Peripheral mononeuropathy associated with valproic acid poisoning in an adult patient

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Abstract. Objective: To present the case of axillary nerve neuropathy associated with valproic acid (VPA) poisoning. Case report: A 26-year-old man was hospitalized because of a suicide attempt with VPA overdose. Toxicology analysis revealed high serum VPA level (2,896 μmol/L; therapeutic range: 350 – 690 μmol/L). Three days after admission, the patient complained of weakness in his right arm. Neurological examination revealed weakness of flexion and abduction of the right arm and loss of sensation in the skin over the lateral upper right arm. A nerve conduction velocity test was normal in the ulnar, radial, median, musculocutaneous, and sural cutaneous nerves. Compound muscle action potential showed reduced amplitude and prolonged latencies in the right axillary nerve taken from Erb’s point and absent taken from distal stimulation point. Right axillary nerve paresis was diagnosed and the patient underwent a physical therapy program, which resulted in gradual recovery. Discussion: In the presented case, other possible causes of neuropathy were excluded by medical history, laboratory and radiological tests, and clinical course of the disease. The temporal relationship between the VPA poisoning and the occurrence of neuropathy supports the hypothesis of a VPA-caused axillary neuropathy. According to the Narangno’s Adverse Drug Reaction (ADR) Probability Scale, VPA-induced neuropathy was rated “probable”. Conclusion: VPA-induced neuropathy may be a serious ADR, but it is potentially preventable and reversible. Thus, clinicians should be aware of this rare ADR.

Case report

A 26-year-old man had been treated for bipolar disorder since 2010. His medical treatment included sertraline 50 mg/day and VPA 1,000 mg/day.

In August 2012, the patient took an unknown amount of VPA in a suicide attempt. A few hours later, he was admitted to the Emergency Department of the University Hospital Dubrava. Physical examination revealed sorer without focal neurological deficit and bilateral symmetrical flexion and abduction of the arms to a painful stimulus. There were no signs of traumatic injury. Computed tomography of the brain showed no pathological changes. Hemoglobin concentration and leukocyte and platelet counts were normal, as were serum glucose, potassium, sodium, chloride, and bicarbonate levels. Kidney and liver function tests, arterial blood pH, and plasma osmolality were all within normal ranges. Urinalysis was negative for hematuria, leukocyturia, and proteinuria. Toxicology analysis revealed a high serum level of VPA (2,896 μmol/L; therapeutic range 350 – 690 μmol/L).

Introduction

Valproic acid (VPA) is a carboxylic acid with a proven efficacy in the treatment of epilepsy and bipolar disorder and a potential for use in the treatment of various central nervous system and neurodegenerative disorders [1, 2]. However, the clinical use of VPA is limited by possible adverse drug reactions (ADRs). The most common ADRs of VPA include weight gain and gastrointestinal symptoms [3, 4]. VPA can also induce neurological ADRs such as sedation and tremor [5].

In this report, we present a case of a patient experiencing axillary neuropathy as a probable result of intentional VPA overdose. To our knowledge, this is the first case of VPA-associated peripheral mononeuropathy.
Table 1. Right axillary nerve conduction study in a patient with valproic acid poisoning.

<table>
<thead>
<tr>
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<th>Latency (normal values &lt; 3.6 ms)</th>
<th>Amplitude (normal values &gt; 5 mV)</th>
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</thead>
<tbody>
<tr>
<td>Distal (shoulder) point</td>
<td>absent</td>
<td>absent</td>
</tr>
<tr>
<td>Erb's point</td>
<td>3.85 ms</td>
<td>3.7 mV</td>
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We suspected that the patient's altered mental status was caused by VPA poisoning. All medications were discontinued and the patient's mental status gradually recovered within 2 days with supportive care. Three days after admission, the patient complained of weakness in his right arm. Neurological examination showed weakness of flexion and abduction of the right arm and loss of sensation in the skin over the lateral upper right arm. Radiograph of the right shoulder showed no signs of dislocation or fracture. No possible cause of neurological symptoms was detected by magnetic resonance (MR) imaging of the brain. No cord or nerve root compression was found on MR of the cervical spine. MR imaging of the right shoulder revealed no pathologic changes. Vitamin B12, serum folate, thyroid function tests, VDRL test, cryoglobulins, antineutrophil cytoplasmic antibodies, antinuclear antibodies, Bence-Jones protein, creatine kinase, myoglobin, and angiotensin-converting enzyme levels were either within normal ranges or negative. Serum antigens for hepatitis B and C viruses and human immunodeficiency virus were also negative.

