JAMA
THE JOURNAL of the American Medical Association
Sept 28, 1979 Vol 242, No. 13

Original Contributions

Reye's Syndrome in Nonpediatric Age Groups

Rajiv R. Varma, MD; David R. Riedel, MD; Richard A. Komorowski, MD; Gregory J. Harrington, MD; Thomas V. Nowak, MD

• Reye's syndrome (encephalopathy and fatty liver) is generally considered a disease of children. Four patients, aged 16, 18, 19, and 23 years, with Reye's syndrome were initially seen by internists. A viral prodrome followed by vomiting and encephalopathy without focal neurological signs or jaundice clinically suggested Reye's syndrome. Normal findings of CSF examination (except for increased opening pressure), abnormal findings of liver function tests, and increased blood ammonia further supported the diagnosis. None was hypoglycemic. Reye's syndrome was related to influenza B virus in three patients and to *Varicella* in another. Three patients survived. Reye's syndrome may be seen initially by general practitioners, emergency room physicians, internists, or psychiatrists. The importance of considering this syndrome in the differential diagnosis of unexplained encephalopathy in adults is stressed.

(*JAMA* 242:1373-1375, 1979)

REYE'S syndrome (encephalopathy and fatty liver) is widely considered to be a disease of the pediatric ages.[1-3] It is characterized by a prodrome of viral illness followed by vomiting and encephalopathy with associated hepatic dysfunction. Although the average reported age in recent years has been higher, Reye's syndrome largely remains an entity seen by pediatricians.[4-6] Occurrence of Reye's syndrome in nonpediatric ages may present diagnostic and management problems to physicians not familiar with the practice of pediatrics.

From the Departments of Medicine (Drs Varma, Riedel, and Nowak), Pathology (Dr Komorowski), and Neurology (Dr Harrington), Milwaukee County General Hospital, Medical College of Wisconsin, Milwaukee.

Reprint requests to Milwaukee County General Hospital, PO Box 105, Milwaukee, WI 53226 (Dr Varma).

REPORT OF CASES

CASE 1.—A 16-year-old boy had congenital absence of the left kidney and a history of ureteropelvic junction obstruction on the right. Surgery had been unsuccessful in halting the progression to chronic renal failure and renal rickets. His renal function was conservatively managed, and his serum creatinine level was relatively stable. The patient was in his usual state of health until six days before admission, when diarrhea and a flu-like illness began. Nausea and vomiting developed shortly thereafter.

At another hospital he was found to be restless, with wandering eyes and noisy respirations. Within two hours he became unresponsive. Laboratory examination disclosed the following values: sodium, 143 mEq/L; potassium, 5.5 mEq/L; carbon dioxide, 8 mEq/L; BUN, 124 mg/dL; creatinine, 8.4 mg/dL; ammonia, 164 μ/L (normal, 10 to 48 μ/L); and SGOT, 81 IU/L. The patient was transferred to Milwaukee County General Hospital. One grand mal seizure occurred en route. His blood pressure (BP) was 160/82 mm Hg; pulse rate, 120 beats per minute; and respirations, 32/min. The optic discs were sharp. Stridor with intercostal retractions was seen. The liver edge was palpated 1 cm below the right costal margin. Rickets deformity of the legs was present. The patient was flaccid and unresponsive to painful stimuli; pupillary reflexes, Doll's eye motions, ciliospinal reflexes, and gag reflex were intact. Kernig's and Brudzinski's signs were normal. Deep-tendon reflexes were 1+ and equal in the upper extremities and 3+ at the knee and ankle. Plantar responses were extensor.

Laboratory examination (Table) was pertinent for elevated SGOT levels, with normal bilirubin levels, prolonged prothrombin time, elevated ammonia levels, and acidosis. Because of chronic azotemia associated with Reye's syndrome, a percutaneous liver biopsy was not performed. The patient was treated with four exchange transfusions during 60 hours by the methods described by us previously.[7] His mental status, blood ammonia, pH, and renal status reverted to premorbid levels. He was discharged on the ninth hospital day. Viral studies were performed by methods described in our previous publication.[8] Acute and convalescent paired sera showed a fourfold increase in titers to influenza B.

CASE 2.—A 19-year-old woman noted a sore throat seven days before admission. Two days later a typical varicelliform rash appeared on her face and trunk. Thirty-six hours before admission, she experienced nausea and vomiting. She was examined in the emergency room of another hospital and was treated with trimethobenzamide

hydrochloride suppositories, antacids, and anticholinergics. Deteriorating mental status prompted her return to the emergency room later that evening. She was irritable, combative, with alternating episodes of agitation and somnolence. She was admitted.

