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50 Years Ago in *THE JOURNAL OF PEDIATRICS*

Aspirin and Reye Syndrome

Strauss RG, McAdams AJ. Arthritis, aspirin, and coma. J Pediatr 1970;77:156-63.

Strauss and McAdams reported a 22-month-old girl who presented with fever, encephalopathy, hepatomegaly, and metabolic acidosis after the initiation of high-dose aspirin for juvenile arthritis. She ultimately developed intracranial hypertension and died. Her autopsy revealed noninflammatory brain edema and fatty infiltration of the liver. The moderators of this clinical-pathological conference proposed salicylate toxicity as the most likely diagnosis. Reye syndrome was considered and dismissed, given the authors' skepticism that this relatively recently described illness represented a distinct clinical entity.

Despite the authors' doubts, Reye syndrome was diagnosed in children with increasing frequency in the decade following publication of this article. The syndrome was characterized by vomiting, followed by encephalopathy, coagulopathy, and, at its most severe, cerebral edema and liver failure with microvesicular fatty infiltration. These manifestations typically appeared shortly after recovery from a viral illness, especially influenza or varicella. Aspirin, widely used at the time for community-onset childhood illnesses, was suspected as a possible inciter owing to the clinical overlap between Reye syndrome and salicylate toxicity. Indeed, several US-based retrospective case-control studies published in the early 1980s repeatedly demonstrated an association between aspirin use during the antecedent illness and the development of Reye syndrome.

These findings prompted public health officials and the Food and Drug Administration to issue a still-extant warning against the routine use of aspirin in children. Nevertheless, these studies came under intense criticism by some based on their small sample sizes and their suspected design flaws, particularly those surrounding ascertainment and recall bias. A multicenter prospective study initiated in the mid-1980s was designed to address these criticisms, but by then both aspirin use and Reye syndrome had decreased dramatically, and hence this study, although again demonstrating the aspirin–Reye connection, suffered low enrollment.

Critics have further noted that with improved genetic testing, some children with a Reye-like syndrome have a defined inborn error of metabolism, raising doubts, like those expressed by Strauss and McAdams, that the illness was ever a single entity. Notably, Reye himself speculated that the syndrome that bears his name may have encompassed a range of etiologies. Nonetheless, it is difficult to ignore the fact that as aspirin use in children declined precipitously in the 1980s, so did the diagnosis of Reye syndrome, which has virtually disappeared today.

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