Carbamazepine-induced interstitial pneumonitis associated with pan-hypogammaglobulinemia

Daniel Gonçalves*, Rute Moura, Catarina Ferraz, Artur Bonito Vitor, Luísa Vaz
Serviço de Pediatria, Hospital de São João, Porto, Portugal

Abstract
Carbamazepine remains a first-line drug for treatment of epilepsy in children. A wide variety of side effects have been attributed to its use, including a mild involvement of the immune system, usually a transient decline in IgA. Pulmonary complications, including interstitial pneumonitis, were mainly described in adults, and are considered rare side effects. In this report we describe the first pediatric patient who developed a severe interstitial pneumonitis and a pan-hypogammaglobulinemia 2 months after starting carbamazepine. A gradual resolution of symptoms and complete immune recovery was observed after the drug withdrawal, but 6 months later our patient still has a marked reduction in lung volumes and decreased exercise tolerance. We suggest that immunoglobulins should be carefully examined after carbamazepine initiation, particularly if the patient develops any sign of immunosuppression.

1. Introduction

Carbamazepine (CBZ) is a drug of choice for treatment of simple or complex partial seizures and generalized secondary seizures in both children and adults. A wide variety of side effects have been attributed to its use, including sleep disorders, anorexia, nausea, vomiting, irritability, ataxia and diplopia. Involvement of the immune system has been studied since the drug was first used and affects as many as 47% of patients, with a decrease in IgA levels being the most commonly noted anomaly. IgG deficiency with B cell aplasia has also been reported in some patients treated with CBZ, due to a B cell maturation defect.

While CBZ pulmonary toxicity is rare, interstitial pneumonitis, bronchiolitis obliterans organizing pneumonia, bronchospasm, pulmonary edema and pulmonary nodules have all been reported.

In this report we describe the case of a boy who developed an interstitial pneumonitis and a pan-hypogammaglobulinemia following CBZ therapy.

2. Patient presentation

A 7-year-old boy was being treated for epilepsy with valproic acid, since he was 3 years old. Following a long asymptomatic period, he had another seizure 2 months before admission, and CBZ was started. Four weeks later, he presented to the emergency room (ER) with fever, cough and dyspnea. Chest x-ray revealed a mild interstitial infiltrate, and he was started on a 10-day course of clarithromycin.

Since there was no clinical improvement, the patient returned to the ER. Pulmonary auscultation revealed fine crackles and wheezing bilaterally. He was discharged under systemic corticosteroid therapy (bethametasone) and inhaled short acting β2-agonist (salbutamol).

Two weeks later he presented again with fever, non-productive cough, asthenia and worsening dyspnea. On examination he had a marked respiratory distress (tachypnea 48 cycles/min – nasal flare, intercostal retractions) and hypoxemia (oxygen saturation of 84% in room air). PA again revealed diffuse crackles and wheezes in both lungs. Initial investigations showed a hemoglobin of 11.5 g/dL, white cell count of 18.2 x 10^9/L (72% neutrophils, 12% lymphocytes), platelet count of 338 x 10^9/L and a C-reactive protein of 35 mg/L. Chest radiograph demonstrated bilateral interstitial infiltrates.

He was admitted under oxygen, ampicillin, oseltamivir, prednisone and salbutamol, with a presumptive diagnosis of pneumonia. Blood culture, viral antigen detection on nasal swab and serology for atypical pneumonia were all negative. Computed tomography (CT)
of the chest (Fig. 1) revealed multiple cylindrical bronchiectasis in all pulmonary lobes, associated with peribronchial condensations in the upper lobes, a pattern compatible with bilateral interstitial pneumonitis. Steroid dosage was increased and ceftriaxone added to the therapeutic regimen. There was no improvement in the following days, with severe hypoxia and sustained fever. Due to a possible need of admission in an Intensive Care Unit, he was transferred to our pediatric department (tertiary care hospital). Workup at this stage revealed pan-hypogammaglobulinemia (IgG = 163 mg/dL, IgA < 6 mg/dL, IgM < 5 mg/dL). Lymphocyte subset showed normal numbers of CD4+ T cells (43.7%), CD8+ T cells (38.9%) and almost absent CD19+ B cells (0.4%). A diagnosis of CBZ hypersensitivity was suspected, and CBZ was replaced with topiramate. An infusion of 600 mg/kg of IgG was performed.

A gradual clinical improvement was noted with a decrease in the respiratory rate, work of breathing and oxygen requirement. The child was discharged after 3 weeks, under a dose reduction scheme of prednisone. Six months after CBZ discontinuation, the patient had normalized quantitative immunoglobulins and improved B cell numbers. Pulmonary function tests show a restrictive pattern with a Forced Vital Capacity (FVC) of 53%, and a normal FEV1/FVC ratio. He still has decreased exercise tolerance and some limitation in performing activities of everyday life.

