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# VALPROIC ACID INDUCED ACUTE HEMORRHAGIC PANCREATITIS WITH TRANSIENT HYPERGLYCEMIA IN A CHILD WITH TEMPORAL LOBE EPILEPSY: A CASE REPORT

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## ABSTRACT

Valproic acid (VPA) is a well-tolerated anti-epileptic drug. It is mainly used for the management of epilepsy, acute mania, bipolar mood disorder, and prophylactic treatment of migraine. Acute pancreatitis is a serious side effect of VPA with an incidence of 1:40,000. A higher number of cases has been reported among children and adolescents. The idiosyncratic reaction is the main cause of pancreatitis; however, a higher dose may aggravate the condition. In most cases, it usually develops on average 11 months afterVPA initiation; however, it is rarely seen before 3 months. Here we are reporting a 6-year-old boy who developed acute hemorrhagic pancreatitis within three months following initiation of VPA for management of temporal lobe epilepsy. The patient was successfully managed by conservative treatment with intensive care support. Finally, we discharged the patient with Levetiracetam and followed up without any side effects or any new episodes of seizure.

**Keywords**: Valproic Acid, Sodium Valproate, Acute Pancreatitis, Hyperglycemia.

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## INTRODUCTION

Valproic acid (VPA) induced acute pancreatitis is an idiosyncratic reaction that was first reported in 1979[1]. Acute pancreatitis is a rare and serious complication of VPA with an incidence of 1:40,000[2]. Generally, pancreatitis develops within 3-24 months following initiation of VPA[3]. Here we are reporting a 6-year-old child who developed acute hemorrhagic pancreatitis within two months following initiation of VPA for management of temporal lobe epilepsy.

## CASE REPORT

A 6-year-old boy was diagnosed as a case of temporal lobe epilepsy on 23rd March 2024, based on clinical symptoms and EEG (Electroencephalogram) findings. The patient was initially treated with VPA, 750mg/day in two divided doses for 7 days followed by 500mg twice daily (1000mg/day) as a maintenance therapy. He was doing well without any further episodes of seizure. On 16th May 2024, he was admitted to our medical college hospital with a sudden onset of severe upper abdominal pain associated with several episodes of vomiting which contained undigested food particles. On examination the patient was very irritable, GCS (Glasgow Coma Scale) score was 12, temperature was 98° Fahrenheit, pulse rate was 130 beats per minute, blood pressure was 90/60 mmHg, and capillary refilling time was <2 seconds.

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There was no dehydration, lungs were clear but tachypnoea was present. The abdomen was soft with diffuse tenderness. Murphy's sign was absent; body weight was 34 kg during hospitalization. Initial investigations revealed ascites upon performing ultrasonogram, bilateral mild pleural effusion on chest x-ray, very high serum lipase and amylase, with random blood glucose level of 23.6 mmol/L (Table-1). Based on the clinical presentations and investigation findings the patient was diagnosed as a case of acute pancreatitis. To find out underlying causes, serum calcium, lipid profile, and imaging of biliary duct structures were done but no abnormalities were seen. Development of acute pancreatitis within the first two months of VPA initiation with no other obvious causes made the causative relationship of VPA with this event as many case reports on this topic have been published worldwide since 1979.VPA was immediately stopped following the diagnosis of acute pancreatitis. The patient was managed conservatively in an ICU (Intensive Care Unit) setting and his condition began to improve very slowly as observed from consecutive investigation reports (Table 2) and vital signs of the patient. Diagnostic laparotomy was later done and a diagnosis of acute hemorrhagic pancreatitis was made based on laparotomy findings. The patient was managed conservatively and improved over 30 days. Initial blood glucose was managed by subcutaneous insulin, within 5 days blood glucose returned to normal range without insulin and no further peak of blood glucose was observed during the follow-up period. The patient was discharged with Levetiracetam and followed up without any side effects or any new episodes of seizure.

**Table 1 : Investigation profile of patient during admission**

| Date | Tests | Result | Unit | Normal range |
|---|---|---|---|---|
| 16.05.2024 | Serum Lipase | 1704 | U/L | 13-60 |
| 16.05.2024 | Serum Amylase | 575 | U/L | <90 |
| 16.05.2024 | Sodium/Potassium/Chloride | 128/5.3/94 | | |
| 16.05.2024 | Hemoglobin<br>WBC<br>Neutrophil<br>Lymphocytes | 16.2<br>11700<br>80<br>13 | g/dl<br>/L<br>%<br>% | 13-18<br>4000-11000<br>40-74<br>20-45 |
| 17.05.2024 | Serum Calcium | 9.3 | mg/dl | 8.2-10.2 |
| 17.05.2024 | Lipid Profile | | mg/dl | |
| | Total Cholesterol<br>HDL Cholesterol<br>LDL Cholesterol<br>Triglyceride | 90<br>21<br>54<br>129 | | <200<br>>40<br><100<br><150 |
| 17.05.2024 | Serum Pro-calcitonin | 0.134 | ng/ml | <0.046 |
| 17.05.2024 | SGPT | 53 | U/L | 16-63 |
| 17.05.2024 | SGOT | 202 | U/L | <37 |
| 17.05.2024 | Serum Albumin | 3.48 | g/dl | 3.4-5 |
| 17.05.2024 | Echo | Minimal Pericardial Effusion | | |
| 17.05.2024 | HbA1C% | 5.5 | % | <5.7 |
| 17.05.2024 | RBS | 23.6 | mmol/L | <7.8 |
| 17.05.2024 | USG abdomen | Features suggestive of perforation of hollow viscus, moderate ascites with bilateral mild pleural effusion | | |
| 18.5. 2024 | CRP | 28.11 | mg/L | <5.0 |
| 18.5.2024 | Serum Creatinine | 0.38 | mg/dl | 0.2-0.7 |

