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Case Study

Interesting Case of Valproate Induced Pancreatitis

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ABSTRACT

Valproate is a commonly prescribed first-line antiepileptic for both primary and secondary generalized seizures. However, it is crucial to be mindful of significant complications, such as acute pancreatitis, linked to sodium valproate, especially when considering its use in populations like children and individuals with intellectual disabilities, who have unique susceptibilities in epilepsy and bipolar disorder treatment. In this case presentation, we discuss an instance of valproate-induced acute pancreatitis in a 22-year-old patient with a known history of mania over the past 6 months. The patient was initially prescribed oral sodium valproate at a dosage of 1g/day. Subsequently, oral valproate was promptly discontinued, and an alternative medication was initiated. Following one week of the new medication, the patient showed improvement, leading to discharge after 10 days with a prescription for Tab. Olanzapine 10 mg HS and Tab. Pacitane 2 mg OD. Notably, there was no recurrence of pancreatitis during subsequent follow-up.

Introduction

Acute pancreatitis is characterized by inflammation of the pancreas, which can manifest as a singular event or recur over time. The severity of this condition varies, ranging from mild inflammation to extensive pancreatic necrosis. Indications and manifestations of acute pancreatitis was illustrated in **figure 1**. While the primary consequence of acute pancreatitis is exocrine dysfunction, recurrent episodes of inflammation and subsequent fibrosis can lead to endocrine insufficiency. This complex disorder is often triggered by various factors, with chronic alcohol use disorder, gallstone disease, severe hypertriglyceridemia, and hypercalcemia being the most prevalent causes[1].

Among the triggers, chronic alcohol use disorder stands out as a leading contributor to the development of acute pancreatitis. The continuous exposure of the pancreas to alcohol can induce inflammation, initiating a cascade of events that culminate in the manifestation of this condition. Gallstone disease is another common instigator, wherein the presence of gallstones obstructs the pancreatic duct, causing inflammation[2]. Severe hypertriglyceridemia, characterized by elevated levels of triglycerides in the blood, and hypercalcemia, an excess of calcium in the bloodstream, further contribute to the multifaceted etiology of acute pancreatitis. In addition to these primary triggers, there are less frequent associations with various factors, including genetic predisposition and infections of viral, parasitic, fungal, or bacterial origin. Genetic factors may render certain individuals more susceptible to the development of acute pancreatitis, while infections with viruses such as mumps, coxsackievirus, cytomegalovirus, varicella, and herpes simplex virus, as well as parasites like toxoplasma, cryptosporidium, and ascaris, can also play a role [3]. Fungal infections, specifically with aspergillus, and bacterial infections caused by mycoplasma, legionella, leptospira, and salmonella, albeit less common, contribute to the diverse array of potential triggers for this inflammatory condition. Graphic illustration of the causes of acute pancreatitis was shown in **figure 2**[4, 5].

Clinically, patients affected by acute pancreatitis present with distinct symptoms that aid in diagnosis. The hallmark feature is acute-onset severe epigastric and left upper quadrant abdominal pain. This pain is often accompanied by nausea and vomiting, further emphasizing the a-

