Recognition and early management of Reye's syndrome

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SUMMARY Reye's syndrome continues to be associated with a high mortality. Out of 12 cases treated on our intensive care unit over a four year period, seven died, one suffered minimal cerebral damage, and four were normal.

Rapid progression through coma stages and high peak ammonia concentrations worsened prognosis. Reye's syndrome was suspected in only 50% of cases at the referring hospital and resulted in prompt referral to the intensive care unit in only one case. Late referral to the unit was associated with a poor outcome.

Sudden neurological deterioration followed diagnostic lumbar puncture in six children. Papilloedema was an unreliable sign of raised intracranial pressure and was absent in all cases. While computed tomography of the brain was useful in providing additional evidence of raised intracranial pressure, this could only be confirmed by direct measurement.

Lumbar puncture in the presence of rapidly progressive coma should be deferred until raised intracranial pressure has been excluded. To this end, early admission to a paediatric intensive care unit with facilities for computed tomography and monitoring of intracranial pressure is recommended.

Despite reports of improved outcome in Reye's syndrome in the United Kingdom,¹ mortality continues to be high in children over 5 years of age.² Twelve children with a diagnosis of Reye's syndrome have been treated on our intensive care unit over a four year period, 10 of whom were aged over 5. We have reviewed these cases to identify adverse factors.

Patients and methods

Twelve cases were identified from the admissions register of the intensive care unit for the four years from 1 December 1981 to 30 November 1985. All fulfilled the case definition of the British Paediatric Association and Communicable Diseases Surveillance Centre Reye's Surveillance Registry.³ In six cases there was histological confirmation of the diagnosis from postmortem liver biopsy specimens.

Coma stages were assigned on the basis of clinical signs and neurophysiological features using Lovejoy's classification (Table 1).⁴ Computed tomograms and ultrasound examinations of the brain were taken at the time of admission and reviewed subsequently by a neuroradiologist who was unaware of diagnosis and outcome.

Results

Apart from two of the children who were aged 13 and 15 months, the mean age of the remaining 10 children was 10.2 years (median 10.5 years, range 7.1-12.8 years). Eleven were white and the remaining child was of Bengali origin. There were eight girls. Seven children died (mortality 58%). On review, four survivors were normal while a fifth suffered minimal cerebral damage.

The prodrome consisted of varicella in three, respiratory symptoms in six, and gastrointestinal illness in two. One child had no recognisable prodromal illness. Duration of prodrome ranged from two to 10 days (median four days); nine children had been given aspirin.

The neurological phase was heralded by profuse vomiting in eight and by lethargy and mild vomiting in three. The 13 month old patient presented with a hypoglycaemic convulsion and an attack of apnoea.

Despite typical presentations, Reye's syndrome was suspected by the referring hospital in only six of the children. Blood ammonia concentration was measured in three in whom Reye's syndrome was the admitting diagnosis. This was raised in one child who was immediately referred to the intensive care

Table 1 *Lovejoy coma scales*⁴

Stage	Level of consciousness	Respiratory pattern	Response to pain	Other central nervous system findings
1	Lethargic, drowsy	Normal	Appropriate	Nil abnormal
2	Disoriented, delirious	Hyperventilation	Appropriate	Pupils normal, hyperreflexic
3	Obtunded, comatose	Hyperventilation	Decorticate posturing	Pupils normal/dilated, hyperreflexic, extensor plantars, dolls eye reflex normal
4	Coma	Hyperventilation or Cheyne-Stokes respiration	Decerebrate posturing	Fixed, dilated pupils $\pm$ hippus, calorics dysconjugate, dolls eye reflex lost
5	Deep coma, seizures	Cheyne-Stokes respiration or respiratory arrest	Flaccid	Fixed, dilated pupils loss of brain stem reflexes, isoelectric electroencephalogram

unit and survived with no neurological deficit. The finding of normal ammonia concentrations in the two remaining children reassured the referring hospital that Reye's syndrome had been excluded, although both had encephalopathic features at the time: other investigations, including lumbar puncture, were then performed in an attempt to establish a diagnosis. On admission to the intensive care unit raised blood ammonia concentration, cerebral oedema, and raised intracranial pressure were present and both died.

In the other three children Reye's syndrome was first suspected only after considerable neurological deterioration. In one child this was some 40 hours after admission and after irreversible cerebral damage sustained in a respiratory arrest in stage 4 coma.

Other referring hospital diagnoses included chickenpox encephalitis, herpes simplex encephalitis, and, in two children, acute dystonic reaction to prochlorperazine, which had been prescribed by the general practitioner for nausea and vomiting.

Mean duration of coma stage 1 was 18 hours (range 0–24) in those who died and 50 hours (range 39–72) in those who survived.

On admission to the referring hospital, only one child was in coma stage 4. On admission to the intensive care unit all except two children had deteriorated neurologically, five being in coma stage 4 and two in coma stage 5. Six of these seven children died.

