology; however, cases with post-infectious origin have been reported. Myasthenia gravis after a *Varicella zoster* infection is even rarer, and is not mentioned in textbooks as a complication of the varicella infection. We report a three-year-old child with post-varicella myasthenia gravis who is, to the best of our knowledge, the second and youngest reported case in the world.

CASE REPORT

A three-year-old boy presented to Department of Paediatrics with a one-day history of fever, and vesicular eruptions starting from the trunk on the same day. Lesions were characteristic of chicken pox (varicella). The child was sent home with symptomatic treatment. After two weeks, the patient presented to us with an abrupt onset of drooping of both eyelids. The symptoms were less noticeable early in the mornings, and became more evident at mid-day, with progressive deterioration as the day advanced. There was no history of change in voice, difficulty in chewing, swallowing or breathing. The patient did not complain of any pain, sensory symptoms or limb weakness. On examination, the patient had marked ptosis of both eyes (Fig. 1). There was no evidence of any other cranial nerve involvement, motor or sensory deficit. The rest of the general and systemic examinations was essentially normal.

The patient was admitted and it was observed that his eyelid weakness definitely increased on exercise and decreased on rest. On investigations, his complete blood counts, erythrocyte sedimentation rate, sodium potassium, sugar, serum glutamic-oxaloacetic transminase, serum glutamate pyruvate transminase, creatinine kinase, and thyroid functions were normal. Anti-acetylcholine receptor (anti-AChR) antibodies were not detectable in his serum. On computed tomography (CT) of his thorax, there was no evidence of thymoma. Repetitive nerve stimulation test (RNST) of the right ulnar nerve at 5 Hz and 10 Hz showed 11% and 5% decrements and that of the left median nerve at 20 Hz showed a 78% decrement in the action potential, which was strongly suggestive of myasthenia gravis (Fig. 2). The patient was given a 0.04 mg/kg test dose of neostigmine intramuscularly and he showed

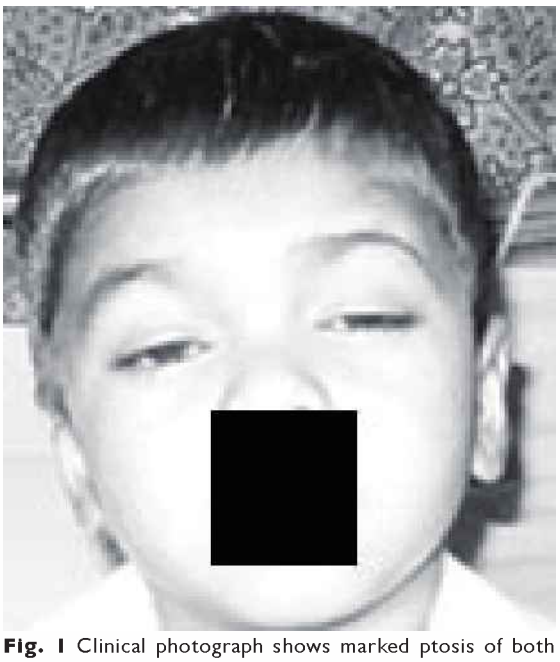

Fig. 1 Clinical photograph shows marked ptosis of both eyelids.

