Consequences Of Reye Syndrome

Although most patients who survive the acute illness of Reye Syndrome (RS) may expect complete recovery, children—especially those who are very young at the time of disease onset or who have very severe RS—may develop transient neurological dysfunctions or minor intellectual deficiencies, according to researchers at the Yale University School of Medicine. Many of these deficits, however, are short term.

"As a group, children with RS remain remarkably intact, and the intense therapeutic efforts of those caring for them will be rewarded not only with survival but with recovery free from significant loss in academic achievement or intellectual function," says Dr. Sally Shaywitz, director of the learning disorders unit at the Yale-New Haven Hospital and associate professor of pediatrics at the Yale University School of Medicine.

In a sibling-matched study of 16 RS survivors, 13 of whom had experienced very severe RS, Dr. Shaywitz and her colleagues found that 8 children had minor and transient neurological abnormalities and 11 manifested attention deficits. Four of the survivors had contracted the disease before age 7. Five of the children with symptoms of attention deficit had experienced significant emotional stress about a month before the onset of RS.

Results of the study clearly indicate that children with early disease onset and severe RS should be examined frequently after recovery for evidence of sequelae, according to Dr. Shaywitz. Because 13 of the 16 survivors had suffered exceptionally severe RS, the results should not be interpreted as being applicable to the status of the average RS survivor, she says.

Reye syndrome is an acute encephalopathy, often fatal, involving acute swelling of the brain, hypoglycemia, and fatty infiltration and dysfunction of the liver. In severe cases, intensely increased intracranial pressure and varying degrees of coma occur, mitochondria in the brain and liver are damaged, and the blood-ammonia concentration increases markedly.

Most often, RS follows an episode of influenza or chickenpox. Repeated vomiting after recovery from an upper respiratory tract infection is one of the most prominent symptoms of the disease. The cause of RS is not known, and there is no specific treatment, according to Dr. Shaywitz. Supportive measures are the only therapy. Intubation of the trachea ensures proper oxygenation of the brain while mannitol and phenobarbital are used to reduce intracranial pressure.

The 16 children studied by Dr. Shaywitz and her colleagues represented all of the RS survivors treated at Yale-New Haven Hospital between January 1977 and December 1978. Twelve children had siblings of appropriate age to serve as controls. Dr. Shaywitz points out that lack of an adequate control group was one shortcoming of previous investigations of sequelae in RS survivors.

In the Yale study, survivors and their sibling volunteers were admitted to the Yale Children's General Clinical Research Center (GCRC) for a battery of neurologic, cognitive, educational, and psychiatric tests. The survivors had been followed in the pediatric neurology clinic for more than 3 years after being discharged from the hospital.

Thirteen of the RS children had experienced very severe disease, resulting in coma of stages three to five on a scale of five. Controlled assisted ventilation, which included intubation of the trachea, was required for each of these patients. Intracranial pressure and blood-ammonia levels were very high. Most patients required at least one dose of mannitol to control intracranial pressure.

By the end of the 3-year followup study, neurological impairment noted in eight of the survivors had disappeared. These deficits had included transient hemiparesis, temporary loss of the ability to carry out familiar and purposeful movements, and transient exaggerated reflexes, tics, grimacing, and drooling. Control siblings did not manifest any of these deficits.

Differences between survivors and controls in measurements of basic IQ were not significant except for those who were affected at a very early age. Compared to control subjects, children who had suffered very severe RS had lower educational test scores, which were obtained through achievement tests such as the Woodcock-Johnson test. A significant correlation was found between the severity of RS and Bender figure-drawing tests. The survivors tended to perform more slowly than their siblings in other tests that demonstrate neurological maturation, according to Dr. Shaywitz.

Psychiatric symptoms of RS survivors consisted mainly of hyperactivity with inattention or anxiety. In 8 of the 11 RS children the symptoms occurred soon after acute illness. Psychiatric ratings of survivors, according to the NIMH Children's Psychiatric Rating Scale, were significantly poorer than those of their siblings and correlated with the severity of RS.

"The pattern of behavior following RS was consistent for all RS survivors interviewed," Dr. Shaywitz says. "During the first 6 months after the illness they were unusually irritable, easily distracted, agitated, inattentive, impulsive, and fidgety as compared to the behavior of the 12 siblings who served as control subjects. Only 2 of the 16 affected children were considered by their parents to be totally back to normal." Behavior returned to normal, however, by the end of the 3-year study, indicating that the abnormalities were only transient, according to Dr. Shaywitz.

A possible relationship between significant emotional stress and the development of RS is suggested by the unusually large number of survivors who had experienced severe stress within a month before onset of the disease, according to Dr. Shaywitz. "We speculate that this commonality indicates that the brain monoaminergic mechanisms may play a role in the pathogenesis of the disorder," she says. "This possibility should be explored."

Additional reading:

1. Shaywitz, S. E., Cohen, P. M., Cohen, D. J., Mikkelson, E., Morowitz, G., and Shaywitz, B. A., Long-term consequences of Reye syndrome: a sibling-matched, controlled study of neurologic, cognitive, academic, and psychiatric function. *Journal of Pediatrics* 100:41–46, 1982.
2. Shaywitz, B. A., Venes, J. L., Cohen, D. J., and Bowers, M. B., Reye syndrome: monoamine metabolites in ventricular fluid. *Neurology* 29:467, 1979.
3. Davidson, P. W., Willoughby, R. H., O'Tuama, L. A., Swisher, C. N., and Benjamins, D., Neurological and intellectual sequelae of Reye syndrome: a preliminary report. *American Journal of Mental Deficiency* 82:535, 1978.
4. Lloyd, K. G., Davidson, K., Price, H. J., et al., Catecholamine and octopamine concentrations in brains of patients with Reye syndrome. *Neurology* 27:985, 1977.

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