CASE REPORT

Pancytopenia associated with levetiracetam in an epileptic woman

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SUMMARY

Haematological toxicity due to antiepileptic drugs is uncommon, but the increased risk of aplastic anaemia has been reported. Few case reports have been published regarding pancytopenia associated with levetiracetam treatment, and its intrinsic pathogenesis is still unknown. We describe the case of a woman aged 77 years who presented with abdominal pain and loss of appetite. She had been taking valproic acid, due to a previous episode of epileptic seizures, and presented with drowsiness and dizziness. Valproate was discontinued and therapy with levetiracetam was initiated. 2 days later, we observed severe anaemia, leucopenia and thrombocytopenia, which were attributed to levetiracetam. Although she recovered soon after the treatment was discontinued, it took 2 weeks for cell counts to return to normal.

BACKGROUND

Levetiracetam is considered a safe antiepileptic drug, in children and adults. It is well tolerated and its side effects are considered benign and central nervous system-related, such as somnolence, drowsiness and fatigue. Furthermore, levetiracetam has no significant drug interactions.¹

There are few case reports published on the topic of blood dyscrasias, such as thrombocytopenia and pancytopenia, which disappear after the drug is discontinued. The clinical data collected, however, do not allow conclusions to be drawn that would shed light on the pathogenesis or the predisposing factors that determine these blood dyscrasias.

CASE PRESENTATION

A woman aged 77 years was admitted to our hospital with digestive difficulties, abdominal pain, loss of appetite and a premature feeling of satiety. She had occasional nausea and vomiting, but no weight loss. She had a 3-year history of extracapillary proliferative glomerulonephritis, and was therefore being treated with prednisone 5 mg daily. At the time of admission, she had no renal failure or skin or blood involvement. She had been taking aspirin and valproic acid for a year due to a single episode of epileptic seizures related to a previous cerebrovascular accident, leaving no sequelae.

Physical examination was normal and did not show any significant findings. Heart and lung sounds, abdominal palpation and neurological examination were all normal.

In the workup that followed, a gastroscopy revealed a bezoar. We therefore initiated treatment with cellulase, with a good clinical outcome.

However, the patient unexpectedly presented with drowsiness and loss of alertness, which were attributed to the treatment with valproic acid: its value was 146 µg/mL (normal range: 50–100 µg/mL). We therefore decided to discontinue valproic acid and initiate levetiracetam 500 mg daily.

INVESTIGATIONS

Her baseline complete blood count showed: white cell count 4420/µL (normal range 4000–10 000/µL), haemoglobin 13.2 g/dL and platelets 218 000/µL (normal range 150 000–450 000/µL).

Two days after initiating levetiracetam, however, the blood smear showed pancytopenia: white cell count 2500/µL with 1200 neutrophils, haemoglobin 6.6 g/dL and platelets 68 000/µL.

DIFFERENTIAL DIAGNOSIS

On admission, initial laboratory tests showed a normal complete blood count. Given the sharp decline in this count, we decided to rule out disseminated intravascular coagulation, haemolysis, infection, autoimmune disorders and thrombotic thrombocytopenic purpura, which were the main differential diagnoses we proposed. However, our first option was a drug side effect.

A peripheral blood smear did not show any schistocytes or abnormalities in blood cells. Bilirubin, liver and kidney functions, haptoglobin and D-lactate dehydrogenase were normal. Reticulocyte count and direct antiglobulin test were also normal.

C3 and C4 levels were normal, and antineutrophil cytoplasmic antibody and antinuclear antibody tests were also normal.

An abdominal ultrasound was performed, which did not show any splenomegaly or other abnormalities.

We therefore believe that this blood dyscrasia was a drug-related effect due to the treatment the patient was taking.

TREATMENT, OUTCOME AND FOLLOW-UP

On the assumption that levetiracetam was the only new drug that had been added, it was suspended.

We transfused 2 units of red blood cells immediately after we noticed the severe anaemia.

While we observed signs of improvement the next day (white cell count 3560/µL, haemoglobin 9.5 g/dL and platelets 123 000/µL), the complete blood count only returned to baseline values 14 days after the discontinuation of this antiepileptic drug.

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Two days after diagnosing the pancytopenia, the patient presented with dyspnoea and fever, and the chest X-ray revealed pneumonia of the lower right lung, which was treated with amoxicillin–clavulanate 2 g every 8 hours for 10 days. Once fully recovered, the patient was discharged. At follow-up, 3 and 6 months after discharge, we observed normal laboratory and radiological findings.

