HOW COMMON IS REYE'S SYNDROME?

TWENTY years ago, the seminal report by Reye et al. drew attention to "encephalopathy with fatty degeneration of the viscera."[1] This clinical entity, now recognized throughout the world, is a major cause of noninfectious neurologic death after viral illness in children.[2] The clinical syndrome is composed of two phases: an infectious phase followed within a few days by an encephalopathic phase. Influenza B or A and varicella account for most of the infections. The temporal constancy between the two phases is remarkable. Recurrent vomiting begins about five or six days after the onset of the infectious symptoms. The vomiting may persist for hours or days before the patient either spontaneously recovers or lapses into the encephalopathic phase. The mechanism underlying the vomiting remains unexplained. Often, the child who has recovered will recall the early vomiting, suggesting that cerebral function, specifically memory, remains intact or nearly so at this point in the illness. The intensity and severity of the encephalopathic phase are highly variable. When first described by Reye and colleagues, it appeared to be a rare but devastating event with a very high mortality rate. Seventeen of 21 children died; the cause of death was massive swelling of the brain with resulting cerebral herniation.

As the years passed, more metabolic clues were uncovered, linking the hepatic dysfunction and the cerebral disturbance. It became increasingly clear that the syndrome was manifested clinically as an encephalopathy and chemically as a hepatopathy. The levels of serum transaminases were always elevated — a feature now regarded as a cornerstone of the diagnosis. Other laboratory abnormalities included hypoprothrombinemia, hypoglycemia, hyperammonemia, free fatty acidemia, elevated organic acids and amino acids, hyperuricemia, and hypophosphatemia.[3] Hypoxia associated with respiratory failure and hypotension associated with volume depletion and failing cardiac output also contributed to the cerebral insult. The serum amino acid profile was distinctive. Concentrations of alanine, glutamine, glutamate, lysine, and alpha-amino-*N*-butyrate were elevated, and citrulline and argininosuccinic acid levels were not detectable.[4,5] Similarly, the serum organic acid profile was characteristic, with elevated levels of lactic, pyruvic, beta-hydroxybutyric, acetoacetic, butyric, isobutyric, propionic, isovaleric, and caprylic acids.[4,6] Several plasma proteins were affected, including very-low-density lipoproteins, various clotting factors, and components of the complement system. Other enzymes were also elevated in the blood, including creatine kinase, lactic dehydrogenase, amylase, and lipase. These observations suggested the involvement of other organs as well, such as skeletal muscle and pancreas.

The observed blood abnormalities were paralleled by a number of observed tissue changes. Distinctive histopathological features were seen in liver-biopsy

specimens, including panlobular accumulation of lipid droplets, glycogen depletion, empty Golgi membranes, proliferating peroxisomes, and distorted mitochondria.[7] Similar mitochondrial alterations were found in biopsy specimens of brain[8] and skeletal muscle.[9] Parallel biochemical abnormalities observed in similar tissue specimens indicated a universal decrease in the activities of several mitochondrial enzymes, with the sole exception of carnitine palmitoyltransferase. There were decreases in the activities of ornithine transcarbamylase, carbamoyl-phosphate synthetase, the pyruvate dehydrogenase complex, pyruvate carboxylase, succinate dehydrogenase, cytochrome oxidase, glutamate dehydrogenase, isocitrate dehydrogenase, and monoamine oxidase.[10,11] Whether all mitochondrial-enzyme systems are affected in Reye's syndrome is still unknown, because a complete biochemical profile has not been undertaken. However, this possibility seems quite likely in view of the current evidence. In contrast, the cytosolic enzymes that have been measured have been normal. For example, electrophoretic resolution demonstrated that the cytosolic isozyme of malate dehydrogenase was normal, whereas the mitochondrial isozyme was decreased.[11] These biochemical and histopathological observations have led to the speculation that Reye's syndrome represents a metabolic response to a universal mitochondrial insult,[10] since most if not all of the laboratory abnormalities could be explained on the basis of a primary mitochondrial injury.

With the proliferation of articles on the subject, Reye's syndrome has been diagnosed more frequently and earlier in the course of the illness. The apparent mortality of 90 per cent in 1963 has been replaced by an equivalent survival rate in 1983. Two studies have surveyed the incidence of Reye's syndrome during periods when influenza B occurred in epidemic proportions. Corey and colleagues analyzed 379 cases between December 15, 1973, and June 30, 1974,[12] and Morens and colleagues analyzed 454 cases between December 1, 1976, and November 30, 1977.[13] The nationwide case-fatality ratio was 41 per cent in 1974 and 42 per cent in 1977. More recent statistics indicate a downward trend in mortality, which is now approaching 10 per cent at most teaching institutions. The apparent incidence is approximately 0.31 to 0.88 per 100,000 children under 18 years of age.

These incidence figures are influenced by several factors, including the regional distribution of the illness and the definition of the disease. Traditionally, Reye's syndrome has been a rural and suburban entity rather than an urban problem. The urban–rural distribution of the syndrome in Ohio that was reported by Sullivan-Bolyai and co-workers differed in this respect from the figures in previous reports, because Sullivan-Bolyai et al. employed a demographic classification that had been redefined according to the 1970 U.S. Bureau of Census definitions.[14] As a result, in their study, the urban noncentral-city standard metropolitan statistical area had the highest incidence (1.62 cases per year per 100,000 persons between the ages of 0 and 17 years).

In this issue of the *Journal* Lichtenstein and colleagues report an even higher incidence of Reye's syndrome (3.5 cases per 100,000 children <1 to 17 years of age) during a one-year prospective study from December 1, 1980, through November 30, 1981, using only biopsy-confirmed cases.[15] In fact, their own statistics suggest that the annual incidence may be even higher (approaching 6.06 cases per 100,000 children <1 to 17 years of age) if one defines Reye's syndrome according to the entry criteria for their study — namely, prodromal upper-respiratory-tract infection or varicella, acute onset of recurrent vomiting, absence of jaundice, levels of serum aspartate or alanine aminotransferase that are three times higher than normal, and lumbar-puncture findings excluding infection.

Lichtenstein and his co-workers have chosen to term liver-biopsy specimens from five patients meeting these entry criteria as "non-Reye's" specimens, because the histochemical reaction for succinic acid dehydrogenase was equivocal or normal. However, all five specimens demonstrated microvesicular steatosis, and three of the five demonstrated mild ultrastructural changes. These distinctions raise the issues of specificity and sensitivity. Were the liver-biopsy findings sufficiently sensitive to identify all cases of Reye's syndrome? What were these cases if they were not Reye's syndrome? There was no evidence of necrosis, inflammation, or cholestasis, nor were there any differences either clinically or demographically between the Reye's and the non-Reye's patient groups. The ultrastructural abnormalities appeared to be highly specific for Reye's syndrome, particularly in the appropriate clinical setting. Many investigators think that the liver biopsy is most useful in evaluation of atypical cases, recurrent disorders resembling Reye's syndrome, and cases occurring in infants. The entry criteria of Lichtenstein and colleagues may, in fact, be the most sensitive criteria currently available to permit recognition of the disease process.

What Lichtenstein et al. have clearly demonstrated is that Reye's syndrome is more common than previously realized, and that it is the most likely explanation for recurrent vomiting and hypertransaminemia several days after an influenzal illness or varicella. Attention should now focus on the pathogenetic link between the antecedent infectious phase and the "mitochondrial phase," to provide further insight into this fascinating clinical problem.

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