Several family members had symptoms suggestive of upper respiratory tract infection but without mental changes. Findings of a lumbar puncture were normal except for an opening pressure of 30 cm of water, which was attributed to the patient's agitated behavior. The blood ammonia level was 261 μ/L (normal, 50 to 70 μ/L), and the SGOT value was 271 IU/L. The next morning the patient was transferred to Milwaukee County General Hospital.

The pulse rate was 120 beats per minute; axillary temperature, 37 °C; respirations, 24/min; and BP, 110/60 mm Hg. There was no icterus. A dark-red, crusting, papular rash was visible over her trunk and face. The patient was intermittently combative and somnolent. The extremities moved equally, and no decerebrate or decorticate activity was noted. The neck was supple. The pupils were dilated but reacted briskly to light. The corneal and oculocephalic reflexes were intact. The optic margins were sharp. The plantar response was extensor bilaterally. The deep-tendon reflexes were symmetrical and hyperactive. Palmomental and snout reflexes were present. The liver was palpable 3 cm below the right costal margin. Except for a mild respiratory alkalosis, the electrolyte levels were normal. The glucose value was 129 mg/dL (Table); BUN, 13 mg/dL; creatinine, 1.1 mg/dL; hematocrit, 42.9%; and WBCs, 12,200/cu mm. The prothrombin time was 15.0 s (control, 12.0 s). The total bilirubin value was 0.7 mg/dL, and the SGOT value was 270 IU/L.

The patient was treated with mannitol and furosemide for incipient cerebral edema. Three and a half hours after admission, spontaneous movements ceased, and decerebrate posturing occurred in response to pain. An EEG showed continuous high-voltage synchronous delta activity. At periodic intervals suppression of activity was also noted in a generalized fashion. These findings were consistent with a metabolic encephalopathy and compatible with Reye's syndrome.

Since the patient's condition was clinically deteriorating, an exchange transfusion with fresh-frozen plasma and saline-washed RBCs' was performed. The patient remained somnolent, but decerebrate posturing was no longer noted, and the deep-tendon reflexes were less hyperactive. A second exchange transfusion was performed on the second hospital day. A percutaneous liver biopsy was performed without complications. Specimens were submitted for light and electron microscopy (Fig 1 and 2), viral culture, and enzyme assays. Early on the third hospital day, she dramatically became oriented and alert. The deep-tendon reflexes became normoactive, and the plantar responses became flexor. On the seventh hospital day, she was discharged.

The liver biopsy specimen was grossly yellow. Light microscopy (Fig 1 and 2) of the liver biopsy specimen disclosed panlobular fatty infiltration consistent with findings of Reye's syndrome. By electron microscopy the hepatocyte cytoplasm contained various-sized lipid vacuoles. Large numbers of residual bodies and microbodies were noted. The mitochondria demonstrated degenerative changes characterized by loss of cristae. No viral particles were found. Carbamoyl phosphate synthetase, ornithine transcarbamoylase, and arginase levels in liver tissue were measured and were 0.6 mg (normal, 1.3± 0.3 [SD]), 19.5 μmole/mg protein (normal, 37.2±8.7 μmole/mg protein), and 253.0 μmole/mg protein (177.0±63.0 μmole/mg protein), respectively. Acute and convalescent sera disclosed a fourfold increase in titers to *Varicella*.

CASE 3.—A 23-year-old obese man was brought to the emergency room by his family. He had been well until a week before admission, when, like other members of the family, an upper respiratory tract infection developed. He treated himself with aspirin twice per day. Thirty-six

Clinical Features in Patients With Reye's Syndrome

Patient	Viral Studies	SGOT, IU/L	Highest Level		
			Serum Bilirubin, mg/dL	Prothrombin Time, s*	Ammonia, μ/L (Normal)
1	Influenza B†	169	1.0	17/12	164 (10-48)
2	*Varicella*†	271	0.7	15/12	261 (50-70)
3	Influenza B†	310	1.0	15/13	170 (30-70)
4	Influenza B‡	528	1.6	Not done	182 (10-40)

*Patient/control.
†Fourfold increase in antibody titers of paired sera.
‡Suspected or epidemiologic evidence.

Fig 1.—Hepatocytes have fine cytoplasmic vacuoles. No hepatocellular necrosis or inflammation (hematoxylin-eosin, ×400).

