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Pancreatitis in a Young Adult on Valproate: A Rare but Serious Adverse Effect

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Abstract: ***Valproic acid (VPA) is a commonly prescribed antiepileptic drug with a favorable safety profile. However, rare but serious adverse effects like acute pancreatitis have been reported, particularly in children and young adults. We describe a 19-year-old male with generalized tonic-clonic seizures on sodium valproate monotherapy who presented with acute epigastric pain, vomiting, and absent bowel movements. Laboratory tests showed markedly elevated serum amylase and lipase. Imaging confirmed acute interstitial pancreatitis. Common etiologies, including alcohol use, gallstones, hypertriglyceridemia, and infection, were excluded. Given the temporal association and resolution following drug withdrawal, a diagnosis of valproate-induced pancreatitis (VIP) was made, supported by a Naranjo score of 6. Valproate was discontinued, supportive care initiated, and levetiracetam introduced for seizure control. The patient showed clinical improvement within 72 hours and remained recurrence-free on follow-up. This case highlights the importance of considering VIP in young patients presenting with pancreatitis of unclear etiology.***

Keywords: Valproate, Acute Pancreatitis, Drug-Induced Pancreatitis, Antiepileptic Drug Toxicity, Case Report

1. Introduction

Valproic acid (VPA) and its derivatives, including sodium valproate, are broad-spectrum antiepileptic medicines (AEDs) frequently recommended for generalized and partial seizures, bipolar affective disorder, and migraine prophylaxis, owing to their effectiveness and comparatively safe profile.[1] Although typically well tolerated, valproate is linked to numerous severe side effects, particularly hepatotoxicity, hyperammonemia, thrombocytopenia, and teratogenicity.[2] Acute pancreatitis is a little acknowledged although potentially life-threatening consequence of valproate treatment.

Valproate-induced pancreatitis (VIP) was initially documented in the 1970s and is currently recognized as an uncommon variant of drug-induced pancreatitis (DIP). The prevalence is estimated to be between 1 in 40,000 and 1 in 400 patients, with an elevated risk in children and young people.[3] The etiology is ambiguous; nevertheless, suggested pathways encompass direct toxic effects on pancreatic acinar cells, oxidative stress accompanied by lipid peroxidation, and the buildup of deleterious metabolites such 4-en-VPA. [4,5]

VIP predominantly manifests within the initial year of treatment, though instances of late-onset have been recorded.[6] It is generally idiosyncratic and not dose-dependent, which complicates prediction. The clinical presentation resembles that of pancreatitis from various etiologies, commonly characterized by epigastric pain, nausea, vomiting, and elevated serum pancreatic enzymes.[7] Imaging can indicate pancreatic enlargement, inflammation, or fluid accumulation. Recurrence has been documented following rechallenge with the drug, highlighting the importance of immediate withdrawal upon suspicion.

Due to its infrequency and the ambiguous characteristics of its symptoms, VIP may be readily disregarded. A high index of suspicion is crucial, especially in patients on valproate who present with acute abdominal pain. This report presents a case of acute pancreatitis induced by valproate in a young adult, emphasizing the need for awareness of this uncommon adverse effect and the significance of prompt recognition and intervention.

2. Case Report

A 19-year-old male, with a known history of generalized tonic-clonic seizures (GTCS) for the past year, presented to the emergency department with acute onset of severe upper abdominal pain for two days. The pain was epigastric in location, radiating to the back, constant, and associated with nausea, multiple episodes of non-bilious vomiting and also non- passage of flatus and faeces. There was no history of alcohol intake, trauma, recent infections, or use of herbal or over-the-counter medications. The patient denied any prior similar episodes.

He had been started on sodium valproate 1 g/day (500 mg BID) as monotherapy three months prior to this presentation for seizure control, with good compliance and no recent dose adjustments. He was not taking any other medications. There was no family history of pancreatitis or metabolic disorders.

On examination, the patient was alert, oriented and vitals were pulse: 90/min, blood pressure: 118/72 mmHg, respiratory rate: 18/min, temperature: 99.1°F and oxygen saturation: 98% on room air. Abdominal examination revealed tenderness in the epigastric region with no guarding or rebound tenderness, bowel sounds were absent and no organomegaly or ascites. There were no signs of hepatosplenomegaly, lymphadenopathy, or skin rashes.

Initial laboratory and imaging workup revealed in table 1:

Table 1: Initial investigations of patient

Name of Test	Measured Values	Reference values
Haemoglobin	13.5 mg/dL	12-16 mg/dL
Total leucocyte counts	11800	3000-11000
Platelet count	2.6 lac	1.5-4.5 lac
T. Bilirubin	0.8 mg/dL	0.5-1.5 mg/dL
AST	27 U/L	<35 U/L
ALT	25 U/L	<35 U/L
ALP	310 U/L	30 – 120 U/L
Total protein	7.4 g/dL	6.0-8.3 g/dL
Serum albumin	4.4 g/dL	3.5-5.5 g/dL
Blood urea	26 mg/dL	20-40 mg/dL
Creatinine	0.7mg/dL	0.7-1.2 mg/dL
Serum amylase	620 U/L	30–110 U/L
Serum lipase	870 U/L	13–60 U/L
Serum Calcium	9.2 mg/dL	8-11 mg/dL
Sreum triglycerides	126 mg/dL	<150 mg/dL

Ultrasound abdomen revealed mildly enlarged pancreas with peripancreatic fat stranding, no gallstones or biliary duct dilatation. CT abdomen: Confirmed findings consistent with acute interstitial pancreatitis; no necrosis or pseudocyst formation. MRI of abdomen was planned to rule out any structural abnormality and turned out to be normal.

