case report

B cell aplasia and hypogammaglobulinemia associated with levetiracetam

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Levetiracetam (LEV) is a second-generation antiepileptic drug approved for the treatment of several types of epilepsy. We report a 45-year-old female who developed hypogammaglobulinemia and B cell aplasia during LEV treatment. The Naranjo probability score for an adverse drug reaction was 6. After LEV discontinuation, the number of B cells gradually increased and reached normal levels within two months. This case suggests that monitoring of immunoglobulin levels and lymphocyte subsets analysis is important in patients treated with LEV, especially in cases of prolonged infections.

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Antiepileptic drugs are known to induce hematological and immunological alterations. Thrombocytopenia, pancytopenia, hypogammaglobulinemia and B cell deficiency have been reported in some patients with the administration of antiepileptic drugs such as carbamazepine, phenytoin and valproate.[1-3]

LEV is a new generation antiepileptic drug reported to have a high degree of efficacy and tolerability in epilepsy treatment since 1999.[4] In systematic reviews, it is also considered a safer alternative monotherapy as an antiepileptic drug in pregnancy.[5] The most commonly observed adverse effects of the drug are somnolence, agitation, asthenia, headache, abnormal behaviour and depression.[4] Hematological disorders such as pancytopenia, thrombocytopenia and platelet dysfunction have been reported.[6-11] Stevens-Johnson syndrome and psychotic disorders have been observed in some cases.[12,13] We report a rare case of B cell aplasia and hypogammaglobulinemia after LEV treatment.

CASE

A 45-year-old female was operated on for a pituitary tumor with transsphenoidal pituitary surgery. A second operation was required to repair the postoperative rhinorrhea (cerebrospinal fluid, CSF leak). After the operation, the patient was re-evaluated due to complaints of headache, nausea, loss of appetite, and fever. Based on CSF microscopy results, she was hospitalized with the diagnosis of meningitis. The patient was started on cefotaxime for 4 days and then switched to meropenem) and vancomycin. At 18 days, when no significant improvement was observed in CSF microscopy, the patient was started on ampicillin for *Listeria monocytogenes meningitis*. As there was no clinical response to the treatment and no improvement in CSF microscopy, the patient underwent brain surgery with a presumptive diagnosis of chemical meningitis. When admitted to the hospital, the patient's cell count in CSF was 2871. After treatment with meropenem plus linezolid therapy for 26 days and one week no-antibiotic treatment, the patient was discharged with an improved CSF cell count of 385 cells. After being discharged, the patient had a seizure at home. Complicated by postoperative epileptic attacks, the patient was started on antiepileptic therapy (LEV at a dosage of 500 mg tablets three times daily). One month later, the patient presented again with complaints of fever and headache. As no clinical response

was obtained by treatment with meropenem for 11 days and chloramphenicol for 10 days, the patient was referred for evaluation of immunodeficiency.

In her clinical evaluation, it was learned that she was healthy before the surgery for the pituitary tumor and there was no family history related to immunodeficiency. Laboratory tests revealed a normal white blood cell count (6.7/10^9/L) and normal platelet count (256/10^9/L). Erythrocyte sedimentation rate (ESR, 5 mm/h) was normal. Viral serologies including hepatitis B, hepatitis C and HIV were negative. *Brucella* agglutination was also negative. Skin tuberculin test was negative. Immunological examination showed decreased levels of IgG (778 mg/dL, normal: 913-1884 mg/dL) and IgA (97 mg/dL, n: 139-378 mg/dL). Her serum level of IgM was normal (108 mg/dL, n: 88-322 mg/dL). Peripheral blood flow cytometric analysis revealed the absence of B cells (CD19+ B cells; <1%) (n: 7-23%) (**Figure 1**). T cell subsets and natural killer cell numbers were normal. Neutrophil function, chemotaxis, phagocytosis and oxidative burst activity were normal. Isohemagglutinin titers, levels of pneumococcal and tetanus specific IgG antibodies were also normal. Immunological studies are shown in **Table 1**.

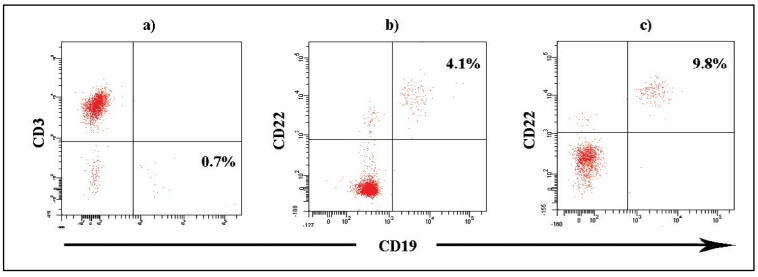

Figure 1. The percentage of CD19+ B lymphocytes; a) at admission b) 20 days after stopping levetiracetam c) 2 months after stopping levetiracetam.

The Naranjo adverse drug reaction probability score[14] was 6 (+2 for occurrence of B cell aplasia and hypogammaglobulinemia after administration of LEV, +1 for improvement of B cell aplasia and hypogammaglobulinemia following discontinuation of LEV, +2 for the absence of an alternative causes for the adverse event, +1 for the confirmation by objective evidence). The antiepileptic drug was discontinued after epileptic seizures were controlled. B cells gradually increased three weeks later (CD19+ B cells: 4%, CD20: 4.1%, CD21:2.8%, CD22: 5.8%) and returned to normal within two months (CD19+ B cells: 9.8%) (**Figure 1**). In the one year follow-up period, the number of B cells was stable and the patient was doing well without any infection.

