

Case Reports

D-Penicillamine induced myasthenia gravis

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ABSTRACT

Myasthenia gravis is a disorder of impaired neuromuscular transmission resulting in weakness and abnormal fatigability on exertion, improved by anti-acetyl cholinesterase drugs. A number of drugs are known to exacerbate myasthenia gravis or interfere with neuromuscular transmission. We report a case of D-penicillamine induced myasthenia gravis who developed ptosis, diplopia and easy fatigability, 4 years after initiation of the drug for Wilson's disease. On stopping the drug, within 3 months all her symptoms disappeared without any anti-acetyl cholinesterase drugs. Thus, the onset of drug induced myasthenia gravis could be insidious but the withdrawal of the drug leads to rapid recovery.

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Myasthenia gravis (MG) is a disorder of impaired neuromuscular transmission resulting in weakness and abnormal fatigability on exertion, improved by anti acetyl cholinesterase drugs. It was only in the late 1970's, that the current understanding of the immune mediated basis of MG was established, although the condition was first described more than 350 years ago by Willis.¹ Myasthenia gravis has a prevalence of approximately 125 cases per million population.² Approximately 11-24% of all MG patients have disease onset in childhood or adolescence.³ There is a slight female preponderance of 3:2, although males predominate in older age groups. Weakness and fatigability of ocular, bulbar and extremity striated muscles often worsening with stress and exertion characterize the disease. The ocular symptoms are ptosis and diplopia with other manifestations being dysarthria, dysphagia and dyspnea. The edrophonium test, electro physiologic repetitive stimulation testing and demonstration of acetylcholine receptor (AChR) antibodies establishes diagnosis.⁴ Treatment includes anti acetyl cholinesterase agents, thymectomy, immunosuppressants, immunoglobulins and plasmapheresis.⁵ A number of drugs known to be

non depolarizing neuro muscular blocking agents, including antibiotics, anesthetic agents, anticonvulsants and rheumatological drugs are known to precipitate symptoms of MG. D-penicillamine is a potent drug used to treat Wilson's disease, rheumatoid arthritis and cystinuria, that can cause MG. Unilateral ptosis could be the first manifestation⁶ and the onset may be insidious. The withdrawal of D penicillamine⁷ usually results in the resolution of the disease even without any anti cholinesterase therapy.⁸

Case Report. A 12-year-old Omani girl, known to have Wilson's disease on D penicillamine therapy was admitted to the pediatric ward with a 3-week history of ptosis, diplopia and easy fatigability on exertion. Born to consanguineous parents by normal delivery with no past history of any significant illness, she was investigated for persistent jaundice of 2-months duration, at the age of 8 years. At that time she had mild jaundice and firm hepatomegaly with no other signs of hepatic failure. Two of her siblings were diagnosed to have Wilson's disease, one of whom eventually died. Based on low serum ceruloplasmin and serum copper, altered

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Figure 1 - D-penicillamine induced ptosis of the left eye.

coagulation profile and elevated liver enzymes, she was diagnosed to have Wilson's disease which was later confirmed by liver biopsy. She was started on D-penicillamine (250mg 4 times a day) and pyridoxine (10mg every day) and has been taking the medicines for the past 4 years.

On examination, she was fully conscious and well oriented. The cranial nerves were normal with normal pupillary reaction to light. She had ptosis of the left eye (**Figure 1**). Systemic examination was unremarkable. Muscle power was normal in all 4 limbs. Electromyogram showed decremental response of more than 20% in both the deltoid muscles and the left orbicularis oculis. Nerve conduction studies were normal and edrophonium test positive. Computerized tomography of brain and mediastinum, thyroid function tests, collagen profile and immunological work up were all normal. Acetylcholine receptor antibodies were strongly positive (29.1 nmol/L). The diagnosis of MG was beyond doubt and D-penicillamine was thought to be precipitating the symptoms. D-penicillamine was stopped and she was put on triethylene tetramine dihydrochloride (500mg three times a day). Three months later, all her symptoms suggestive of MG disappeared with all her hepatic parameters remaining normal. She has been on regular follow-up for more than a year after stopping the D-penicillamine, and her AChR antibodies subsequently became negative.

