

Reye's syndrome in children under three years old

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SUMMARY The National Childhood Encephalopathy Study identified 37 cases of Reye's syndrome in children aged between 2 and 36 months in a 3-year period, giving an estimated incidence in Great Britain of 0.7/100 000 children a year. The diagnostic features were neither consistently positive in these cases, nor negative in 11 others later considered not to have Reye's syndrome. The prognosis was poor; the fatality rate was 46%, and 60% of the survivors were handicapped. A surveillance scheme to investigate pathological, clinical, and epidemiological factors in this rare condition is required. This has now been set up in the UK.

A case of acute encephalopathy with fatty infiltration of the liver in a child was first described in 1929,¹ but the association was not recognised as a clinico-pathological entity until 1963.² The syndrome was quickly recognised in several countries and attracted much clinical and pathological investigation.³⁻⁵ A conclusive diagnosis can be made on the findings of a severe acute neurological illness of unexplained origin with the characteristic fatty liver degeneration on histology.⁶ There is however, debate on whether other pathological indices of liver dysfunction, short of the morbid histology, are acceptable diagnostic criteria.⁷

The cause of Reye's syndrome (RS) is unknown, although epidemiological studies have suggested various factors including toxins, drugs, and infections possibly occurring in an individual with a genetically-determined metabolic abnormality.⁸

It occurs most often in school-aged children but the prognosis is worst in the younger age groups.^{9,10}

Much of the available information about RS is derived from several large series of cases from North America¹¹⁻¹⁴ and from the results of surveillance carried out by the Center for Disease Control,¹⁵ based in Atlanta, Georgia.

The neurological conditions studied by the National Childhood Encephalopathy Study (NCES)¹⁶ included RS, and therefore the cases notified provide an opportunity to investigate pathological, clinical, and epidemiological data on RS in young British children.

Patients and methods

The NCES was set up to investigate serious neurological disorders in children aged between 2 and 36

months. Every paediatrician, infectious disease physician, and neurosurgeon in England, Scotland, and Wales was asked to notify the NCES of all children admitted to hospital suffering from certain defined illnesses, including RS. Clinical information and the results of investigations were recorded on a standard questionnaire. Two control subjects matched for sex, age, and geographical area of residence were chosen for each case from a community-based register. The period of case collection was 3 years from July 1976 to June 1979. A monthly reminder letter was sent to all participants in order to encourage case reports. All patients were followed up, either by post if they had apparently recovered within 15 days after admission, or by a visit from a paediatrician and member of the research team if there was evidence of sequelae. The visited cases were assessed using an adaptation of the Stycar sequences.¹⁷

Case definition

The diagnosis on each of the 1180 cases reported to the NCES was reviewed critically in the light of all existing information. This sometimes included data not available to the referring clinician at the time of the acute illness. The final diagnosis was decided by consensus of the NCES paediatricians and epidemiologists, taking account of all reported information and the results of subsequent enquiries. The diagnosis of RS was considered *definite* in patients who had an acute encephalopathy of unknown cause and in whom liver histology during the illness showed the characteristic fatty changes. If the liver was not examined microscopically, either by biopsy or at necropsy, RS was accepted as the *probable*

diagnosis if an acute encephalopathy was associated with either transaminases (aspartate or alanine) above 100 IU/l or a macroscopically pale fatty liver on post-mortem examination. Hepatomegaly, hyperammonaemia, hypoglycaemia, and an increased prothrombin time were not included in the diagnostic criteria.

A diagnosis of RS was suggested by the notifying clinician in 48 cases. According to the above criteria, 6 patients had definite RS and 31 had probable RS. In 11 cases the notified diagnosis of RS was not supported and they were therefore recategorised on review.

In 8 cases notified with a diagnosis other than RS there was an acute encephalopathy associated with evidence of liver dysfunction. In view of the positive alternative diagnosis made by the paediatrician during the acute illness, these cases were not included in the RS groups but their clinical and pathological findings are reported for comparison.

The 6 cases of definite RS and 31 probable RS cases were grouped together and their outcome and epidemiology are discussed in this report.

