Recognizing a Case of Reye's Syndrome

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Although the incidence of Reye's syndrome is declining, it remains a deadly disease. Early recognition and initiation of supportive measures can decrease the mortality rate from this disorder. Glucose levels should be maintained and electrolyte imbalances and coagulopathies should be corrected in patients with early Reye's syndrome. Comatose patients require specialized care at a tertiary care facility that has the capability to prevent and treat intracranial hypertension. Survivors of Reye's syndrome may have subtle neuropsychologic deficits but generally recover very well considering the gravity of the disease.

Reye's syndrome was first described in 1963 as a syndrome of fatty degeneration of the liver and acute encephalopathy. In 1977, 454 cases were reported nationwide, with a case fatality rate of 42 percent.[1] The number of cases dropped to only 25 in 1989,[1] possibly due to an increased awareness of the association between Reye's syndrome and salicylate use. Early recognition and treatment are important in decreasing the morbidity and mortality associated with this potentially fatal disorder.

Illustrative Case

An eight-year-old girl in a stuporous state was brought to the hospital emergency department. The girl's mother related that the child had been sick for approximately one week with an upper respiratory infection, but that she seemed to be improving.

On the morning of admission, her condition worsened and she was brought to the office. Bronchitis was diagnosed, and erythromycin was prescribed. Several hours later, she began vomiting, and shortly thereafter became very agitated and began screaming incoherently. She had received no aspirin or other products containing salicylate.

The patient was lethargic on presentation to the emergency department. Her eyes were open but she made no purposeful movements and did not seem to regard her environment. Painful stimuli would elicit a shrill, cat-like scream. Blood pressure was 97/58 mm Hg; pulse, 122; respiratory rate, 24; and temperature, 97.5°F (36.4°C). Her skin was pale and cool, and her neck was supple. Examination of her heart, lungs, abdomen and reflexes was unremarkable.

A computed tomographic (CT) scan of the head was normal. Fingerstick blood glucose measurements were less than 40 mg per dL (2.2 mmol per L) in spite of three boluses of 25 percent dextrose. On admission, laboratory values showed a white blood cell count of 10,700 per mm^3 (10.7×10^9 per L) with 90 percent polymorphonucleocytes and 2 percent band forms. Sodium was 130 mEq per L; potassium, 7.0 mEq per L; chloride, 94 mEq per L; and carbon dioxide content, 21 mEq per L. Plasma glucose was 45 mg per dL (2.5 mmol per L); and blood urea nitrogen, 44 mg per dL (15.7 mmol per L); and creatinine, 0.9 mg per dL (79.6 μmol per L). A urine toxicology screen was negative. Aspartate aminotransferase level was 15,400 units per L, and alanine aminotransferase level was 1,225 units per L. Total

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bilirubin was 0.5 mg per dL (8.55 µmol per L) and ammonia was 141 µmol per L. Prothrombin time was elevated at 38.9 seconds (control value: 11.6 seconds, equivalent to International Normalization Ratio of 10) and activated partial thromboplastin time was 46 seconds. Albumin level was 1.2 g per dL (12 g per L).

A lumbar puncture was performed and the cerebrospinal fluid was clear, with 72 red blood cells per mm^3 and three white blood cells per mm^3. Cerebrospinal fluid glucose was 28 mg per dL (1.55 mmol per L) and protein was 22 mg per dL (0.22 g per L). No organisms were seen on the CSF Gram stain.

Arterial blood gases showed a pH of 7.5; Pco_2, 22 mm Hg; Po_2, 112 mm Hg; bicarbonate level, 21 mEq per L; and oxygen saturation, 96 percent on room air.

The patient was admitted to the pediatric intensive care unit with a diagnosis of Reye's syndrome. Supportive therapy was initiated. Mannitol was administered to combat elevation of intracranial pressure. Intravenous fluids with 20 percent dextrose were given at approximately two-thirds maintenance rate to maintain blood glucose levels.