In an attempt to reach an accurate diagnosis, nerve conduction studies and electromyography were performed. Nerve conduction velocity was normal in the ulnar, radial, median, musculocutaneous, and suprascapular nerves. Compound muscle action potential showed reduced amplitude and prolonged latencies in the right axillary nerve taken from Erb's point and absent taken from distal stimulation point (Table 1).

Clinical examination and electrodiagnostic abnormalities indicated isolated right axillary nerve paresis. The patient underwent a physical therapy program, which gradually led to recovery. Therapy with VPA was not restarted, while sertraline was re-introduced before the hospital discharge. Three months after the diagnosis, his neurological and electrophysiological findings were normal. The patient remained asymptomatic during 1 year of follow-up.

**Discussion**

Peripheral neuropathy has a wide variety of causes [6], but most of them could be excluded in the presented case. The most common causes of neuropathy are diabetes mellitus and alcohol abuse, followed by malignant diseases. However, these were excluded since the patient was non-diabetic and non-alcoholic. Also, radiological and laboratory examinations did not reveal any signs of malignancy and the patient remained asymptomatic during the follow-up period. Treponema pallidum, human immunodeficiency virus, and hepatitis B and C viruses' infections as possible causes of neuropathy were excluded by serological testing. Laboratory tests showed no signs of hypothyroidism, vitamin deficiencies, autoimmune, kidney, or liver diseases. Both the clinical presentation and the course of the disease were not indicative for Guillain-Barré syndrome. There was no history of exposure to environmental toxins or drugs other than VPA and sertraline. Possibility that sertraline was a cause of neuropathy was excluded by the clinical course of the disease and a negative re-challenge.

The axillary nerve originates from the posterior cord of the brachial plexus. The most common cause of axillary neuropathy is trauma, usually with shoulder dislocation or humeral fracture [7]. Axillary neuropathy can also occur as a neurological complication after regional anesthesia and following general anesthesia or sleep in a prone position with the arms raised above the head [8]. Atraumatic causes of neuropathy include quadrilateral space syndrome and neuralgic amyotrophy syndrome [9, 10]. These causes of axillary neuropathy in the presented case were excluded by the history of the disease and radiological examinations.

Drug-induced peripheral neuropathies are uncommon and account for only 2 – 4% of cases [11]. Chemotherapy and antiretroviral drugs are the most important causes of drug-induced neuropathy [12]. Certain antiepileptics, e.g., phenytoin and carbamazepine, were also reported to cause peripheral neuropathy [13, 14]. Neuropathy usually occurs
after prolonged use of antiepileptic drugs. However, rare cases of acute neuropathy were also reported after a short course of antiepileptic therapy [15]. Previous studies did not reveal any effects of VPA on the peripheral nerve conduction [16].

In our patient, the cause of axillary neuropathy was suspected to be VPA poisoning. Other possible causes of neuropathy were excluded by medical history, laboratory and radiological findings, as well as by the clinical course of the disease. The temporal relationship between the VPA poisoning, which was confirmed by a high serum level of the drug, and the occurrence of neuropathy supported the hypothesis of a VPA-induced axillary neuropathy. The hypothesis was further supported by the recovery of axillary nerve function with no further neurological signs and symptoms after withdrawal of the drug. According to the Naranjo’s Adverse Drug Reaction Probability Scale, VPA-induced neuropathy was rated “probable” [17]. However, some rare causes of neuropathy (e.g., Lyme disease, amyloidosis) were not studied in this case, which should be taken into consideration as a limitation of the report.


