Valproic Acid Administration in Management of Status Epilepticus Causing Reye’s Syndrome

Pooja Prabhakar Kamath

1Department of Pediatrics, V. N. Desai, Hospital, Mumbai, Maharashtra, India

Address for correspondence Pooja Prabhakar Kamath, MBBS, MD, Ultra Co Op Hsg Soc, Lt Dilip Gupte Marg, Mahim, Mumbai 400016, Maharashtra, India (e-mail: drpoojakamath@gmail.com).

Introduction

Valproic acid is commonly used to treat seizures in children. Regular use of valproic acid is known to cause hepatic dysfunction, and in extremely rare cases, it is known to have caused Reye’s syndrome. There are very few reports of Reye’s syndrome caused by valproic acid use.

Methods

A 2-year asymptomatic girl underwent modified Blalock–Taussig shunt surgery for correction of tetralogy of Fallot. Postoperatively the girl developed status epilepticus, which did not subside with initial use of intravenous midazolam and phenytoin sodium. She eventually responded to two doses of intravenous valproic acid administered 10 minutes apart. She developed depressed sensorium and was put on mechanical ventilation. The following day’s laboratory investigations revealed raised levels of serum ammonia, serum glutamic-oxaloacetic transaminase (SGOT), and serum glutamic-pyruvic transaminase (SGPT) with normal serum bilirubin. Thus, a diagnosis of Reye’s syndrome was established. The patient succumbed to disease 2 days later.

Discussion

Reye’s syndrome is a rare and a fulminant illness seen typically in children following a viral illness and/or use of salicylates or other medications. There are rare reports of Reye’s syndrome following use of medications like valproic acid. This patient had a noninflammatory encephalopathy with hepatic dysfunction following two doses of valproic acid.

Conclusion

There are very few reports on Reye’s syndrome in the literature as it is a rare condition and diagnosis is difficult. Knowledge of the presentation of Reye’s syndrome is essential for treatment and management. When using drugs like valproic acid in children, liver enzymes and serum ammonia levels should be monitored.

Keywords

- hyperammonemia
- mitochondrial injury
- non-inflammatory hepatic encephalopathy

Abstract

Introduction

Valproic acid is commonly used to treat seizures in children. Regular use of valproic acid is known to cause hepatic dysfunction, and in extremely rare cases, it is known to have caused Reye’s syndrome. There are very few reports of Reye’s syndrome caused by valproic acid use.

Methods

A 2-year asymptomatic girl underwent modified Blalock–Taussig shunt surgery for correction of tetralogy of Fallot. Postoperatively the girl developed status epilepticus, which did not subside with initial use of intravenous midazolam and phenytoin sodium. She eventually responded to two doses of intravenous valproic acid administered 10 minutes apart. She developed depressed sensorium and was put on mechanical ventilation. The following day’s laboratory investigations revealed raised levels of serum ammonia, serum glutamic-oxaloacetic transaminase (SGOT), and serum glutamic-pyruvic transaminase (SGPT) with normal serum bilirubin. Thus, a diagnosis of Reye’s syndrome was established. The patient succumbed to disease 2 days later.

Discussion

Reye’s syndrome is a rare and a fulminant illness seen typically in children following a viral illness and/or use of salicylates or other medications. There are rare reports of Reye’s syndrome following use of medications like valproic acid. This patient had a noninflammatory encephalopathy with hepatic dysfunction following two doses of valproic acid.

Conclusion

There are very few reports on Reye’s syndrome in the literature as it is a rare condition and diagnosis is difficult. Knowledge of the presentation of Reye’s syndrome is essential for treatment and management. When using drugs like valproic acid in children, liver enzymes and serum ammonia levels should be monitored.

