Seronegative Myasthenia Gravis and Human Immunodeficiency Virus Infection: Response to Intravenous Gamma Globulin and Prednisone

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ABSTRACT: ***Background:*** There are only rare reports of myasthenia gravis complicating human immunodeficiency virus infection. The role of immunomodulatory therapy is unknown. ***Methods:*** Case report and literature review. ***Results:*** The diagnosis of human immunodeficiency virus infection followed that of myasthenia gravis in a 35-year-old man. Clinical and electrophysiological features were diagnostic of generalized myasthenia gravis but two edrophonium chloride tests and acetylcholine receptor antibodies were negative. Prednisone therapy and intravenous gamma globulin were associated with rapid clinical recovery. ***Conclusions:*** Prednisone therapy and intravenous gamma globulin may be helpful in patients with generalized myasthenia gravis complicating HIV infection.

RÉSUMÉ: Myasthénie grave séronégative et infection par le virus de l'immunodéficience humaine: réponse à l'administration de gamma globuline intraveineuse et de prednisone. ***Introduction:*** Il y a peu de cas rapportés de myasthénie grave comme complication de l'infection par le virus de l'immunodéficience humaine (VIH). Le rôle de la thérapie immunomodulatrice est inconnu. ***Méthodes:*** Histoire de cas et revue de la littérature. ***Résultats:*** Le diagnostic d'infection par le VIH a été fait après celui de myasthénie grave chez un homme de 35 ans. Les manifestations cliniques et électrophysiologiques étaient pathognomoniques de la myasthénie grave généralisée. Cependant, deux tests au chlorure d'édrophonium et le dosage des anticorps contre le récepteur de l'acétylcholine étaient négatifs. Le traitement par la prednisone et la gammaglobuline intraveineuse a donné lieu à une amélioration rapide de l'état clinique. ***Conclusions:*** Le traitement par la prednisone et la gamma globuline intraveineuse peut être utile chez les patients qui présentent une myasthénie grave comme complication de l'infection par le VIH.

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Human immunodeficiency virus (HIV) infection has been associated with several autoimmune disorders including thrombocytopenic purpura,[1] systemic lupus, erythematosis,[2-5] and other neurological disorders with a presumed autoimmune aetiology.[6] A presumptive link between HIV and myasthenia gravis (MG) has been suggested by a number of case reports that have shown myasthenic symptoms occurring concurrently with HIV seroconversion.[7-14]

We report a patient who developed generalized but seronegative and edrophonium chloride unresponsive myasthenia gravis that preceded the diagnosis of HIV infection. Electrophysiological studies of neuromuscular transmission provided the diagnosis and the patient recovered with intravenous gamma globulin (IVIG) and prednisone therapy.

Case Report

A 35-year-old previously well homosexual male, presented with a two week history of double vision, loss of strength for chewing solid food, and dysarthria when he was tired. He denied the use of intravenous or street drugs, and had been tested negative for HIV approximately one year prior to his presentation.

Neurological examination identified ptosis, weakness of eye closure, mild dysarthria and ophthalmoplegia. The remainder of the neurologic examination was normal. A single-masked (to the patient) intravenous injection of edrophonium chloride 10 mg did not improve the ophthalmoplegia. A subsequent MRI of the brain including brainstem without and with gadolinium and a 2D time of flight MR angiogram were both normal. Ten days later he returned with increasing weakness, dysphagia and weight loss. A repeat single-masked 10 mg intravenous edrophonium test was negative. Repetitive conduction studies identified a significant decremental response at 2 Hz stimulation of the facial nerve recording over orbicularis oculus (maximum resting decrement was 25% in amplitude and 30% in area), and over trapezius following stimulation of the accessory nerve (maximum post exercise decrement was 20% in amplitude and 29% in area). Repetitive stimulation of the ulnar nerve with recording over abductor digit minimi before and after exercise was normal. A CT chest scan did not identify thymoma and the patient improved on oral pyridostigmine. Acetylcholine receptor antibodies were absent (Dr. Joel Oger, University of British Columbia). HIV serology was positive by ELISA and Western blot with a CD4 count of 250 x 10^6 per litre (17%). Two weeks later he developed shortness of breath, worsened weakness and further diplopia despite an escalating dose of pyridostigmine. His forced vital capacity had fallen from 4.4 L to 2.5 L.

