RECERTIFICATION SERIES

Reye's Syndrome Update

Patricia Dockery Weavil, MD
Gale Harkness, PA-C

The *Physician Assistant* Recertification Series provides a definitive review and update of major areas of primary care medicine. Articles are selected by a distinguished panel of PA educators and clinicians. The Series is designed to help PAs maintain current clinical standards.

ABSTRACT

The declining incidence of Reye's syndrome in recent years has paralleled an increasing awareness of the risk factors—especially the use of aspirin in children. Although the majority of cases may be mild, the illness can progress to severe encephalopathy, increased intracranial pressure, coma, and death. Children between the ages of 4 and 12 are most susceptible. In a typical case, apparent recovery from a viral infection is followed by the abrupt onset of vomiting. Changes in mental status appear, liver function tests show abnormalities, and fatty infiltration of the liver is seen on biopsy. Early treatment consists of dextrose and fluid support. Later interventions may include sedation, respiratory assistance, control of intracranial pressure, and specific treatment of complications. Early diagnosis and prompt intervention can reduce mortality and the risk of permanent sequelae.

Reye's syndrome was first described in 1963, by Reye and colleagues[1] in Australia, as a devastating illness characterized by acute encepl alopathy and fatty degeneration of the liver; the syndrome was fatal in 17 of 21 children described in the initial report. Since then, research data have implicated a number of factors in the development of Reye's syndrome, including viral infections and the use of aspirin-containing products. However, the cause and physiology of the syndrome remain unclear.

Prevention is currently the best strategy for controlling Reye's syndrome. The steadily declining incidence in recent years has paralleled a growing awareness of the risk factors. Diagnosis and treatment have also improved over the past decade. Cases are often diagnosed earlier, at milder stages, when cures are more common. All clinicians who care for children must know how to prevent, recognize, and treat this potentially fatal illness.

CASE REPORT

A 5-year-old girl had been in good health until the onset of a temperature of 100.4 °F (38 °C), rhinorrhea, and cough. For the first 3 days of her illness she was treated with a multidrug cold preparation containing aspirin, and she began to recover on days 4 and 5. She became irritable during the fifth night and began vomiting early on the morning of the sixth day. Her parents telephoned her pediatrician, who recommended instituting clear

Patricia Dockery Weavil is Assistant Professor, Department of Pediatrics, Physician Assistant Program, and *Gale Harkness* is Instructor, Physician Assistant Program, Bowman Gray School of Medicine, Wake Forest University, Winston-Salem, NC.

liquids and bringing the child to the office if the vomiting did not cease.

The patient became increasingly irritable when aroused and was reacting violently to stimulation by the time her mother brought her to the physician's office later that morning. On physical examination, the child was very uncooperative and irritable. Notable physical findings included respirations, 40/min; heart rate, 110/min; rectal temperature, 101°F (38.3°C); and a slightly enlarged liver that was palpable 2 cm below the right costal margin. Laboratory studies showed a peripheral white blood cell (WBC) count of 18,000/μL with 60% neutrophils and 6% band forms. The child was taken to the emergency department of the local hospital.

At the hospital, analysis of cerebrospinal fluid (CSF) showed 4 WBCs/μL with 100% lymphocytes; protein, 44 mg/dL; and glucose, 40 mg/dL. Gram's stain of the CSF was negative, as was counterimmunoelectrophoresis (which detects bacterial antigens in CSF). Results of blood chemistry analysis included sodium, 139 mEq/L; CO_2, 13 mEq/L; blood urea nitrogen, 33 mEq/L; creatinine, 0.5 mEq/dL; glucose, 40 mg/dL; aspartate aminotransferase (AST), 287 U/L; alanine aminotransferase (ALT), 155 U/L; and ammonia, 190 μmol/L. Diagnoses of sepsis and Reye's syndrome were considered, based on the patient's history and test results.

