



Case report

Prophylactic levetiracetam-induced pancytopenia with traumatic extra-dural hematoma: Case report



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ABSTRACT

Background: Pancytopenia has only rarely been reported with Levetiracetam use. It is a potentially life threatening adverse effect that requires cessation of therapy.**Case description:** We describe a case of an otherwise well thirty-two-year-old man who underwent an emergent craniotomy for evacuation of a traumatic extra-dural haematoma. Post-operatively, he developed pancytopenia which corrected with cessation of levetiracetam.**Conclusion:** This report aims to increase awareness of this rare side effect and reiterates the judicious use of prophylactic levetiracetam in brain trauma.

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1. Introduction

The prophylactic use of anti-epileptic drugs (AEDs) for short durations following supra-tentorial surgery is common practice. Levetiracetam is a pyrrolidone derivative that is water soluble and is filtered by the kidneys with a half-life of 6–8 h. Its anti-epileptic effect is thought to be by modulation of neurotransmitter release via its adherence to the synaptic vesicle protein SV2A. Its advantages compared to older antiepileptics include a limited side effect profile, no requirement for therapeutic level monitoring in most cases and minimal drug interactions[1].

Levetiracetam can cause several adverse effects predominantly related to the central nervous system including dizziness, headache, behavioural changes and somnolence. Haematological side effects such as anaemia, mild thrombocytopenia and leukopenia are uncommon and do not usually require cessation of the drug[2]. However, pancytopenia, though exceedingly rare, is a potentially life-threatening side effect and this does require cessation of therapy[3]. The pathogenesis and predisposing factors leading to these haematological dyscrasias are unknown. We report a case of levetiracetam-induced pancytopenia in the context of a traumatic extradural hematoma.

Abbreviations: AEDs, anti-epileptic drugs; CT, computed tomography; Hb, haemoglobin; INR, international normalized ratio; Neuts, neutrophils; Plts, platelets; RBCs, red blood cells; TBI, traumatic brain injury; WCC, white cell count.

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2. Case report

A thirty-two-year-old male presented to the emergency department unconscious. He fell on the ground six hours prior following a punch to his right temple. On examination, his GCS (Glasgow Coma Scale) score was 8, with anisocoria and left sided hemiplegia. Following resuscitation and urgent imaging, he underwent a right sided craniotomy and a large parietotemporal extra-dural haematoma evacuated (Fig. 1). As prophylaxis 1 g loading dose of levetiracetam was administered prior to surgery and continued 500 mg twice daily planned for 7 days as per our institution protocol. Biochemistry prior to surgery was unremarkable; haemoglobin (Hb) 146, white cell count (WCC) 15.4, platelets (Plt) 217, internationalized normal ratio (INR) 1.0, activated partial thromboplastin time 26.7 with normal renal and hepatic function. Repeat Hb was 116 immediately post-operatively.

On post-operative day 1, repeat imaging demonstrated almost complete resolution of haematoma and the pupils were equal and reactive to light. Haemoglobin was noted to be 93, Plt 223. On post-operative day 3 Hb fell to 62 with the patient tachycardic despite adequate fluid volume. A unit of packed red blood cells (RBCs) was administered. In addition, his Plt count, neutrophils, lymphocytes, monocytes, eosinophils, basophils all were down trending, consistent with the picture of bone marrow suppression (Fig. 2). A further unit of RBCs was administered, and Hb raised to 66. There was no evidence of occult gastrointestinal bloods loss, haematuria or external signs of haemorrhage at bedside examination. There were no features of infection, his septic screen was negative. Peripheral blood smear did not reveal any schistocytes or