A neurologist was consulted and an electroencephalogram (EEG) revealed diffuse slow background activity consistent with stage II Reye's syndrome.

Approximately 30 hours after admission, the patient rapidly regained consciousness. Over the next few days, her liver enzymes gradually returned to normal. A thorough metabolic workup was performed, including measurements of plasma amino acids and organic acids and urine amino acids. On admission, these tests showed gross generalized amino acidemia. One week later, repeat tests were normal. The patient was discharged from the hospital one week after admission, without apparent residual problems.

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Definition and Pathogenesis

Reye's syndrome is associated with viral illness and involves encephalopathy and profound changes in the liver. It has also been associated with salicylate use, but neither a history of viral illness nor salicylate use is necessary to make the diagnosis.

In 1989, 76 percent of children diagnosed with Reye's syndrome had an identifiable viral illness within three weeks before the diagnosis; 12 percent of the children had a preceding varicella infection.[1] The Centers for Disease Control and Prevention definition of Reye's syndrome is given in *Table 1*.

The major metabolic derangement in Reye's syndrome is a marked decrease in the activity of hepatic intramitochondrial enzymes. Several inborn errors of metabolism may mimic the presentation of Reye's syndrome, including deficiencies of ornithine transcarbamylase, carnitine, pyruvate dehydrogenase and pyruvate carboxylase. These conditions should be included in the differential diagnosis of Reye's syndrome.[2,3]

The use of aspirin has long been associated with development of Reye's syndrome.[4] The reason for the association has not been clearly defined, but salicylates, in conjunction with certain viral infections, may inhibit mitochondrial enzymes in susceptible individuals.[5] No dosage of salicylates is safe during a viral infection.[5] Although the studies linking salicylates and Reye's syndrome have limitations, it is recommended that salicylates be used cautiously, if at all, in children with chickenpox or influenza, especially since other analgesics/antipyretics are readily available.[6]

The liver and brain are the organs most prominently affected in Reye's syndrome. The liver shows microvesicular lipid deposits in the cytoplasm, without inflammation or necrosis. Electron microscopy

TABLE 1

Centers for Disease Control Case Definition of Reye's Syndrome

1. Acute, noninflammatory encephalopathy documented by:
   a. Alteration in the level of consciousness and, if available, a record of cerebrospinal fluid containing <8 leukocytes per mm^3
   or
   b. Histologic specimen demonstrating cerebral edema without perivascular or meningeal inflammation
2. Hepatopathy documented either by a liver biopsy or autopsy considered to be diagnostic of Reye's syndrome or by a threefold or greater rise in the levels of either serum aspartate aminotransferase, serum alanine aminotransferase or serum ammonia
3. No more reasonable explanation for the cerebral and hepatic abnormalities

shows marked disruption of the mitochondria. Central nervous system tissue demonstrates a similar pattern of fatty deposition and cerebral edema without inflammation.[7]

Other organ systems may show fatty infiltration as well, including the heart, pancreas and kidneys. Patients may die of heart failure, gastrointestinal bleeding, renal failure or shock, but the usual cause of death is cerebral edema leading to herniation.[8]

Clinical Manifestations

Any pediatric patient with a history of a viral illness followed by a sudden change in mental status should be evaluated for possible Reye's syndrome. Most cases occur in children aged four to 12 years, and the peak age for occurrence is about six years.[1] Reye's syndrome typically develops five to seven days after the onset of a viral illness, such as an upper respiratory tract infection or varicella. The child begins to have protracted vomiting and mental status changes such as delirium, stupor or inappropriate behavior. These neurologic symptoms may progress to coma and death. Focal neurologic signs are uncommon. The liver may be enlarged, but jaundice does not develop.[8]

Laboratory abnormalities relate to the liver involvement. Elevation of liver enzymes without hyperbilirubinemia is the rule. Tests of liver function such as prothrombin time, partial thromboplastin time and albumin may be abnormal, reflecting the underlying liver dysfunction. The serum glucose level is frequently low and the ammonia level is usually elevated.[8]

