Annotations

Aetiology of Reye's syndrome

The 'discovery' of an apparently new disease may be expected to generate much interest and research and looking back from the 20th anniversary of the original report of encephalopathy and fatty degeneration of the viscera in childhood,¹ this has certainly been true of Reye's syndrome (RS). Much important information has emerged from surveillance carried out by the Centers for Disease Control (CDC) in the United States. More than 2000 cases have now been studied² and some possible aetiological factors have been identified. Nevertheless, understanding of the role of these factors and of pathogenetic mechanisms remains poor.

Definition

Precise definitions are crucial in epidemiological investigation and comparison of data from different sources. There is much debate about the diagnostic precision of liver histology in RS. Diagnosis based on light or electron microscopy may be considered conclusive but to demand it in every case is impracticable. Simpler laboratory measures of hepatic dysfunction correlate well with liver microscopy³ but none may be relied upon as a consistent marker.⁴ It seems reasonable therefore to accept the following definition:

- 1) Acute encephalopathy (without cerebrospinal fluid pleocytosis);
- 2) Characteristic liver histology or raised transaminase or ammonia values ($\geq 3\times$ normal);
- 3) No other explanation for the illness.

Pathophysiology

Early ammonia values seem to be correlated positively with the severity and outcome of RS.^{5,6} The encephalopathy is due to cerebral oedema and is the major prognostic factor, as in survivors the liver returns to normal. It is not, however, inevitable that the cerebral disorder is caused by hyperammonaemia as both may be secondary to derangement of common metabolic pathways. This concept is supported by the presence in brain mitochondria of ultrastructural abnormalities similar to those in the liver.⁷ Early ammonia estimations and neurological assessments are essential to identify high risk patients who need aggressive treatment with cerebral decompression and intracranial pressure monitoring.⁶

Associated epidemiological factors

Age and social class. Most cases of RS in the United States occur in middle class white children over the age of 3 years whereas a high proportion of infant cases come from the lower class black community. Most cases reported during the first year of the United Kingdom RS surveillance scheme were under 3 years old and all were white. In infants it may be difficult to distinguish RS from other causes of encephalopathy such as toxic or metabolic abnormalities and heatstroke.

Genetic susceptibility. Reports of family clusters of RS (though none in identical twins) and recurrent episodes in the same individual do not allow distinction between genetic and environmental factors. In these cases it is important to identify metabolic disorders that may simulate RS.⁵ The fact that siblings may suffer similar prodromal illnesses but whereas one recovers another develops RS, suggests idiosyncratic mechanisms.

Environmental factors.

Viruses

There is now substantial evidence from the United States linking geographical, temporal, and age distributions of RS with influenza.⁸ As in British children⁴ the virus is usually type B. RS is also associated epidemiologically with antecedent varicella infection. The age distribution is younger than after influenza reflecting the age specific attack rates of the infections.⁸ Many other viruses have been anecdotally associated with RS but the evidence is insufficient to support a causal relation.

Aflatoxin

Aflatoxin poisoning produces an RS like illness and a causal relation has been suggested.⁹ However, liver histology is not consistent with RS and a controlled study¹⁰ found no difference in aflatoxin isolation rates between RS patients and controls.

Insecticides

A relation between RS and crop spraying with chemicals such as DDT or fenitrothion has been supported by experimental evidence.¹¹ This may be a more likely cause in rural communities than aflatoxin poisoning.

Table Case control studies of Reye's syndrome and salicylate consumption

Study	Prodromal illness matched?		No in study	Taking salicylates (%)
Starko <i>et al.</i> ¹²	No	Cases	7	100
		Controls	16	50
Waldman <i>et al.</i> ¹³	a) Nature	Cases	25	96
		Controls	46	73
	b) Nature and temperature	Cases	12	100
		Controls	29	45
Halpin <i>et al.</i> ¹⁴	Nature and temperature (multivariate analysis)	Cases	97	97
		Controls	156	71

Salicylates

Isolated case reports of RS after taking drugs such as valproic acid and warfarin suggest no more than a chance association but there is more extensive evidence relating to antiemetics and salicylates both of which are drugs used for symptomatic treatment of the prodromal illness of RS. A crucial point against a causal relation between RS and antiemetics is that they are usually taken after the onset of vomiting, which is probably a symptom of the RS pathophysiological process. This argument, however, does not apply to salicylates which are often taken earlier.

Three American retrospective controlled studies found a statistically significant association between salicylate consumption and RS (Table) but the results have been criticised on several grounds:

1) Selection bias—cases were not all histology proved and therefore some children with a non-RS diagnosis may have been included. For valid comparison of exposure to a risk factor, cases and controls should have an equal chance of exposure. The crucial matching criterion for RS is severity of prodromal illness and relevant variables include nature, duration, temperature, and specific infecting virus. Only part of 1 study¹³ matched prospectively on nature and peak temperature, and another¹⁴ included both variables only by multivariate analysis.