Cefuroxime, 225 mg/kg/d intravenously (IV), was initiated for presumed sepsis. For treatment of presumed Reye's syndrome, an infusion of 10% dextrose in electrolyte solution was started, and the patient was placed under close observation. Preliminary results of a liver biopsy included microvesicular fatty infiltration and mitochondrial changes that were consistent with early Reye's syndrome.

Dextrose was continued IV, and after 3 days, the child's ammonia and liver enzyme levels had returned to normal. Cefuroxime was discontinued when cultures of blood and CSF showed no growth over 3 days. The patient was discharged from the hospital 7 days after admission. No residual physical or neurologic effects from Reye's syndrome were noted at discharge.

RISK FACTORS

A number of studies have reported an increased risk of Reye's syndrome in children taking aspirin for symptomatic therapy during viral illness.[2-9] Awareness of this risk factor has grown in recent years, among both clinicians and the public, and warning labels are now required by the Food and Drug Administration (FDA) on all nonprescription aspirin products (see *Box*, "FDA Mandates Stronger Warning on Aspirin Preparation Labels"). However, some children continue to receive aspirin inappropriately because caregivers are uninformed or because older aspirin-containing products (predating the FDA regulation) lack warning labels. Reye's syndrome also has developed in children requiring aspirin therapy for chronic conditions, such as rheumatoid arthritis.[10]

FDA MANDATES STRONGER WARNING ON ASPIRIN PREPARATION LABELS

The FDA has published an updated regulation revising the label warning that must be affixed to all nonprescription products containing aspirin. The new label reads: "WARNING: Children and teenagers should not use this medicine for chicken pox or flu symptoms before a doctor is consulted about Reye syndrome, a rare but serious illness reported to be associated with aspirin."

The new regulation took effect on December 9, 1988. For one year following that date, all nonprescription aspirin products must prominently display an attention-getting statement alerting consumers to the stronger Reye's syndrome warning. The statement must include the words "new" and "warning."

Some cases of Reye's syndrome have occurred in children who have *not* taken aspirin. Other risk factors, including viruses and exogenous toxins, have been implicated in such cases. The strongest viral links appear to be with influenza B and the varicella-zoster (chickenpox) virus.[11,12] Other viruses that have been associated with outbreaks of Reye's syndrome include the enteroviruses, Epstein-Barr virus, and myxoviruses. Occasional links to ingestion of toxic substances, such as aflatoxin, have also been reported. Although Reye's syndrome has developed among siblings, no evidence has been found for a genetic predisposition.[13]

EPIDEMIOLOGY

Reye's syndrome appeared in the United States only sporadically until 1974, when more than 400 cases were reported, with a case-fatality rate of 40%.[13] The declining incidence in recent years (*Fig 1*)[14] has been attributed to a decrease in the use of aspirin in children[15,16] as well as to a low rate of major influenza epidemics.

Fewer than 100 cases per year are currently reported in the United States, with a case-fatality rate of approximately 30%.[17] However, because the vast majority of

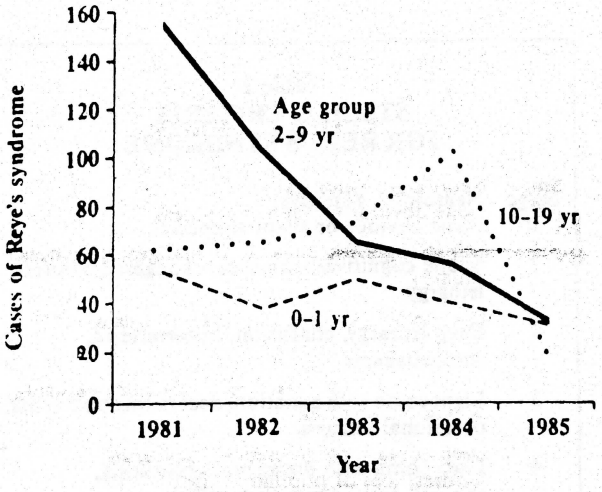

Fig 1. Reported cases of Reye's syndrome in the United States from 1981 to 1985, by age group (as of January 15, 1986). Source: Centers for Disease Control.[14]

cases may be mild and undiagnosed, the actual incidence may be much greater than reported.

