

Reye's Syndrome: Lessons for Family Physicians

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Thirty years have passed since Reye's syndrome was first described, yet the precise pathophysiologic mechanism initiating this feared childhood condition remains elusive. Epidemiologic studies have now confirmed that avoidance of aspirin in children is a potent preventive measure. As a result, the incidence of Reye's syndrome has been almost completely eliminated.

Family physicians, as the primary caregivers to a substantial percentage of the pediatric population, are in a key position to continue the successes of primary prevention, to recognize suspected cases early and to submit case reports, such as in this month's issue of *American Family Physician*,¹ to aid in further defining the etiology of Reye's syndrome.

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There is a lesson in the history of Reye's syndrome. In October 1963, Reye, an Australian pathologist, reported on a "new" clinicopathologic entity occurring in children.² Reye's series comprised 21 cases collected over a period of 10 years; 14 of these children were under two years of age. The condition was characterized by severe vomiting and profound disturbances in the sensorium, often leading to coma and death. Autopsies revealed cerebral edema and fatty infiltration of the viscera, particularly the liver. The etiology was unknown.

Also in 1963, Johnson, an epidemiologist with the U.S. Public Health Service, independently reported on 16 children (11 were over five years of age) who manifested a severe neurologic illness during a four-month period in association with an outbreak of influenza B.³ The illness in some of these children was strikingly similar to the illness described by Reye.

Epidemiologic studies in the United States, published in the early 1980s, revealed that the vast majority (more than 90 percent) of children who developed Reye's syndrome received aspirin to relieve the symptoms of viral illnesses, particularly influenza and chickenpox.⁴⁻⁶ Between July 1980 and June 1982, the Centers for Disease Control and Prevention, in four *Morbidity and Mortality Weekly Report* articles (including an advisory from the Surgeon General),⁷ expressed increasing concerns about an association between Reye's syndrome and a salicylate. As a result of this association and subsequent confirmatory studies, aspirin fell out of favor as a pediatric antipyretic, and the incidence of Reye's syndrome fell dramatically.

In contrast to the epidemiology of

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Reye's syndrome in the United States (about 80 percent of the cases before 1981 involved children over the age of four and were aspirin-associated), Reye's syndrome in Australia continued to mirror the typical cases originally reported (children under two years of age). Acetaminophen, not aspirin, was the pediatric antipyretic of choice in Australia at the time. The Australian experience of Reye's syndrome occurring presumably independent of aspirin seemed to support initial concerns of some physicians about the validity of an association between Reye's syndrome and aspirin. Responding to these concerns, a USPHS task force was formed to study this relationship.⁸

The results of the USPHS study supported those of the initial studies confirming and validating the strong association between aspirin and Reye's syndrome. The findings reinforced the need to avoid aspirin use in children with viral illnesses, and continued efforts at primary prevention have made Reye's syndrome an exceedingly rare condition in the United States.

Inherited metabolic diseases provide a possible explanation for the broad spectrum of clinical and epidemiologic characteristics observed in patients diagnosed with Reye's syndrome. Since Reye's syndrome and inherited metabolic diseases share similar hepatic pathophysiology, the two conditions may be clinically indistinguishable. A systematic search for inherited metabolic diseases in all patients with Reye's syndrome has only recently been recommended, thus some of these metabolic mimics of Reye's syndrome have only recently emerged.^{9,10}

The possibility exists that many cases of inherited metabolic diseases, particularly in the very young, were misdiagnosed as Reye's syndrome. Retrospective reports support this claim, leading one author to suggest the possibility that the very young

patients described by Reye and the older children described by Johnson may actually have represented groups of patients affected by distinctly different illnesses. Reye's cases may have represented children with inherited metabolic diseases, whereas Johnson's cases may have had Reye's syndrome.¹¹

The case described by Quam in his article, "Recognizing a Case of Reye's Syndrome," typifies the changing pattern of Reye's syndrome in the 1990s. Aspirin has traditionally been associated with the vast majority of cases in the United States, but today an increasing proportion of the small number of cases of Reye's syndrome are not associated with aspirin. Though the etiology of aspirin-independent Reye's syndrome is unknown, it appears that this disorder represents a heterogeneous variety of undiagnosed and yet-to-be identified metabolic diseases, some of which may require only subtle hepatic injury (e.g., from non-aspirin salicylates or other drugs, viral infection or other nonspecific stresses) for symptoms to develop.

The family physician's role in the management of Reye's syndrome covers three areas: primary prevention, recognition and stabilization, and reporting cases to appropriate authorities. When evaluating children with mental status changes, clinicians must consider such conditions in the differential diagnosis as head injury, toxic ingestions, anoxic/hypoxic insults, central nervous system infections and inherited metabolic diseases, initiate a broad-based work-up and begin supportive empiric therapy. While a specific diagnosis may not be initially possible, recognition of the life-threatening characteristics (elevated intracranial pressure, hypoglycemia and coagulopathies) of Reye's syndrome and other hepatopathies can be truly life-saving.

After initial stabilization, most patients

should be referred to a center with pediatric critical care services. With the assistance of a metabolic specialist, patients with suspected Reye's syndrome should undergo thorough investigations to rule out inherited metabolic diseases. All cases of Reye's syndrome should be reported. Most important, physicians who care for children younger than 18 years of age must continually remind parents and teens who self administer medication that aspirin is closely associated with Reye's syndrome. By managing these patients in this way, the metabolic mimics of Reye's syndrome will be better defined and the incidence and mortality of Reye's syndrome will be minimized. Continued primary prevention and unmasking of previously unrecognized metabolic disorders may some day reduce Reye's syndrome to an obsolete diagnosis of only historical interest.

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