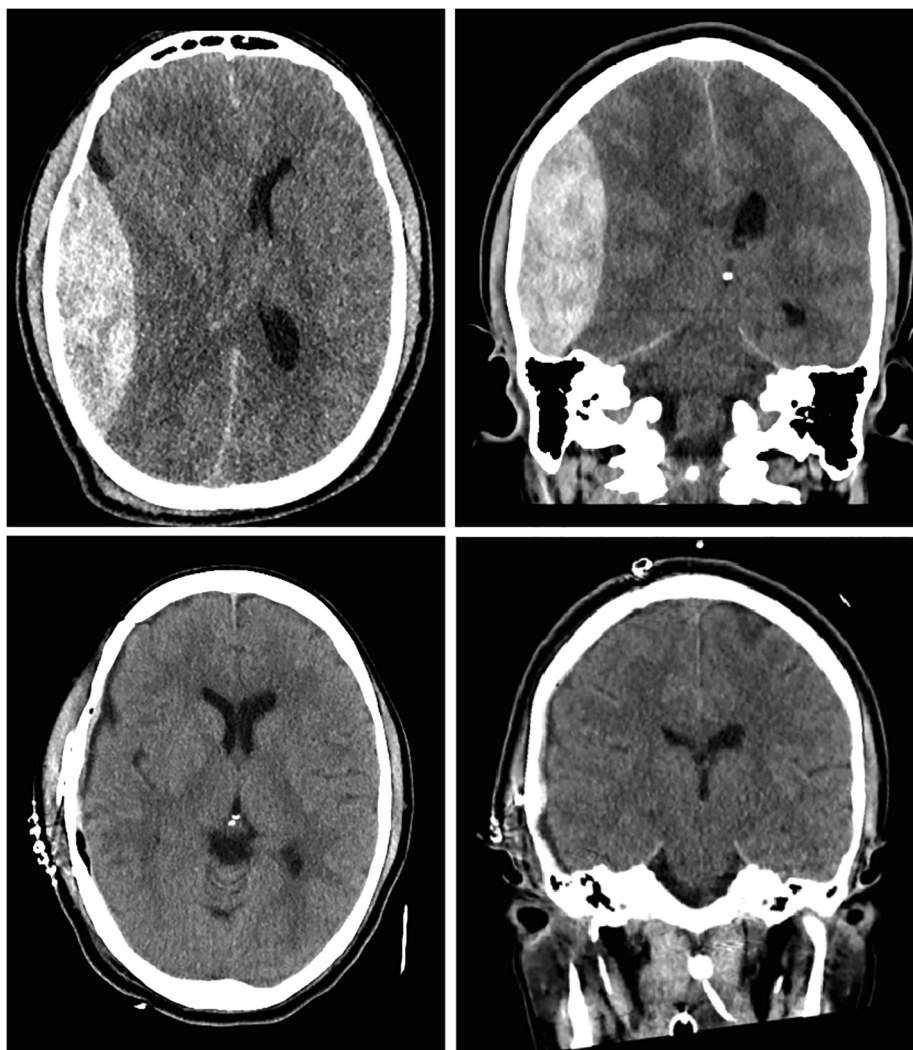


Fig. 1. Preoperative (upper panels) and postoperative (lower panels) CT scan showing axial (left panels) and coronal (right panels) views of the parietotemporal extradural hematoma evacuated by craniotomy.

blood cell abnormality. Renal and hepatic function were normal, as were haptoglobin and lactate dehydrogenase levels. Haematinics showed normal stores of ferritin, B12, folate though his plasma ferritin was low at $2 \mu\text{mol/L}$ (Range $9\text{--}30 \mu\text{mol/L}$) as was his plasma transferrin $18 \mu\text{mol/L}$ (Range $23\text{--}43 \mu\text{mol/L}$) consistent with a response to inflammation. A CT scan of his abdomen and pelvis demonstrated no evidence of intra-abdominal bleeding or solid organ injury. The differential diagnoses included disseminated intravascular coagulation, thrombotic thrombocytopenic purpura and infection. Given investigations were otherwise unremarkable the possibility of a drug side effect was considered. Levetiracetam was ceased on post-operative day 4. A levetiracetam level was not taken because a dose-dependent mechanism was unlikely and there was no clear indication to continue the drug. The next day his haemoglobin was noted to have increased from 66 to 78 g/L , WCC 5.7 to 5.8 , Neuts from 3.43 to 3.99 and Plt from 119 to 170 . His tachycardia had settled, with no clinical signs of anaemia and he was neurologically intact with normal cognition. Blood counts continued to improve with Hb 98 , Plts 258 on the day of discharge.

3. Discussion

The current report highlights the rare, though potentially life-threatening complication of pancytopenia caused by levetiracetam.

Although other differential diagnoses were considered, haematological abnormalities resolved with cessation of levetiracetam making it the most likely cause. The pathogenesis between levetiracetam and pancytopenia remains unclear and to the best of our knowledge this is the first report describing this side effect in the context of traumatic brain injury. This raises concern regarding the liberal use of prophylactic levetiracetam in patients with traumatic brain injury (TBI).

The use of prophylactic AEDs in patients with TBI remains contentious with no level 1 evidence supporting their use [4]. Their use though is still recommended in the Brain Trauma Foundation guidelines to reduce to incidence of early-post traumatic seizures [5]. The most recent Cochrane review on the prophylactic use of AEDs following brain surgery concluded there remains no consistent evidence to suggest they are efficacious in reducing early or delayed seizures following surgery or associated mortality [6]. One could argue, that in our patient, the presence of a purely extra axial lesion may not have necessitated seizure prophylaxis, because of the low epileptogenic rate of extradural hematomas reported in the literature. When compared to subdural hematomas, or intra-axial traumatic injuries, such as contusions, risk of seizures appears to be relatively low in extradural hematomas [7,8]. We believe that despite levetiracetam-induced pancytopenia being a rare side-effect it may have been avoided with careful patient selection for seizure prophylaxis.

