Myasthenia Gravis in a Patient with Epilepsy Treated with Long-Term Cyclosporine Therapy

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Abstract

We report the case of a 36 years old female affected by myasthenia gravis (MG) and generalized epilepsy treated with cyclosporine A (CsA) and phenobarbital. The patient had a long history of MG that was resistant both to high corticosteroids dosage and other immunosuppressive therapy (azathioprine).

We evaluated cyclosporine efficacy by the improvement in neuromuscular function and reduction in steroid dosage. On the basis of mechanism of action of CsA the onset of therapy was preceded by two plasma-exchanges.

After one year patient reached an asymptomatic state and steroid dosage was reduced at 70% of the starting dose. A successive reduction of CsA dosage was due to lack of compliance and was followed by worsening of myasthenic signs while MG score improved after full CsA dosage was resumed.

No difference in anti-acetylcholine-receptor antibodies was noted in the course of treatment.

To avoid side effects, accurate CsA plasma levels and serum creatinine were monitored. No signs of nefrotoxicity were observed. Only minor side effects such as hypertricosis and gengival hyperplasia appeared after six months of therapy.

Key words: cyclosporine A, Myasthenia Gravis treatment, autoimmune disease.

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Myasthenia Gravis (MG) is an autoimmune T-cell dependent disorder in which anti-acetylcholine receptor antibodies are pathogenetic. Anti-acetylcholine-receptor antibodies impair neuromuscular transmission affecting the properties of acetylcholine binding to its receptor and causing complement-mediated destruction of junctional folds. The therapy of MG involves thymectomy and the use of steroids and azathioprine as immunosuppressant drugs, whose efficacy has been established.

Cyclosporine A (CsA) is a cyclic undecapeptide that has immunosuppressive role both in transplantation tolerance and in many autoimmune disorders.

CsA, like FK 506 and rapamycin inhibits IL2 and IL2R gene expression at a pretranscriptional level that results in inhibition of T4-helper cells, and reduces production of lymphokines in the thymus gland [1, 2]. Its action is mediated by cyclophilin, a cytosolic protein with prolyl-isomerase activity [3].

In MG treatment CsA was studied in a 12 months trial involving 20 patients, with a significant improvement in the treated group [4]. Results of two double-blind comparative trials have shown a similar efficacy of cyclosporine versus azathioprine in a 12 months period [5] and prednisone in a 6 months period [6].

Further studies are necessary to understand the role of cyclosporine in long term therapy of MG, its efficacy in reduction of steroid dosage, its safety and the interaction with other drugs.

Here we report the case of a myasthenic patient with epilepsy, showing a severe myasthenic form: the patient was resistant to traditional immunosuppressive therapy and was therefore treated with cyclosporine. The reduction of cyclosporine dosage caused disease relapse, but an appropriate CsA level controlled MG symptoms.

Case report

Cyclosporine was administered to a 36 years-old woman with a long history of MG resistant to the traditional immunosuppressive therapy. The diagnosis of MG was performed according to Engel criteria [7]. Since years of age 19 the patient is affected by generalized epilepsy treated with fenobarbital 100 mg/die with good control of seizures. At the end of 1985 the patient showed important systemic asthenia, ptosis and bulbar symptoms. At one year from the beginning of the disease the patient under-

went thymectomy. Thymic histology showed a benign thymoma.

After a first brief period with minimal myasthenic signs, at 3 years from onset the patient had to undergo plasmapheresis weekly, high dosage steroids were necessary to obtain an improvement in bulbar symptoms and for frequent respiratory crises.

Azathioprine 100-150 mg daily resulted in slight improvement however nasal voice, disphagya and swallowing difficulties were still present.

In the thirty months before cyclosporine therapy, the patient underwent 34 plasmapheresis cycles with a mean of 1 pheresis/month. and steroid dosage was 25-55 mg prednisone on alternate day.

Cyclosporine was tried in 1992 for the presence of cushingoid features and new myasthenic crisis.

The patient had severe weakness of limb girdle muscles and was not able to sit from a supine position. She had severe weakness of facial muscles, difficulty in chewing, hypomotility of palatine veil and nasal voice, her steroid dosage was 55 mg prednisone on alternate day.