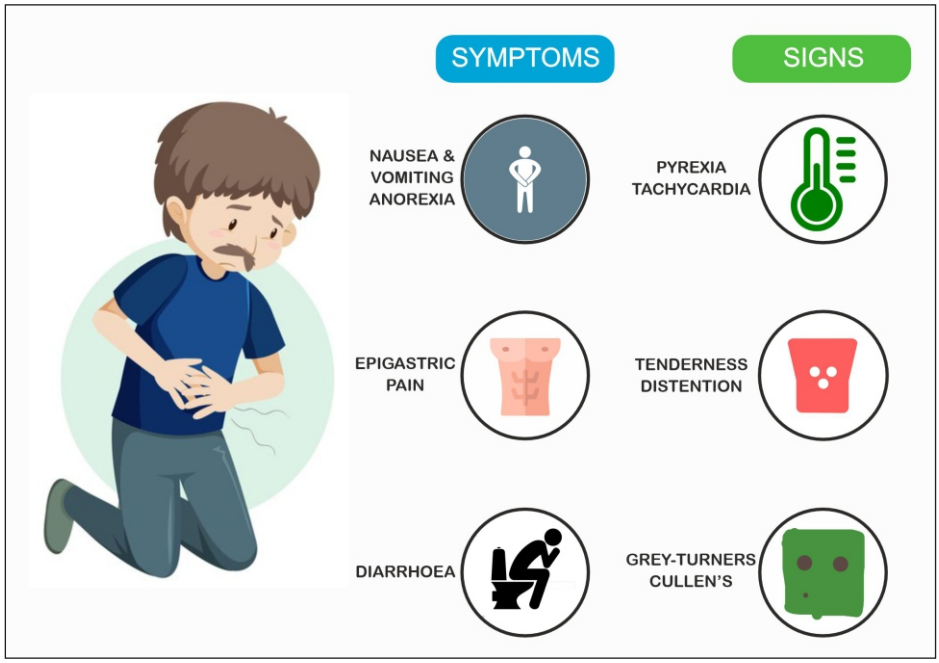

Figure 1: Signs and symptoms of acute pancreatitis (Gapp J *et al.*, 2024).

-cute and intense nature of the inflammatory process [6]. The localization of the pain to the upper abdominal regions corresponds with the anatomical location of the pancreas and is indicative of the organ's involvement. The sudden onset and severity of symptoms necessitate prompt medical attention and intervention to mitigate complications and optimize patient outcomes. Understanding the triggers and clinical presentation of acute pancreatitis is essential for accurate diagnosis and timely intervention [7]. The recogniti-

-on of chronic alcohol use disorder, gallstone disease, severe hypertriglyceridemia, and hypercalcemia as primary contributors highlights the importance of addressing these underlying factors in the management of the condition. Additionally, awareness of the less common associations with genetic predisposition and various infections broadens the diagnostic perspective, ensuring a comprehensive approach to patient care [8].

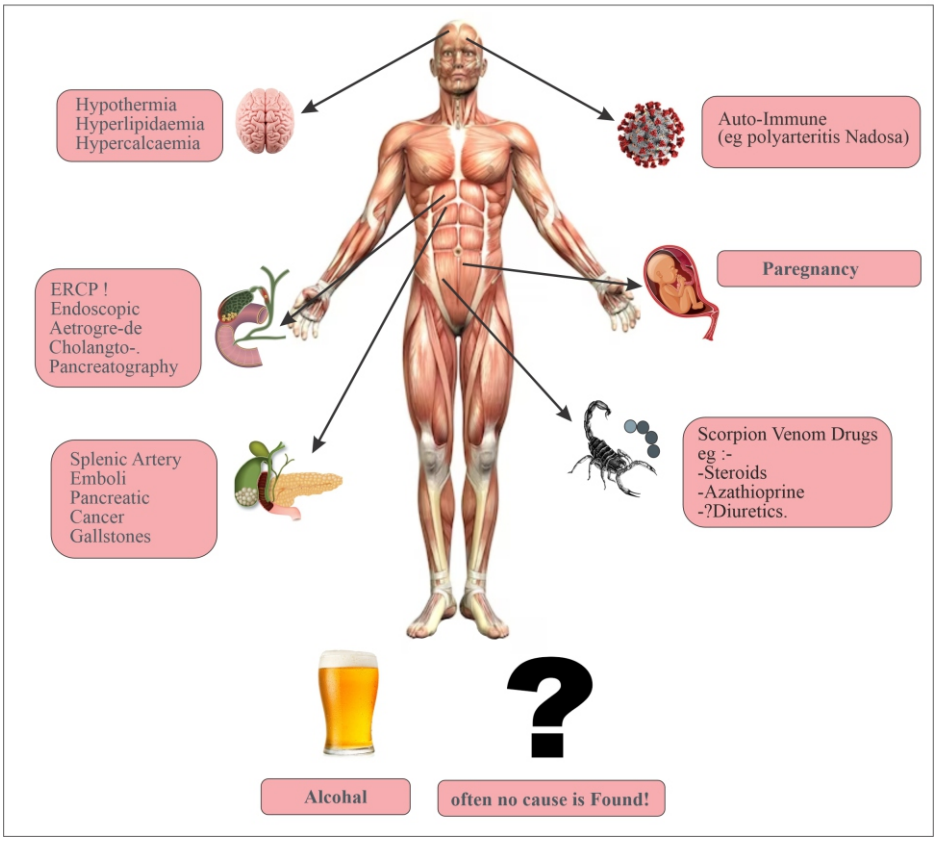

Figure 2: Factors leading to acute pancreatitis (Gapp J *et al.*, 2024).