DISCUSSION

Levetiracetam is a safe drug, given its low rate of drug-related adverse events and its lack of interaction with other drugs. Nevertheless, levetiracetam can cause neurological side effects during treatment, such as fatigue, dizziness or unusual mood or behavioural changes, but these usually disappear throughout the course of the treatment.^{1 2}

There are a few cases reporting some rare side effects, such as blood dyscrasias. According to the FDA Safety Information,² the reported haematological abnormalities include decreased red blood cell counts, increased eosinophil counts, decreased white cell count and neutrophil counts, and cases of agranulocytosis.²

However, several cases of thrombocytopenia have also been reported,^{3–6} which have eventually led to the discontinuation of the antiepileptic drug. We searched the medical literature to find reliable studies or case reports and found four case reports regarding pancytopenia,^{7–10} which are summarised in table 1. This review revealed that the clinical data are quite heterogeneous with regard to doses, predisposing factors and infectious complications. All cases were women and three of them were over 65 years of age. In two patients, the underlying disease was a neoplasm. Levetiracetam was the first-choice drug in two of the cases, whereas in the other two cases, it replaced the existing antiepileptic drug. Our patient was also over 65 years of age, but her underlying condition was an immunological disease (extracapillary proliferative glomerulonephritis). She was on antiepileptic treatment because of a cerebrovascular event 1 year earlier, for she presented with epileptic seizures. We believe the bezoar was no related to the pancytopenia, for it was just the cause of her digestive symptoms.

Since she presented with drowsiness, which we believed was a side effect of valproic acid, we decided to replace it with levetiracetam. Therefore, we considered this drug-related effect as an incidental finding during admission.

Although not all complete blood counts were provided, the four patients in table 1 received red blood cell transfusions, as did our patient. In all reported cases, the haematological abnormalities were detected a few days after the beginning of the treatment with levetiracetam and these alterations were not subtle, but very noticeable.

Only Gallerani *et al*⁸ performed a bone marrow biopsy, which revealed medullary hypoplasia (no further details provided). The case reported by Gallerani *et al* also presented with severe infectious complications: liver abscesses and pneumonia, which were correlated to the leucopenia. Our patient presented with pneumonia of the lower right lung within the first 2 days after the pancytopenia was diagnosed; by then, her neutrophil count was 1200/ μ L.

In order to withdraw the levetiracetam therapy, the Naranjo probability scale¹¹ was applied by the four authors. When applied to our patient, the score determined the adverse reaction followed a temporal sequence after levetiracetam was given, improved when the drug was discontinued, and could not be reasonably explained by the patient's clinical state or an alternative cause. These findings suggested that the recently initiated levetiracetam had induced the pancytopenia.

Table 1 Features of previously reported patients with levetiracetam-induced pancytopenia

Author/year	Gender/age	Neurological disorder	Event leading to initiation of LEV	Previous AED	Levetiracetam dose	Baseline CBC	Time of treatment with LEV* (days)	Lowest CBC, if provided	Response time after discontinuation of LEV	Infectious complications
Elouni, 2009	Female, 76	Ischaemic stroke	Status epilepticus	Clonazepam	1 g daily	Hb: 11.5 g/dL WCC: 22 300/ μ L Platelets: 290 000/ μ L	2	Hb: 9.8 g/dL WCC: 5700/ μ L Platelets: 83 000/ μ L	2 days	None
Gallerani, 2009	Female, 65	Meningotheliomatous meningioma	First epileptic seizure	None	750 mg twice a day	Hb: 14.1 g/dL WCC: 7500/ μ L Platelets: 273 000/ μ L	9	Not provided	6 days	Pneumonia, liver abscesses
Aydogan, 2012	Female, 16	Lafora's disease	Not provided	Sodium valproate	1 g twice a day	Hb: 8.4 g/dL WCC: 7200/ μ L Platelets: 280 000/ μ L	4	Hb: 6.2 g/dL WCC: 2200/ μ L Platelets: 7383/ μ L	4 days	None
Alzahani, 2015	Female, 79	Glioblastoma multiforme	Seizure prophylaxis	None	Not reported	Reported as normal	5	Platelets <100 000/ μ L	24 hours	None
García Carretero, 2016 (current case report)	Female, 77	First epileptic seizure, transient ischaemic attack	Neurological valproate toxicity	Sodium valproate	500 mg daily	Hb: 13.2/dL WCC: 4420/ μ L Platelets: 218 000/ μ L	2	Hb: 6.6 g/dL WCC: 2500/ μ L Platelets: 68 000/ μ L	24 hours	Pneumonia of the lower right lung

*Until pancytopenia is observed.

