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Case report

Carbamazepine-induced hypogammaglobulinemia

Nihal Ozaras [a], Nadir Goksugur [b], Saliha Eroglu [a], Omur Tabak [c], Billur Canbakan [d], Resat Ozaras [d,*]

[a] Bezmialem Vakif University, Istanbul, Turkey
[b] Abant Izzet Baysal University, Bolu, Turkey
[c] Bakirkoy Education-Training Hospital, Istanbul, Turkey
[d] Istanbul University, Istanbul, Turkey

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ABSTRACT

Carbamazepine is used to control seizures. Its common side effects are sleep disorders, anorexia, nausea, vomiting, polydipsia, irritability, ataxia, and diplopia. Involvement of the immune system is rare, and few cases of decreased immunoglobulin levels have been reported. We describe a patient with low immunoglobulin levels due to carbamazepine use who presented with recurrent urinary tract infection. Intravenous immunoglobulin was administered, and immunoglobulin levels increased to safer levels after discontinuation of carbamazepine. Previous reports describe severe infection after carbamazepine-induced hypogammaglobulinemia. Therefore, in patients using antiepileptics, particularly carbamazepine, serum immunoglobulin levels should be checked in those with recurrent infections.
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1. Introduction

Carbamazepine is used to control certain types of seizures. The most commonly encountered side effects include sleep disorders, anorexia, nausea, vomiting, polydipsia, irritability, ataxia, and diplopia.[1] Involvement of the immune system, manifesting as dermatitis, eosinophilia, leukopenia, lymphadenopathy, and splenomegaly, has also been reported.[1,2]

Decreased immunoglobulin levels after carbamazepine use is rare, and few cases have been reported.[3–7] We report on a patient with transiently low immunoglobulin levels due to carbamazepine use who presented with recurrent urinary tract infection.

2. Case report

A 37-year-old male was first admitted with Jacksonian seizures involving the left side of his body and loss of consciousness. He was found to have a right parietal mass and underwent surgery for a subtotal removal of the mass. The histology of the mass was consistent with oligodendroglioma (World Health Organization classification, Grade II). He was prescribed carbamazepine, lamotrigine, and clonazepam. He continued to have some hemidysesthesia, and his seizures increased. Because his seizures were intractable, right then left sided stereotactic thalamotomies were performed. His seizures improved and carbamazepine (800 mg/day) was continued. Within 6 years he required a ventriculo-atrial shunt operation and revision operations for hydrocephalus. Blood carbamazepine levels were within normal limits on several occasions. A physical therapy program was initiated. He did not need a urinary catheter.

In the 6 months prior to presentation the patient developed 3 episodes of urinary tract infections, all associated with systemic signs and symptoms (fever, flank pain, leukocytosis and increased C-reactive protein levels) The infections were due to *Escherichia coli* (treated with ceftriaxone), *Klebsiella* sp. (treated with meropenem), and *Pseudomonas aeruginosa* (partially sensitive to meropenem and amikacin and treated with a combination of these drugs). Concurrently, a pink-red maculo-papular rash on the face and trunk was noted, with the lesions varying in size from 2 mm to 10 mm. The platelet counts ranged from 100,000/mm^3 to 150,000/mm^3. An ultrasound scan of the renal tract was negative. His complete blood count and leukocyte differential (55% neutrophils, 40% lymphocytes, 3% eosinophils, and 2% monocytes) were normal except for a slightly low platelet count (135,000/mm^3). He had not been given any drug with known immunosuppressive properties. The immunoglobulin assay revealed low IgG and IgM levels: IgG 275 mg/dL (normal: 884–1912 mg/dL), IgM 31 mg/dL (*n*: 50–196 mg/dL), IgA 94 mg/dL (*n*: 68–423 mg/dL). Ig subclasses were also determined: IgG1 132 mg/dL, IgG2 100 mg/dL, and IgG3 3 mg/dL. Urinalysis revealed leukocytes, and urine culture yielded *P. aeruginosa*, which was resistant to all the antibiotics tested. The C-reactive protein level was 30 times higher than normal.

Although the carbamazepine level was 7 mcg/mL (normal range: 4–12 mcg/mL), it was discontinued. The rash disappeared

* Corresponding author at: Istanbul University, Cerrahpasa Medical School, Department of Infectious Diseases, TR-34098, Cerrahpasa, Istanbul, Turkey. Tel.: +90 212 5299565; fax: +90 212 5299565.
E-mail address: rozaras@yahoo.com (R. Ozaras).

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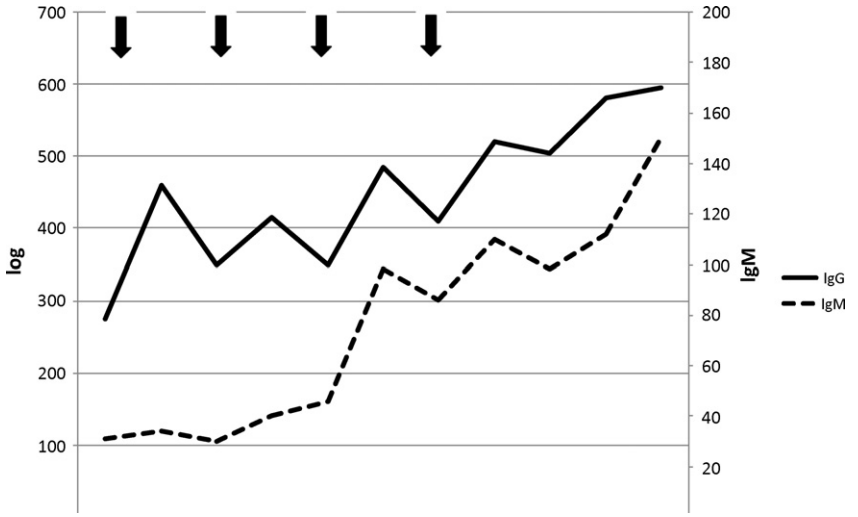


Fig. 1. Immunoglobulin G (solid line) and M (dashed line) levels after discontinuation of carbamazepine. Black arrows show intravenous immunoglobulin administrations. Unit for both IgG and IgM is mg/dL.

within 4 days, and the platelet counts returned to normal within 10 days. The urinary tract infection was successfully treated with colistin. The patient was given intravenous immunoglobulin (400 mg/kg, 32 g); because the immunoglobulin levels remained low, it was administered three more times. Four months after discontinuation no more immunoglobulin was needed (Fig. 1). During a follow-up of 1 year, the patient was doing well, without any rash or infection.