TABLE 2

National Institutes of Health Consensus Conference Clinical Staging System for Reye's Syndrome

Stage	*Level of consciousness*	*Posture*	*Response to pain*	*Pupillary reaction*	*Oculocephalic reflex*
I	Lethargy, follows verbal commands	Normal	Purposeful	Brisk	Normal
II	Combative or in stupor; verbalizes inappropriately	Normal	Purposeful or nonpurposeful	Sluggish	Conjugate deviation
III	Coma	Decorticate	Decorticate	Sluggish	Conjugate deviation
IV	Coma	Decerebrate	Decerebrate	Sluggish	Inconsistent or absent
V	Coma	Flaccid	None	None	None

Adapted from National Institutes of Health Consensus Conference. Diagnosis and treatment of Reye's syndrome. JAMA 1981;246:2441-4.

TABLE 3

Fatality Rates for Reye's Syndrome Based on Clinical Stage at Admission*

Stage	*Range (%)*
I	12 to 19
II	25 to 32
III	35 to 47
IV	50 to 71
V	63 to 100

**—Fatality rate data for 1977-1980.*

Data from Hurwitz ES, et al.[11]

A clinical staging system for Reye's syndrome was first described by Lovejoy and colleagues[9] in 1974; this staging system included EEG findings for each stage. This system was subsequently modified in 1981 by a National Institutes of Health Consensus Conference but this classification system does not include EEG findings (*Table 2*).[10] The staging system provides some prognostic data (*Table 3*), and can help guide clinical management.[11]

Differential Diagnosis

Many disorders may present in a manner similar to that of Reye's syndrome (*Table 4*). Certain medications and toxins, including endotoxin, isopropyl alcohol, aflatoxin, aspirin, acetaminophen, valproic acid, antiemetics, warfarin and hypoglycin, may produce a similar syndrome. Hypoglycin is a toxin found in the akee tree (*Blighia sapida*), which grows in Africa, the Caribbean region, southern California, southern Florida and Hawaii.[8] Several inborn errors of metabolism may mimic Reye's syndrome, and metabolic screening should be performed in patients in whom Reye's syndrome is suspected.[3] Finally, infections of the central nervous system must be ruled out.

Management

In all stages of Reye's syndrome, certain treatment principles should be followed. Serum glucose levels should be maintained with infusions of 10 to 15 percent dextrose or higher, with frequent glucose determinations (every two to four hours). Serum electrolyte levels and calcium, phosphorous and magnesium levels should be corrected and monitored at least daily. Neurologic status should be assessed hourly. Liver enzyme and ammonia levels should be determined daily. Significant coagulopathy should be corrected with fresh frozen plasma (10 mL per kg), especially before any invasive procedure, and vitamin K should be given (3 to 5 mg intramuscularly).[8] Evidence shows that correction of any electrolyte imbalances and maintenance of serum glucose levels in patients with stage I disease may prevent further progression.[11-13]

Patients with stage II disease require monitoring in an intensive care unit, since the condition of these patients may rapidly progress to a comatose state. If progression toward stage III is evident, urgent transfer to a tertiary care center is recommended.[8]

Patients with stage III involvement and worse (i.e., a comatose patient) require aggressive treatment at a tertiary care center. Elective intubation is mandatory and, aside from the basic supportive care also given for stages I and II, possibilities for treatment include measurement and control of intracranial pressure and attempts to decrease ammonia levels.

