Clinical features and prognosis of Reye's syndrome

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SUMMARY Twenty three sporadic cases of Reye's syndrome diagnosed according to widely accepted criteria were seen between 1979 and 1982. The patients were younger than those reported from North America (median age 9 months), girls were twice as common as boys, and the syndrome presented twice as frequently in the summer 6 months. The annual incidence was 1.4 cases/100 000 among children aged less than 4 years. The prodrome consisted of upper respiratory symptoms in 61% of the children and even less specific features in more than 25%; two patients had varicella. Six of the 23 patients presented after a prodrome of less than 24 hours with 'acute collapse', simulating 'near miss' cot death associated with profound hypoglycaemia, and in four of these there was an unfavourable outcome. Intensive care methods including judicious fluid restriction coupled with 'prophylactic' hyperventilation (87%), direct monitoring of intracranial pressure (70%), and barbiturate coma (52%) achieved neurologically intact survival in 74% of patients. Failure to recognise the syndrome early enough or to manage it appropriately resulted in four deaths. To help reduce overall mortality in the United Kingdom paediatricians have a duty to acquaint family doctors and emergency department staff of the earliest clinical features of Reye's syndrome and of the need for immediate hospital referral.

It is 20 years since the late Dr R D K Reye described the syndrome of acute encephalopathy and visceral fatty infiltration.¹ Reye's syndrome is the most common type of acute hepatocellular failure in childhood, the encephalopathy is unpredictable, and its management and prognosis are still far from satisfactory. We believe that it occurs more frequently than is thought, and that published reports from the rest of the United Kingdom have probably underestimated the true incidence.^{2,3} Our aim in reporting recent experience of Reye's syndrome in Northern Ireland is to heighten diagnostic awareness, improve early recognition, and encourage a more aggressive approach to diagnosis and management.

Patients and methods

The total provincial population of Northern Ireland is 1.5 million, of which there are approximately 330 000 children aged less than 13 years. Since January 1973 we have seen 46 patients with Reye's syndrome of whom 23, treated between 1979 and 1982, form the subject of this report.

Diagnostic criteria were as follows:

- (1) A prodromal history of either upper respira-

tory tract or gastroenteric symptoms often accompanied by fever, or of varicella.

- (2) Hepatic dysfunction, characterised by a threefold rise in blood ammonia and/or serum aspartate aminotransferase or alanine aminotransferase and a very prolonged prothrombin time (<40% compared with control).

- (3) Abrupt onset of a central nervous system disorder manifested by changes in the level of consciousness (often with other abnormalities).

- (4) Exclusion of other disease states that have similar clinical features.⁴

Between January 1979 and December 1982, 23 patients (18 seen personally) fulfilled these criteria; five others with similar clinical features were excluded because of inadequate confirmatory laboratory data. To abstract the relevant data from the paediatric case notes a protocol was devised covering symptoms and duration of the present illness and details of the past obstetrical, developmental, social, and family histories. All drugs (particularly salicylate, paracetamol, phenothiazine, antitussives, antibiotics, and sodium valproate) prescribed either by the family doctor or given by the parents, or both, within 96 hours before admission were recorded. Details of the clinical examination and laboratory

data on admission to the intensive care unit were noted and the level of consciousness was graded according to the scheme of Lovejoy *et al.*⁴ The facets of hospital management were categorised, together with outcome and any complications that supervened.

Histopathological specimens of liver were available in 17 cases, 12 of which had been obtained by needle biopsy, and these were reviewed by Dr Denis O'Hara. With the exception of case 13 (below) all showed the presence of panlobular microvesicular fatty infiltration of the liver without appreciable cellular necrosis or inflammation. The data were analysed using the Statistical package for the social sciences and parametric statistical tests.

Results

Clinical features. Fifteen of the 23 patients with Reye's syndrome were girls, and all had previously been well and developing normally. The age range was 0.2–5.9 (median 0.75) years and 14 patients were seen between May and October, most commonly during the month of August (4 patients).