Valproate received approval in the United States in 1978 for treating absence seizures and has since been utilized as monotherapy or in combination with other anticonvulsants. Its applications include the treatment of mixed and complex partial seizures, acute manic episodes in bipolar disorder, and prophylaxis for migraines. valproate is also effective against myoclonic, simple partial, and generalized tonic-clonic seizures [9, 10]. Despite an unknown mechanism, it is believed to be associated with the metabolism of the neurotransmitter GABA. Compared to older anticonvulsants , valproate generally presents fewer adverse effects, with a lower frequency of cognitive dysfunction and central nervous system impacts, allowing patients to remain more alert and functional [11]. Common side effects encompass nausea, vomiting, tremor, and weight gain. However, its toxic effects can manifest in a dose-dependent or idiosyncratic manner, with notable idiosyncrasies including alopecia, bone marrow aplasia, immune-mediated hepatotoxicity, and pancreatitis. Although fewer than 120 cases of valproate related acute pancreatitis have been reported in literature, the majority are mild and self-limiting. This report details a case of severe acute pancreatitis associated with valproate, presenting with a large pseudocyst [12-14].

In this case study, the authors describe an uncommon case of acute pancreatitis induced by valproate in a 22 years old gentleman, a known case of mania for the past 6 months. He was prescribed oral sodium valproate1g/day and had continued the same for 6 months without a psychiatric review.

CASE PRESENTATION

We present a rare case of valproate induced pancreatitis. The patient was a 22 years old gentleman, a known case of mania for the past 6 months. He was prescribed oral sodium valproate1g/day and had continued the same for 6 months without a psychiatric review. After 6 months, the patient presented with progressively worsening abdominal pain for 10 days duration with multiple episodes of vomiting. There was history of alcohol and drug abuse for 4 years and had stopped 6 months back. There was no history of smoking, gallstones, trauma, viral infection. On examination, he was tachycardic and dehydrated. Abdomen was distended with severe epigastric tenderness. Routine tests were within normal limits. Serum Amylase(396 U/L) and serum lipase(654U/L) were markedly high. Abdomen imaging showed diffusely enlarged pancreas with peri-pancreatic fluid collection and a CT Severity index of 6.

After ruling out other causes of pancreatitis, he was managed as a case of valproate induced pancreatitis. Oral valproate was immediately stopped and matdication was started on Tab.Olanzapine 10 mg in the night and Tab.Pacitane 2 mg OD. He was kept Nil per oral for the first two days of admission with supportive I.V Fluids and antibiotics.Once abdominal pain subsided, he was started on orals and gradually stepped up. The patient improved after 1 week and was discharged after 10 days with Tab.Olanzapine10 mg HS and Tab.Pacitane 2 mg OD. There was no recurrence of pancreatitis on subsequent follow-up.

DISCUSSION

While numerous drugs have been identified as potential contributors to acute pancreatitis, it's worth noting that drug-induced pancreatitis is a relatively infrequent occurrence. Specifically, pancreatitis induced by valproate is a rare phenomenon, with an estimated incidence of 1 in 40,000 cases [15]. This complication typically arises within the initial year of treatment or following a dosage increase, demonstrating a higher occurrence in young individuals, those engaged in polytherapy (especially with carbamazepine, phenytoin, phenobarbital, and certain benzodiazepines), individuals with chronic encephalopathies, and those undergoing dialysis treatments. Cases of valproate induced pancreatitis have been reported as early as 1970s. Around 120 cases have been published in medical literature including few fatal cases. Basic management includes stoppage of the offending drug and providing supportive care. But, patient's spectrum of presentation varies from good recovery to mortality[16-18].

The precise mechanism through which valproate induces pancreatitis remains unknown. However, a prevailing theory suggests that patients receiving valproic acid may experience depletion of free radical scavengers, such as superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase. This depletion could potentially lead to an excess of free radicals, subsequently causing endothelial permeability and lipid peroxidation, ultimately resulting in tissue damage. Another suggested mechanism involves the reduction of carnitine due to valproic acid use, which is proposed to play a significant role in the pancreatic damage incurred[19, 20].