Median duration of stay in the referring hospital before transfer to the intensive care unit was 22.5 hours (range 7–41.5) for those who died and 8 hours (range 5–30) for those who survived.

Papilloedema was not seen in any child during admission to referring hospital and there were no demonstrable signs of meningitis. Lumbar puncture was attempted at the referring hospital in all 12

children and was successful in 11. Cerebrospinal fluid (CSF) was normal in all cases. Manometric CSF pressure was recorded in three children and was reported as being normal.

In three children a provisional diagnosis of 'coning' after lumbar puncture was made before referral to intensive care. One child, sufficiently delirious and combative (coma stage 2) to require sedation for lumbar puncture, became unresponsive to commands two to three hours later. A second child, unable to recognise his parents and delirious and irritable with dilated poorly reacting pupils (coma stage 2) at the time of lumbar puncture, became unconscious immediately afterwards. The third child was responding to deep pain only, had dilated but reactive pupils, and was hyperreflexic (coma stage 3) at the time of lumbar puncture. Her level of consciousness seemed to improve transiently after CSF was removed. Two hours later, however, she developed fixed and dilated pupils in conjunction with systemic hypertension and Cheyne-Stokes respiration for which she required intubation and ventilation. She subsequently died.

There was evidence of deterioration after lumbar puncture in a further three children. One child, comatose and tachypnoeic with a full fontanelle (coma stage 3), developed episodes of bradycardia and apnoea, necessitating intubation and ventilation 30 minutes after lumbar puncture. Two other children, in coma stage 4 at the time of lumbar puncture, developed progression of brain stem signs, culminating in respiratory arrest. Four of the six children who deteriorated after lumbar puncture died.

On admission to the intensive care unit it was elected to monitor intracranial pressure in all but two of the children, one who was brain dead on arrival and one who had a normal scan when in

coma stage 2. In the course of the four years under review three different methods of monitoring intracranial pressure were employed: subdural solid state pressure transducers, subdural fluid filled catheters, and subarachnoid screws. Because of technical problems with the first two methods and the need to ensure minimal disturbance to the patient, we now use a subarachnoid screw inserted at the bedside.

Intracranial pressure was raised (> 20 mmHg) on or shortly after monitoring was begun in five out of eight children whose computed tomograms of the brain suggested cerebral oedema. Monitor malfunction precluded accurate intracranial pressure measurement in the other three, but clinical signs in two of these strongly suggested surges in intracranial pressure. Initial intracranial pressure was < 20 mmHg in both children whose computed tomograms of the brain yielded normal results but became raised after 24 hours in one child.

Principles of management of Reye's syndrome on the intensive care unit did not change substantially over the four years. All children were intubated and hyperventilated to maintain arterial carbon dioxide tension between 2.7 and 3.3 kPa (20–25 mmHg) and were nursed in the head up, midline position with all nursing procedures performed under full sedation and paralysis. A serum osmolality of 300–310 mOsm/kg was achieved by fluid restriction and regular treatment with mannitol. Blood sugar was regularly monitored and normoglycaemia maintained with 10–15% dextrose infusions with added electrolytes. Acute rises in intracranial pressure were treated with hyperventilation, sedation, muscle relaxants, and infusion of mannitol. If there was no response to these manoeuvres a slow bolus of intravenous thiopentone was given. Barbiturate coma was maintained with an infusion of thiopentone in the severe cases.

Hypoglycaemia was found at admission to referring hospital in three children and recurred in one shortly after admission to the intensive care unit. Mean peak blood ammonia concentrations (upper limit of normal = 50 $\mu\text{mol/l}$) on admission to the intensive care unit were 147 $\mu\text{mol/l}$ (range 77–210) in those who survived and 396 $\mu\text{mol/l}$ (range 160–484) in those who died. The blood ammonia concentration continued to rise after admission in two children who both deteriorated neurologically after an apparently stable period and died. In all other children ammonia concentrations reached their peak on the day of admission to the intensive care unit. Alanine and aspartate transaminase activities and prothrombin time on admission were raised in all cases (Table 2).

Detailed metabolic investigations were performed in seven cases and revealed amino acid profiles

Table 2 Laboratory results of the fatal cases compared with survivors of 12 cases of Reye's syndrome

	Cases		Normal upper limit
	Died (n=7)	Survived (n=5)	
Peak ammonia ($\mu\text{mol/l}$):			
Mean	396	147	50
Range	(160–900)	(77–210)	
Alanine transaminase (U/l)*:			
Median	1125	507	40
Range	(253–6710)	(336–848)	
Aspartate transaminase (U/l)*:			
Median	967	385	50
Range	(228–5972)	(187–534)	
Prothrombin time (secs)*†:			
Median	14	10.5	3
Range	(7.5–42)	(4.5–11.5)	

*Values on admission to intensive care unit.

†Given as seconds prolonged beyond control value.

consistent with Reye's syndrome (raised alanine, glutamine, lysine, and alpha-amino-N-butyrate).