3. Discussion

The combination of worsening dyspnea, prolonged fever without improvement, chest CT pattern of interstitial pneumonitis and pan-hypogammaglobulinemia, along with a 2-month interval between the beginning of CBZ and the onset of symptoms, led to the presumptive diagnosis of CBZ hypersensitivity. Furthermore, a gradual resolution of symptoms and immune recovery was observed after CBZ suspension. To our knowledge, this is the first case report of a pediatric patient with both an interstitial pneumonitis and a pan-hypogammaglobulinemia in association with CBZ therapy.

Although the exact mechanisms of CBZ induced hypogammaglobulinemia are unknown, absence of B cells, impairment of immunoglobulin synthesis in B cells and a disorder of the class-switch have all been implied.4,7 Recovery usually requires 4 months to 6 years after drug withdrawal.5 In our patient, the most likely mechanism was the absence of B cells, probably due to direct bone marrow suppression, as previously suggested.9 Since the patient did not exhibit signs or symptoms of immunodeficiency before CBZ administration, and the hypogammaglobulinemia with absent B cells resolved after CBZ suspension, it is likely that CBZ therapy was responsible for this serious defect in humoral immune response. Confirmation of the diagnosis with a further challenge with CBZ was not thought to be justified.

CBZ-induced interstitial pneumonitis is a rare but well-described complication in adults. The mechanism of lung injury is believed to be an immune–mediated hypersensitivity response.10 In the present case, the thoracic CT findings and the clinical improvement after CBZ withdrawal, suggest a CBZ-induced interstitial pneumonitis. Despite the gradual improvement after the drug withdrawal, our patient still has some exercise intolerance, probably related to the marked decrease in lung volumes. Various patterns of lung disease months to years after an initial CBZ exposure have been reported before, mainly bronchiolitis obliterans organizing pneumonia and drug induced lupus.5,6,11 Further clinical follow-up along with thoracic CT imaging will reveal any residual lung damage.

CBZ continues to be a first-line drug for the treatment of epilepsy in children. The present report calls attention to the need for clinical follow-up of CBZ-treated children, due to its various side effects, particularly affecting the immune system. We suggest that immunoglobulins should be carefully examined in these children, particularly after CBZ initiation. Moreover, concomitant CBZ therapy should always be considered as a cause of interstitial pneumonitis, since CBZ withdrawal is the only effective treatment for further reducing lung injury.

Disclosure statement

The authors report no biomedical financial interests or other potential conflicts of interest in this manuscript. There were no sponsors in this study.

Contributor’s statement

Daniel Gonçalves — conception and design of the manuscript, drafting of the article.
Rute Moura — conception of the manuscript, data collection.
Catarina Ferraz — manuscript revision.
Bonito Vitor — manuscript revision.
Luisa Vaz — final approval of the version to be published.

References

1. Loiseau P. Carbamazepine: clinical efficacy and use in epilepsy. In: Levy RH, Mattsson RH, Meldrum BS, Perucca E, editors. Antiepileptic drugs. 5th ed. Philadelphia: Lippincott Williams & Wilkins; 2002. p. 262–72 [ch 23].
2. Sorrel TC, Forbes J. Depression of immune competence by phenytoin and carbamazepine. Clin Exp Immunol 1979;20:273–85.
3. Rice CM, Johnston SL, Unsworth DJ, et al. Recurrent herpes simplex virus encephalitis secondary to carbamazepine induced hypogammaglobulinaemia. J Neurol Neurosurg Psychiatry 2007;78:1011–2.

4. Go T. Carbamazepine-induced IgG1 and IgG2 deficiency associated with B cell maturation defect. Seizure 2004;13:187–90.

5. Archibald N, Yates B, Murphy D, Black F, Lordan J, Dark J, et al. Carbamazepine-induced interstitial pneumonitis in a lung transplant patient. Respir Med 2006;100:1660–2.

6. Banka R, Ward MJ. Bronchiolitis obliterans and organising pneumonia caused by carbamazepine and mimicking community acquired pneumonia. Postgrad Med J 2002;78:621–2.

7. Tamada T, Nara M, Tomaki M, Ashino Y, Hattori T. Secondary bronchiolitis obliterans organising pneumonia in a patient with carbamazepine-induced hypogammaglobulinaemia. Thorax 2007;62:100.

8. Castro AP, Redmerski MG, Pastorino AC, de Paz JA, Fomin AB, Jacob CM. Secondary hypogammaglobulinemia after use of carbamazepine: case report and review. Rev Hosp Clin Fac Med Sao Paulo 2001;56:189–92.

9. Yamamoto T, Uchiyama T, Takahashi H, Himuro K, Kanai K, Kuwabara S. B cell aplasia and hypogammaglobulinemia after carbamazepine treatment. Inter Med 2010;49:707–8.

10. Mauri-Hellweg D, Bettens F, Mauri D, Brander C, Hunziker T, Pichler WJ. Activation of drug-specific CD4+ and CD8+ T cells in individuals allergic to sulfonamides, phenytoin, and carbamazepine. J Immunol 1995;155(1):462–72.

11. Milesi-Lecat A, Schmidt J, Aumaitre O, et al. Lupus and pulmonary nodules consistent with bronchiolitis obliterans organising pneumonia induced by carbamazepine. Mayo Clin Proc 1997;72:1145–7.