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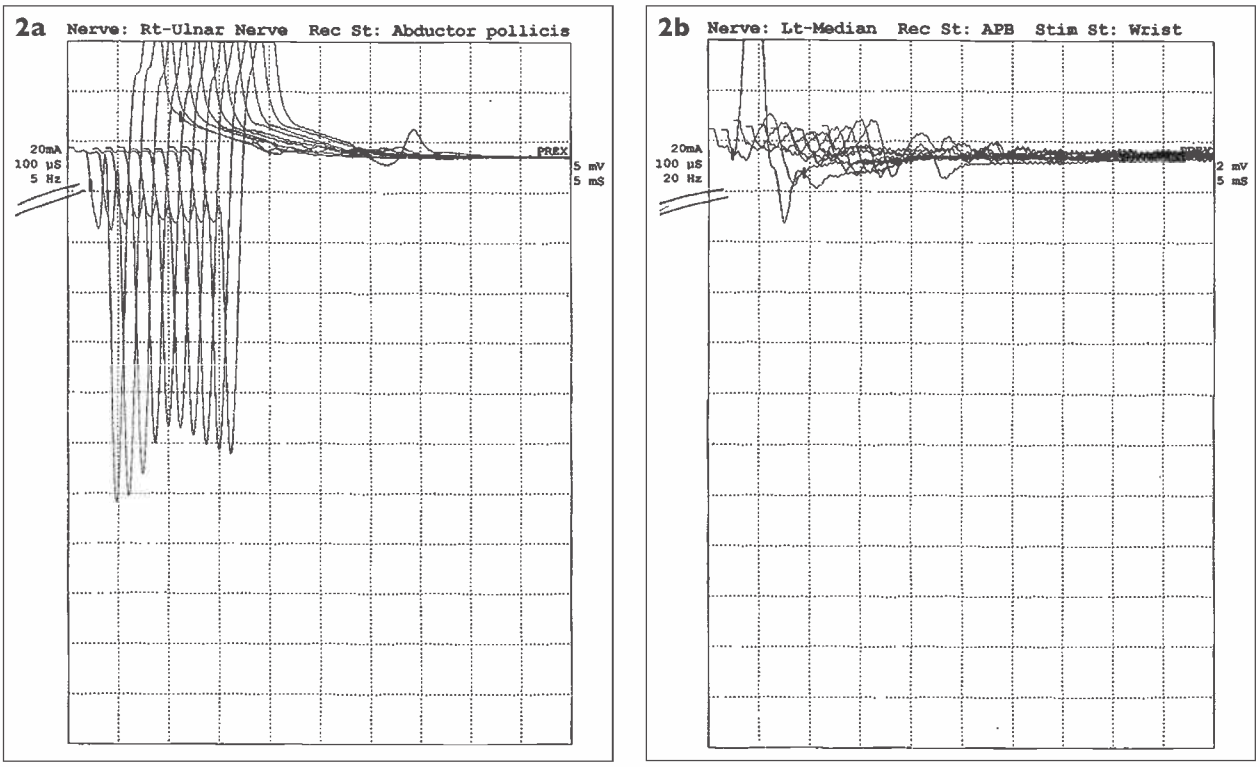

Fig. 2 Repetitive nerve stimulation test of (a) right ulnar nerve at 5 Hz; and (b) left median nerve at 20 Hz.

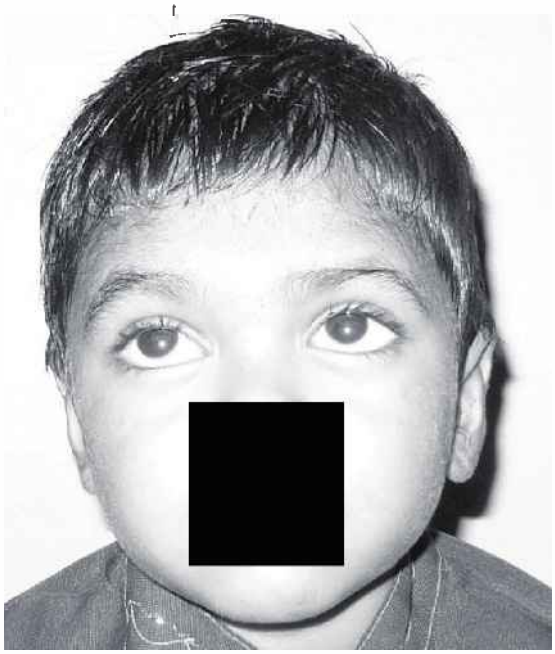

Fig. 3 Clinical photograph shows normal eyelids after the neostigmine test.

remarkable improvement within 30 minutes. This improvement was transient (Fig. 3). A diagnosis of post-varicella myasthenia gravis was made and the patient was put on oral pyridostigmine. The patient was discharged on a maintenance dose of oral pyridostigmine, in six divided doses, and has been on close follow-up for the last six months without any recurrence of symptoms. Repeat RNST after six months was normal.