Introduction

Australian pathologist R.D.K. Reye first described this syndrome in 1963. It is a rare syndrome characterized by an acute, life-threatening, noninflammatory encephalopathy and fatty degeneration of the liver with minimal or no clinical signs of liver involvement often following a mild illness notably viral in nature. Classic Reye’s syndrome has a severe disturbance of mitochondrial structure and associated enzymatic disturbances.

The incidence of Reye’s syndrome among the reported cases was 0.11 cases per 100,000 in 1990 to 1991 in United Kingdom, with only 3 reported cases between 2001 and

©2021. Medical and Surgical Update Society.

This is an open access article published by Thieme under the terms of the Creative Commons Attribution-NonDerivative-NonCommercial-License, permitting copying and reproduction so long as the original work is given appropriate credit. Contents may not be used for commercial purposes, or adapted, remixed, transformed or built upon. (https://creativecommons.org/licenses/by-nc-nd/4.0/).

Thieme Medical and Scientific Publishers Pvt. Ltd. A-12, 2nd Floor, Sector 2, Noida-201301 UP, India
2009. It is typically seen in children with a median age of 7 years (equally in males and females). This condition is quite fatal with mortality rates as high as 31%.

Case Summary
A 2-year-old asymptomatic girl underwent modified Blalock–Taussig shunt surgery for corrective repair of tetralogy of Fallot. Postoperatively she developed status epilepticus due to shunt block. The seizures lasted for 45 minutes requiring intravenous midazolam at 0.1 mg/kg twice 5 minutes apart, followed by intravenous phenytoin sodium 20 mg/kg, and then subsequently two doses of intravenous sodium valproate 20 mg/kg 10 minutes apart. The seizures subsided after the second dose of intravenous sodium valproate. Though the seizure was eventually controlled, the girl continued to remain critical with a poor Glasgow Coma Scale (E1M2V1), unequal pupils not reacting to light with retinal hemorrhages and early papilledema, and further on developed signs of shock for which the patient was intubated and put on mechanical ventilator at the pediatric intensive care unit. Blood investigation report the following day was as follows: serum glutamic-pyruvic transaminase (SGPT) 5,489 IU/L; serum glutamic-oxaloacetic transaminase (SGOT) 2,496 IU/L; international normalized ratio (INR) 1.5; serum bilirubin 0.3 mg/dL; and serum ammonia 1,118 mg/dL. The hemo-glucose test showed low readings. However, serum bilirubin was within normal limits. The patient was suspected to have Reye’s syndrome based on the clinical presentation and blood investigations. She was treated with intravenous dextrose saline drip, inotropes for shock, hypertonic saline for raised intracranial pressure, mechanical ventilation for respiratory support, and intravenous sodium benzoate, syrup lactulose, high bowel wash, for hyperammonemia. She continued to be in depressed sensorium and did not respond to the treatment. She succumbed to the illness 2 days later. Diagnosis of Reye’s syndrome was confirmed by postmortem liver biopsy, which showed fatty change.

Discussion
The Centers for Disease Control and Prevention (CDC) has outlined the clinical criteria for Reye’s syndrome as an acute, noninflammatory encephalopathy that is documented clinically by an alteration in consciousness and, if available, a record of the cerebrospinal fluid (CSF) containing ≤8 leukocytes/mm³, or a histology demonstrating cerebral edema without perivascular or meningeal inflammation. It has to be associated with hepatic dysfunction either by a liver biopsy or an autopsy or a threefold or greater increase in the levels of the SGOT, SGPT, or serum ammonia, and no more reasonable explanation for the cerebral and hepatic abnormalities.

Clinical Staging of Reye’s Syndrome
Clinical staging of Reye’s syndrome is as follows:

- **Stage 1**: usually quiet, lethargic, and sleepy; vomiting; and laboratory evidence of liver dysfunction.
- **Stage 2**: deep lethargy, confusion, delirium, combative, hyperventilation, and hyper-reflexia.
- **Stage 3**: obtunded, light coma ± seizures, decorticate rigidity, and intact pupillary reaction.
- **Stage 4**: seizures, deepening coma, decerebrate rigidity, loss of oculocephalic reflexes, and fixed pupils.
- **Stage 5**: coma, loss of deep tendon reflexes, respiratory arrest, fixed dilated pupils, flaccidity/decerebrate, and isoelectric electroencephalogram.

