GRADE I REYE'S SYNDROME

A Frequent Cause of Vomiting and Liver Dysfunction after Varicella and Upper-Respiratory-Tract Infection

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Abstract In a one-year prospective study we assessed the incidence of Reye's syndrome in children presenting with the acute onset of vomiting after a prodromal upper-respiratory-tract infection or varicella, and with serum alanine or aspartate aminotransferase levels at least three times higher than normal, and a paucity of neurologic findings. Of 25 patients meeting the above criteria, 19 had liver biopsies yielding adequate tissue for diagnostic purposes. Biopsy specimens from 14 of these 19 patients (74 per cent) were diagnostic of Reye's syndrome, according to rigorous light-microscopical, histochemical, and ultrastructural criteria. None of the biopsy specimens contained evidence of other acute pathologic processes, including hepatitis. A wide spectrum of mitochondrial alterations existed at the ultrastructural level, ranging from mild to severe lesions that were indistinguishable from those seen in comatose patients with Reye's syndrome. Our findings suggest that the clinical complex of vomiting, hepatic dysfunction, and minimal neurologic impairment after varicella or an upper-respiratory-tract infection usually represents Reye's syndrome. This syndrome occurs more frequently than previously recognized. (N Engl J Med 1983; 309:133-9.)

SINCE the initial description of it in 1963,[1] Reye's syndrome has been perceived as an illness generally associated with neurologic deterioration and death. This perception was reinforced during the influenza B epidemic of 1973-1974, when the Centers for Disease Control[2] reported a national mortality rate of 41 per cent among 379 patients, 75 per cent of whom presented with clinical Grade II or more severe illness (i.e., with evidence of central-nervous-system involvement). Similar mortality rates were reported in association with influenza A epidemics[3] and in association with influenza A and B during years when there were no epidemics of these viruses.[4] In 1978 Partin and coworkers[5] expanded the spectrum of clinical presentation and outcome in Reye's syndrome when they described liver-biopsy findings in 14 patients with Grade I Reye's syndrome (i.e., vomiting and elevated levels of aminotransferase but no neurologic findings). In 12 of these patients the disease did not progress to more advanced grades. Partin et al. suggested that mild, nonprogressing cases of Reye's syndrome are diagnosable both clinically and histologically; it was further suggested that such patients may, in fact, account for the majority of cases of Reye's syndrome.

We designed a study to examine prospectively the hypothesis that vomiting and elevated levels of serum aspartate or alanine aminotransferase, when preceded by either a viral upper-respiratory-tract infection or varicella, are manifestations of mild Reye's syndrome. The aims of the study were, first of all, to establish the frequency of Reye's syndrome among children who present with vomiting, a threefold or greater elevation of serum aminotransferase, and a paucity of neurologic signs after a viral upper-respiratory infection or varicella; secondly, to characterize the hepatic morphology in Grade I Reye's syndrome; and thirdly, to estimate a minimum annual incidence of the syndrome in children under the age of 17 years.

METHODS

Clinical Aspects

The one-year study period lasted from December 1, 1980, through November 30, 1981. The major influenza activity during this year was from influenza A (H3N2/H1N1). The annual reported incidence of varicella in Cincinnati closely approximated the mean annual incidence for the preceding four years.[6] All patients who presented in the Children's Hospital emergency room and who met the following criteria (based on the inclusion criteria of the Centers for Disease Control)[7] were candidates for entry: prodromal upper-respiratory-tract infection (as defined by fever, cough, rhinorrhea, and coryza) or varicella, acute onset of recurrent vomiting, absence of jaundice, levels of serum aspartate or alanine aminotransferase that were three times higher than normal, and lumbar-puncture studies that excluded cerebrospinal-fluid infection. It should be noted that patient identification was aided in the metropolitan Cincin-

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nati area by a high-visibility, multimedia community-awareness program that has been operative since the mid-1970s. This program has resulted in numerous emergency-room visits initiated by both physicians and parents, for the specific purpose of ruling out Reye's syndrome.