An alternative theory regarding valproate induced pancreatitis revolves around the impact of valproic acid on mitochondrial beta-oxidation. Valproic acid is primarily metabolized through mitochondrial beta-oxidation, an enzyme system also implicated in the metabolism of branched-chain amino acids [21]. A research group found that valproic acid inhibited beta-oxidation enzymes associated with the metabolism of both branched-chain amino acids and straight-chain fatty acids. This led them to suggest that individuals with a genetic deficiency in the enzymes responsible for the mitochondrial beta-oxidation of valproic acid might experience an accumulation of toxic metabolites[22]. In contrast, another research group conduc-

-ted a screening of serum and urine amino acid levels in patients who developed pancreatitis during valproic acid therapy. Their findings did not reveal any significant changes in amino acid levels, and as a result, they dismissed the theory of beta-oxidizing enzyme deficiency as a cause for valproic acid-induced pancreatitis[23-25].

The diagnosis of pancreatitis relies on clinical signs and symptoms, with notable indicators including localized abdominal pain in the epigastrium, accompanied by nausea, potential vomiting, abdominal distension, fever, and malaise. Crucial to the diagnostic process is the measurement of blood amylase and lipase levels, as their elevation helps guide diagnosis and can confirm clinical suspicions [26]. It's important to note that amylase levels may increase in some patients receiving valproic acid without necessarily indicating pancreatitis. In cases involving valproic acid, a pancreatitis diagnosis requires elevated levels of pancreatic enzymes alongside the presence of clinical symptoms [27, 28]. Lipase, specific to the pancreas, serves as a more precise indication of pancreatic damage. Depending on the clinical context, additional investigations such as abdominal ultrasound and a CT scan may be necessary. Ultrasound proves valuable in the initial assessment of individuals suspected of acute pancreatitis and should be conducted within the first 24 to 48 hours of symptom onset. Ultrasonography of the pancreatic duct is particularly useful in diagnosing and monitoring pancreatitis in children. In cases of severe acute pancreatitis, an abdominal CT scan becomes essential, playing a critical role in assessing the extent of the inflammatory process, identifying necrosis, and evaluating other local complications[29, 30].

The diagnosis of valproate related acute pancreatitis is primarily one of exclusion, and it should be considered when other plausible causes of pancreatitis are ruled out. In this specific case, a thorough investigation eliminated all other potential causes of pancreatitis. Notably, there was no evidence of gallstones, and serum values of calcium and triglycerides were within normal range. Additionally, there was no family history of pancreatitis, and the patient was not taking any medication other than valproic acid [31]. While many cases of valproate related pancreatitis are mild and self-limiting, discontinuation of valproic acid typically leads to the normalization of amylase levels and the resolution of clinical symptoms. However, in this particular case, the patient continued to experience symptoms, indicating a severe episode of pancreatitis with the formation of a pseudocyst. It is advisable to avoid the use of valproic acid in patients who have previously experienced acute pancreatitis associated with its use, given the high likelihood of recurrence and potential complications[32-34].

We observed full recovery of the patient after discontinuation of therapy. The cause of this varied presentation and the caus-e of such a wide spectrum of morbidity and mortalities remains unclear. Proposed mechanism of action of valproate induced acute pancreatitis are probably due to the direct toxic effects of the free radicals on the pancreas and a depleted superoxide dismutase, catalase, and glutathione peroxidase enzymes responsible for free radical scavenging.

CONCLUSION

The presence of gastrointestinal symptoms in patients undergoing valproate treatment should always prompt consideration of acute pancreatitis, a potentially challenging complication to diagnose. Elevated levels of pancreatic amylase and lipase serve to confirm the clinical suspicion. Utilizing a CT scan aids in evaluating local complications. In instances of acute pancreatitis, it is imperative to discontinue valproate administration, and resuming the drug post-recovery is strictly contraindicated.

ETHICS APPROVAL

Not Applicable.

AVAILABILITY OF DATA AND MATERIAL

Not Applicable.

CONFLICT OF INTERESTS

Authors declared that there is no conflict of interest.

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