Abstract

Introduction: Oxaliplatin is a cytotoxic platinum compound that is in widespread use in the treatment of gastrointestinal cancers. It has been occasionally associated with acute motor neuropathy, but the precise mechanism is uncertain. To the best of our knowledge, we report the first case of a patient demonstrating post-tetanic facilitation in the setting of transient bilateral abducens neuropathy and hypokalemia, after being infused with oxaliplatin.

Case presentation: A 47-year-old Indian woman with metastatic gastric cancer was receiving an oxaliplatin infusion at the initiation of her third cycle of palliative chemotherapy. She developed acute bilateral abducens neuropathy with post-tetanic facilitation alongside acute laryngopharyngodysesthesia and hypokalemia. Following supportive management, including potassium infusion and warming, her neurological signs and symptoms were spontaneously resolved. This syndrome did not recur in subsequent cycles following prolongation of infusion duration and the addition of supportive calcium and magnesium infusions.

Conclusion: The novel clinical observation of post-tetanic facilitation highlights a possible involvement of voltage-gated channels at the presynaptic terminals in the mechanism of acute oxaliplatin neurotoxicity.
The patient had not taken any oral medications other than capecitabine up to one week previously. The patient demonstrated physical signs consistent with bilateral abducens neuropathy, with bilateral gaze-evoked diplopia. Surprisingly, post-tetanic facilitation was observed, with unilateral resolution of diplopia and abducens neuropathy following sustained lateral gaze over one minute. Contralateral abducens neuropathy remained unchanged following apparent resolution of the unilateral abducens neuropathy. The apparently resolved unilateral abducens neuropathy recurred following a two-minute rest. Decreased tendon reflexes diffusely were noted, but no focal or generalized weakness was found. New electrocardiographic changes in terms of diffuse T-wave inversions were noted, as well as mild elevation of her serum creatine kinase-MB (CK-MB) levels by mass assay. Also noted was a serial decrease over 16 hours (7.0 µg/L immediately, 5.2 µg/L 8 hours later and 3.9 µg/L 16 hours later), but the diffuse T-wave inversions persisted. Corresponding serial serum creatine kinase (CK) levels were 72 µg/L, 63 µg/L and 52 µg/L, and troponin-T levels were not elevated at any of these three-time points.

Baseline blood counts and electrolytes drawn two days prior were unremarkable; in particular, her potassium level was 3.5 mmol L⁻¹ (3.3-4.9 mmol L⁻¹). She was asymptomatic up till this event. In particular, there was no intervening symptom of vomiting or diarrhoea, and the patient did not report the use of any oral medications. The patient did not have prior hypokalemia up to this point. Electrolytes drawn immediately upon onset of neurological symptoms revealed acute hypokalemia, with a serum potassium level of 2.5 mmol L⁻¹ (3.3-4.9 mmol L⁻¹). She was asymptomatic up till this event. In particular, there was no intervening symptom of vomiting or diarrhoea, and the patient did not report the use of any oral medications. The patient did not have prior hypokalemia up to this point. Electrolytes drawn immediately upon onset of neurological symptoms revealed acute hypokalemia, with a serum potassium level of 2.5 mmol L⁻¹ (3.3-4.9 mmol L⁻¹). She was asymptomatic up till this event. 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calcium chelation as the primary mechanism of acute oxaliplatin-induced neurotoxicity, but it is conceivable that a specific locations along the peripheral nerve may be more vulnerable to accumulation of oxaliplatin or its metabolites [1]. For example, platinum has been shown to accumulate in dorsal root ganglia in rodents administered oxaliplatin.

We considered the possibility of the acute hypokalemia causing the post-tetanic facilitation that we observed. Acute hypokalemia is associated with axonal and muscle membrane hyperpolarization [14,15]. It must be acknowledged that although our review of the literature did not report a previous association between hypokalemia and post-tetanic facilitation, the mechanisms of hypokalemia in inducing weakness are complex and as-yet poorly understood. Hence, a possible contribution of hypokalemia to post-tetanic facilitation cannot be definitively excluded. However, recent electrophysiological investigations of patients with acute hypokalemia highlight its contribution to axonal hyperpolarization, with a resulting activity-dependent conduction block worsening, rather than improving weakness [14]. Hence, this data suggests that hypokalemia is not the primary mechanism for post-tetanic facilitation.

Conclusion
In summary, while the mechanism of acute oxaliplatin-induced neuropathy remains uncertain, our novel clinical observation of post-tetanic facilitation alongside acute hypokalemia highlights voltage-gated channels at the presynaptic nerve terminal for investigation in the mechanism of acute oxaliplatin neurotoxicity.

Consent
Written informed consent was obtained from the patient’s family for publication of this case report. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

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Authors’ contributions
MHT wrote the manuscript. JHN and LC obtained data and reviewed the literature. CWT and BTT helped write the manuscript. All authors read and approved the final manuscript.

Competing interests
The authors declare that they have no competing interests.

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