Cases were clinically graded at the time of presentation, using the five-stage Cincinnati grading system.[8] According to this system, patients with Grade I illness are quiet and sleepy but respond to verbal commands. Patients with Grade II illness are stuporous and have thick speech and difficulty counting. Grades III through V are characterized by progressively deepening coma.

All patients were treated in a standardized manner with intravenous infusions of 10 per cent dextrose and electrolytes at a rate of 1500 to 1800 ml per square meter of body-surface area per day. More severely affected patients were treated with continuous intracranial-pressure monitoring, elective endotracheal intubation with controlled ventilation, intravenous mannitol, and pentobarbital.

The following studies were performed at admission on all patients meeting the entry criteria. Blood was analyzed for levels of electrolytes, glucose, blood urea nitrogen, creatinine, bilirubin, serum aspartate, and alanine aminotransferase, alkaline phosphatase, ammonia, uric acid, creatine kinase, salicylate, and toxic substances. Prothrombin time, partial thromboplastin time, and complete and differential blood counts were measured, and blood cultures and serologic studies were performed to detect the presence of hepatitis A, hepatitis B, cytomegalovirus, and Epstein–Barr virus. Urine specimens were obtained for urinalysis and bacterial culture. Tests of cerebrospinal fluid included a cell count, Gram's stain, bacterial and viral cultures, and measurement of glucose and protein. Stool and nasopharyngeal-secretion specimens were tested for viral culture. All laboratory measurements and cultures were performed with standard techniques in the Children's Hospital laboratories.

A percutaneous liver biopsy was performed with a Menghini needle as soon as possible after case identification in the emergency room. Tissue was collected at the bedside, and processing was initiated immediately. Portions were fixed in formalin and embedded in paraffin for routine light microscopy. Additional tissue was fixed in 3 per cent glutaraldehyde and embedded in epoxy resin for electron microscopy and was snap-frozen in liquid nitrogen. Cryostat sections of the frozen piece were used for lipid stains (Sudan black, Oil Red O) and enzyme histochemical assay of succinic acid dehydrogenase (a mitochondrial enzyme) and reduced nicotinamide adenine dinucleotide dehydrogenase (a multicompartmental enzyme). These techniques have been described previously.[9-13]

Morphologic Criteria

The histologic and histochemical criteria that we used for making the diagnosis of Reye's syndrome by light microscopy have previously been established. These included panlobular accumulation of small lipid droplets and depletion of succinic acid dehydrogenase in the absence of other abnormalities, such as zonal or cellular necrosis, cholestasis, and inflammation of the lobule or portal tract.

The ultrastructural criteria for the diagnosis of Reye's syndrome[9,14-16] included the following mitochondrial features: presence of an electron-lucent flocculent matrix, diminished matrix granules, variable severity of mitochondrial expansion, and irregularity of the mitochondrial membrane. Other alterations that accompanied those seen in the mitochondria were also evaluated, including peroxisomal proliferation and swelling, proliferation of smooth endoplasmic reticulum, and glycogen depletion. These features did not increase the diagnostic specificity achieved with mitochondrial assessment alone. Using these criteria, we assessed the severity of damage at the ultrastructural level (Fig. 1).

Mild involvement (Fig. 1B) was characterized by localized areas of mitochondrial alterations partially satisfying the four criteria described above; some areas in the specimen appeared normal. These changes are not diagnostic of Reye's syndrome and can be considered supportive of that diagnosis only in the presence of the described clinical setting and a positive diagnosis by light microscopy. Moderate involvement (Fig. 1C) was defined as alterations in all mitochondria, with at least some areas in which all four criteria were satisfied. Severe involvement (Fig. 1D) was present when all areas of the specimen met all four criteria.