Reye's syndrome develops most commonly during the "flu season," from January through March. More cases are reported in suburban and rural areas than in cities.[18] The greatest susceptibility appears to occur between the ages of 4 and 12 years (*Table I*), with a peak at age 6.[19] However, cases have been reported occasionally in both infants and adults.

RECERTIFICATION RECAP

Reye's syndrome is a potentially life-threatening illness characterized by acute encephalopathy and fatty degeneration of the liver. Although cases have been reported in infants and adults, the highest incidence is in children between 4 and 12 years of age, with a peak at age 6. The use of aspirin has been identified as a major risk factor; viral infection (especially influenza B and varicella zoster) and ingestion of toxic substances also have been implicated. Decreased use of aspirin in children and a low rate of major influenza epidemics have contributed to a declining incidence of reported cases in recent years. The majority of cases may be mild and undiagnosed.

CLINICAL PRESENTATION

Reye's syndrome most often presents with a biphasic course in a previously healthy child. In 90% of cases, the prodromal illness is an upper respiratory tract infection (URI); in 5% to 7% of cases, the prodromal illness is chickenpox.[19] In the first phase, the initial viral illness is usually followed by apparent recovery. The second phase begins with an abrupt onset of persistent vomiting, usually 5 to 7 days after the beginning of the prodromal illness. Progression to coma may occur within several hours.[19]

The diagnosis of Reye's syndrome should be considered whenever vomiting accompanies or follows a viral infection in a child. In mild cases, the initial vomiting spell may be followed by 1 or 2 days of persistent nausea, anorexia, and listlessness.[20] Even at this stage, results of liver function tests will usually show abnormalities. Many cases of Reye's syndrome do not progress beyond this stage.

In progressive cases of Reye's syndrome, initial hyperactivity of the sympathetic nervous system may produce hyperreflexia, agitation, combativeness, and fear, as well as persistent vomiting. Hypoglycemia may develop, accompanied by increasing sleepiness and lethargy. Jaundice is rarely seen, but moderate hepatomegaly is

Table 1
DIAGNOSTIC GUIDELINES FOR REYE'S SYNDROME

Typical Patient Profile
4–12 years of age (peak at age 6)
Prodromal viral illness (usually URI or chickenpox)
Previously healthy

Presenting Complaints
Onset of vomiting after resolving illness
Sleepiness, subtle cognitive changes in early stages
Agitation and stages of coma later

Physical Findings
Varying degrees of mental disorientation
Moderately enlarged liver

Laboratory Findings
Hypoglycemia
Serum liver functions: elevated AST, ALT, and ammonia

Liver Biopsy Findings
Microvesicular fatty infiltration
Characteristic changes in mitochondria

present in about 40% of cases.[21] Intracranial pressure may increase in association with cerebral edema. Advanced cases of Reye's syndrome are characterized by deepening levels of coma.

Complications of Reye's syndrome include diabetes insipidus, cardiac arrhythmias, gastrointestinal bleeding, hypotension, respiratory insufficiency/arrest, pancreatitis, aspiration pneumonia, and metabolic abnormalities such as mixed respiratory alkalosis/metabolic acidosis and disturbances of fluid and electrolytes.[21]

Several systems for staging Reye's syndrome have been developed. The staging system shown in *Table 2* includes the earliest diagnostic criteria.[22]

Table 2
STAGING CRITERIA FOR REYE'S SYNDROME

Stage	Neurologic Findings
0	None obvious or slight sleepiness
1	Subtle cognitive/behavioral changes; quietness, lethargy
2	Deep lethargy, confusion, hyperreflexia, combativeness
3	Light coma with agitation, decorticate posturing, occasional seizures
4	Deep coma with decerebrate posturing, seizures, loss of pupillary reflex
5	Deep coma, flaccidity, flat electroencephalogram

