

Carbamazepine induced transient monoclonal gammopathy and immunodeficiency

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ABSTRACT

Immune abnormalities have been found in many patients receiving anti-epileptic drugs. However, the effects of carbamazepine are still conflicting. We report the case of a 31-year-old woman who began carbamazepine treatment because of idiopathic epilepsy of adulthood. After three years of treatment she developed arthralgias and malaise. Complete immunologic evaluation showed a total absence of immunoglobulin M with decreased levels of immunoglobulin A, positive antinuclear antibodies and monoclonal paraproteinemia type IgG-kappa. The possibility of B cell lymphoma or myeloma was ruled out. Skin testing was negative. Bone marrow examination was normal. After carbamazepine discontinuation, levels of IgA and IgM increased until reaching normal values over 3 years. The monoclonal gammopathy of undetermined significance also disappeared over this period. During this period of immunodeficiency, the patient did not complain of any infectious complications.

Key words: Carbamazepine. IgA deficiency. IgM deficiency. Monoclonal gammopathy. IgG-kappa paraproteinemia. Immunodeficiency.

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RESUMEN

Se han detectado alteraciones inmunitarias en muchos pacientes que reciben antiepilépticos; sin embargo, los efectos de carbamacepina siguen siendo contradictorios. Describimos el caso de una mujer de 31 años que empezó a tomar carbamacepina por epilepsia idiopática en adultos. Después de tres años de tratamiento, experimentó artralgias y malestar. Una evaluación inmunológica completa reveló la ausencia total de inmunoglobulina M y disminución de la concentración de inmunoglobulina A, anticuerpos antinucleares positivos y una paraproteinemia monoclonal de tipo IgG-kappa. Se descartó la posibilidad de linfoma de los linfocitos B o mieloma. Las pruebas cutáneas fueron negativas. La exploración de la médula ósea fue normal. Después de suspender la carbamacepina, las concentraciones de IgA e IgM aumentaron hasta alcanzar sus valores normales a lo largo de 3 años. La gammapatía monoclonal de significación indeterminada también desapareció a lo largo de ese período. Durante ese período de inmunodeficiencia, la paciente no experimentó ninguna complicación infecciosa.

Palabras clave: Carbamacepina. Déficit de IgA. Déficit de IgM. Gammapatía monoclonal. Inmunodeficiencia. Paraproteinemia IgG-kappa.

INTRODUCTION

Carbamazepine, a widely employed and often safe drug, has been involved in severe hypersensitivity and several adverse reactions^{1,2}. Moreover, hemato-

logical and immunologic abnormalities have been found in many patients receiving antiepileptic drugs^{1,3}. Carbamazepine has been also implicated in other several alterations of humoral immune parameters but the effects of carbamazepine on the immune response are still conflicting^{1,3-8}. Monoclonal gammopathy of undetermined significance (MGUS) and myeloma have been associated with antiepileptic drugs^{3,9-11}. However, carbamazepine has been rarely implicated in these diseases³. We present a rare case where carbamazepine induced a monoclonal gammopathy with humoral immunodeficiency, mainly affecting immunoglobulin M (IgM).

CASE REPORT

A 31 years-old woman was diagnosed of epilepsy. She did not suffered any structural damage of the central nervous system. She began treatment with Tegretol® (carbamazepine) 300 mg, three times daily, with excellent control of her symptoms. After 3 years, she developed an intense pain in left wrist with functional impotence and diffuse arthralgias of larger joints; the symptoms persisted more than two months. Physical and joints radiological examinations of the joints were normal. It was not detected any lymphadenopathy. Bacteriological findings were negative. Acute-phase reactants were normal. IgM rheumatoid factor was not detected. Antibodies anti-nuclear antigens (AAN) were detected by immuno-fluorescent technique, 1/80 (positive > 1/40); and they showed a granular pattern. Determination of serum immunoglobulins showed a total absence of serum immunoglobulin M (IgM) (0 mg/dl), a partial deficit of serum immunoglobulin A (IgA) (7 mg/dl) and normal immunoglobulin G (IgG) level (984 mg/dl). Serum protein values were normal, but electrophoresis showed a marked production of a single monoclonal immunoglobulin, IgG type with kappa light chain. An abdominal and thoracic scan tomography did not show any abnormal finding. Both, the analysis of peripheral lymphocyte populations and the cytology of bone marrow aspiration were normal; plasma cells accounted less than 1 % of marrow cellularity. The anatomo-pathological findings of the bone marrow examination showed several intertravicular lymphoid elements of variable morphology with adequate T and B cellularity, and a polyclonal plasmocytosis without malignity. All these findings supported the diagnosis of benign monoclonal gammopathy of undetermined significance (MGUS). Skin testing with carbamazepine was negative.

After analyzing the case we decided to stop the carbamazepine, since she had not had any epileptic

attack in three years. Recovering of symptoms and laboratory parameters was seen during the following months. The serum levels of IgM and IgA recovered normal values along 3 years, 0 mg/dl to 60 mg/dl, and 7 mg/dl to 45 mg/dl respectively. During this time, she did not complain of any infectious disorder or other complication. A clear decrease of the production of paraprotein IgG-kappa has been observed during these years.

DISCUSSION

Hypersensitivity syndrome is not rare in anticonvulsant therapy^{1,2}. Hematological disorders can also be found^{1,3-8}.

Lymphadenopathy associated with prolonged treatment with anticonvulsants, notably phenytoin, is a rare but well-established disorder that may mimic clinically and pathologically a malignant lymphoma, and had been called anticonvulsant induced pseudolymphoma^{1,8}. This disorder, which can also be caused by carbamazepine, usually subsides within weeks after the drug is stopped, and reappears promptly on re-administration of the offending drug⁸.

Monoclonal gammopathy of undetermined significance (MGUS) is characterized by a serum M-protein level less than 30 g/l, fewer than 10 % plasma cells in the bone marrow, and no or only small amounts of M-protein in the urine; by the absence of lytic lesions, anemia, hypercalcaemia, and renal insufficiency; and most importantly, by the stability of the M-protein and by the failure of other abnormalities to develop¹². Monoclonal gammopathy is a disturbance in immunoglobulin synthesis in which there is an homogeneous increase in a monoclonal immunoglobulin produced by a clone of plasma cells arising from the abnormal rapid multiplication of a single cell line. Monoclonal gammopathy has been also described in relation with antiepileptic drugs^{3,9-11}. These drugs have been also associated with the developing of myeloma⁹⁻¹⁰. However, carbamazepine is not frequently reported as the etiologic agent in cases of myeloma or monoclonal gammopathy³.

Drugs may induce hypogammaglobulinemia¹ Some reports show that long-term treatment with carbamazepine has exhibited immunosuppressant effects on T cells, and also on serum immunoglobulin levels³⁻⁷. Other reports did not show changes on immune response caused by carbamazepine⁶. There are several reports of carbamazepine-induced hypogammaglobulinemia^{1,13-16}. Some of these cases happen within the complex of symptoms of the anticonvulsant hypersensitivity syndrome^{3,13} or with immunoblastic lymphoma.

hadenopathy⁸. Our patient did not develop any infectious complication; however, in other case with carbamazepine induced hypogammaglobulinemia, a visceral leishmaniasis was diagnosed¹⁶.

In most cases of carbamazepine induced hypogammaglobulinemia, all immunoglobulins were affected, by contrast, in our patient the main affected immunoglobulin was IgM.

To our knowledge, it is the first case that combines an IgM and IgA deficit with a monoclonal gammopathy due to carbamazepine treatment. In this case both immunologic disorders disappeared several months after discontinuation of the drug.

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