Microbiological studies were undertaken in all patients and no causative organisms were isolated. Varicella was diagnosed clinically in three children. Influenza B infection was diagnosed serologically in one case.

Liver biopsy was not performed in the survivors. Consent for postmortem examination was refused by the parents of one child while liver biopsy only was permitted in another. Liver histology and histochemistry in six children confirmed the diagnosis of Reye's syndrome. Neuropathology in five children confirmed cerebral oedema in all and herniation in four (two of whom had apparently deteriorated after lumbar puncture).

Discussion

Reye's syndrome is being increasingly reported as a cause of encephalopathy in the United Kingdom.³ The mortality has fallen from 66% for the year 1981–82 to 48% for 1984–85. (S Hall. Personal communication.) Of 23 cases of Reye's syndrome recently reported from Northern Ireland,¹ 22% died, with 74% achieving normal survival. It is noteworthy that the median age in this series was 9 months and that no child was over 6 years of age. This contrasts with our smaller series with a mortality of 58% but older age group.

An excess mortality among older children has been noted since 1981 when the Reye's syndrome surveillance scheme was first established. There is no clear explanation for this finding. In the period from 1981–85, when overall mortality was 51%, the mortality for children aged over 5 years was 66%

compared with 41% for those aged 1 year and under. (S Hall. Personal communication.) This is in contrast to the United States where mortality is highest in the younger child.⁵

In our series survivors were distinguished from those who died by longer duration of stage 1 coma. This has been previously observed by Lovejoy.⁶ Peak ammonia concentrations, considered to be a prognostic indicator in Reye's syndrome,⁷ were higher in the fatal cases discussed here, although there is overlap between the two groups.

The timing of diagnosis of Reye's syndrome and referral to an intensive care unit has a strong influence on outcome.⁸ A provisional diagnosis of Reye's syndrome was made at the referring hospital in six of our children, but in only one did this result in prompt referral (less than five hours) to the intensive care unit. Initially normal ammonia concentrations delayed referral in two, while in three Reye's syndrome was considered only after considerable neurological deterioration.

It is of concern that, despite classic features of a biphasic illness, profuse vomiting, and progressive coma, Reye's syndrome had not been considered as a possible diagnosis before referral in 50% of cases. Reye's syndrome shares these features in common with potentially fatal inborn errors of metabolism such as ornithine carbamyl transferase deficiency and medium chain acyl-CoA dehydrogenase deficiency. Such conditions can only be distinguished from Reye's syndrome by detailed metabolic investigations.^{9, 10} All, however, require urgent treatment and investigation.

These cases highlight some of the problems in making an early diagnosis. Normal blood ammonia concentrations, though not typical, may occur in Reye's syndrome.¹¹

Indications for lumbar puncture and the association of this procedure with acute neurological deterioration in children already suffering from an altered level of consciousness have been the subject of much controversy.^{12, 13} Reye's syndrome has been considered by some as a contraindication to lumbar puncture,¹⁴ while others have considered this justified if papilloedema or deep coma are not present.¹⁵ Although it is difficult to distinguish the clinical evolution of Reye's syndrome from the adverse effects attributable to lumbar puncture, we found that lumbar puncture was rapidly followed by pronounced deterioration in six children.

Raised intracranial pressure is difficult to diagnose clinically and is not reliably excluded by the absence of papilloedema. Indeed, we found that papilloedema was rarely present even when there was obvious cerebral oedema seen on the computed tomogram. When there is clinical suspicion of raised

intracranial pressure lumbar puncture should be deferred. The appearances of cerebral oedema on computed tomogram of the brain would be an indication for direct measurement of intracranial pressure, and lumbar puncture should not be performed. It should be remembered, however, that raised intracranial pressure can occur in the presence of a normal computed tomogram of the brain, and, if there is any doubt, intracranial pressure should be directly monitored. It is our current practice to initiate monitoring of intracranial pressure in any child who has progressed to stage 2 coma or beyond, even if a computed tomogram of the brain yields normal results. Our unit now favours the use of subarachnoid screws, which can be inserted at the bedside.

Until more is understood about the aetiology (or aetiologies) of Reye's syndrome, treatment remains supportive with control of raised intracranial pressure fundamental to survival. Our experience and that of other centres suggests that survival is unlikely if a child has already progressed to coma stage 4 or 5.

Delay in referral to the intensive care unit was associated with a poor outcome, particularly for children with rapidly advancing coma. These children should be admitted for assessment to an intensive care unit.

In conclusion, outcome for Reye's syndrome in the UK has not improved appreciably over the last four years. Our experience suggests that it is not being recognised or referred at an early stage in the illness, both of which are factors that could influence outcome. Clinical history and examination cannot satisfactorily exclude acutely raised intracranial pressure. This possibility should be considered when deciding to lumbar puncture an encephalopathic child, particularly where dilated pupils, decorticate or decerebrate posturing, or altered brain stem signs are present. In these circumstances early referral to a paediatric intensive care unit with facilities for computed tomography and monitoring of intracranial pressure with full neurosurgical support should be arranged.

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