Two courses of plasmaexchange were performed at the beginning of the treatment and CsA was started at a dose of 6 mg/proKg/daily. At six months patient had only slight symptoms with asthenia of facial muscles, weakness of flexors muscles of neck and deltoid muscles (4/5 according to Medical Research Council scale) and few bulbar symptoms, steroid dosage was reduced to twenty mg alternate day. In the next two months the patient became asymptomatic and steroids were reduced again (15 mg/Kg alternate day) [Fig 1 and 2].

During the following year our patient remained asymptomatic with minimal steroid dosage.

At this point, the patient reduced CsA dosage to four and two mg/Kg/daily respectively for lack of compliance; this resulted in worsening of myasthenic and severe bulbar symptoms.

We had to adjust CsA level, but plasmapheresis and steroid dosage increase were necessary. When patient had reached asymptomatic state cyclosporine dosage was reduced at 5 mg/Kg/daily, based on minimal efficacy dose. The follow up of the patient is three years.

Methods

Neuromuscular function was measured with a MG score [Table 1] in relation to functional importance of the involved muscle districts and the grade of compromission. Anti-acetylcholine receptor antibodies were measured at different intervals from the beginning by a modified radioimmunoassay previously described [8]. Cyclosporine side effects, serum creatinine, blood pressure and adverse effects such as hypertrichosis and gengival hyperplasia were carefully monitored.

Results

Our patient had improvement in her myasthenic symptoms just after 1 month of therapy and slight symptomatology was present at six months. At the end of the first year she was asymptomatic for 1 year (Fig. 1). No plasma-exchanges were necessary during the correct use of cyclosporine. Steroid dosage was reduced over 70% of the initial dose (Fig. 2). The worsening of myasthenic symptoms was caused by the reduction in cyclosporine dosage under 4,5 and 2 mg/Kg/daily respectively points out the importance of appropriate blood cyclosporine levels. In a follow-up of three years no important side effects were present. Serum creatinine had a slight but not progressive increase under 1,2 mg/dl. Minor side effects like hypertricosis and gengival hyperplasia were present.

At difference with previous studies [4, 6] we found no reduction in anti-acetylcholine receptor antibodies titles.

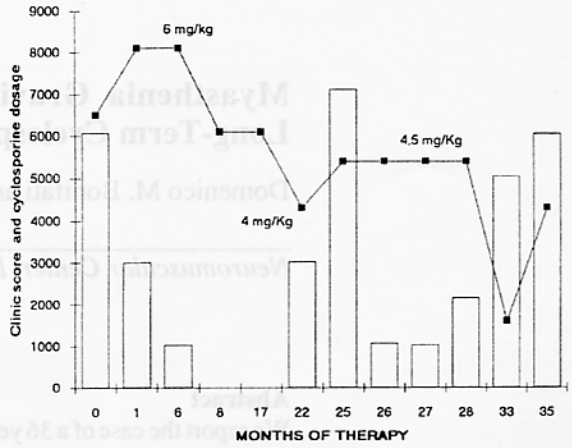

Figure 1. Clinical score evaluated by MG score and plasma cyclosporine levels: the worsening of myasthenic symptoms were due to decrease of the cyclosporine dosages.

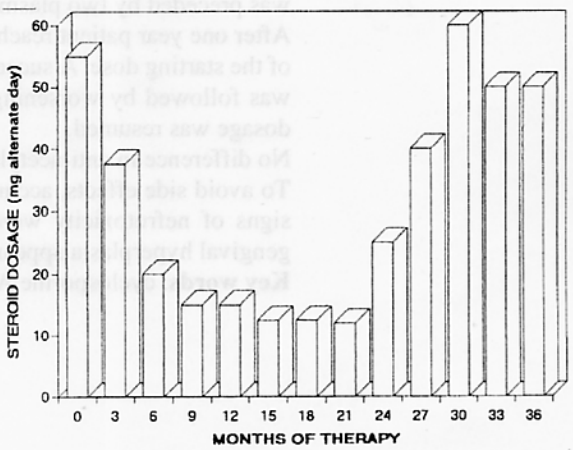

Figure 2. Corticosteroids dose during three years of treatment.

Discussion

Cyclosporine acts binding to a cytosolic protein cyclophilin [3]. The cyclosporine.cyclophilin complex inhibits calcineurin, a calcium- and calmodulin-dependent serine/threonine phosphatase. Inhibition of calcineurin ac-

Table 1. MG score used to evaluate our MG patients. The score is graded differently in various muscle districts according to their functional importance.