The prodromal illness of this biphasic disorder lasted 1 to 8 (median 3) days and consisted of upper respiratory symptoms in 14 (61%) patients, 7 of whom had been coughing and 10 of whom had fever. Severe diarrhoea and fever occurred in two others, one of whom also had upper respiratory symptoms and had been referred initially to a communicable disease unit. Two others had had varicella. Six

patients (26%) had had none of these symptoms; their parents gave a history of non-specific complaints—anorexia, listlessness, drowsiness, and either restlessness or screaming episodes, or both, of sufficient severity in five of the 6 to have been seen by their family doctor; two of them on three occasions before hospital admission.

The second or neurological phase of the syndrome was marked in 22 of the 23 patients by the abrupt onset of vomiting, which was repeated in most (78%) on at least three occasions; in 13 (57%) children altered blood was present in the vomitus. One child passed a single melaena stool (Table). When first examined at this centre all patients had a reduced level of consciousness—two were drowsy (Lovejoy stage 1), 9 were delirious or extremely restless with tachypnoea (Lovejoy stage 2), 9 were in coma (Lovejoy stage 3), and one was more deeply comatose with decerebrate posturing of the limbs (Lovejoy stage 1). On admission to hospital 6 of the 14 who had had upper respiratory symptoms and four of the 6 with a non-specific prodrome were in coma. Fourteen of the 23 patients taken first to peripheral hospitals (two of which did not have paediatric staff) had a mean Lovejoy stage of almost 3, but the mean Lovejoy stage of the 9 who lived in or near Belfast and were brought directly to this centre was 2. The respiratory rate was raised in all patients (in 8 children >50/min). The liver was judged to be abnormally firm in 19 (83%), but was not pathologically large in 12 (52%). Seizures occurred in 11 (48%) patients before or shortly after admission.

Table Clinical features in 6 infants with Reye's syndrome who presented with acute collapse simulating a 'near miss' cot death

Case no	Sex	Age (yr)	Prodromal features	Duration of prodrome (days)	Recent medication	Level of consciousness (Lovejoy stage)	Occurrence of seizures	Glucose value (mmol/l)		Outcome
								Blood	Cerebrospinal fluid	
7	M	0.82	Upper respiratory symptoms, fever (40°C)	3	Salicylate, antihistamine	3	+	2.1	0.8	Full recovery
9	M	0.76	Fever, diarrhoea, undue irritability	1	Salicylate	3	+	1.3	0.5	Full recovery
13	M	0.92	Upper respiratory symptoms, fever	1	Salicylate	2	+	3.0	0.6	Died
15	F	0.78	Upper respiratory symptoms, fever, non-specific rash	1	—	4	—	0.5	0.5	Died
16	M	0.21	Upper respiratory symptoms, fever (40°C), non-specific rash, irregular respiration	1	—	3/4	+	1.0	—	Died
19	F	0.66	Fever, non-specific rash	1	Salicylate	3	+	0.1	0.9	Neurologically handicapped

Presentation with acute collapse/encephalopathy. Six young infants who had been febrile (two with a pyrexia of 40°C or more) with or without upper respiratory symptoms, five for less than 24 hours (Table), were found by their parents in a 'collapsed' condition, simulating a 'near miss' cot death. This subgroup of the series were also liable to have seizures, to be more deeply unconscious, and ultimately to have a worse prognosis.

Laboratory investigations. All patients fulfilled the stated diagnostic criteria, and most had a raised blood ammonia value as well as an increase in each of the transaminases. When first seen, 22 patients were hypoglycaemic (median 1.45 mmol/l) and in 16 the cerebrospinal glucose value was reduced (median 0.80 mmol/l). In the 6 'collapsed' infants, blood glucose concentrations were lower than in the other 17 patients (mean (SD), 1.33 (1.07) and 1.78 (1.26) mmol/l, respectively). The difference in cerebrospinal fluid glucose values was even more striking, and was mean (SD), 0.66 (0.18) mmol/l and 1.84 (1.84) mmol/l, respectively. Initial blood ammonia concentrations were also lower in 'collapsed' infants mean (SD), 178 (1.44) μ mol/l compared with 357 (224) μ mol/l, possibly reflecting the very short prodrome. The 6 patients who died or sustained neurological damage could be distinguished from the survivors only by the initial higher bilirubin concentration ($P < 0.004$).