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Table: Reported Cases of Myasthenia Gravis and HIV infection.

Sex/Age (Years)	Initial CD4 cell count (CD4/CD8)	Involvement	Respiratory Failure	Tensilon Test	CMAP decrement > 10% (3Hz)	Anti-AchR Serology	Use of steroids as treatment	Use of IVIG
M/15	NT (0.82)	G	–	++	+	negative	–	–
M/36	371 (0.65)	G	–	++	+	uncertain	–	–
M/20	NT (0.62)	G	–	++	+	positive	–	–
F/38	NT (0.3)	G	–	++	+	positive	–	–
M/45	270 (NT)	G	–	++	+	positive	–	–
M/48	60 (NT)	G	–	++	unknown	positive	–	–
F/62	340 (0.4)	G	–	++	+	negative	–	–
M/35	250 (0.26) (present case)	G	+	–	+	negative	+	+

M = male; F = female; NT = not tested; CMAP = compound muscle action potential; AChR = acetylcholine receptor; G = generalized

On examination he had dysarthria, mild use of accessory muscle groups for breathing, near complete ophthalmoplegia, facial weakness, inability to close his jaw, neck flexion and extension weakness and generalized upper limb weakness with fatiguability. Treatment was begun with IVIG (35 grams/day for 5 days) and prednisone 50 mg daily. Five days later his vital capacity had increased to 3.9 L, his weakness had improved and his opthalmoplegia had begun to resolve. No deterioration in his myasthenia after starting prednisone was observed during the first few days of treatment. Anti-retroviral therapy was begun with zidovudine and lamivudine. By 3 weeks from the time of the second admission he had residual jaw closure weakness and fatiguability, a "pseudo" left internuclear ophthalmoplegia but normal neck and limb motor function. By 2 months after the second admission he had mild jaw closure weakness but normal extraocular movements. He returned to work by 3 months after admission and was neurologically normal at 6 months follow up with a stable CD4 count (250 x 10^6 per litre [21%]) and an increase in weight. Prednisone had been tapered to 35 mg on alternate days.

Discussion

Our patient demonstrated several clinical features worth emphasizing: (i) MG may be associated with early HIV infection but may be associated with negative edrophonium chloride testing and absent acetylcholine receptor antibodies; (ii) IVIG and prednisone may help MG in the setting of HIV infection.

There have been seven other cases of HIV-associated myasthenia gravis reported in the literature thus far[7-14] summarized in the Table. Seronegativity occurs in 10-30% of patients with myasthenia gravis, and alone is not a unique feature of our case.[15] Our patient however also had limited responsiveness to anticholinesterase medication and two negative edrophonium chloride tests. As a result other therapeutic strategies were considered. The CT scan of our patient's chest revealed no evidence of thymoma. Thymectomy was not carried out because it was judged to pose a greater risk and the possibility of a delayed benefit to an HIV infected patient. We also chose to defer thymectomy in this case because of previous suggestions that MG symptoms in HIV-infected individuals are transient and improve with declining CD4 counts by 8-14 months.[7-14]

We used prednisone immunosuppression to treat this patient's MG symptoms. Although the utilization of prednisone for the treatment of MG has been advocated for years with success,[16,17] the inherent problems of further immunosuppressing HIV patients with corticosteroid therapy are clearly evident. Prednisone has been utilized in the treatment of other HIV-associated conditions including *Pneumocystis carinii* pneumonia,[18] and idiopathic esophageal ulcerations[19] with moderate success and limited side effects. In our patient, the addition of prednisone was tolerated very well and a significant improvement in his clinical condition was noted within days of initiation of therapy. The addition of the intravenous gamma globulin during the initial corticosteroid therapy was also well tolerated, may have contributed to his clinical improvement, and may also have prevented the early, transient deterioration in the strength often accompanying corticosteroid therapy.[16] The improvement with both forms of treatment developed too rapidly to be ascribed to spontaneous remission.

The addition of steroids to the treatment protocol of HIV-associated MG presents one other theoretical problem. Corticosteroids are regarded as a prolonged commitment in the treatment of MG due to the high probability of relapse associated with discontinuation.[17] However, since myasthenic symptoms associated with HIV infection have been transient, in some cases decreasing with the declining CD4 count, more rapid tapering of prednisone should probably be considered earlier in this clinical setting.

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