I)	*OCULAR MOTILITY*
0	normal
1	partial nystagmus, moderate ptosis.
2	lateralized diplopia, monolateral ptosis
3	diplopia in primary position, bilateral ptosis
4	ophtalmoplegya
II)	*MUSCULAR STRENGTH*
1)	FACIAL MUSCLES
0	normal
10	gives away but resists
20	gives away and does not resist
30	lagophthalmus or no movements of the lips
2)	FLEXORS MUSCLES OF THE NECK
	0 10 20 30 40 50
3)	ABDOMINAL MUSCLES
0	hands to the neck
10	hands to the chest
20	holds up arms
30	holds up arms (fixing legs)
40	not able to sit down
4)	DELTOID MUSCLE
	0 10 20 30 40 50
5)	MUSCLES OF INFERIOR LIMBS
0	10/15 squats
10	5/10 squats
20	1/5 squats
30	squats with support
40	not able to get up
100	not able to stand up
III)	*OROPHARINGEAL FUNCTION*
1)	CHEWING
0	normal
1000	exhaustibility
2000	gives
3000	jaw ptosis
2)	TONGUE
0	normal
1000	does not push effectively against the cheek
2000	does not catch up superior frenulum
3000	immovable
3)	SWALLOWING
1000	hypomotility of palatine veil or exhaustibility at the end lunch
2000	dysphagia for liquid or solid food, time of lunch is increased
20000	impossible, only with naso-gastric tube
4)	SPEECH
0	normal
2000	rhinolalia or slight hypophonia
3000	exhaustibility until aphonia or grave nasal voice but intelligible
3000	aphonia or grave disphonia unintelligible

tivity may prevent activation of some nuclear factors involved in transcription of interleukin 2 and other cytokines [9].

Interleukin 2 has a central role in the immune cascade and stimulates its own and interleukin 2-receptor upregulation [10] and the production of other lymphokines like interferon γ [9, 11] that stimulates the function or expansion of T-cells [12, 13]. Cyclosporine inhibits both antibody- and cell-mediated immunity.

Probably because its mechanism of action, CsA acts in the early phases of *in vitro* lymphocytes stimulation [14, 15] and in experimental autoimmune diseases.

CsA has shown to be effective in allograft rejection and in many autoimmune disorders. The usual therapy in generalized MG involves either corticosteroid therapy or azathioprine. Many patients, however, are resistant to steroid therapy or present important side effects in long-term treatment. Azathioprine therapy has been reported to be effective in MG [6] but some patients have shown to be resistant and present multiple side effects such as hematologic changes (33%) [17].

The efficacy of CsA in MG treatment was first observed in a trial of 12 months involving 20 patients, that showed a significant improvement in cyclosporine group [4]. The role of cyclosporine in long term MG treatment and the minimal effective dose are not clear and further studies are necessary.

Our patient was resistant at azathioprine associated and had important steroids side effects (Cushingoid appearance). Moreover frequent plasma exchanges were necessary to maintain her life quality. An asymptomatic state was reached after a period of 8 months from onset of CsA therapy.

This prompt improvement may be due also to the association of plasma-exchange treatment.

Plasma-exchange reduce anti-acetylcholine receptor antibodies and is associated with corresponding short-term clinical improvement [18, 19].

Cyclosporine could acts also on successive T-cell proliferation and indirectly on the production of anti-acetylcholine receptor antibodies. Therefore CsA could act in a synergistic way with plasma exchange.

The clinical course in our patient confirms that cyclosporine effect has a short period . Prompt worsening of MG score appeared following the first reduction at 4,3 mg/Kg CsA plasma level, this is probably due to concomitant phenobarbital therapy that induces cytochrome P450 enzymes. Gradual reduction of CsA and concomitant slight increase of corticosteroids may be necessary to avoid sudden worsening.

No reduction in anti-acetylcholine receptor antibodies was noted in this case. No important side effects were present in our patient and in particular no signs of nefrotoxicity were present. A greater decrease in glomerular filtration rate and creatinine clearance rate have been observed in patients with psoriasis receiving higher CsA dosages in a dose-finding study [20].

In conclusion cyclosporine may be efficacious in the treatment of MG patients resistant to the traditional immunosuppressive therapy. A brief plasma-exchange course increases the immunosuppressive action of cyclosporine. Suspension of cyclosporine therapy should be slow to avoid sudden worsening. According to previous studies concomitant phenobarbital use requires a higher cyclosporine dosage.