Adapted from Behrman and Vaughan.[22]

RECERTIFICATION RECAP

Reye's syndrome should be considered whenever vomiting accompanies or follows a viral illness in a child. The most typical presentation involves a biphasic course. The first phase is characterized by apparent recovery from URI, chickenpox, or other viral illness. In the second phase, vomiting begins abruptly 5 to 7 days after the onset of the prodromal illness. Mild cases may not progress beyond 1 or 2 more days of nausea, anorexia, and listlessness. In progressive cases, agitation is followed by lethargy and sleepiness. Moderate hepatomegaly may be present. In advanced cases, increased intracranial pressure is associated with deepening levels of coma.

LABORATORY AND BIOPSY FINDINGS

Laboratory findings often become abnormal in early stages of Reye's syndrome. The peripheral WBC count may be normal or moderately elevated; serum electrolyte levels usually reflect the degree of dehydration and acidosis. However, these findings are not specific to Reye's syndrome.

Abnormalities of liver function develop rapidly, producing serum elevations of AST, ALT, and ammonia. Serum ammonia levels correlate with the degree of encephalopathy. Other indicators of liver function, including prothrombin time, are also commonly abnormal; however, bilirubin levels may be normal.[21]

Hypoglycemia is moderate in the early stages of Reye's syndrome, but becomes marked in later stages. In some dehydrated patients, laboratory values are difficult to assess owing to the presence of hemoconcentration; however, a low glucose level despite hemoconcentration provides additional evidence of Reye's syndrome.

Liver biopsy is the most definitive diagnostic modality for Reye's syndrome. In a typical case, the biopsy specimen shows both microvesicular infiltration of fat into the cells and characteristic changes in the mitochondria.[23] Biopsy is indicated if a definitive diagnosis will affect the choices of treatment for a very sick child, and it is often essential in the differential diagnosis of a very young child or infant. Biopsy also may be considered in any patient suspected of having Reye's syndrome beyond stage 1. However, the procedure is not without risk and is sometimes contraindicated in the unstable or bleeding patient. In many cases, the diagnosis of Reye's syndrome can be made without a liver biopsy.

The differential diagnosis of Reye's syndrome includes other causes of abnormal liver function and coma, such as inborn errors of metabolism,[24,25] sepsis, hyperthermia, viral encephalitis or meningoencephalitis, acute hepatitis, and poisoning with salicylates, carbon tetrachloride, or other substances.[21]

No reliable clues have been discovered to help predict which patients with Reye's syndrome will progress to advanced stages. For this reason, all children at risk should receive careful evaluation and consideration for therapy.

RECERTIFICATION RECAP

Abnormalities of liver function develop early in the course of Reye's syndrome, with serum elevations of AST, ALT, and ammonia. Hypoglycemia is moderate in early stages and marked in later stages. Liver biopsy is indicated when definitive diagnosis will affect treatment choices; characteristic findings are microvesicular fatty infiltration and mitochondrial changes. The likelihood of progression to advanced stages cannot be predicted from early findings; all children with Reye's syndrome should receive careful evaluation and treatment.

TREATMENT

Most patients with Reye's syndrome are best managed in an intensive care unit by clinicians with experience in treating the syndrome. Early treatment is supportive, with institution of IV dextrose and fluid support and careful observation for progression of signs and symptoms. An infusion of 10% dextrose in electrolyte solution is usually given; further adjustments of the dextrose concentration are tailored to the patient's response. Vitamin K (1 mg at onset of treatment) may be given IV for hypoprothrombinemia. Fluid intake is usually restricted to two thirds of the usual maintenance level—that is, 750 mL/m²/d.

