

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 exogenous² (lead or mercury poisoning) or endogenous³ (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 $4 \times 10^9/l$, 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

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Table 1 *Drugs inducing myasthenia gravis*

<i>Antibiotics</i>	Colistin	Neomycin
	Gentamicin	Polymyxin
	Kanamycin	Streptomycin
<i>Cardiovascular</i>	Oxprenolol	
	Practolol	
	Trimethaphan	
<i>Anticonvulsants</i>	Phenytoin	
	Trimethadione	
<i>Others</i>	Tetanus antitoxin	
	Oral contraceptives	
	D-Penicillamine	

diseases – rheumatoid arthritis (31 patients), Wilson's disease (two patients), and progressive systemic sclerosis (one patient) – underwent treatment with D-penicillamine and developed ocular myasthenia. Ptosis and diplopia were present in all cases in which symptoms and signs were reported. Serum globulin assay in more than 75% of those cases that were tested showed an acute, usually transient, elevation of antibodies to acetylcholine receptors^{11 14 16 21 24 31 33} and, in another report, to striated muscle.¹¹ Electromyographic tracing of the muscle response to double-step stimulation showed the typical myasthenia decremental response on repetitive nerve stimulation.³¹

The differentiation of drug induced from spontaneous myasthenia gravis is usually on clinical grounds. In the drug induced type the onset of symptoms is usually six to seven months after starting therapy but ranges from less than one month to eight years. Muscular weakness usually resolves two to three

months after stopping D-penicillamine, but recovery may occur after only several weeks or up to several years. It has been noted that two patients with myasthenia gravis induced by D-penicillamine had the HLA-DRI antigen in contrast to patients with idiopathic myasthenias, who typically have HLA-DR3 antigen.²⁴ This difference suggests a different genetic background, that these are two distinct populations, and that the drug induced myasthenias are not simply unmasked from a susceptible stage. Moreover, recurrence after discontinuing D-penicillamine has been reported.^{10 31} Usually a concomitant improvement in electromyographic tracings²⁵ and a decline in antiacetylcholine receptor antibodies^{21 24 25 30} are observed during clinical recovery, though the antibodies may remain raised.³² Some patients may require oral anticholinesterase treatment. Rarely, plasmapheresis may be necessary for short-term maintenance.¹²

The pathogenesis of drug-induced myasthenia gravis is not clear. D-Penicillamine has no direct effect on cell membrane miniature end plate potential,³⁰ amplitude, or ocular potential.³⁴ The increase in serum antibodies to acetylcholine receptors, as in primary myasthenia gravis,³⁵ implies a common pathogenesis. However, there are patients on D-penicillamine therapy who never develop antibodies³⁰ and there are also those who have antibodies but no myasthenic weakness.¹¹ Current theories on the mechanism of drug induced myasthenia gravis focus on altered immunological reactivity. A population of B cell lymphocytes has apparently been induced to manufacture antibodies to the acetyl-

Table 2 *Review of literature: myasthenia gravis following D-penicillamine treatment*

<i>Author</i>	<i>Year</i>	<i>No of Patients</i>	<i>Underlying disease</i>	<i>Duration of treatment (months)</i>	<i>Time of recovery (months)</i>	<i>Antibody to acetylcholine receptor</i>	<i>Ocular myasthenia</i>
Bucknall <i>et al.</i> ¹⁰	1975	4	RA	4,5,8,9	1,1–1/3,NA,NA	NA	+
Czlonkowski ²⁰	1975	1	W	13	1–1/2	NA	+
Masters <i>et al.</i> ¹¹	1977	8/1 (9)	RA/W	NA/100	NA/NA	4+,1–/+	NA/+
Gordon and Burnside ¹⁹	1977	1	RA	4	7	NA	+
François <i>et al.</i> ²⁵	1978	1	RA	5	3	NA	+
Russell and Lindstrom ²¹	1978	1	RA	2	8	+	+
Atcheson and Ward ¹⁷	1978	1	RA	1/15	1	–	+
Vincent <i>et al.</i> ³³	1978	3	RA	6,20,9	NA	3+	+
Sundstrom and Schuna ¹⁵	1979	2	RA	6,7	2 26 mo.	NA	+
Keesey and Novom ¹²	1979	1	RA	9	8	+	+
Argov <i>et al.</i> ³¹	1980	2	RA	10,18	NA	+	+
Rousseau and Diendonne ¹¹	1980	1	RA	6	2	+	+
Albers <i>et al.</i> ¹⁴	1980	1	RA	7	6	+	+
Torres <i>et al.</i> ¹⁶	1980	1	PSS	6	10 mo.	+	+
Bocanegra <i>et al.</i> ¹⁸	1980	1	RA	3	2+	–	+
Lang <i>et al.</i> ¹²	1980	2	RA	6,7	6,6	1+1–	+
O'Keefe <i>et al.</i> ²⁴	1985	2	RA	9,36	4,4+	+/+	+

RA=rheumatoid arthritis. W=Wilson's disease. PSS=progressive systemic sclerosis. NA=not available.

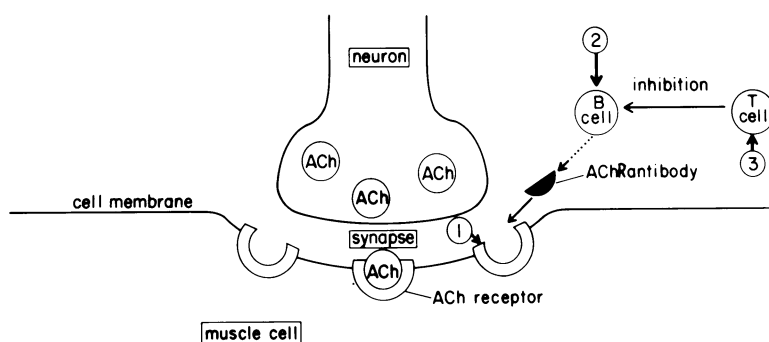


Fig. 1 Possible sites of penicillamine action: (1) Alteration of acetylcholine receptor. (2) Stimulation of B cell lymphocytes. (3) Inhibition of suppressor T cell lymphocytes.

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 E₁ synthetase to produce prostaglandin E₁, 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.

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