Reye’s syndrome is presumed to be multifactorial in nature. The exact cause of Reye’s syndrome remains unknown. The condition typically occurs after a viral illness, particularly an upper respiratory tract infection or gastroenteritis. Organisms commonly involved are influenza virus, varicella virus, and *bacillus cereus*. Use of salicylates during viral illness may precipitate Reye’s syndrome. Other drugs like paracetamol, tetracycline, valproic acid, zidovudine, didanosine, and antiemetics have been known to be associated with Reye’s syndrome.

The patient’s case scenario met the criteria for Reye’s syndrome having presented with status epilepticus and following use of valproic acid developed encephalopathy with a poor GCS score and markedly elevated levels of SGOT, SGPT, and serum ammonia with no explanation for the hepatic dysfunction and confirmation of fatty change in post mortem liver biopsy. However, it was difficult to stage the girl’s condition as she went into encephalopathy following status epilepticus and had a fulminating course over the next 2 days.

The liver biopsy histology of the patient showed changes of diffuse panlobular microvesicular steatosis in hepatocytes, swelling, and degeneration of hepatocytes. Electron microscopy showed multiple small fat globules in cells, swollen mitochondria with degenerative changes, and prominent nucleoli. The histologic appearance of liver biopsy of the patient classically appeared as that of Reye’s syndrome.

Reye’s syndrome involves mitochondrial injury, which inhibits oxidative phosphorylation and fatty acid β-oxidation. Accumulation of high concentration of ammonia leads to encephalopathy and anicteric hepatitis with threefold rise in liver enzymes. Induction of the mitochondrial permeability transition (MPT) is a common pathophysiological mechanism.

The prognosis of a patient of Reye’s syndrome is seen to be associated with the severity of involvement of the nervous system. Raised blood ammonia level is also significantly associated with a poor prognosis. When diagnosed early and aggressive treatment is initiated with peritoneal dialysis, intracranial decompression, and exchange transfusion, there have been claims of improvement.

In this patient, use of valproic acid to control status epilepticus was inferred to be the cause of Reye’s syndrome in the absence of any preceding viral illness or salicylate use. Valproic acid is known to cause elevated liver enzymes and
Valproic Acid Administration in Management of Status Epilepticus Causing Reye’s Syndrome

Valproic acid causes hyperammonemic encephalopathy in individuals with baseline normal liver function, despite use of therapeutic doses and normal serum levels of valproic acid after prolonged use in susceptible individuals.\(^8\)

In our patient, two doses of valproic acid given to control status epilepticus caused elevated serum ammonia levels, SGOT, and SGPT levels, and precipitated Reye’s syndrome. Hypoxic encephalopathy as a result of status epilepticus and sedative effect of antiepileptic drugs can delay the diagnosis of Reye’s syndrome having overlapping presentation.

Less hepatotoxic drugs like levetiracetam may be considered for management of status epilepticus in children so as to avoid an occurrence of Reye’s syndrome.

**Conclusion**

Knowledge of the syndrome and a good clinical acumen are required to diagnose Reye’s syndrome.

Aspirin or any salicylate compound should not be used to treat febrile viral illness in children. Monitoring of liver enzymes must be essentially done in patients on initiation of valproic acid at frequent intervals. This may help determine the onset of Reye’s syndrome at the initial stages.

Use of less hepatotoxic drugs may be considered for control of seizures instead of valproic acid.

Since the mortality rate is high in this illness, index of suspicion should be high and approach should be quick when the patient has developed altered sensorium and raised intracranial pressure following valproic acid use.

**Conflict of Interest**

None declared.

**References**