Ultrastructural involvement was graded by two morphologists skilled in electron microscopy, who worked independently and without knowledge of the specific clinical histories and the light-microscopical findings. When possible, the areas examined were panlobular.

Patients were diagnosed as having Reye's syndrome when the histologic and histochemical criteria were met and at least mild mitochondrial involvement was present.

Statistical Methods

The relation between laboratory measurements on admission and ultrastructural grade was assessed with Student's two-tailed t-test.

Informed Consent

This project was carried out according to the principles of the Declaration of Helsinki and was approved by the Institutional Review Board on Investigations Involving Human Beings. Informed written consent was obtained from the patients' parents before the patients were studied.

Results

Study Population

During the study period, 31 patients met all five entry criteria (Fig. 2), and 25 of them presented with what clinically appeared to be Grade I disease. Six patients presented with more advanced disease (five with Grade II and one with Grade III). In one case the disease rapidly progressed from Grade III on admission, and the patient subsequently died.

Liver biopsies were performed in 19 of the 25 patients with clinical and laboratory findings compatible with Grade I disease. The study group consisted of these 19 patients. Six of the 25 patients were not enrolled in the study. Biopsies were attempted in three of these six patients. In two the procedure was unsuccessful. In the third patient adequate tissue was obtained only for light microscopy; all the diagnostic criteria for Reye's syndrome were met at this level. The parents of two patients refused to allow a biopsy. The procedure was not performed in the sixth patient because of persistently abnormal results of clotting studies.

The 19 study patients with Grade I disease did not differ in any important way from previously studied groups of patients with Reye's syndrome.[17-21] Their average age was 6½ years (range, 6 months to 13½ years). There were 10 boys and 9 girls. Eighteen were white, and one was black. Seven came from urban areas, and 12 lived in suburban sectors of the metropolitan Cincinnati area. Eleven patients had upper-respiratory-tract infections as their prodromal illness; the other eight had varicella. The patients were sick for an average of 6.3 days before the onset of vomiting (range, 3 to 16 days); the period tended to be longer for patients with upper-respiratory-tract prodromal illnesses (6.9 days vs. 5.3 days for patients with varicella). On the average, patients vomited for 1.2 days (12 to 66 hours) before being admitted to the hospital; there was no difference between patients with upper-respiratory-tract infection and those with varicella with respect to this index. There were no differences, either clinically or demographically, between the patients whose biopsy specimens were diagnostic of

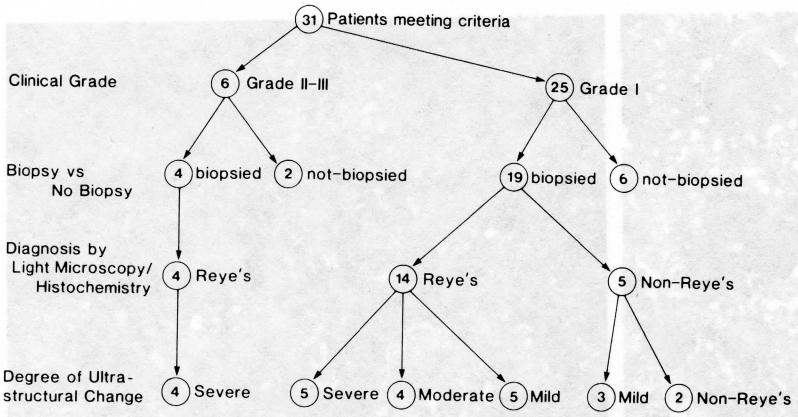

Figure 2. Findings on Light and Electron Microscopy in Biopsy Specimens from Patients Clinically Diagnosed as Having Reye's Syndrome.

Reye's syndrome and those whose specimens did not meet the diagnostic criteria.

All patients had taken medication (average, 2.5 medications per patient) before being seen in the emergency room. Salicylates were taken most frequently (by 15 patients), followed by decongestants (7), antiemetics (6), acetaminophen (6), antibiotics (5), and diphenhydramine (3).

