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FAILURE OF TREATMENT OF MYASTHENIA GRAVIS BY CYCLOSPORIN-A

A CASE REPORT

*PAULO E. MARCHIORI * — J. LAMARTINE DE ASSIS ** — MILBERTO SCAFF ***

SUMMARY — Recently, cyclosporin-A (Cy-A) has been used in the treatment oy myasthenia gravis (MG). This drug could be employed in some patients refractory to classic treatments or that develop undesirable side effects. It is reported the case of a 22 year-old woman with generalized and severe MG, and diabetes mellitus. She had been submitted to thymectomy and reoperated, to the classic ethiopathogenic methods of therapy, and to total body irradiation. No therapeutical results were observed. Also, she developed transient and slow bone marrow depression, and liver dysfunction. Owing to these limitations and to the absence of response to treatments mentioned, Cy-A use was attempted in this case. Unfortunately, Cy-A did not influence the myasthenic symptomatology. Cy-A also failed in suppressing anti-AChR production, which increased during Cy-A therapy. Results observed in this case are in disagreement with literature data on the subject.

Ausência de resposta ao tratamento da miastenia grave por ciclosporina-A: registro de um caso.

RESUMO — A ciclosporina-A (Ci-A) foi incluída, recentemente, no esquema de tratamento da miastenia grave (MG). A droga tornou-se opção válida para pacientes refratários a outros métodos terapêuticos de base etiopatogênica ou em virtude de efeitos colaterais e contra-indicações importantes a tais procedimentos. É registrado o caso de mulher de 22 anos de idade com forma generalizada e severa de MG adquirida e com diabetes mellitus. Foi timectomizada e reoperada ulteriormente. O diabetes se agravou com glicocorticóides e a paciente desenvolveu depressão da medula óssea e, por último, comprometimento hepático após uso de citostáticos. Não tendo havido resposta à irradiação de corpo inteiro, optou-se, então, pelo uso da Ci-A que também não influenciou a sintomatologia miastênica. É de notar que dosagens repetidas de anti-receptor de acetilcolina durante o uso de Ci-A, mostrou produção aumentada do anticorpo, em desacordo com os dados da literatura.

Myasthenia gravis (MG) is an immunologic disease with reduction in the acetylcholine receptors (AChR) turnover at neuromuscular junctions (NMJ) by an autoimmune response [1,4,9]. Circulating autoantibodies against post-synaptic AChR are responsible for transmission failure at NMJ which is the cause of fatigability and abnormal weakness of the skeletal muscle in myasthenics [6,10]. Antibodies against AChR (anti-AChR) are present in 60-85% of myasthenic patients [5,6]. At present, the etiopathogenic treatment of MG commonly involves thymectomy and immunosuppressive agents [5]. Although these treatments are generally effective, a proportion of patients submitted to immunosuppressive treatment remain refractory despite the prolonged use of the maximum tolerated doses. Undesirable side effects develop and the medication cannot be discontinued without precipitating a relapse of MG [4]. In view of these limitations, cyclosporin (Cy-A) could be a valuable adjunct in the treatment of MG [2,4]. The results observed in one case are reported.

Department of Neurology, Faculty of Medicine, University of São Paulo (FMUSP): * Assistant Professor; ** Associate Professor.

Clínica Neurológica, FMUSP — Caixa Postal 3461 - 01051 São Paulo SP - Brasil

CASE REPORT

The patient (CAVS; RG 2295567-K) is a Brazilian 22 year-old woman whose MG began in 1981 with respiratory failure, dysphagia, dysphonia, weakness of limbs and variable anti-AChR levels: 0.6 nM/l (November 14, 1984); 22.3 nM/l (August 15, 1985); 23.4 nM/l (December 2, 1986) She was submitted to: anticholinesterasic drugs and thymectomy; reoperated; prednisone (60-80 mg/day) alone or in combination with cytolytic drugs (azathioprine, 100 mg/day for 1.8 years; cyclophosphamide, 100 mg/day for 6 months, and chlorambucyl, 2-4 mg/day for 1.5 years); plasma exchange, and total body irradiation (TBI). All those treatments were ineffective. She also developed transient and slow bone marrow depression and liver dysfunction, and diabetes mellitus. An attempt to treat by Cy-A was made. The Cy-A dosage schedule was: 7.5 mg/kg/day in the first week (December, 1986); 5 mg/kg/day in the second week, and 6 mg/kg/day for remainder 4 months treatment period. The serum level of Cy-A was 220ng/ml (25-1200 ng/ml) by radioimmunoassay in March 24, 1987. The serum levels of anti-AChR during and on going the Cy-A treatment were: 91.0 nM/l on January 21, 1987; 54.0 nM/l on February 23, 1987; and 107.0 nM/l on March 19, 1987. Cy-A did not influence the myasthenic symptomatology.