DISCUSSION

Myasthenia gravis is a disease of the neuromuscular junction, with a prevalence of 50–125 per million population.[1] It is a disease of the older age group, with only 4.3% of patients having onset at less than ten years of age.[2] Myasthenia gravis is an autoimmune disorder and is characterised by decreased neuromuscular transmission. Approximately 90% of patients with myasthenia gravis have circulating anti-AChR antibodies directed against the nicotinic acetylcholine receptors present on the postsynaptic membrane at the neuromuscular junctions. The result is either a decrease in the number of AChRs at neuromuscular junctions, or certain morphological changes in the pattern of presynaptic membrane folding, or an increased gap between the nerve terminal and postsynaptic muscle membrane. Once AChR concentration is reduced to less than 50%, endplate action potential fails to generate an action potential required to cause the muscle contraction upon repetitive nerve stimulation.

10% of patients with myasthenia gravis are seronegative for anti-AChR antibodies. These patients are labelled as having seronegative myasthenia gravis

(SNMG). In some of these patients, IgG antibodies against muscle specific kinase (anti-MuSK) have been demonstrated.[3] In a series of 78 SNMG patients by Evoli et al, 37 patients were positive for anti-MuSK; with a female gender predominance. These patients had a predominant involvement of bulbar muscles (100%) and ophthalmoplegia (94.6%), and high incidence of respiratory crises (46%).[3] These anti-MuSK positive patients had more severe forms of the disease, 46% of them belonging to Class V according to Myasthenia Gravis Foundation of America classification (2000).[4] Response to pyridostigmine was poor in these patients and most of these (35/37) required immunosuppressive therapy and 22/37 required plasmapheresis. Our patient belonged to the SNMG group; but the clinical presentation of weaknesses were confined to ocular muscles only (Class I). He responded well to pyridostigmine. Gender and age of onset practically ruled out the possibility of anti-MuSK positive entity, though we could not demonstrate this due to non-availability of the test.

Though myasthenia gravis is known to be autoimmune in aetiology, viral infections have been proposed by many authors to play some role as well. Korn and Abramsky found evidence of preceding viral infection in five out of 50 cases of myasthenia gravis at their centre, where one of them developed it after herpes zoster and surprisingly, one after receiving a measles vaccine.[5] There have been previous isolated reports of myasthenia gravis after other viral infections, and even after immunisations and vaccines. In the present era of human immunodeficiency virus (HIV) pandemic, myasthenia gravis has also been reported as a complication of HIV and after dual infection with HIV and human t-lymphotropic virus (HTLV).[6]

A viral aetiology has been given attention recently in other autoimmune and collagen vascular disorders as well. Association of myasthenia gravis with HLA-B8 antigen, which is also linked to increased susceptibility to certain viral infections, gives supportive evidence for a possible viral aetiology.[7] Molecular mimicry has been demonstrated between the human AChR α subunit and a specific domain on *Herpes simplex* virus glycoprotein D with specific immunological cross reactivity.[8] This suggests viruses as a possible initiating agent in some cases of myasthenia gravis. A similar kind of sharing of antigenic determinants have been shown between α subunit of AChR and membrane proteins in *Escherichia coli*, *Klebsiella pneumoniae*, and *Proteus vulgaris*; this supports the hypothesis of the post-infectious origins of the disease.[9] Similar detailed immunological studies are required to prove the role of varicella in myasthenia gravis.