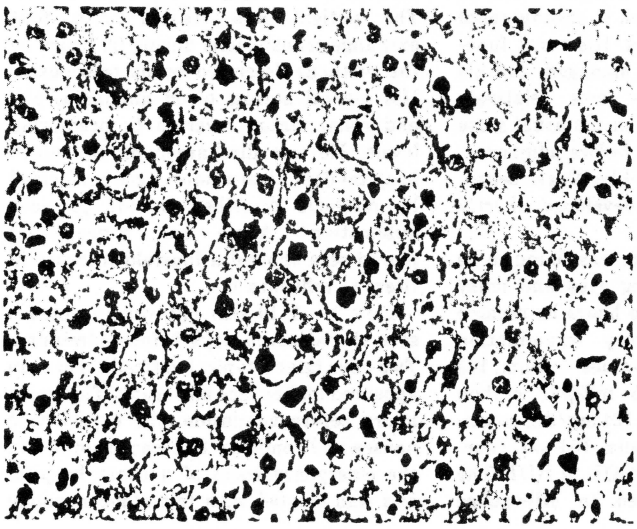
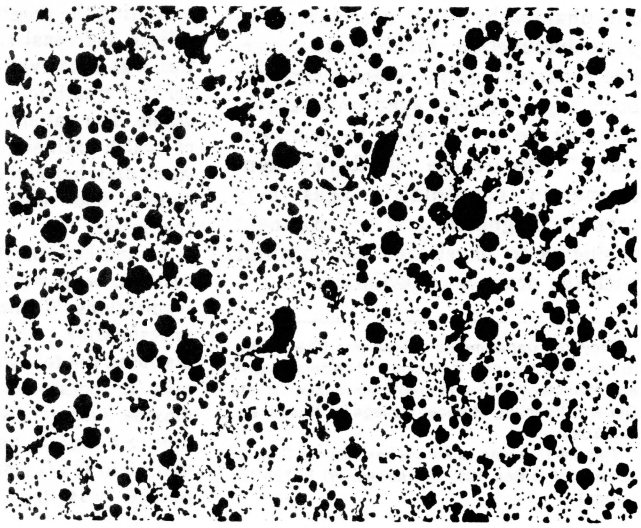


Fig 2.—Hepatocytes contain numerous variable-sized lipid vacuoles (oil red O stain on frozen section, ×400).



hour before admission, he started vomiting, which persisted until the day before admission. Subsequently he became more lethargic. Six hours before admission, his family noticed bizarre behavior and unprovoked violent outbursts. Physical examination disclosed a restless, intermittently screaming man disoriented to place and time. His BP was 120/80 mm Hg, and his pulse rate was 108 beats per minute. There was neither icterus nor peripheral cutaneous stigmas of chronic liver disease. An enlarged, firm, smooth, nontender liver 4 cm below the right costal margin was noted. Papilledema was absent.

Neurological examination showed increased muscle tone in all extremities, with hyperactive but symmetrical deep-tendon reflexes. Plantar reflexes were extensor. There were no focal neurological signs. Lumbar puncture showed an opening pressure of 21 cm of water, and the CSF was unremarkable. All bacterial cultures (including CSF) were negative. The admitting SGOT value was 310 IU/L, the SGPT value was 325 IU/L, the bilirubin value was 1.0 mg/dL, and the prothrombin time was 15/13 s. The blood ammonia level was 170 μ/L (normal, less than 70 μ/L). Blood glucose level varied between 100 and 140 mg/dL. Findings of a complete blood cell count were normal except for an occasional atypical lymphocyte. The hepatitis B surface antigen and the Monospot test were negative. The patient received intravenous fluid therapy and was observed. During the ensuing two days, his condition improved. By the fifth day, his liver had clinically returned to normal size, and he was discharged. He refused a liver biopsy. Acute and convalescent sera showed a fourfold increase in the influenza B titers.

CASE 4.—An 18-year-old woman was seen and treated at another institution. She had viral prodromes that were followed by anorexia, nausea, vomiting, and then encephalopathy without localizing signs or jaundice. She died of the complications of cerebral edema with diabetes insipidus and brain-stem herniation. Her clinical picture was difficult to evaluate because of the possible nonparenteral drug abuse. Her clinical, biochemical, EEG, and histological findings at autopsy, including that of electron microscopy, were, however, consistent with the diagnosis of Reye's syndrome. It seems likely that cases such as this exist but are often not reported.

COMMENT

Although Reye's syndrome is a disease of children, our patients were initially seen and treated by internists. This suggests that the nonpediatric physician must be aware of the features of this syndrome. Correct diagnosis is important, because treatment may differ from that of other CNS disorders.