**SGOT**: Serum Glutamic-Oxaloacetic Transaminase; **SGPT**: Serum Glutamic Pyruvic Transaminase; **USG**: Ultrasonogram; **RBS**: Random Blood Sugar; **CRP**: C-reactive protein; **Echo**: Echocardiogram; **LDL**: low Density Lipoprotein; **HDL**: High Density Lipoprotein.

**Table 2 : Investigation profile of patient 5 days after admission.**

| Date | Tests | Result | Unit | Normal range |
|---|---|---|---|---|
| 21.05.2024 | Serum Lipase | 23 | U/L | 13-60 |
| 21.05.2024 | Serum Amylase | 27 | U/L | <90 |
| 21.05.2024 | Sodium/Potassium/Chloride | 132/3.3/96 | | |
| 21.05.2024 | Hemoglobin | 9.9 | g/dl | 13-18 |
| | WBC | 9500 | /L | 4000-11000 |
| | Neutrophil | 70 | % | 40-74 |
| | Lymphocytes | 22 | % | 20-45 |
| 21.05.2024 | Serum Calcium | 8.4 | mg/dl | 8.2-10.2 |
| 21.05.2024 | Total Cholesterol | 90 | | <200 |
| | HDL Cholesterol | 21 | | >40 |
| | LDL Cholesterol | 54 | | <100 |
| | Triglyceride | 129 | | <150 |
| 21.05.2024 | Serum Pro-calcitonin | 0.134 | ng/ml | <0.046 |
| 21.05.2024 | SGPT | 53 | U/L | 16-63 |
| 21.05.2024 | SGOT | 202 | U/L | <37 |
| 21.05.2024 | Serum Albumin | 3.48 | g/dl | 3.4-5 |
| 21.05.2024 | Echo | Structurally normal heart | | |
| 21.05.2024 | Serum Creatinine | 0.38 | mg/dl | 0.2-0.7 |

**SGOT**: Serum Glutamic-Oxaloacetic Transaminase; **SGPT**: Serum Glutamic Pyruvic Transaminase; **USG**: Ultrasonogram; **RBS**: Random Blood Sugar; **CRP**: C-reactive protein; **Echo**: Echocardiogram; **LDL**: low Density Lipoprotein; **HDL**: High Density Lipoprotein.

## DISCUSSION

A nationwide survey in Japan observed that, 1.2% of all cases of acute pancreatitis was caused by drugs[4]. Approximately 500 drugs are known to cause pancreatitis, with VPA being one of the most common[5]. Due to the serious side effects of VPA, the US Food and Drug Administration issued a black box warning in 2000 regarding the potential risk of fatal pancreatitis caused by the use of VPA[6]. The mechanism of VPA-induced pancreatitis is not fully understood. It is hypothesized that VPA may cause depletion of free radical scavengers such as catalase, superoxide dismutase, and glutathione peroxidase.
This depletion may lead to the generation of excess free radicals, causing endothelial permeability, lipid peroxidation, and, tissue damage that can contribute to the development of pancreatitis[7,8].

Serum amylase levels may rise in some patients taking VPA, even if there are no signs of pancreatitis. If typical symptoms of pancreatitis such as abdominal pain, nausea, vomiting, and fever are not present, VPA-induced pancreatitis should not be diagnosed solely based on a slight increase in serum amylase and lipase[9]. Our patient developed symptoms of acute pancreatitis after initiation of VPA, which was confirmed by biochemical parameters (e.g. high serum amylase and lipase). After cessation of offending medication (VPA) and, changing to another group did not cause the same condition. We also excluded the other possible causes of pancreatitis like hypercalcemia, hypertriglyceridemia and gallstone disease before suspecting the VPA induced pancreatitis. Viral infection, which was not

excluded by the polymerase chain reaction test, has a low probability as the patient did not complain of any prodromal symptoms of fever, myalgia, or body aches before the development of pancreatitis.

Based on the World Health Organization–Uppsala Monitoring Centre (WHO-UMC) causality rating scale, we can say this acute pancreatitis was caused by VPA.
The primary treatment for acute pancreatitis is conservative measure. It is important to discontinue VPA and use caution when considering reintroducing it after recovery, as there is a high risk of recurrent pancreatitis in over 80% of cases[3]. So it is better not to start the VPA again if serious side effects like pancreatitis are reported.

## CONCLUSION

Patients with epilepsy if treated with VPA, should be carefully monitored regarding its serious side effects (e.g. bone marrow suppression, and pancreatitis). Early detection of serious complications and timely intervention may save the lives of many patients.

## CONSENT

Informed written consent from the legal guardian of the patient was taken.

## CONFLICT OF INTEREST

There is no conflict of interest.

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