Results

Clinical and pathological features. The clinical and pathological findings in the cases reported are shown in Table 1.

The 6 definite RS cases were so categorised because liver histology characteristic of RS was found at post-mortem examination. In 4 of these cases the liver was enlarged. No laboratory investigations were performed in 3 patients who were moribund on arrival in hospital. Transaminases were measured in 2 of the remaining 3 patients and were raised in 1 but normal in the other who had an increased level of blood ammonia and a prolonged prothrombin time.

Of the 31 probable RS cases, 28 had raised transaminases and the other 3 had a pale fatty liver at necropsy but microscopical examination was not performed and there was no other evidence of liver

dysfunction. Transaminases were measured and found to be normal in 2 of these 3 cases. Blood ammonia levels were measured in 13 of the probable cases and were above 100 $\mu\text{mol/l}$ (170 $\mu\text{g}/100\text{ ml}$) in eight.

On review 11 cases were considered not to have RS. In 5 of them transaminases were raised but liver histology was negative for RS in 4, and the fifth patient was eventually re-diagnosed as having ornithine transcarbamylase deficiency. In 2 other cases the liver looked macroscopically fatty but microscopical examination did not show the typical changes. In the remaining 4 cases in this group transaminases were not raised and neither necropsy nor liver biopsy was performed, although hypoglycaemia (blood glucose $<2.4\text{ mmol/l}$, $<40\text{ mg}/100\text{ ml}$) was present and 2 had a prolonged prothrombin time. Blood ammonia concentration was measured in 4 cases in this group and in all of them it was less than 100 $\mu\text{mol/l}$ (170 $\mu\text{g}/100\text{ ml}$).

In 8 cases with an 'other diagnosis', transaminases were above the normal range and in 5 they were above 100 IU/l. Two had hypoglycaemia, one of whom had a prolonged prothrombin time. Another 2 of these cases were found to have a normal blood ammonia concentration.

The clinical symptoms of the cases are shown in Table 2. All patients presented with an acute encephalopathy manifested by convulsions or coma.

Table 2 *Clinical symptoms*

	<i>Symptoms</i>				
	<i>Prodromal illness</i>	<i>Vomiting</i>	<i>Convulsions</i>	<i>Coma</i>	<i>Haemorrhage</i>
Definite RS n=6	4	3	3	4	1
Probable RS n=31	20	20	24	25	2
Not RS n=11	8	9	8	7	3
Other diagnosis n=8	8	5	8	6	1

Table 1 *Clinical and pathological findings*

	<i>Hepatomegaly</i>	<i>Raised serum transaminases (>100 IU/l)</i>	<i>Raised blood ammonia >100 $\mu\text{mol/l}$ (>170 $\mu\text{g}/100\text{ ml}$)</i>	<i>Prolonged prothrombin time (>2 \times control)</i>	<i>Hypoglycaemia <2.4 mmol/l (<40 mg/100 ml)</i>	<i>Fatty liver appearance</i>	
						<i>Macroscopical</i>	<i>Microscopical</i>
Definite RS n=6	4	1	1	2	1	5	6
Probable RS n=31	8	28	8	9	14	7	Not done
Not RS n=11	4	5	0	2	5	2	0
Other diagnosis n=8	1	5	0	1	2	Not done	Not done

or both of these. A preceding history of minor inflammatory illness was present in two-thirds of the 48 cases originally notified as RS and all of those notified with another diagnosis. Vomiting was a prominent symptom, occurring in half of the definite cases, 65% of the probable cases, and in 82% of the not RS cases. It also occurred in 63% of those with an 'other diagnosis'. Convulsions and coma were common features in all groups. Haemorrhage was a rare symptom but again occurred in all groups of cases.

Epidemiology. The 37 cases of definite or probable RS are considered together. Sex and age are shown in Fig. 1. There was no significant difference in the sex ratio of 17 males to 20 females. The median age at presentation was 12 months.