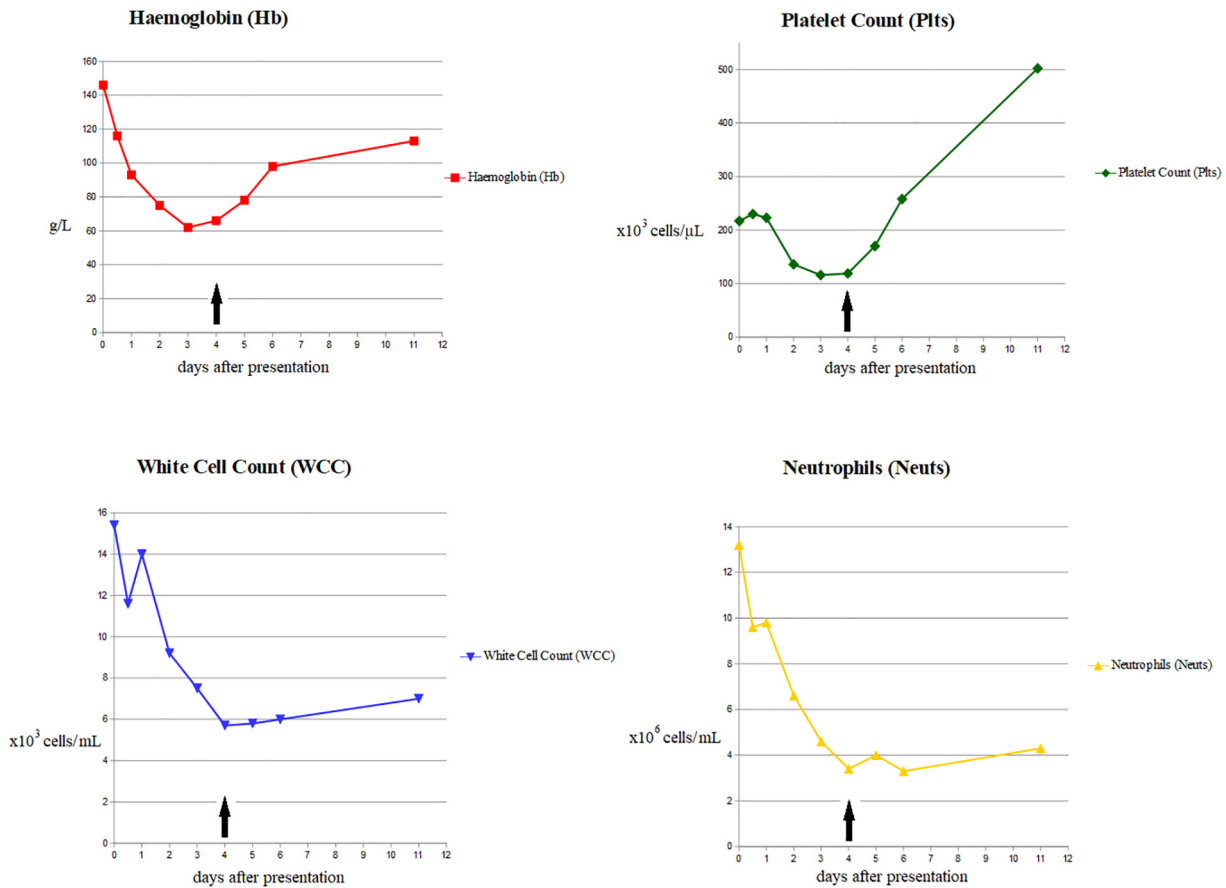


Fig. 2. Graphs showing Haemoglobin (Hb) (left upper panel), Platelet Count (Plts) (right upper panel), white cell count (WCC) (left lower panel), Neutrophils (Neuts) (right lower panel) values over time. An arrow indicates the cessation of Levetiracetam (day 4).

Six cases of levetiracetam induced pancytopenia have previously been reported in the medical literature [3,9–11]. Clinical data on these cases are heterogeneous with regards to predisposing factors, indication for therapy, dosing and complications. Two of these patients underwent surgery for intracranial neoplasm, with one patient commenced for first seizure and the other as prophylaxis [3,11]. Both patients were female and over 65 years of age. Three of the six patients reported suffered infectious complications including liver abscess, pneumonia and upper respiratory tract infection. One mortality has been attributed to levetiracetam induced pancytopenia in a 4-month-old infant treated for seizures who developed pneumonia, septic shock and multi-organ failure [10]. Luckily, in our case, there was almost no impact of the pancytopenia on the outcome of the patient. The haematological markers were back to normal at 1 month-follow-up.

In addition to clinical review, neurosurgical patients should be monitored for haematological toxicity following commencement of levetiracetam.

4. Conclusion

Pancytopenia is a known adverse effect of levetiracetam. Although extremely rare, this case serves to highlight that it may occur after seizure prophylaxis following traumatic brain injury and clinicians must be mindful of this complication. Judicious use of this medication may be advocated, especially for traumatic extradural hematoma.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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