Light Microscopy/Histochemistry

When examined by light microscopy for morphology and histochemistry, 14 of the 19 biopsy specimens were diagnostic of Reye's syndrome (Fig. 2). The five that did not meet the criteria had various degrees of microvesicular fat-droplet deposition within the hepatocytes but failed to qualify on the basis of either equivocal or normal succinic acid dehydrogenase staining. None of the five specimens had findings that were consistent with any other known acute liver disease. More specifically, none of the 19 specimens, including the five non-Reye's specimens, had any findings suggestive of either viral or toxic hepatitis (e.g., focal hepatocellular necrosis, acute or chronic inflammatory-cell infiltrate, canalicular or hepatocellular cholestasis, or viral inclusions). A biopsy specimen from 1 of the 14 patients with Reye's syndrome had features suggestive of alpha$_1$-antitrypsin deficiency; this patient was subsequently found to have an SZ phenotype. One of the patients with a specimen that was not diagnostic of Reye's syndrome was found incidentally to have congenital hepatic fibrosis.

Ultrastructure

The ultrastructural pathology was evaluated independently by two skilled morphologists (C. C. Daugherty and J. S. Partin). Their evaluations showed a 90 per cent concordance rate (17 of 19 cases).

All 14 patients meeting the clinical and light-microscopical criteria for Reye's syndrome had some mitochondrial damage. Considerable ultrastructural diversity existed among these patients (Fig. 2). Five had severe mitochondrial changes that were indistinguishable from the damage seen in previously studied patients who had presented with clinical Grade II or III disease (Fig. 1D). Four patients had moderate mitochondrial abnormalities (Fig. 1C), and the other five had mild ultrastructural changes (Fig. 1B).

Of the five patients who did not meet the histologic and histochemical criteria for Reye's syndrome, three had mild mitochondrial changes by electron microscopy that were indistinguishable from the mild ultrastructural changes observed in five of the patients with positive histologic and histochemical findings. The other two patients with nondiagnostic specimens had mitochondria that appeared to be normal. In this context, it is important to note that changes other than those associated with the spectrum of lesions in Reye's syndrome were not observed in this group, thus strongly supporting the concept of Reye's syndrome as a distinct entity with a unique clinical and pathological presentation.

Laboratory Features

An attempt was made to correlate the degree of ultrastructural abnormality with various clinical characteristics and biochemical measurements (Table 1). No correlation was observed between the severity of the ultrastructural lesion and the duration of illness and vomiting before admission to the hospital or the levels on admission of serum aspartate aminotransferase, serum salicylate, ammonia, uric acid, or creatine kinase. The level of serum alanine aminotransferase on admission was higher ($P<0.05$) in the patients with moderate ultrastructural changes than in those with severe changes but did not differ from the level in patients with mild changes.

Incidence

Using only biopsy-proved cases (4 patients with Grade II or higher diseases and 14 with Grade I disease), we attempted to estimate the minimal incidence of Reye's syndrome in metropolitan Cincinnati during the one-year study period. On the basis of an estimated population for the area of 511,550 children under the age of 17 years, the incidence was calculated to be 3.5 cases per 100,000 children per year. Population estimates were derived from the U.S. Census Bureau's 1980 data for the 11 counties that make up the Children's Hospital primary catchment area.

Discussion

During a prospective study of Grade I Reye's syndrome performed between December 1, 1980, and November 30, 1981, at the Children's Hospital Medical Center in Cincinnati, 74 per cent (14 of 19) of the patients meeting accepted clinical and laboratory cri-

Table 1. Correlations between Severity of Hepatic Ultrastructural Involvement and Various Clinical and Chemical Indexes in Patients with Grade I Reye's Syndrome.*