Salicylate medication during the prodrome. In the 96 hours before admission, 18 of the 23 patients had received one or more drugs, 14 of them salicylates (two had also had paracetamol). The usual salicylate dosage was the 75 mg tablet of soluble aspirin (Disprin). This had been given up to four times in all. Using the Students's *t* test or the χ^2 test, comparison was made of epidemiological, clinical, and laboratory data in those who had or had not received salicylate. No statistically valid relation could be found between salicylate and any parameter studied, including the presence of fever or of blood in the vomit, the occurrence of 'collapse' or seizures, the respiratory rate, the Lovejoy stage, outcome, blood glucose value, prothrombin time or acid base data.

Serum salicylate, measured in 14 patients, was detectable in only 8. Concentrations between 1.5 and 2.0 mmol/l (20 and 27 mg/dl) were found in four and above this range in one child. The serum salicylate concentration correlated significantly with blood pH ($r = -0.74$) and with base deficit ($r = +0.71$), but not with P_{aCO_2} , prothrombin time, or any other laboratory test.

Management. Patients with suspected Reye's syndrome were admitted to the intensive care unit where monitoring was begun, neurological assessment and Lovejoy stage determination carried out, and laboratory tests done to confirm the diagnosis. Often hypoglycaemia had already been corrected, but an infusion of 10 to 15% glucose was continued. In all cases this was combined with a regimen to combat accumulation of nitrogenous products as a result of hepatocellular failure, using lactulose and neomycin given by nasogastric tube. A gentle enema was given, leaving a small quantity of neomycin in the lower bowel. The policy for managing the encephalopathy was founded on experience in North America and was introduced during 1980. In three patients little more than the above measures were instituted. Twenty patients (87%) were managed using 'prophylactic' hyperventilation under neuromuscular blockade, accompanied in 16 (70%) patients by monitoring of the intracranial pressure by means of a subdural Richmond screw in 12 (52%) or an extradural probe linked to a chart recorder in four others. High dosage phenobarbitone (barbiturate coma) was employed in 12 (52%) patients and dexamethasone in 18 (78%). Infusions of 20% mannitol were required to attempt reduction of transiently raised intracranial pressure in 11 (48%) patients; more commonly in those who were in Lovejoy stage 3 or 4. Two patients (cases 4 and 19 below) were given intravenous thiopentone in an attempt to control either persistently raised intracranial pressure, or uncontrollable seizures that did not respond to conventional anticonvulsant treatment.

Pulmonary complications were generally mild and transient; 11 patients developed atelectasis or consolidation—one a pneumothorax and another transient subglottic stenosis caused by laryngeal oedema.

Prognosis and reasons for failure. Follow up at 12 months to 5 years, showed that 17 (74%) children seemed to have made a complete neurological recovery. Five patients died and one is severely physically and mentally handicapped. It is salutary to examine the sequence of events in this latter group.

The diagnosis was not suspected in an infant aged 5 months (case 4) admitted to a peripheral hospital without paediatric staff. Transfer was delayed and on arrival at this centre the child's neurological level of consciousness was at least Lovejoy stage 4. Definitive management was therefore started late. In two infants (cases 15 and 16, Table), who were seen in 1979, warning signs of rising intracranial pressure (deepening coma, extensor spasms, and either pupillary dilation or third nerve palsy, or