AED, antiepileptic drug; CBC, complete blood count; Hb, haemoglobin; LEV, levetiracetam; WCC, white cell counts.

On the basis of these five case reports, it is difficult to draw firm conclusions. They are probably very few cases to get evidence-based findings. The specific mechanisms of action are unknown, but it would be reasonable to assume that the pancytopenia was related to aplastic pancytopenia or bone marrow aplasia, rather than microangiopathic haemolytic anaemia or thrombotic thrombocytopenic purpura. Although not reported by any of the four case reports, we did not find ghost cells or schistocytes which could have pointed to microangiopathic aetiology. Further studies are needed to better understand the factors associated with the bone marrow aplasia: idiosyncratic drug reaction (type B reaction), immune-mediated, toxins, etc.

It is also not clear whether there is a toxic dose, or there is an aberrant reaction or hypersensitivity to levetiracetam (idiosyncratic drug reaction), without connection to the pharmacology of the drug. Nevertheless, our hypothesis rests on the assumption that the current adverse drug reaction did not involve overdose (type A reaction), but appeared to be concentration independent. Therefore, we believe it was an idiosyncratic drug

reaction, which occurs rarely and unpredictably among the population.

In the four case reports, as well as ours, the pancytopenia resolved quite rapidly (between 1 and 6 days after discontinuation of the drug).

What we do consider important is the high risk of severe infectious complications, probably related to leucopenia. The patient reported by Gallerani *et al*⁸ presented with pneumonia and liver abscesses, and our patient also presented with pneumonia of the lower right lung, which appeared in an unexpected way, while no underlying condition was present in either of the two patients. Anaemia, leucopenia and thrombocytopenia can therefore be life-threatening conditions clinicians should be aware of. Hence, we should look for any evidence of haematological toxicity due to antiepileptic drugs.

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Contributors RGC wrote the first draft; MRB and MO-V made interesting suggestions; IS-R helped in the translation into English.

Competing interests None declared.

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Learning points

- ▶ Available data on predisposing factors or clinical conditions regarding the likelihood of an adverse event such as pancytopenia due to levetiracetam therapy are limited. Few case reports have been published on this subject to establish a population-based evidence.
- ▶ Most of the side effects of levetiracetam are minor, and are usually related to neurological symptoms. Our hypothesis is that pancytopenia related to levetiracetam is an idiosyncratic drug reaction.
- ▶ When the pancytopenia is present, the first step would be to withdraw the treatment with levetiracetam, and be aware of severe infectious complications, because haematological abnormalities can be unexpected, but life-threatening situations.
- ▶ While it is true that clinicians must be aware of certain adverse effects regarding antiepileptic drugs, blood dyscrasias are very rare and can be diagnosed within the first few days after initiating levetiracetam therapy.

REFERENCES

- 1 Kayani S, Sirsi D. The safety and tolerability of newer antiepileptic drugs in children and adolescents. *J Cent Nerv Syst Dis* 2012;4:51–63.
- 2 U.S. Food and Drug Administration. Keppra (levetiracetam) tablets and oral solution. (Cited 5 August 2016). <http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm284241.htm>
- 3 Kimland E, Höjberg B, von Euler M. Levetiracetam-induced thrombocytopenia. *Epilepsia* 2004;45:877–8.
- 4 Meschede A, Runge U, Sabolek M. Thrombocytopenia during levetiracetam therapy. *Epilepsy* 2008;80:91–2.
- 5 Oghlakan R, Nock C, Koubeissi M. A case of levetiracetam-induced thrombocytopenia. *Epileptic Disord* 2010;12:335–7.
- 6 Sahaya K, Goyal MK, Sarwal A, *et al*. Levetiracetam-induced thrombocytopenia among inpatients: a retrospective study. *Epilepsia* 2010;51:2492–5.
- 7 Elouni B, Ben Salem C, Biour M. Levetiracetam-induced pancytopenia. *Ann Pharmacother* 2009;43:985.
- 8 Gallerani M, Mari E, Boari B, *et al*. Pancytopenia associated with levetiracetam treatment. *Clin Drug Investig* 2009;29:747–51.
- 9 Aydogan H, Yalçın S, Karahan MA, *et al*. Pancytopenia associated with levetiracetam treatment in Lafora's disease. *Blood Coagul Fibrinolysis* 2012;23:175.
- 10 Alzahrani T, Kay D, Alqahtani SA, *et al*. Levetiracetam-induced pancytopenia. *Epilepsy Behav Case Rep* 2015;4:45–7.
- 11 Naranjo CA, Busto U, Sellers EM, *et al*. A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther* 1981;30:239–45.

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