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References

[1] Bader P, Bendings S, Wagner H, Heeg K: Cyclosporine A (CsA) prevents the generation of mature α/β T cells but spares γ/δ T lymphocytes. *Current Topics in Microbiology and Immunology* 1991; 173: 81-89.

[2] Jenkins MK, Schwartz RM, Pardoll DM: Effects of cyclosporine A on T cell development and clonal deletion. *Science* 1988; 241: 1655-1658.

[3] Harding MV, Handschumacher RE, Speicher DW: Isolation and aminoacid sequence of cyclophilin. *J Biol Chem* 1987; 261: 8547-8555.

[4] Tindall RSA, Rollins JA, Phillips JT, et al: Preliminary results of a double-blind, randomized placebo controlled trial of cyclosporine in Myasthenia Gravis. *N Engl J Med* 1987; 316: 719-724.

[5] Schalke BCG, Kappos L, Rohrbach E, et al: Cyclosporine vs azathioprine in the treatment of myasthenia gravis: final results of randomized control double-blind clinical trial. *Neurology* 1988; 38 (Suppl. 1): 135.

[6] Tindall RSA, Phillips JT, Rollins JA, et al: Cyclosporine in the treatment of Myasthenia gravis. *Monogr Allergy* 1988; 25: 135-147.

[7] Engel AG: Acquired Autoimmune Myasthenia Gravis, in Engel AG, Franzini-Armstrong C (eds): *Myology, Basic and Clinical 2nd edn.* New York, McGraw-Hill, 1994, pp 1769-1797.

[8] Zotti M, Faella LR, Sartori V, Bonifati DM, Rizzotti P, Angelini C: Dosaggio degli anticorpi antirecettore dell'acetilcolina nella miastenia gravis. *Monogr di Medicina di Laboratorio* Galeno, 1994; Vol. 1, n° 1: pp 25-32.

[9] Bierer BE, Cyclosporine A, FK 506 and Rapamycin: binding to immunophilins and biological action. *Chem Immunol* Basel, Karger, 1994; 59: 128-155.

[10] Malek TR, Ashwell JD: Interleukin 2 upregulates expression of its receptor on a T cell clone. *J Exp Med* 1985; 161: 1575-1580.

[11] Inaba K, Granelli-Piperno A, Steinman RM: Dendritic cells induce T lymphocytes to release B cell-stimulating factors by an interleukin 2-dependent mechanism. *J Exp Med* 1988; 158: 2040-2057.

[12] Erard F, Corthesy P, Nabholz M, Lowenthal JW, Zaech P, et al: Interleukin 2 is both necessary and sufficient for the growth and differentiation of lectin-stimulated cytolytic T lymphocyte precursors. *J Immunol* 1985; 134: 1644-1562.

[13] Nakagawa T, Hirano T, Nakagawa N, Yoshizaki K, Kishimoto T: Effect of recombinant IL-2 and gamma-INF on proliferation and differentiation of human B cells. *J Immunol* 1985; 134: 959-966.

[14] Green CJ: Immunosuppression with Cyclosporine A: a review. *Diagnostic histopathology* 1981; 4: 157-174.

[15] Gauchat JF, Khandjian LW, Weil R: Cyclosporin prevents induction of interleukin-2 receptor gene in cultured murine thymocytes. *Proc Natl Acad Sci USA* 1986; 83: 6430-6434.

[16] Mertens HG, Hertel G, Reuther P, Rieker K: Effect of immunosuppressive drugs (azathioprine). *Ann NY Acad Sci* 1981; 377: 691-699.

[17] Wilensky R, Dwyer B, Mayer RF: Relapses in patients with Myasthenia Gravis treated with azathioprine. *Ann NY Acad Sci* 1993; 591-593.

[18] Pinching AJ, Peters DK, Newsom-Davis J: Remission of Myasthenia Gravis following plasmaexchange. *Lancet* 1976; II: 1373-1376.

[19] Lewis RA, Selwa JF, Lisak RP: Myasthenia Gravis: immunological mechanism and immunotherapy. *Ann Neurol* 1995; 37 (51): 551-562.

[20] Ellis CN, Fradin MS, Messana JM, Brown MD, Siegel MT, et al: Cyclosporine for plaque type psoriasis. Results of a multidose, double-blind trial. *N Engl J Med* 1991; 324: 277-284.