both) were overlooked in this hospital and each progressed rapidly from Lovejoy stage 3 to 4 or more, before aggressive treatment was begun. In neither child was intracranial pressure monitored directly. A 6 month old baby (case 23) presented with brown vomiting, tachypnoea, and the liver palpable 3 cm below the costal margin, but little initial reduction in consciousness. For 5 days she had been lethargic and refusing feeds. She was thought to be in cardiac failure, possibly caused by viral myocarditis, and died abruptly, less than 12 hours from admission after several bouts of intractable tachyarrhythmia. One infant (case 19, Table) who had had profound and probably prolonged hypoglycaemia (the family live remote from their local hospital), initially presented as a 'near miss' cot death. After four days of intensive care and after endotracheal extubation, she had generalised seizures which were difficult to control by conventional treatment. She required reintubation, a further three days of intermittent positive pressure ventilation, and several infusions of thiopentone. She has severe neurological handicap. Case 13 who presented initially in a similar fashion, developed acute pulmonary oedema ('shock lung') after intermittent positive pressure ventilation and in spite of vigorous treatment died three weeks later—after 25 days of ventilatory support.

Histopathology of the liver in cases 4, 15, 16, 19, and 23 was characteristic of Reye's syndrome, but that in case 13 was not typical as the necropsy was done more than three weeks after the onset of the illness. In the patient in case 23 fatty infiltration was present in many organs including the myocardium and endothelium of vessels of the brain; there was, however, neither histological nor virological evidence of acute viral myocarditis. The patient in case 16, had a distinct peribronchiolar lymphocytic infiltration. Necropsy in all cases showed considerable cerebral swelling and in two there was evidence of herniation of the uncus and cerebellar tonsils.

Discussion

Reye's syndrome in Northern Ireland has been shown to be a less than rare disorder with a local incidence similar to that of phenylketonuria (approximately 1/5000 live births); it had a variable prodrome and an unpredictable natural history. With early recognition and optimal management, however, a prognosis as good as that reported from North America may be achieved.

Although data on incidence^{2,3} suggest that Reye's syndrome is more frequent in Northern Ireland than in the rest of the United Kingdom, this difference is probably more apparent than real. If this is true it

may be predicted that in the second year of the British Paediatric Association/Communicable Disease Surveillance Centre (BPA/CDSC) survey approximately 200 cases will be seen in the United Kingdom—that is a sixfold increase compared with 1982–3 when several large and populous regions reported few if any cases of Reye's syndrome.

Twenty three patients have been managed in Belfast in the past four years and the epidemiology indicates certain differences from experience in North America. Most patients in Belfast were less than 4 years of age, the median age was strikingly low at 9 months, and there was a 2:1 excess of girls compared with a mean age of 8 years and a similar but much smaller sex ratio in North America.⁵⁻⁸ Our cases occurred most frequently in the latter half of the year, especially in August, while in 1982 five cases occurred between September and December. (Five cases also occurred between September and November 1983). In North America, however, late winter peaks have often been reported^{5,7,8} and the BPA/CDSC survey also recorded some clustering between February and March 1982.³

The prodrome of Reye's syndrome was varied, and our experience was similar to that of other reports^{2,8} including the BPA/CDSC survey.³ Six patients had vague and even less specific features and although they differed little from the 14 with upper respiratory symptoms in other respects including prodrome duration and prognosis, they were more likely to be in coma on admission.

In our experience the most useful pointer to early recognition of Reye's syndrome is the abrupt onset of repeated vomiting in a young child who has had trivial upper respiratory symptoms or varicella, or in whom behaviour or responsiveness is altered. This is especially likely if altered blood is also present in the vomitus. Although reduction in consciousness or seizures, or both, may have occurred, these are less specific in suggesting Reye's syndrome. Early diagnosis depends to a large extent upon a high level of suspicion in the medical profession. It is important therefore for paediatricians to acquaint local family doctors and accident and emergency department staff of the early clinical features and of the necessity for urgent hospital referral to confirm the diagnosis and begin optimal management. Immediate minimum laboratory tests include blood ammonia, serum transaminases, and prothrombin time as well as blood glucose (see below) and cerebrospinal fluid examination. Needle biopsy of liver will afford even greater diagnostic certainty and it is our policy to perform a biopsy as soon as the patient's coagulation status allows or can be sufficiently improved with fresh frozen plasma.