COMMENTS

Recently cyclosporin A (Cy-A), a new and potent immunosuppressive hydrophobic and undecapeptide agent derived from two different strains of fungi, *Cylindrocarpon lucidum* Booth and *Trichoderma polysporum* Rifai [7], has been widely used in transplantation surgery for preventing graft rejection. The drug has been also used in a few cases of MG, rheumatoid arthritis, and polymyositis [2]. Based on favorable preliminary results referred in the literature we have decided to use Cy-A alone in this patient because besides that she has also developed bone marrow depression. No significant changes in myasthenic symptoms were observed, and it has also shown failure in suppressing anti-AChR production which increased during Cy-A therapy, in disagreement with the literature data [2,4,11]. This finding results from the fact that Cy-A preferentially inhibits the activity of T-helper cell lymphocytes and the receptor of interleukin-2, spares a population of suppression white cells completely blocking the clonal expansion of alloreactive T cells, and interferes with other B-lymphocytes activating mechanisms [3,7,8,12].

As a result, the ultimate value of Cy-A in the therapy of MG remains to be determined and the absence of response in the present case should not incentivate its eventual use in refractory MG in spite of the low toxicity. Although the Cy-A treatment has been used in only a few presumed conditions, as yet there are no well controlled studies of its effects [4].

REFERENCES

1. Appel SH, Blosser, JC, McManaman JL, Ashizawa T — Acetylcholine receptor turnover in myasthenia gravis. Am J Physiol 243:E31, 1982.

2. Besinger VA, Mraz W, Fateh-Moghadam A — Cyclosporin (CyA) in myasthenia gravis. In Schindler R (ed): Cyclosporin in Autoimmune Diseases, First International Symposium, Bade Springer, Berlin, 1985, pg 100.

3. Dos Reis GA, Shevach EM — Effect of cyclosporin-A on T cell function in vitro: the mechanism of suppression of T cell proliferation depends on the nature of the T cell stimulus as well as the differentiation state of the responding T cell. J Immunol 129:2360, 1982.

4. Drachman DB, Adams RN, McIntosh K, Pestronk A — Treatment of experimental myasthenia gravis with cyclosporin A. Clin Immunol Immunopathol 34:174, 1985.

5. Engel AG, Sahashi K, Fumagalli G — The immunopathology of acquired myasthenia gravis. Ann NY Acad Sci 377:158, 1981.

6. Fambrough BM, Drachman DB, Satyamurti S — Neuromuscular junction in myasthenia gravis: decreased acetylcholine receptors. Science 182:293, 1973.

7. Hess AD, Tutschka PJ — Effect of cyclosporin A on human lymphocyte responses in vitro: I. C_s A allows for the expression of alloantigen-activated suppression cells

while preferentially inhibiting the induction of cytolytic effector lymphocytes in MLR. J Immunol 124:2601, 1980.

8 Hess AD, Tutschka PJ, Santos GW — Effect of cyclosporin-A on human lymphocyte responses in vitro: II. Induction of specific alloantigen unresponsiveness mediated by a nylon wool adherent suppressor cell. J Immumol 126:961, 1981.

9 Lennon VA, Lindstrom JM, Seybold ME — Experimental autoimmune myasthenia: a model of myasthenia gravis in rats and guinea pigs. J Exp Med 141:1365, 1975.

10. Lindstrom JM, Seybold ME, Lennon VA, Whittinghams S, Duane DD — Antibody to acetylcholine receptor in myasthenia gravis: clinical correlates and diagnostic values. Neurology 26:1054, 1976.

11. Nyberg-Hansen R, Gjerstad L — Cyclosporin in the treatment of myasthenia gravis: preliminary results from pilot study. In Schindler R (ed): Cyclosporin in Autoimmune Diseases, First International Symposium, Bade Springer, Berlin, 1985, pg 96.

12. Wang BS, Heacock EH, Chang-Xue Z, Tilney NL, Strom TB, Mannick JA — Evidence for the presence of suppressor T lymphocytes in animals treated with cyclosporin-A. J Immunol 128:1382, 1982.