Discussion. Myasthenia gravis is the best understood autoimmune disease of the nervous system, with antibodies directed against the skeletal muscle acetylcholine receptors. Acetylcholine receptor antibody has also been shown to block neuromuscular transmission and accelerate turnover of acetylcholine receptors cross linked by immunoglobulin G.²

As with adults, ptosis is the most common clinical finding in children frequently accompanied by

ophthalmoparesis. Ptosis is usually unilateral at onset in one third of juvenile MG patients, but subsequently spreads to the other eye in 90% of cases.⁹ Myasthenia gravis is frequently associated with other immune mediated diseases such as rheumatoid arthritis, thyroid disease, systemic lupus erythematosus and diabetes mellitus.⁹ Non immune disorders associated with juvenile MG include epilepsy, various forms of neoplasia particularly thymoma and later in life, breast carcinoma.¹⁰ Sound clinical examination is most often the basis of MG diagnosis, however, the edrophonium (tensilon) test, decremental response of the compound muscle action potential to repetitive stimulation of a motor nerve and demonstration of AChR antibody in the serum, all contribute to its confirmation. Pyridostigmine, an anti acetyl cholinesterase drug is recommended as the standard initial treatment.⁴ Immunosuppressants, antimetabolites, and intravenous immunoglobulins are indicated for refractory cases. Thymectomy is mandatory for all patients except in those cases of drug induced MG where no intervention is required other than withdrawal of the incriminating drug.

Children, as adults with MG, are sensitive to non-depolarizing neuromuscular blocking agents. Intermediate acting non-depolarizing blockers such as atracurium and vecuronium should be used with care.¹¹ There are a number of drugs known to exacerbate MG or interfere with neuromuscular transmission including antibiotics (aminoglycosides, erythromycin, tetracycline, penicillins, sulfonamides, fluoroquinolones, clindamycin and lincomycin); anesthetic agents (neuromuscular blocking agents, lidocaine and procaine); anti convulsants (phenytoin, mephenytoin and trimethadione); cardiovascular drugs (beta blockers, procainamide and quinidine); rheumatologic drugs (D-penicillamine and chloroquine); and other drugs like iodinated contrast, chlorpromazine and lithium.² Drug induced MG is uncommon in clinical practice. Although many of the drugs mentioned above, including D-penicillamine, reduce the safety margin of neuromuscular transmission, overt MG induced by a drug in a previously well child is rare. D-penicillamine induced MG has been previously reported.^{12,13} Penicillamine is a monoclonal chelating agent which is a degradation product of all penicillins. Only the D isomer of penicillamine is used clinically which is available commercially as a synthetic product. D-penicillamine chelates copper, iron, mercury, lead and probably other heavy metals to form soluble stable complexes, which are readily excreted by the kidneys. Copper is chelated by the combination of 2 molecules of D-penicillamine with one atom of the metal. In vitro, one gram of D-penicillamine is definitely superior to other chelating agents and is well tolerated orally. In a series of 71 patients with rheumatoid arthritis 5 of them developed MG within 2 years.¹⁴ They all

responded to discontinuation of the drug. However, there are reports of patients who needed short term anti cholinesterase therapy after developing D-penicillamine induced MG.⁷ On re-introducing D-penicillamine in a patient with D-penicillamine induced MG, it was found that myasthenic syndrome recurred, thus excluding beyond doubt the remote possibility of spontaneous remission in drug induced MG.¹² Even with minor myasthenic symptoms, the treating physician should immediately discontinue the drug.¹⁴

D-penicillamine induced MG is not associated with human leukocyte antigen (HLA) – DR3, which is found in most patients with idiopathic MG.¹⁵ It is more likely to find HLA – DR1 and BW35 antigens in patients with D-penicillamine induced MG,¹⁶ suggesting that penicillamine induced MG and its idiopathic counterpart occur in patients with different genetic backgrounds.