DISCUSSION

Levetiracetam (LEV) is a well-tolerated and efficacious anticonvulsant drug against a broad range of seizure types.[15,16] To our knowledge, this is the first report of B cell aplasia due to the use of LEV. In the literature, B cell aplasia has been described with the use of antiepileptic drugs as carbamazepine in a few cases.[1,17,18] Yamamoto et al[1] reported a case of hypogammaglobulinemia associated with aplasia of B lymphocytes after carbamazepine treatment in a 33-year-old man who suffered status epilepticus. This case presented with bilateral interstitial pneumonia and an absence of B cells that persisted for more than three months.

Table 1. Serum concentrations of immunoglobulins during and after LEV therapy.

	Serum concentrations (mg/dL)						
	IgG	**IgA**	**IgM**	**IgG1**	**IgG2**	**IgG3**	**IgG4**
84 days after starting LEV	778	97	108	594	167	17	19.7
100 days after starting LEV	876	107	136	NT	NT	NT	NT
19 days after stopping LEV	816	99.6	140	744	117	29	18
63 days after stopping LEV	1190	99.6	135	NT	NT	NT	NT
181 days after stopping LEV	1630	182	543	NT	NT	NT	NT
404 days after stopping LEV	1140	226	181	1030	183	27	19
Normal ranges	913-1884	139-378	88-322	643-1071	179-435	17-83	14-80

NT: not tested, LEV: levetiracetam

Our case exhibited symptoms of chronic meningitis and the signs of infections that resolved after disconnection LEV.

The mechanism of B cell aplasia related to antiepileptic agents remains unclear. Elouni et al[8] reported on a 76-year-old patient who suffered confusion, hemianopsia and seizure secondary to ischemic stroke. Two days after treatment with intravenous LEV, the patient had pancytopenia.[8] Gallerani et al[6] described a 65-year-old woman who underwent surgical removal of a meningioma; pancytopenia developed the ninth day after the start of LEV. Meschede et al[10] observed a 64-year-old who suffered from epilepsy with complex partial seizures who developed thrombocytopenia after the first LEV dose. All of these patients were in good condition after LEV discontinuation. In our patient, the recovery of B lymphocyte counts was observed 2 months after drug discontinuation. Although LEV may induce pancytopenia in some patients, primary hematological disease was unlikely because of the normal blood cell count other than B cell lymphocytes in our case. Our case indicates that LEV may be associated with reversible B cell aplasia as a rare adverse reaction of possible idiosyncratic origin.

Reversible hypogammaglobulinemia secondary to the use of LEV was reported in a case in the literature. Azar and Ballas[19] reported a 19-year-old man with panhypogammaglobulinemia after LEV treatment. Surgical drainage was performed due to brain abscess and he was given oral LEV (500 mg twice daily) for seizure prophylaxis. In his immunologic evaluation, they found a decreased IgG level after 1 month and serum IgG, IgA and IgM levels declined after 2 months. B, T and natural killer cell numbers were normal. Serum immunoglobulin changes returned to normal when the drug was discontinued 25 months later.[19] In our patient, an initial assessment of immunodeficiency was performed 3 months after the initiation of LEV therapy and it was discontinued after seizures were controlled. In our patient, serum IgG and IgA levels reached normal levels about 2 and 6 months later, respectively.

Svalheim et al[20] investigated immunoglobulin levels in patients with epilepsy using antiepileptic drugs (levetiracetam, lamotrigine, carbamazepine). No significant differences were observed for patients treated with LEV in 21 women (44.7%) and 26 men (55.3%).[20] In another study, Li et al[21] investigated the in vitro effect of levetiracetam and valproate on apoptosis and cytotoxic function of CD8+ T lymphocytes in humans. They showed that LEV had a moderate depressive effect on degranulation of CD8+ T lymphocytes, indicating that levetiracetam can disturb the antiviral function of the immune system.[21] This case illustrated that LEV may affect immune system cells.

Our patient had specific antibody levels indicating previous normal function of the immune system and had no personal or family medical history suggestive of immunodeficiency prior to the surgery for pituitary tumor. Almost every patient receiving intracranial surgery that involves opening the dura mater is given antiepileptic drugs. In our patient, the other causes of B cell aplasia and hypogammaglobulinemia include protein-losing enteropathy, malabsorption, hematologic malignancies, and infectious diseases (e.g. human immunodeficiency virus). Autoimmunity had been ruled out by careful evaluation of clinical features and laboratory examinations.

Based on the information available in the literature, we suspected that the patient may have developed a secondary immunodeficiency induced by antiepileptic drugs. The Naranjo adverse drug reaction probability score indicated that LEV was related to the development of reversible B cell aplasia and hypogammaglobulinemia.

We suggest that LEV was the most likely cause of our patient's hypogammaglobulinemia and B cell aplasia. Patients requiring LEV should have serum immunoglobulins measured and lymphocyte subsets analysis performed if they experience recurrent or persistent infections.

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