Presentation in 25% of our 23 patients was

atypical and was precipitated by an abrupt episode of 'collapse' simulating 'near miss' cot death after a very short prodrome (Table). This clinical subgroup has not previously been highlighted, although 20% of cases in the BPA/CDSC survey may have had a similar type of onset.³ Reye's syndrome presenting in this fashion, may also be a cause of actual sudden infant death syndrome. Two recent local cases of sudden infant death syndrome each had striking microvesicular panlobular fatty infiltration of the liver characteristic of Reye's syndrome (J Crane, personal communication). Similar histopathological findings have also been reported in an infant who died suddenly and unexpectedly at 20 weeks of age.⁹

The pathogenesis of the abrupt 'collapse' in these babies is currently the subject of further study, but on the basis of these data may be related to the rapid development of severe hypoglycaemia. The cerebrospinal fluid glucose values were uniformly extremely low and probably more accurately reflected this development than did blood glucose values, since several of these profoundly ill infants may have been given a bolus of high concentration glucose before the initial blood sample was taken. The occurrence of abrupt hypoglycaemia may represent an extreme form of defective gluconeogenesis,¹⁰ although the part played by hormonal factors which influence glucose homeostasis also requires study.¹¹ Clearly Reye's syndrome should be considered seriously in any collapsed child or 'near miss' cot death. Early recognition of the hypoglycaemia and immediate correction by the first doctor to see the patient might improve the prognosis, which seems to be particularly bad in this subgroup (Table).

Optimal management of Reye's syndrome is possible only within an intensive care unit, where the ratio of staff to patients is favourable and facilities exist to monitor vital functions continuously. This approach coupled with careful restriction of fluid intake to two thirds the normal requirement and in recent years with techniques aimed at controlling and monitoring intracranial pressure directly, have contributed greatly towards effective treatment of progressive brain swelling and to improvement in the prognosis of Reye's syndrome. Experience with 22 of these 23 patients has led us to conclude that all patients exhibiting extreme restlessness or delirium accompanied by tachypnoea or incoordinated respiration—that is Lovejoy stage 2—ought to be managed using 'prophylactic' hyperventilation to regulate Paco_2 and hence intracranial pressure.¹² Since this necessitates the use of neuromuscular blockade, the ability to detect further deterioration in the neurological level is largely removed and renders direct monitoring of intracranial pressure mandatory.^{13 14} The decision to insti-

tute such aggressive management from the onset of Lovejoy stage 2, rather than awaiting stage 3, is reasonable in an intensive care unit which is both experienced and skilled in all aspects of these techniques. It is also important in a disorder where neurological deterioration may occur rapidly and unpredictably, as in cases 15 and 16 (in 1979).

A number of other methods for lowering intracranial pressure, some of which are more controversial, have also been employed. Large doses of phenobarbitone are also known to lower intracranial pressure possibly by reducing afferent stimuli.¹⁵ The use of intravenous mannitol or thiopentone, or both, has been held in reserve should these other methods fail to control, or reduce intracranial pressure to within an acceptable range.¹⁴ The latter two methods have been used particularly in patients in Lovejoy stage 3 and 4. In the past four years the use of exchange transfusion^{14 16} and peritoneal dialysis¹⁷ has been abandoned. In each of the 23 patients, however, neomycin and lactulose were given by nasogastric tube to reduce the production of various toxic nitrogenous metabolites, such as ammonia, in the colon. Although this is a relatively simple and innocuous form of treatment, whether it is as important in Reye's syndrome as in fulminant hepatic failure has been challenged and should be evaluated.¹¹

The use of salicylate during the prodrome has been suggested as a possible co-factor in pathogenesis.^{18 19} Recent case control studies showed that children with Reye's syndrome were significantly more likely to have received aspirin during the prodrome than controls.¹⁸⁻²⁰ These researches have, however, been criticised as biased, most importantly in that those patients who developed Reye's syndrome were more ill during the prodrome and hence were more likely to have been given aspirin.^{21 22} Although our review was limited in size and did not set out to investigate specifically the role of salicylate, we were unable to find a statistical association between any clinical or laboratory parameter, and particularly between the severity or outcome of Reye's syndrome, and the giving of aspirin during the prodrome.

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