Incidence

The average mid-year population of children aged 2 to 36 months in England, Wales, and Scotland during the NCES case collection period was about 1 800 000. Therefore the approximate incidence of reported cases of RS in this age group in Great Britain was 0.7 per 100 000 children a year.

Seasonal distribution

The total number of cases presenting in each month during the 3-year study period is shown in Fig. 2. Cases occurred throughout the year with the highest aggregate incidence in February.

Association with vaccines

In the 7-day period before the onset of symptoms one case had received diphtheria-tetanus-pertussis immunisation and another diphtheria-tetanus immunisation. No patient had been given measles

vaccine within 14 days. Thus no significant association of RS with any type of vaccine has been shown.

Prodromal illness

Twenty-four (65%) of the 37 cases had an apparently minor illness between 6 hours and 2 weeks before the acute encephalopathy of RS (Table 3). Fifteen cases had an upper respiratory tract infection, associated with vomiting in 10 and diarrhoea in five. Six cases had a combination of vomiting and diarrhoea diagnosed as gastroenteritis.

Social class, birthweight, and breast feeding

Case-control analyses were carried out for each factor. There was no statistically significant difference between the cases and controls with regard to social class distribution or birthweights. Infant feeding history was known in 27 cases, of whom 4 (15%) had been breast fed for at least 4 weeks. The corresponding figures in controls were 24 (30%) out of 82. However although the incidence of breast feeding in cases was only half that in controls the numbers are small and do not achieve statistical significance.

Outcome. The condition of the cases at follow-up 1 year after onset of RS is shown in Table 4. Three children were moribund on arrival in hospital and died within a few hours, and a further 14 died between 1 and 7 days after admission. Six patients had recovered by the time of discharge from hospital between 7 and 31 days after admission. These, and an additional 2 children who still had sequelae on discharge home, were found to be normal on follow-up 1 year later. Twelve cases had a neurodevelopmental handicap on follow-up. Nine of these were

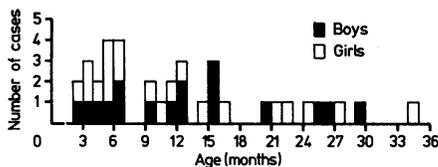


Fig. 1 Age distribution.

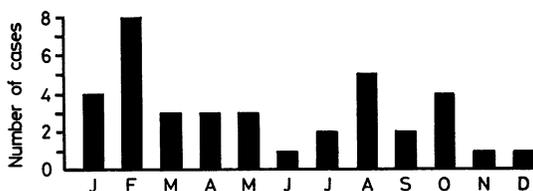


Fig. 2 Month of onset, 1976-79.

Table 3 Prodromal illness

	Cases	
	No	%
Upper respiratory tract infection	15	41
Gastroenteritis	6	16
Non-specific pyrexia	1	3
Urinary tract infection	1	3
Minor surgery	1	3
None	13	35

Table 4 Outcome 1 year later of 37 cases

	Cases	
	No	%
Normal	8	22
Mild developmental retardation	1	3
Severe developmental retardation	2	5
Gross neurological and developmental handicaps	9	24
Dead	17	46

totally unresponsive and had grossly retarded arrested development, and the remaining 3 had a lesser degree of developmental handicap.

Discussion

The fatty infiltration of the liver in RS was described by Reye, Morgan, and Baral in their original paper² and they implied that it should be present in all cases of the syndrome. This ultimate proof is demanded by some American authorities before making a diagnosis of RS.^{6 18 19} Others however, accept raised serum transaminases as an index of liver dysfunction with^{7 10 20} or without^{15 21} high levels of blood ammonia.