Hepatic Ultrastructural Involvement (no. of patients)	Prodromal URI: Varicella	Duration of Illness	Duration of Vomiting	SGOT †	SGPT ‡	Ammonia	Serum Salicylate	Uric Acid
	no. of patients	*days*	*hr*	*IU*		*μg/dl*	*mg/dl*	*mg/dl*
Mild (5)	2:3	8	39	744±214	726±151	23.5±5.4	2.2±0.7	7.4±1.1
		(5–11)	(12–48)	(266–1466)	(236–1174)	(11.2–42)	(0–4.4)	(5.2–10.5)
Moderate (4)	4:0	8.8	36	1156±317	1242±366 §	36.5±13.7	2.2±0.1	8.7±0.4
		(5–12)	(30–48)	(364–1912)	(308–1692)	(13.2–74)	(1.9–2.5)	(7.5–8.9)
Severe (5)	3:2	6	30	666±134	526±89	39.2±8.6	6.8±2.1	6.4±1.5
		(4–7)	(17–48)	(338–976)	(330–824)	(19.6–61.6)	(1.9–14.0)	(2.6–10.7)

*Plus–minus values are ±S.E.M. Figures in parentheses are ranges. URI denotes upper-respiratory-tract infection. To convert values for ammonia to micromoles per liter, multiply by 0.5872. To convert values for salicylate to millimoles per liter, multiply by 0.07240.

†SGOT denotes serum aspartate aminotransferase. ‡SGPT denotes serum alanine aminotransferase. §$P<0.05$, as compared with severe involvement.

teria for Reye's syndrome were found on liver biopsy to have histologic, histochemical, and ultrastructural changes characteristic of the syndrome. None of the patients from whom biopsy specimens were obtained, including the five who met some but not all histopathologic criteria, had light-microscopical or ultrastructural changes that were suggestive of hepatitis, drug-induced hepatic injury, or any other recognizable acute liver disease. The changes found in three of the five nondiagnostic biopsy specimens suggested Reye's syndrome more strongly than any other diagnosis.

These findings confirm the hypothesis that children who present with vomiting, a threefold or higher elevation in the level of serum alanine or aspartate aminotransferase, and a paucity of neurologic signs while recovering from varicella or a viral upper-respiratory-tract infection have Reye's syndrome. When recognized clinical and biochemical criteria are used to identify cases of Reye's syndrome, the liver-biopsy findings, evaluated according to the strictest histologic, histochemical, and ultrastructural criteria, are confirmatory. This observation suggests that the clinical and biochemical criteria used in our study are adequately selective (and sufficiently sensitive) for identifying patients with mild Reye's syndrome. In addition, our study refutes recently published reports suggesting that vomiting and elevated levels of aminotransferase occurring in children while they are infected with varicella represent varicella hepatitis.[22-24] Biopsy specimens were not obtained from any of the patients described in these other reports, and all the cases fulfilled all the clinical and biochemical criteria for Reye's syndrome. The distinction between these two diseases is an important one. Varicella hepatitis is usually observed in the context of generalized viral dissemination, which results in multisystem involvement and eventual death.[25-27] Affected patients are usually immunocompromised, with hepatitis evolving in conjunction with congenital infection,[28] generalized debilitation, or chemotherapy for cancer.[24] In contrast, Reye's syndrome follows varicella in an otherwise normal host.

Considerable heterogeneity in the hepatic mitochondrial damage was observed in our 14 patients with Grade I illness. These findings confirm the electron-microscopical observations made earlier by Partin et al. in a group of 14 patients with Grade I Reye's syndrome.[5]

Although none of our biopsy-proved cases progressed clinically to more advanced disease, the potential for such progression in patients with Grade I illness is well recognized. Partin et al.[5] observed such a progression in 2 of 14 patients (14 per cent). Between 1973 and 1981, the frequency of disease progression among children with Grade I Reye's syndrome reported to the Centers for Disease Control was 34 per cent (Rowley D: personal communication).

