A Case of Reye Syndrome Caused by Influenza A Virus

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Background: Reye syndrome is a rare and potentially life-threatening disease characterized by liver failure and hepatic encephalopathy. Multiple possible etiologies have been suggested, but only aspirin (acetylsalicylic acid) has been statistically proven to be a causative factor. We describe a case of Reye syndrome secondary to influenza A virus.

Case Report: A 2-year-old male with a recent history of influenza-like symptoms presented with neurologic deterioration. He had elevated liver enzymes, hyperammonemia, elevated creatinine, and hypoglycemia. Liver biopsy showed microvesicular steatosis consistent with Reye syndrome. He was given supportive care and recovered after 17 days with normalization of metabolic derangements. At 4-month follow-up, the patient had reached age-specific developmental milestones.

Conclusion: The incidence of Reye syndrome has decreased since 1980 when the Centers for Disease Control and Prevention issued a warning against aspirin use in children. Consequently, any new incidence of Reye syndrome warrants investigation of other etiologies. This case adds to the evidence that causes other than aspirin can result in Reye syndrome.

Keywords: Hepatic encephalopathy, influenza A, Reye syndrome

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INTRODUCTION

In 1963, Reye et al first described a distinct clinicopathologic entity characterized by “disturbed consciousness, fever, convulsions, vomiting, disturbed respiratory rhythm, altered muscle tone, and altered reflexes” with an unknown cause.1 This rare and potentially fatal disease entity affecting multiple organ systems was later termed Reye syndrome. Various agents have been suggested as etiologies of Reye syndrome, including an intrinsic toxin causing disruption in the mitochondrial system, dysfunctional lipid and ammonia metabolism, an extrinsic toxin altering the patient’s response to bacterial or viral prodrome, and genetic susceptibility.2 The only agent, however, that has been statistically proven to be a cause of Reye syndrome is aspirin (acetylsalicylic acid) intake during the viral prodromal phase in young children, a finding that led to issuance of a warning against aspirin use in children in 1980.3 Since then, Reye syndrome incidence in the United States has declined sharply, although rare incidents have been reported from other etiologies.4 We describe a case of Reye syndrome from influenza A virus in a 2-year-old male.

CASE REPORT

A 2-year-old male with no significant medical or family history presented to the emergency department (ED) after he was found unresponsive with vomitus in his mouth. He had influenza-like symptoms including cough, rhinorrhea, diarrhea, vomiting, and fatigue without fever 3 days prior to presentation. His parents gave him acetaminophen twice daily for symptom control. On initial physical examination in the ED, the patient had a Glasgow Coma Scale score of 8 and was somnolent but arousable, withdrawing to pain, spontaneously breathing, and had bilateral clonus. Pupils were equal size and constricted with light. Vital signs were normal for his age. Rapid viral testing was positive for influenza A virus. Significant laboratory results included anemia (hemoglobin 9.2 g/dL), hypernatremia (serum sodium 152 mmol/L), transaminitis (aspartate aminotransferase [AST] 3,460 U/L and alanine aminotransferase [ALT] 1,956 U/L), hyperbilirubinemia (total bilirubin 2.4 mg/dL, direct bilirubin 1.9 mg/dL), elevated international normalized ratio (INR 4.7), hyperammonemia (serum ammonia 96 μmol/L), lactic acidosis (serum lactic acid 3.2 mmol/L), azotemia (blood urea nitrogen 50 mg/dL), hypercreatinemia (serum creatinine 0.92 mg/dL), elevated creatine phosphokinase (544 U/L), elevated procalcitonin (25.9 ng/mL), elevated C-reactive protein (1.44 mg/dL), and hypoglycemia (serum glucose 5 mg/dL). Gamma-glutamyltransferase was normal (12 U/L); salicylate, ethanol, and urodynamic studies were negative. The patient was admitted to the hospital. His initial serum acetaminophen level of 30 mcg/mL had decreased to 8 mcg/mL at admission.