Diagnosis in our case was made by the classical clinical history, decremental response on RNST, and dramatic response with oral pyridostigmine. There was no evidence of thymoma on CT of the thorax, which is seen in 10%–15% cases of myasthenia gravis. However, thymic hyperplasia could not be ruled out as only a biopsy can give a definite diagnosis of the condition. RNST was also done at higher frequency of 20 Hz to differentiate it from the Lambert-Eaton syndrome, while occuring only in an older age group, has a similar presentation to myasthenia gravis. Patients of Lambert-Eaton syndrome may show a similar decremental response at lower frequencies of 3–5 Hz, but show a characteristic incremental response on stronger or high frequency nerve stimulation. This is diagnostic of the condition. Our patient showed a decremental response on RNST at 5, 10 and 20 Hz as well.

Patients with post-infectious origin of myasthenia gravis respond well to acetylcholine esterase inhibitors. Immunosuppressive therapy is rarely required in this group. Out of the previously-reported cases of post-viral myasthenia gravis,[5,10] four patients showed an excellent response to acetylcholine esterase inhibitors, two patients required steroids in addition, and only one patient needed azathioprine. Other drugs which have been tried in resistant cases include mycophenolate mofetil, cyclosporine A, and cyclophosphamide. Other modalities of treatment include intravenous immunoglobulin and plasmapheresis, which are required for managing the state of crises in myasthenic patients.

We could find only one previous report of post-varicella myasthenia gravis during an extensive literature search.[10] This patient was a five-year-old boy with oculo-bulbar weakness. Our patient is probably the youngest and second reported case of post-varicella myasthenia gravis. These two cases, as well as other reports of post-infectious origin of the disease, and gradual recovery over time suggest a causative association of myasthenia gravis with infectious diseases. This is a relatively mild condition, and if diagnosed correctly and treated promptly, the patient can lead a good quality life with self-recovery over a span of a few years. Myasthenia gravis is not yet mentioned as a complication of varicella in textbooks and can be missed at times. We recommend the inclusion of this condition in textbooks.

REFERENCES

1. Drachman D. Myasthenia gravis. N Eng J Med 1994; 330:1797-810.
2. Brett EM, Lake BD. Neuromuscular disorders: I. Primary muscle disease and anterior horn cell disorders. In: Brett EM, ed. Pediatric Neurology. 3rd ed. London: Churchill Livingstone, 1997:51-118.

3. Evoli A, Tonali PA, Padua L, et al. Clinical correlates with anti-MuSK antibodies in generalized seronegative myasthenia gravis. Brain 2003; 126:2304-11.
4. Hohlfeld R, Melms A, Schneider C, Toyka KV, Drachman DB. Therapy of myasthenia gravis and myasthenic syndromes. In: Brandt T, Caplan L, Dichgans J, Diener HC, Kennard C, eds. Neurological Disorders Course and Treatment. USA: Academic Press Elsevier Science 2003:1341-68.
5. Korn IL, Abramsky O. Myasthenia gravis following viral infection. Eur Neurol 1981; 20:435-9.
6. Verma A, Berger J. Myasthenia gravis associated with dual infection of HIV and HTLV-I. Muscle Nerve 1995; 18:1355-6.
7. Feltkamp TEW, van den Berg-Loonen PM, Nijenhuis LE, et al. Myasthenia gravis, autoantibodies, and HLA antigens. Br Med J 1974; 1:131- 3.
8. Schwimmbeck PL, Dyrberg T, Drachman DB, Oldstone MBA. Molecular mimicry and myasthenia gravis. An autoantigenic site of the acetylcholine receptor alpha-subunit that has biologic activity and reacts immunochemically with herpes simplex virus. J Clin Invest 1989; 84: 1174-80.
9. Stefansson K, Dieperink ME, Richman DP, Gomez CM, Marton LS. Sharing of antigenic determinants between the nicotinic acetylcholine receptor and proteins in Escherichia coli, Proteus vulgaris and Klebsiella pneumoniae. Possible role in the pathogenesis of myasthenia gravis. N Eng J Med 1985; 312:221-5.
10. Felice KJ, DiMario FJ, Conway SR. Postinfectious myasthenia gravis: report of two children. J Child Neurol 2005; 20:441-4.