Later interventions in the sicker child may include barbiturate sedation to decrease metabolic activity of the central nervous system, endotracheal intubation with mechanical ventilation, and monitoring of intracranial pressure. Agents such as mannitol may be used to control intracranial pressure. Close monitoring of cardiovascular, neurologic, respiratory, metabolic, fluid, and electrolyte status should be maintained; significant changes should be managed promptly. *Table 3* summarizes some of the interventions that are appropriate for each stage of Reye's syndrome.

The prognosis for a patient with Reye's syndrome is usually determined by the severity of intracranial pressure, central nervous system depression, and coma. Children who recover from advanced stages of the illness may be left with residual neurologic impairment. However, early and appropriate treatment may help to prevent progression of the manifestations of Reye's syndrome and forestall permanent sequelae.

Table 3
MANAGEMENT GUIDELINES FOR REYE'S SYNDROME

Stage	Treatment
0	10% dextrose IV in electrolyte solution Observation
1	10% dextrose IV in electrolyte solution Observation
2	Elective intubation 20% dextrose IV in electrolyte solution Central line placement Head-of-bed elevation
3	Required intubation Intracranial pressure monitoring 20% dextrose IV in electrolyte solution
4, 5	Same as stage 3

Note: Common additions to these therapies include fluid restriction and administration of vitamin K, mannitol, and barbiturates. Dextrose concentrations should be tailored to the patient's response. Most patients are best managed in an intensive care unit by experienced clinicians.

PREVENTION

The use of aspirin in children has been identified as a major risk factor for development of Reye's syndrome. Continuing educational efforts, focused on this risk, must be directed toward parents, other caregivers, and all health personnel. Particular emphasis should be given to the need to identify *all* ingredients of multidrug preparations before giving them to children. Caregivers should understand that there is no reason to use aspirin for control of fever in a child with a possible viral illness. Nonsalicylate analgesics and antipyretics (eg, acetaminophen) should be used instead. Since 1985, about 40% to 65% of reported cases of Reye's syndrome have occurred in patients ≥ 10 years of age; thus, older children and their parents should also be warned about the risks of aspirin use.[17]

Aspirin is, however, crucially important for certain children. The control of chronic illnesses such as rheumatoid arthritis often requires continuing aspirin therapy. Data suggest that children on such therapy may indeed be at increased risk for Reye's syndrome.[10] The increasing incidence of acute rheumatic fever, for which aspirin therapy is often given, may also be cause for concern.

continued

Continued

Our experience suggests that no single answer is best for children who need aspirin for chronic illnesses. Some children may be controlled as well on nonsteroidal anti-inflammatory agents; others do not benefit from these drugs. If a child must be continued on aspirin therapy, it may be advisable to interrupt the regimen whenever likely exposure to influenza or chickenpox in family members, playmates, or other contacts has occurred, as well as during significant community outbreaks of viral illness.

RECERTIFICATION RECAP

Treatment of Reye's syndrome is best administered in an intensive care unit by experienced clinicians. Initial measures include IV dextrose and fluid support with careful observation. Later interventions may include sedation, endotracheal intubation with ventilation, and administration of agents to control intracranial pressure. Early and appropriate treatment may reduce the risk of permanent neurologic sequelae. All parents and other caregivers should be aware of the link between aspirin and Reye's syndrome in children; continuing educational efforts are needed. Special precautions should be taken when aspirin therapy is unavoidable.

CONCLUSION

Prevention and early diagnosis are the keys to reducing the incidence, morbidity, and mortality of Reye's syndrome. All health professionals can help to minimize the risks by avoiding or limiting the use of aspirin in children, educating parents and other caregivers, and being prepared to recognize the early symptoms of Reye's syndrome and institute appropriate treatment.