On day 1 of his hospitalization, the patient’s liver function deteriorated; AST increased to >20,000 U/L, ALT to 9,509 U/L, and ammonia to 180 μmol/L. Two days after admission, he was transferred to the pediatric intensive care unit for...
hepatic failure. He became delirious, agitated, and combat-
tive and had unintelligible speech. He was intubated and
placed on mechanical ventilation for grade 3 hepatic en-
cephalopathy. All tests in an extensive diagnostic evaluation,
including testing for autoimmune, inflammatory, infective,
toxicologic, metabolic, hematologic, and oncologic etiolo-
gies, were negative. Urinalysis on the fourth day of ad-
mission revealed proteinuria (urine protein 100 mg/dL)
indicative of rhabdomyolysis, but the urine was negative
for urobilinogen and nitrites.

Because of the patient’s liver failure and positive result for
influenza A, Reye syndrome was the leading differential.
Liver biopsy revealed central hepatic venous collapse with
surrounding microvesicular steatosis of the hepatocytes
consistent with Reye syndrome (Figures 1 and 2).

In addition to supportive care, the patient was treated with
lactulose every 6 hours and rifaximin 10 mg/kg twice daily to
lower serum ammonia levels. This treatment continued for 8
days. The patient was extubated on day 7. His liver function
gradually improved with supportive care, fresh frozen plas-
ma, and vitamin K 10 mg/kg as needed. His liver enzymes
trended down from AST 4,986 U/L and ALT 5,841 U/L on
day 3, to AST 421 U/L and ALT 1,744 U/L on day 6, and to
AST 53 U/L and ALT 208 U/L on day 17 of his hospitalization.
His INR trended down from 3.2 on day 2, to 1.9 on day 5,
and to 1.2 on day 10. He developed hypertension thought
to be caused by acute kidney injury secondary to rhabdo-
myolysis. Maximum blood pressure was 169/98 mmHg on
day 14, and he was treated with labetalol 2 mg/kg/day initially.
He remained on labetalol through discharge with good
response. His total duration of hospital stay was 17 days,
and he was discharged home. On follow-up 4 months fol-
dowing discharge, the patient’s guardians reported that he
was achieving normal developmental milestones.

DISCUSSION

The Centers for Disease Control and Prevention defines
Reye syndrome as an acute, noninflammatory encephalo-
pathy characterized by alterations in the level of conscious-
ness.5 The encephalopathy must be associated with either
fatty changes of the liver or at least a 3-fold increase in the
levels of ALT, AST, or serum ammonia with no other reason-
able explanation for the hepatic and cerebral abnormalities.5

The National Reye Syndrome Surveillance System classi-
fies Reye syndrome into 6 stages:4

- Stage 1 – Difficult to arouse, lethargy, sleepiness
- Stage 2 – Delirious, combative, disoriented with purpose-
  ful and semipurposeful movements
- Stage 3 – Coma, decorticate rigidity, with preservation of
  pupillary light and ocular reflexes
- Stage 4 – Deepened coma, decerebrate rigidity, loss of
  pupillary reflexes
- Stage 5 – Unarousable, flaccid paralysis, areflexia, and
  pupillary unresponsiveness to light
- Stage 6 – Treated with curare or other medications and
  therefore unclassifiable

Our patient met the criteria for stage 2 Reye syndrome
with markedly elevated liver enzymes, fatty infiltration
shown in the liver biopsy, disorientation, delirium, and com-
bativeness without posturing. Influenza A virus is the sus-
pected etiology for this patient’s Reye syndrome, as an
extensive evaluation was negative for other causes.

From December 1980 through November 1997, more
than 1,200 cases of Reye syndrome were reported in the
United States.4 The fatality rate of Reye syndrome has
been 31%, with the highest rate seen among children <5
years old.4 Since a warning was placed on aspirin in 1980,
no more than 36 new cases have occurred per year.4 There-
fore, any incidence of the disease warrants investigation to
identify possible etiologies as well as treatments to potential-
ly reduce fatality. In our case, influenza A virus directly preceded
the onset of disease course, and supportive care with careful
monitoring led to functional recovery.

CONCLUSION

The incidence of Reye syndrome has decreased since the
Centers for Disease Control and Prevention issued a warning
against giving aspirin to children. Aspirin was not given to
the patient in this case, but he still had a classic presentation
of hepatic encephalopathy and met the clinical criteria for Reye syndrome. Although aspirin is the only statistically proven agent to cause Reye syndrome, our case adds to the evidence that other etiologies, including influenza A, can result in Reye syndrome.

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