3. Discussion

Transient hypogammaglobulinemia has been associated in reports with the administration of carbamazepine as well as phenytoin.[8] Depression of one or more parameters of cellular and/or humoral immune responses was observed in 49% of general hospital patients treated with carbamazepine and 60% of patients treated with phenytoin.[9] Despite this, these findings may not translate into clinical complications (for example recurrent infections). Even among patients admitted with recurrent infections, carbamazepine-induced immune deficiencies are considered rare.[3–7,10]

The mechanisms underlying hypogammaglobulinemia induced by carbamazepine are not well understood. Marcoli et al.[11] reported lymphocyte and immunoglobulin abnormalities in 65 patients undergoing long-term monotherapy (at least 3 months) with phenytoin, carbamazepine, or phenobarbital. A significant decrease of OKT4+ cells was observed with all drugs, while other lymphocyte subpopulations were differently affected depending on the drug used; they concluded that these drugs produce immunosuppressant effects through a complex action involving more than one lymphocyte subpopulation. Gilhus et al. found reductions of IgG2, IgA, and IgM in epileptic patients treated with carbamazepine but no significant changes in lymphocyte numbers or in vitro responses to mitogens.[12–14] Basaran et al.[15] have investigated the effects of phenytoin or carbamazepine on humoral and cellular immunity and found that B lymphocyte numbers were unaffected by carbamazepine but IgM concentrations were significantly low; this effect was most pronounced in the first year.

Garcia Rodriguez et al.[16] described a patient with rash, fever, absence of B lymphocytes, and profound hypogammaglobulinemia: these changes returned to normal when the drug was discontinued. Spickett et al.[10] reported a case of symptomatic hypogammaglobulinemia with absent B lymphocytes and agranulocytosis in association with carbamazepine treatment. They suggested that the regular association of anticonvulsant treatment with hypogammaglobulinemia may be due to the sharing of key surface molecules between the lymphoid and nervous systems. Based on these reports, carbamazepine-induced immune disorders can be classified into three groups: an absence of B cells, extensive impairment of the synthesis of Igs in B cells, and a class-switch disorder of Igs in B cells.[3,4,10,16,17] Our case seems to belong to the second group. Side effects on immune functions do not seem to depend on the dose or on the serum concentration, or on the duration of treatment.[3]

Our patient revealed slight thrombocytopenia. Carbamazepine-induced thrombocytopenia is uncommon. It most often develops 2 weeks after the initiation of the drug and improves within 1 week after discontinuation.[18] Although the exact mechanism is unknown, the detection of carbamazepine-dependent antibodies suggested an immune mechanism.[19,20]

The immunosuppression attributed to anticonvulsants is generally reversible following drug withdrawal, and this was the case with our patient. Although the rash disappeared within a few days, immunoglobulin levels increased over a period of months and needed to be replaced. The recovery of immunoglobulin levels after antiepileptic use usually occurs 4 months to 6 years after the discontinuation of the drug.[21] Because the exact mechanism of low immune globulin levels during carbamazepine use is not known, it is difficult to speculate why the recovery period is so long. It is possible that each of the proposed mechanisms (an absence of B cells, extensive impairment of the synthesis of Igs in B cells, and a class-switch disorder of Igs in B cells) may need months to recover. IgG values higher than 500 mg/dL are considered to be protective in patients with hypogammaglobulinemia for the purpose of reducing the recurrence of infections.[22,23] Accordingly we replaced immunoglobulins until IgG values were higher than 500 mg/dL.

Immunoglobulins play an important role in adaptive immunity; low levels of immunoglobulins are well known to be associated with an increased risk of infections.[23] The type of infection generally depends on which immunoglobulin species is deficient. Sustained very low levels of IgA, IgG, and IgM are associated with significantly increased risk of infections, especially respiratory tract infections of bacterial origin. The threshold level of IgG that is associated with an increased risk of infection is not known. The general consensus is that intravenous Ig treatment should aim to achieve a serum IgG level of >500 mg/dL.[23] Although transient

drug-induced depletion of immunoglobulins is not considered to be associated with an increased risk of infection, the presence of certain comorbidities and failure to treat the infection, as in our case, may require the replenishment of IgG.

The disorders observed after carbamazepine-induced hypogammaglobulinemia may be severe: case reports describe bronchiolitis obliterans organizing pneumonia (BOOP),[5] acute interstitial pneumonia,[24] herpes encephalitis,[6] recurrent sinusitis,[3] reactivation of human herpesvirus 6 infection,[7] and visceral leishmaniasis.[4] BOOP is suggested to be a side effect of the drug or a sequela of drug-induced lupus[25] or repeated respiratory infections caused by carbamazepine-induced hypogammaglobulinemia.[5]

The presence of rash and thrombocytopenia raised the suspicion of a drug-related event in our case. However, these findings are not always associated. Therefore, in patients using antiepileptics, especially carbamazepine, serum immunoglobulins levels should be checked in those with recurrent infections.

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