Management of the cerebral edema associated with Reye's syndrome is the major factor that affects the outcome. When and whether to use devices to directly measure intracranial pressure (subarachnoid bolt, intraventricular drain) is controversial. Some authors recommend the use of such devices for stage II[7,14]; others for stage III.[8] The NIH Consensus Conference makes no specific recommendations for such use.[10]

Controlling intracranial pressure requires balancing two goals: maintenance of adequate cerebral perfusion and prevention of herniation. To adequately gauge progress, a continuous reading of intracranial pressure and arterial pressure is essential. Thus,

TABLE 4

Differential Diagnosis of Reye's Syndrome

Central nervous system infections
Meningitis
Encephalitis
Hemorrhagic shock with encephalopathy
Drug ingestion
Salicylate
Valproic acid
Warfarin
Antiemetics
Acetaminophen
Toxins
Endotoxin
Aflatoxin
Hypoglycin
Isopropyl alcohol
Insecticides
Margosa oil
Metabolic disorders
Organic acidemias
Urea cycle defects
Carnitine deficiency
Transcarbamylase deficiency
Pyruvate dehydrogenase deficiency
Pyruvate carboxylase deficiency
Aminoacidurias
Disorders of carbohydrate metabolism

if aggressive attempts are made to reduce intracranial pressure (i.e., measures other than moderate doses of mannitol), use of an arterial line and an intracranial pressure monitor is mandatory.[8]

Fluid restriction and the use of osmotically active agents may be useful in the treatment of increased intracranial pressure. To prevent a decrease in cerebral perfusion pressure, severe dehydration must be avoided; serum osmolality should be maintained at around 300 mOsm,[7,8] using mannitol only in moderate doses (0.25 g per kg every four to six hours). Because excess free water may contribute to cerebral edema, fluids containing only dextrose and water should be avoided.[8]

Hyperventilation is another effective method of temporarily decreasing intracranial pressure through the potent vasoconstrictive effect of decreased carbon dioxide tension. Although this effect decreases cerebral blood flow, hyperventilation is critical in the management of acute herniation and increased intracranial pressure. Carbon dioxide tension should be maintained between 25 and 35 mm Hg.[8]

If hyperventilation and osmotherapy are ineffective in controlling intracranial pressure, barbiturates may be tried. Pentobarbital (5 to 10 mg per kg) and thiopental (3 to 6 mg per kg) are effective in rapidly reducing intracranial pressure. Barbiturates also decrease perfusion pressure (especially at higher doses), so care must be used when administering these agents, and pentobarbital levels should be maintained in the range of 20 to 30 mg per L.[8]

Decompressive craniotomy and hypothermia have been attempted in the management of Reye's syndrome. Neither has been shown to be of any benefit.[8] Various methods to decrease ammonia levels have also been tried, including dialysis, exchange transfusion, charcoal hemoperfusion, total body washout and metabolic interventions, none of which have been shown to be of any benefit.[8,10]

Long-Term Prognosis

Patients who survive the acute phase of Reye's syndrome recover remarkably well, considering the gravity of the disease. The NIH does not recommend extensive psychologic or educational testing of survivors.[10] However, sibling-matched studies have shown some mild neuropsychologic deficits in survivors, particularly in those who had Reye's syndrome at a younger age.[15,16] Survivors may have some emotional disruption, exhibiting frequent somatic complaints, anxiety and depression.[17] The National Reye's Syndrome Foundation (P.O. Box 829, 426 N. Lewis St., Bryan, OH 43506; telephone: 800-233-7393) is an excellent source of information and support for families affected by Reye's syndrome.

Final Comment

Reye's syndrome, though decreasing in incidence, remains a deadly disease. With

proper management, however, the potential for an adverse outcome can be decreased. Any clinician who provides care to pediatric patients needs to keep a high index of suspicion for Reye's syndrome when a child presents with neurologic symptoms. All children with Reye's syndrome need careful supportive therapy that emphasizes maintenance of glucose levels and correction of any electrolyte imbalances or coagulopathy. Comatose patients require intensive care in a tertiary care center, and specific measures to prevent and treat intracranial pressure elevation should be instituted. Although mortality can be quite high in the advanced stages, long-term sequelae are few and seem to be confined to patients with severe disease or patients who were very young at the time of the illness.

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