2) Recall bias—parents of RS patients would inevitably remember previous drug intake better than control parents and the interview delay was longer for controls than cases.

3) Data collection bias—interviewers knew whether they were seeing patients or controls and in the 2 later studies knew the research hypothesis. Drug identification by direct sighting was facilitated for controls who were interviewed at home whereas patients were interviewed in hospital.

4) Timing of salicylate consumption—this important variable was not consistently stated.

Although these studies were not conclusive, the Food and Drug Administration (FDA) considered that their limitations did not explain the strength of the observed association between salicylates and RS. Additional evidence was the biological plausibility of this association on clinical and pathological grounds.¹⁵ Thus the FDA recommended:

- 1) Avoidance of salicylates for children with varicella or influenza like illnesses;
- 2) A warning label on drug containers;
- 3) A public service warning campaign.

The implications of such actions are enormous¹⁶ and they are currently under review by the American authorities.

The issue therefore is confused. In the United Kingdom it has not (yet) become a major public controversy. The committee on safety of medicines decided that no action was indicated unless more conclusive evidence was produced.

It is therefore essential that further studies are undertaken in spite of the methodological difficulties. In the United Kingdom widespread use of paracetamol may help to prove whether an appreciable difference between salicylate usage in RS patients and controls exists.

We hope that all paediatricians will wish to support a United Kingdom study aimed at settling this controversy and in the meantime will ensure that all patients meeting the accepted diagnostic criteria are notified promptly to the RS surveillance register.

References

- 1 Reye RDK, Morgan G, Baral J. Encephalopathy and fatty degeneration of the viscera: a disease entity in childhood. *Lancet* 1963; ii: 749-52.
- 2 Hurwitz ES, Nelson DB, Davis C, Morens D, Schonberger LB. National surveillance for Reye syndrome: a five-year review. *Pediatrics* 1982; 70: 895-900.
- 3 Corey L, Rubin RJ, Bregman D, Gregg MB. Diagnostic criteria for influenza B-associated Reye's syndrome: clinical vs pathologic criteria. *Pediatrics* 1977; 60: 702-8.
- 4 Bellman MH, Ross EM, Miller DL. Reye's syndrome in children under three years old. *Arch Dis Child* 1982; 57: 259-63.
- 5 DeLong GR, Glick TH. Encephalopathy of Reye's syndrome: a review of pathogenetic hypotheses. *Pediatrics* 1982; 69: 53-63.
- 6 Fitzgerald JF, Clark JH, Angelides AG, Wyllie R. The prognostic significance of peak ammonia levels in Reye syndrome. *Pediatrics* 1982; 70: 997-1000.
- 7 Partin JS, McAdams AJ, McLaurin RL, Schubert WK, Partin JC. Brain ultrastructure in Reye's syndrome; acute injury and repair. In: Crocker JFS, ed. *Reye's syndrome II*. New York: Grune & Stratton, 1979: 237-49.
- 8 Sullivan-Bolyai JZ, Corey L. Epidemiology of Reye syndrome. *Epidemiol Rev* 1981; 3: 1-26.
- 9 Olson LC, Bourgeois CH, Jr, Cotton RB, Harikul S, Grossman RA, Smith TJ. Encephalopathy and fatty degeneration of the viscera in Northeastern Thailand. Clinical syndrome and epidemiology. *Pediatrics* 1971; 47: 707-16.

- ¹⁰ Nelson DB, Kimbrough R, Landrigan PS, Hayes AW, Yang GC, Benanides J. Aflatoxin and Reye's syndrome. A case control study. *Pediatrics* 1980; **66**: 865-9.
- ¹¹ Crocker JFS, Rozee KR, Ozere RL, Digout SC, Hutzinger O. Insecticide and viral interaction as a cause of fatty visceral changes and encephalopathy in the mouse. *Lancet* 1974; **ii**: 22-4.
- ¹² Starko KM, Ray CG, Dominguez LB, Stromberg WL, Woodall DF. Reye's syndrome and salicylate use. *Pediatrics* 1980; **66**: 859-64.
- ¹³ Waldman RJ, Hall WN, McGee H, Van Amburg G. Aspirin as a risk factor in Reye's syndrome. *JAMA* 1982; **247**: 3089-94.
- ¹⁴ Halpin TJ, Holtzhauer FJ, Campbell RJ, *et al.* Reye's syndrome and medication use. *JAMA* 1982; **248**: 687-91.
- ¹⁵ Starko KM, Mullick FG. Hepatic and cerebral pathology findings in children with fatal salicylate intoxication: further evidence for a causal relation between salicylate and Reye's syndrome. *Lancet* 1983; **i**: 326-9.
- ¹⁶ Brown AK, Fikrig S, Finberg L. Aspirin and Reye syndrome. *J Pediatr* 1983; **102**: 157-8.

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