REFERENCES

1. Reye RDK, Morgan G, Baral J: Encephalopathy and fatty degeneration of the viscera: A disease entity in childhood. *Lancet* 1963;2:749-752.
2. Tarlow M: Reye syndrome and aspirin. *Br Med J* 1986;292:1543-1544.
3. Starko KM, Ray CG, Dominguez LB, et al: Reye's syndrome and salicylate use. *Pediatrics* 1980;66:859-864.
4. Waldman RJ, Hall WN, McGee H, et al: Aspirin as a risk factor in Reye's syndrome. *JAMA* 1982;247:3089-3094.
5. Centers for Disease Control: Reye's syndrome—Ohio, Michigan. *MMWR* 1980;29:532,537-539.
6. Halpin TJ, Holtzhauer FJ, Campbell RJ, et al: Reye's syndrome and medication use. *JAMA* 1982;248:687-691.
7. Hurwitz ES, Barrett MJ, Bregman D, et al: Public Health Service study on Reye's syndrome and medications: Report of the pilot phase. *N Engl J Med* 1985;313:849-857.
8. Hurwitz ES, Barrett MJ, Bregman D, et al: Public Health Service study on Reye's syndrome and medications: Report of the main study. *JAMA* 1987;257:1905-1911.
9. Forsyth BW, Horwitz RI, Acampora D, et al: New epidemiologic evidence confirming that bias does not explain the aspirin/Reye's syndrome association. *JAMA* 1989;261:2517-2524.
10. Pribble C: Reye syndrome and aspirin therapy. *Am J Dis Child* 1986;140:966.
11. Sullivan-Bolyai JZ, Corey L: Epidemiology of Reye syndrome. *Epidemiol Rev* 1981;3:1-26.
12. Centers for Disease Control: Reye syndrome—United States, 1984. *MMWR* 1985;34(13):6.
13. Dodge PR, Brown SB, Ector WL, et al: Diagnosis and treatment of Reye's syndrome. *JAMA* 1981;246:2441-2444.
14. Centers for Disease Control: Reye syndrome—United States, 1985. *MMWR* 1986;35(5):66-74.
15. Taylor JT, Gustafson TL, Johnson CC, et al: Antipyretic use among children during the 1983 influenza season. *Am J Dis Child* 1985;139:486-488.
16. Arrowsmith JB, Kennedy DL, Juritsky JN, et al: National patterns of aspirin use and Reye's syndrome reporting, United States, 1980 to 1985. *Pediatrics* 1987;79:858-863.
17. Centers for Disease Control: Reye syndrome surveillance—United States, 1987 and 1988. *MMWR* 1989;38:325-327.
18. Nelson DB, Sullivan-Bolyai JZ, Morens DM, et al: The epidemiology of Reye syndrome: A review with emphasis in recent observation. *Am J Dis Child* 1986;140:1231-1235.
19. Rudolphs A: *Pediatrics* ed 18. E Norwalk, Conn, Appleton & Lange, 1987, p 1591.
20. Lichtenstein PK, Heubi JE, Daugherty CC, et al: Grade I Reye's syndrome: A frequent cause of vomiting and liver dysfunction after varicella and upper-respiratory-tract infection. *N Engl J Med* 1983;309:133-139.
21. Berkow R (ed): *The Merck Manual of Diagnosis and Therapy.* Rahway, NJ, Merck Sharp & Dohme Research Laboratories, 1987, pp 2047-2049.
22. Behrman RE, Vaughan VC (eds): *Nelson Textbook of Pediatrics*, ed 13. Philadelphia, WB Saunders Co, 1987, p 841.
23. Thaler MM: Metabolic mechanisms in Reye syndrome. *Am J Dis Child* 1976;130:241-243.
24. Rowe PC, Valle D, Brusilow SW: Inborn errors of metabolism in children referred with Reye's syndrome. *JAMA* 1988;260:3167-3170.
25. Green G, Blitzer M, Shapira E: Inborn errors of metabolism and Reye syndrome: Differential diagnosis. *J Pediatr* 1988;113:156-159.