A diagnosis of acute pancreatitis was made based on:
- Classical clinical features (epigastric pain radiating to the back)
- Elevated serum lipase/amylase (≥3× upper limit)
- Imaging evidence of pancreatic inflammation

Common etiologies including alcohol consumption, gallstones, hypertriglyceridemia, hypercalcemia, trauma, and infection were excluded. In light of the lack of alternative causes and the temporal relationship with valproate administration, a diagnosis of valproate-induced pancreatitis was proposed. Causality was assessed using the Naranjo Adverse Drug Reaction Probability Scale, which yielded a score of 6 (probable ADR).

Patient was managed with immediate cessation of sodium valproate. Commencement of supportive care: intravenous fluids (Ringer Lactate), bowel rest (nothing by mouth), analgesia with intravenous paracetamol. Continuous assessment of pancreatic enzyme levels and clinical condition was done. A neurology consultation was conducted; valproate was substituted with levetiracetam 500 mg administered twice daily, with titration based on tolerance.

The patient demonstrated progressive clinical improvement over a period of 48 to 72 hours. Oral intake was reinstated on day 4. By day 7, serum amylase and lipase levels normalized.

The patient was discharged on day 8, with scheduled follow-up appointments in outpatient.

No recurrence of pancreatitis was observed during follow-up assessments at 1-, 3- and 12-months post-discharge. Seizures were effectively managed with levetiracetam monotherapy.

3. Discussion

Acute pancreatitis (AP) is a serious inflammatory condition of the pancreas that can be life-threatening and has various causes. Gallstones and alcohol consumption are the primary causes of pancreatitis; however, drug-induced pancreatitis (DIP) represents approximately 0.1–2% of all cases, with over 500 medications identified as potential contributors to this condition. [9,10] Valproic acid (VPA) is an uncommon yet acknowledged cause of epilepsy, especially in pediatric and young adult populations.[2]

This case report details a young male who experienced acute pancreatitis following six months of valproate monotherapy, with no presence of typical risk factors including alcohol consumption, gallstone disease, hypertriglyceridemia, hypercalcemia or structural abnormalities. The temporal relationship, resolution following drug withdrawal, and exclusion of alternative causes provide substantial evidence for a diagnosis of valproate-induced pancreatitis (VIP), which was additionally validated using the Naranjo Adverse Drug Reaction Probability Scale.

The pathophysiology of VIP is not fully elucidated. It is proposed to be idiosyncratic and non–dose-dependent, potentially involving:
- The direct cytotoxic effects of valproate or its toxic metabolites, such as 4-en-VPA, on acinar cells.
- Mitochondrial dysfunction and the inhibition of fatty acid β-oxidation.
- Oxidative stress and lipid peroxidation result in inflammation and acinar cell necrosis [3,4].

A comprehensive review by Gerstner et al. identified 80 cases of VIP, indicating that most cases occurred within the first year of therapy (median onset time: 4–5 months), and that the majority resolved following drug discontinuation.[2] Mortality rates reached as high as 15% in cases where diagnosis was delayed. Clinically, VIP manifests similarly to other types of pancreatitis, characterized by epigastric pain, nausea, vomiting, and elevated pancreatic enzyme levels. Consequently, it frequently serves as a diagnosis of exclusion. Imaging findings are generally nonspecific, often revealing an enlarged or edematous pancreas, with or without associated peripancreatic fluid.[8] The diagnosis was established through classical clinical presentation, elevated enzyme levels, imaging findings, and the absence of alternative etiologies.

Upon suspicion of VIP, it is crucial to promptly discontinue valproate, as its ongoing administration may result in recurrent or exacerbated pancreatitis. Rechallenge is contraindicated due to the potential for severe recurrence or fatal outcomes.[11] In this patient, valproate was effectively replaced with levetiracetam, a medication not linked to pancreatitis.

This case underscores the necessity of a heightened awareness for drug-induced pancreatitis in patients presenting with acute abdominal pain who are on chronic medication. VIP should be evaluated in young patients presenting with new-onset pancreatitis and lacking identifiable common risk factors. Timely identification and cessation of the problematic medication are essential for a positive result.

4. Conclusion

Valproate-induced pancreatitis is an uncommon yet significant adverse effect that clinicians should recognize, particularly in young patients undergoing valproate treatment who exhibit unexplained abdominal pain. Due to its nonspecific clinical presentation and risk of severe complications, early recognition, immediate cessation of the causative agent, and supportive management are essential for positive outcomes. This case underscores the significance of evaluating drug-induced causes in the differential diagnosis of acute pancreatitis and emphasizes the necessity for caution in the long-term prescription of antiepileptic medications.

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