These patients had a history of recent viral illness followed by nausea, vomiting, and then encephalopathy. Physical findings were limited to encephalopathy without localizing signs and variably present hepatomegaly in the absence of jaundice. As in our patients, the CSF is characteristically normal, with the exception of mildly elevated opening pressure, making encephalitis or meningitis unlikely. Increases in aminotransferase and ammonia levels and prolongation of prothrombin time are consistent with findings of Reye's syndrome. Elevation of the ammonia level is associated with deficiency of mitochondrial enzymes of the Krebs urea cycle, especially ornithine transcarbamoylase[8-10] as seen in our second patient.

Though most of the disorders associated with an elevated ammonia level in adults are also associated with clinical jaundice, this does not occur in Reye's syndrome. Hypoglycemia, though emphasized by Reye, is generally limited to younger children and was absent in our patients. The clinical impression of viral infection associated with Reye's syndrome was confirmed by serological studies in three cases and was suspected in another. A percutaneous liver biopsy performed in two of our patients showed a distinctive pathological picture on light and electron microscopy. Although the findings of liver biopsy are characteristic, this procedure is not mandatory for arriving at the diagnosis in patients with typical features.

Reye's syndrome in recent years has become one of the most common causes of encephalopathy in children. Our own data[4] and those of the Center for Disease Control derived from the 1973 to 1974 and the 1977 to 1978 epidemics indicate the apparent changing age pattern. In these epidemics the peak incidence occurred between the ages of 11 to 14 years. In the 1973 to 1974 epidemic associated with influenza B infection, 4% of the cases occurred in persons older than 16 years.[5] These findings and our own experience suggest that Reye's syndrome can and does present to physicians not exclusively involved with pediatric ages and includes family practitioner, emergency room physician, internist, and psychiatrist.

The presentation of an encephalopathic patient (ranging from bizarre or combative behavior to coma) of any age should alert the physician to the possibility of Reye's syndrome. Careful history taking should include specific questions about recent viral illness and vomiting (often persistent) predating the mental status changes.

The importance of arriving at the diagnosis of Reye's syndrome is threefold: it should prevent incorrect pharmacologic approaches, it should place the patient in the intensive care unit in the hands of a team experienced in the management of the syndrome, and it should allow for consideration of recently proposed modes of therapy.

Hepatic arginase and mitochondrial enzyme assays were performed by Ruth Heimler, MD. Michael B. Weinstein, MD, and Joseph L. Teresi, MD, brought specific cases to our attention.

References

1. Reye DRK, Morgan G, Baral J: Encephalopathy and fatty degeneration of viscera: A disease entity in childhood. *Lancet* 2:749-752, 1963.

2. Kapila CC, Kaul S, Kapur SC, et al: Neurologic and hepatic disorders associated with influenza. *Br Med J* 2:1311-1314, 1958.

3. Schubert WK, Partin JC, Partin JS: Encephalopathy and fatty liver (Reye's syndrome). *Prog Liver Dis* 4:489-510, 1972.

4. Varma RR, Casper JT, Lewis JD, et al: Changing patterns of Reye's syndrome, in Pollack JD (ed): *Reye's Syndrome.* New York, Grune & Stratton Inc, 1975, pp 416-417.

5. Corey L, Rubin RJ, Hattwick MAW, et al: A nationwide outbreak of Reye's syndrome: Its epidemiological relationship to influenza B. *Am J Med* 61:615-625, 1976.

6. Morse RS, Holmes AW, Levin S: Reye's syndrome in an adult. *Am J Dig Dis* 20:1184-1190, 1975.

7. Casper JT, Varma RR, Lewis JD, et al: Exchange transfusion in Reye's syndrome with saline washed red blood cells. *Transfusion* 16:130-134, 1976.

8. Tang TT, Siegesmund KA, Sedmak GV, et al: Reye syndrome: A correlated electron-microscopic, viral, and biochemical observation. *JAMA* 232:1339-1346, 1975.

9. Snodgrass PJ, DeLong GR: Urea-cycle enzyme deficiencies and an increased nitrogen load producing hyperammonemia in Reye's syndrome. *N Engl J Med* 294:855-860, 1976.

10. Brown TA, Hug G, Lansky L, et al: Transiently reduced activity of carbamyl phosphate synthetase and ornithine transcarbamoylase in liver of children with Reye's syndrome. *N Engl J Med* 294:861-867, 1976.