Ocular myasthenia gravis after D-penicillamine administration

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SUMMARY A 68-year-old black woman who was put on D-penicillamine therapy (250–500 mg per day, total dose 15 g) for rheumatoid arthritis developed ocular myasthenia gravis. Two weeks after she discontinued D-penicillamine her signs and symptoms cleared with no other treatment. Review of previous cases and possible immunological mechanisms are discussed.

D-Penicillamine is an invaluable therapeutic agent in a variety of illnesses. It is an amino acid that is a pyridoxine antagonist produced by hydrolysis of penicillin.1 Beneficial use has been made of its chelating properties in metallic toxic states whether exogenous (lead or mercury poisoning) or endogenous (Wilson’s disease). Since combination with cysteine yields a more soluble complex, it is potentially useful in cystinuria.4 It has been used in rheumatoid arthritis,5,6 progressive systemic sclerosis,7 primary biliary cirrhosis,8 and haemophilic arthritis.9 With increasing long-term use of D-penicillamine, immune mediated disorders such as myasthenia gravis,10–25 polymyositis,26 systemic lupus erythematosus,27 pemphigus,28 and Goodpasture’s syndrome29 have occurred. This case report provides an illustrative example of reversible myasthenia gravis related to D-penicillamine therapy.

Case report

The patient was a 68-year-old black woman who had had rheumatoid arthritis for 30 years. After four months of D-penicillamine therapy (250–500 mg/day for a total dose of 15 g she noticed the onset of diplopia and right ptosis, which increased in severity at night. No other muscular weakness was noted.

On examination a right ptosis was observed, with palpebral fissures in primary gaze measuring 5 mm on the right and 10 mm on the left. In primary gaze a left hypertropia of 20 prism diopters was recorded. Prolonged upward gaze for two minutes yielded a positive fatigue test with increasing droop of the right upper eyelid. Cogan’s lid twitch sign was also present. Her vision was 20/20 in both eyes. Her pupils, visual fields, slit-lamp appearances, and fundus were normal. Further neurological evaluation revealed no other focal or diffuse neuromuscular difficulty. A Tensilon (edrophonium) test was positive. Computerised axial tomography and lumbar puncture gave normal results. Laboratory tests gave normal values for thyroid function indices (T4-RIA, T3 uptake, TSH), serum vitamin B12 and folate levels, and cerebrospinal fluid protein and glucose. The fasting blood glucose was 9.4 mmol/l (170 mg/100 ml). Complete blood count yielded a packed cell volume of 51% and a white cell count of 4×109/l, with a normal differential count. No antibody to acetylcholine receptor was detected in her serum. Ten days after cessation of D-penicillamine signs and symptoms cleared. The patient never required anticholinesterase therapy.

Discussion

Several drugs may produce a myasthenia gravis-like state (Table 1).30 Since 1975, 10 case reports of 34 patients have strongly suggested an association between D-penicillamine and myasthenic gravis (Table 2). Patients with one of three underlying
Antibiotics
Colistin Neomycin
Gentamicin Polymyxin
Kanamycin Strepromycin

Cardiovascular
Oxprenolol Practolol
Pranolol Trimethaphan
Phenytoin Phenothiazine
Trimethadione

Anticonvulsants

Others
Tetanus antitoxin
Oral contraceptives
D-Penicillamine

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There have been several reports of drug-induced myasthenia gravis, but it is not clear whether this condition is a distinct entity or simply an exacerbation of an underlying autoimmune disorder. Moreover, the pathogenesis of drug-induced myasthenia gravis is not well understood. However, it is thought that drugs may induce myasthenia gravis by altering the balance between anti-acetylcholine antibodies and anti-acetylcholine receptors, leading to a failure of the neuromuscular junction.

The treatment of drug-induced myasthenia gravis is supportive and may include plasmapheresis, corticosteroids, and other immunosuppressive agents. The discontinuation of the offending drug is also important. In some cases, the condition may resolve spontaneously with time.
choline receptors. This could be the result of several possibilities. (Fig. 1): (1) Acetylcholine receptor antigenic properties are altered, which would make self recognition more difficult. 36 (2) There is a loss of suppressor T cell control over B cell production of antibodies. In-vitro studies demonstrate that D-penicillamine decreases T cell division. 37 (3) Direct stimulation of B cells, specific or non-specific, which would lead to increased levels of antibodies.

Although D-penicillamine has been extensively used for several disease states, most patients who develop myasthenia gravis are those with autoimmune disease, suggesting an inherent susceptibility to D-penicillamine. For example patients with rheumatoid arthritis have demonstrable defects in suppressor T cell function. 38

An alternative explanation, not based on an immunological model, is that D-penicillamine stimulates prostaglandin E2 synthetase to produce prostaglandin E2, which occupies an allosteric site on the acetylcholine receptors. 39 This may alter acetylcholine coupling with receptors.

With increasing use of D-penicillamine more patients will undoubtedly present with drug induced secondary myasthenia gravis. Since ocular features are predominant, ophthalmologists should bear in mind the association of myasthenia gravis with D-penicillamine.

References


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