In the 48 cases notified to the NCES as RS liver histology was examined at necropsy in 11 cases, and by biopsy one day after admission in 1 case. Typical changes were reported as present in 6 and absent in six. Serum transaminases were measured in 39 patients but were not consistently abnormal in the definite RS cases, nor were they consistently normal in the not RS group. The pathological investigations merely reflect the severe disturbance of metabolic function, and, like the clinical symptoms, had no constant pattern of distribution. However, although the role of hyperammonaemia in RS is unknown²² it was the only abnormal investigation consistently found to be negative in cases ultimately considered not to have RS. In the USA blood ammonia is widely regarded as an important criterion and is generally measured. However in Great Britain facilities for its urgent estimation are not always available and it was done in only 37% of the 48 cases initially considered to have RS. Even necropsy may not be conclusive because, although RS was suggested by a macroscopically fatty liver in 14 cases, microscopical examination was carried out in only 7 of these and was negative in two. Conversely, the liver at necropsy did not look fatty in a further 6 cases, of whom one showed typical changes of RS on microscopical examination.

In the USA, RS typically occurs in children aged between 3 months and 18 years.¹⁸ Cases have been reported in neonates²³ as well as in adults^{13 24} and the median age appears to have risen from under 6 years in 1962–67 to 11 years in 1971.¹⁴ We therefore expected the majority of cases notified to the NCES to be at the upper end of the age range of 2 to 36 months; however this was not so, the median age being 12 months.

The reported incidence of RS in the USA population aged under 18 years during a 6-month period varied from 0.42 to 1.8/100 000, with a national mean of 0.58/100 000.¹³ The observation period was during an apparent epidemic of RS and the

baseline incidence could be considerably lower. The NCES included only children under 3 years old and therefore the incidence of RS derived from it cannot be directly compared with that from an American series in which the majority of cases were older. However, even taking this into account, our estimated incidence in British children aged 2 to 36 months of 0.7/100 000 a year was higher than expected.

An important feature of RS is the frequent occurrence of a prodromal illness,² confirmed by the present series. This has been related in the USA to infection with several viruses, the most common being influenza B and varicella.^{11–14 18} More cases of RS were reported to the NCES to have occurred in February 1979 than in any other month. This coincided with the beginning of an epidemic in this country of influenza B infection (Communicable Disease Surveillance Centre, 1980, unpublished data). Influenza virus A is found more often than virus B in England and Wales and also is most common in February. Neither these nor any other virus was isolated in any of the cases.

The poor prognosis of RS, particularly in very young children,²⁵ is clearly seen in the NCES cases. The fatality rate was 46% and only 40% of the survivors were normal one year later. In the USA the case fatality rate has been steadily falling from 83% in cases reviewed up to 1967,⁹ to 41% in 1974,¹³ and to 23% in 1980.¹⁵ The recent improvement is claimed to be due to earlier and more aggressive treatment with peritoneal dialysis,⁷ intracranial decompression,²⁶ and exchange transfusion.²⁷ Greater awareness of the disease however, may also have resulted in increased reporting of less serious cases. In the present series 4 cases were treated in university hospitals with aggressive therapy using peritoneal dialysis or exchange transfusion. Two of these children died and 2 survived, one being normal on follow-up. Thirty-three cases were given supportive management only. Of these, 15 died and of the 18 survivors 7 recovered completely. The number of aggressively-treated cases in this series is too small to allow meaningful comparison of outcome. In addition the untreated cases may have been managed conservatively because they were less severely ill on admission to hospital, although early consideration of vigorous therapy has been advocated.²⁸

Conclusion

The NCES has identified an unexpectedly high incidence of RS in children under 3 years old in Britain. A partial explanation may be that diagnostic criteria are not as strict as in the USA where facilities for pathological investigation seem to be used more

often. However the 37 cases reported had good evidence of encephalopathy and liver dysfunction and, in view of the apparent reluctance in this country to perform a liver biopsy, justify the diagnosis of RS. The lack of standardisation of diagnostic criteria evident among paediatricians makes analysis of epidemiological data and evaluation of treatment difficult. In America, the Center for Disease Control has made important contributions to the understanding of RS with its prospective surveillance scheme. A similar survey for the UK has been set up by the PHLS Communicable Disease Surveillance Centre in collaboration with the British Paediatric Association. It will investigate cases of acute encephalopathy and liver dysfunction (throughout all ages in children) and, it is hoped, will elucidate a definition of RS as well as pursuing clinical and epidemiological factors.

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