Thus, MG should be suspected with ptosis without other cranial nerve involvement or miosis, even if the ptosis is unilateral, in patients receiving D-penicillamine. The onset could be insidious and symptoms may manifest even after 4 years. Withdrawal of the drug invariably leads to recovery, although short term anti cholinesterase drugs have been used in some patients. Our patient with Wilson's disease responded well to discontinuation of D-penicillamine and all her myasthenic symptoms disappeared within 3 months and AChR antibody was negative on follow-up. The patient has had monthly visits to the outpatient clinic for more than a year and no myasthenic symptoms have been reported. Triethylene tetramine dihydrochloride proved to be a safe and good alternative for Wilson's disease in the dose of 500 mg twice daily.

References

1. Sanders DB, Howard JF Jr. Disorders of neuromuscular transmission. In: Bradley WG, Daroff RB, Tenichel GM editors. *Neurology in clinical practice*. Boston (MA): Butterworth Heinemann; 2000. p. 2167-2185.
2. Wolfe GI, Barohn RJ. Neuromuscular junction disorders of childhood. In: Swaiman KF, Ashwal S editors. *Pediatric Neurology*. Baltimore (MD): Mosby; 1999. p. 1216-1234.
3. Millichap JG, Dodge PR. Diagnosis and treatment of Myasthenia gravis in infancy, childhood and adolescence. *Neurology* 1960; 10: 1007-1010.
4. Snead OC, Benton JW, Dwyer D. Juvenile Myasthenia gravis. *Neurology* 1980; 30: 732-735.
5. Engel AG. Myasthenia gravis and Myasthenia syndromes. *Ann Neurol* 1984; 16: 519-522.
6. Raynauld JP, Lee YS, Kornfeld P, Fries JF. Unilateral ptosis as an initial manifestation of D-penicillamine induced myasthenia gravis. *J Rheumatol* 1993; 20: 1592-1593.
7. Kimbrough RL, Mevis L, Stewart RH. D-penicillamine and the ocular myasthenic syndrome. *Ann Ophthalmol* 1981; 13: 1171-1172.
8. Liv GT, Bienfang DC. Penicillamine-induced ocular Myasthenia gravis in rheumatoid arthritis. *J Clin Neuroophthalmol* 1990; 10: 201-205.
9. Afifi AK, Bell WE. Tests for Juvenile Myasthenia gravis: comparative diagnostic yield and prediction of outcome. *J Child Neurol* 1993; 8: 403-407.
10. Rodriguez M, Gomez MR, Howard FM. Myasthenia gravis in children: long term follow up. *Ann Neurol* 1983; 13: 504-505.
11. Baraka A. Anaesthesia and Myasthenia gravis. *Can J Anesth* 1992; 39: 476-478.
12. Dubost JJ, Soubrier M, Bouchet F, Kemeny JL, Lhopitaloux R, Bussiere JL et al. Neuromuscular complications of D-penicillamine in rheumatoid arthritis. *Rev Neurol* 1992; 148: 207-211.
13. Vincent A, Newsom-Davis J. Acetyl choline receptor antibody characteristics in Myasthenia gravis: patients with penicillamine induced myasthenia gravis and idiopathic myasthenia of recent onset. *Clin Exp Immunol* 1982; 49: 266-272.
14. Andonopoulos AP, Terziz E, Tsibiri E, Papaslerlades CA, Papapetropoulos T. D-penicillamine induced Myasthenia gravis in rheumatoid arthritis: an unpredictable common occurrence? *Clin Rheumatol* 1994; 13: 586-588.
15. O'Keefe M, Morley KD, Haining WM, Smith A. Penicillamine – induced ocular Myasthenia gravis. *Am J Ophthalmol* 1985; 99: 66-67.
16. Huavx JP, Delreux V. Myasthenia induced by D-penicillamine. Apropos of 2 case reports. *Acta Neurol Belg* 1986; 86: 297-303.