The reasons for the differences in observed rates of progression in mildly affected patients among the two Cincinnati-based study groups and those reported to the Centers for Disease Control are unknown. Several explanations are possible. First of all, reports to the Centers during the eight-year surveillance period were made by physicians located throughout the country at a time when the criteria for diagnosing Reye's syndrome clinically were not standardized. Since in most of the reported cases biopsies were not performed, it is possible that some of the patients did not have Reye's syndrome. In addition, there may have been a propensity to report cases with a more dramatic course or a more unfavorable outcome and, concomitantly, a tendency to underreport nonprogressing cases because of the prevalent concept at that time that Reye's syndrome was an invariably progressive disease.

Secondly, differences in the rate of progression among the three study populations may have reflected differences in the host–virus interactions. Many of the cases reported to the Centers for Disease Control occurred in conjunction with influenza B (during the 1973-1974 epidemic), whereas most of the cases in the study by Partin et al. and all the cases in our study occurred during years when influenza B was not prevalent in the community.

Thirdly, it is possible that some as yet unidentified environmental factor exists in southwestern Ohio and results in less severe disease. Finally, the more benign course observed in our patients may relate to differ-

ences in the time of recognition and subsequent initiation of fluid therapy. Increased public awareness of Reye's syndrome in southwestern Ohio has resulted in early case identification, with patients frequently being seen within 24 hours after the onset of vomiting. All patients were routinely given intravenous infusions of hypertonic glucose and electrolyte solutions, with the intention of correcting mild alterations in hydration and of repleting hepatic glycogen stores (which are usually reduced in Reye's syndrome). Restoration of fluid and metabolic homeostasis may account for the low rate of progression and the absence of mortality observed in Grade I Reye's syndrome. Studies in which patients are randomly assigned to various regimens, including fluids versus no fluids or fluids that contain glucose versus those that do not, will be necessary to test this hypothesis adequately. However, these studies may be difficult to justify on ethical grounds.

Because of the recognized potential for Grade I cases to progress to more advanced stages, we hypothesized that patients with more severe ultrastructural changes were at greater risk of progression to a higher grade of disease and that various commonly measured biochemical markers might have predictive value. However, we were unable to establish a correlation between ultrastructural grade and any initial or peak biochemical marker.

Our study suggests that the incidence of Reye's syndrome, estimated using only biopsy-proved cases, was at least 3.5 cases per 100,000 children under the age of 17 years in metropolitan Cincinnati during the one-year study period (2.7 cases of Grade I illness per 100,000 children, and 0.8 cases of Grade II or higher illness per 100,000 children). This figure represents an 11-fold higher incidence than that calculated by the Centers for Disease Control for the same period (0.31 cases per 100,000 children [17 years or less]).[29] The incidence in the present study probably represents the minimal incidence of Reye's syndrome for the Cincinnati area. It is certain that some of the patients not included in our study population had Reye's syndrome; in fact, all of them (13 of the original 31 patients) met the criteria of the Centers for Disease Control and were included in their surveillance statistics. If all these patients (except for the two shown by biopsy not to have Reye's syndrome) are included in the calculation, the incidence rises to 5.6 cases per 100,000 children under 17 years of age. In addition, the number of children with mild disease who were living within the referral area and never required hospital evaluation (presumably because of the combination of mild disease and adequate oral fluid intake) is unknown.

Finally, several patients were excluded from the present study because their serum alanine or aspartate aminotransferase levels were elevated but were less than three times the normal value. Recent surveillance studies in other areas of the country have suggested that considerable numbers of children have transitory transaminase elevation (higher than twice the normal value) in conjunction with otherwise uncomplicated influenza A and varicella.[30-32] It has been suggested that these patients may have had "anicteric hepatic dysfunction accompanying viral illness"[17,32,33] or "subclinical hepatic changes accompanying varicella infection."[32] Our data suggest that these patients may, in fact, have had Reye's syndrome. Additional studies are needed to determine the pathological alterations under these circumstances, and they may help to define further the complete clinical spectrum of Reye's syndrome.

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