Controversy

Preadmission antipyretics in Reye's syndrome

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SUMMARY The parents of 106 children who had had Reye's syndrome and those of 185 comparison children who had febrile illnesses were interviewed in order to compare preadmission medication exposure rates in the two groups. Although comparable proportions of case and comparison patients had taken antipyretics in the three weeks before admission, a significant excess of cases (59% compared with 26% in the comparisons) had been given aspirin, whereas significantly more comparison children (49% compared with 25% in the cases) had taken paracetamol. There was an excess exposure to aspirin in children under 5 years of age; the excess observed in older patients just failed to reach significance. Separate analyses within Northern Ireland and England also showed a case-comparison difference. A significant correlation was shown between aspirin (but not paracetamol) exposure and the closeness with which cases conformed to the diagnostic criteria of Reye's syndrome, measured by an arbitrary score.

The many difficulties of conducting and interpreting the findings of an epidemiological risk factor study of an association between aspirin and Reye's syndrome are reviewed and emphasised. Inherent biases were present in this as in previous studies and it did not conform to the classical case-control design. Nevertheless the findings suggested that an association between Reye's syndrome and preadmission aspirin may exist in some children.

Reye's syndrome is a rare, serious childhood encephalopathy preceded by a viral prodrome and associated with curiously selective hepatic dysfunction.¹ Although its aetiology and pathophysiology are poorly understood, causation is believed to be multifactorial.² Various toxic agents have been implicated, including aflatoxins, insecticides, and their emulsifiers. An association with aspirin, first mooted 20 years ago,³ was a consistent finding in five case-control studies conducted in the United States from 1978-86.⁴⁻⁸ Although these studies have been criticised,^{9 10} the strength and consistency of the evidence was such that in 1985, the United States public health authorities required warning labelling on aspirin-containing products and initiated a public education campaign against use of aspirin in children with feverish illnesses.

The British Reye's Syndrome Surveillance Scheme (BRSSS), which began in August 1981, is an ongoing joint venture of the British Paediatric

Association and the Public Health Laboratory Service Communicable Disease Surveillance Centre.¹¹ Its principal aims are to document the epidemiology of Reye's syndrome in the British Isles and to provide a case registry for future more detailed studies.

This report, based on cases notified to the BRSSS, presents some of the findings of a two year risk factor study. The aim was to collect detailed preadmission data in cases of Reye's syndrome in order to generate aetiological hypothesis that might then be tested in controlled studies. Initially the study was designed to gather information on a wide range of possible risks rather than to focus on any single hypothesis. After publication of the fourth (pilot) study from the United States⁷ and preliminary analysis of our data, however, it was decided to recruit two comparison groups of patients in order to clarify findings in relation to preadmission medication.

Patients and methods

(1) ASCERTAINMENT OF CASES OF REYE'S SYNDROME AND COMPARISON PATIENTS

Cases of Reye's syndrome were ascertained by the BRSSS from voluntary reporting by paediatricians, other health professionals, parents, and from copies of death drafts supplied by the Office of Population Censuses and Surveys and the General Registry Office for Scotland. Parental permission for an interview was sought after agreement of their paediatricians and family doctors. Comparison groups consisted of children admitted with acute febrile illnesses to two teaching hospitals—one each in South London and Belfast.

(2) DATA COLLECTION

Cases of Reye's syndrome and London comparison patients were interviewed by the same person; two senior medical students conducted the Belfast comparison interviews. These took place in the homes of the cases of Reye's syndrome; parents of comparison patients were seen on the wards. A prepiloted, semistructured questionnaire was used to seek information from the parents of cases of Reye's syndrome on social background; the child's and the family's medical history; symptoms, severity, and duration of the prodromal illness. Questions were also asked on risk factor exposure: (a) details of all medications given in the three weeks before admission—for example, names (visual verification was also requested), dates, dosages, and whether ever given before; (b) contact illness history; (c) travel history; (d) environmental exposures—for example, chemicals, insecticides, sick animals; and (e) diet. Finally, parents were asked about prior knowledge of specific risk factors.

The comparison patients' questionnaire was identical to that used for the cases of Reye's syndrome but omitted questions relating to risk factors other than medications.

(3) DIAGNOSTIC CRITERIA

Cases of Reye's syndrome conformed to the BRSSS definition.¹¹ As even with 'typical' histology this definition is relatively non-specific and distinction must be made from other encephalopathies,¹² each case was also allotted a score (see appendix). This was based on all the clinicopathological features of Reye's syndrome and was an arbitrary measure of how closely the patient fulfilled the diagnostic criteria. Scores ranged from zero to 17—low scores reflecting those in whom the diagnosis was not confirmed and maximum scores reflecting patients who were characteristic in all aspects. Scoring was done without knowledge of risk factor exposure.

Comparison patients consisted of previously healthy children with an acute febrile respiratory, intestinal, or other (infectious) illness who did not develop Reye's syndrome. Any selection was entirely dependent upon interviewer availability.

(4) DATA ANALYSIS

Completed questionnaires were coded, entered on computer, and checked for coding errors using a quality assurance sample. Statistical analysis was performed using the 'Minitab' package and probability values calculated using Fisher's exact test (two tailed).

(5) ETHICAL APPROVAL

This was obtained from the ethical committee of the Public Health Laboratory Service and from the appropriate ethical committees for the comparison group studied.

Results

CASES OF REYE'S SYNDROME

Altogether 264 cases were reported to the BRSSS between 1 August 1981 and 31 July 1985 when recruitment to the risk factor study terminated. The parents of 106 patients were interviewed between April 1984 and October 1985. The median admission to interview interval was 10 months (range, 11 days–5.7 years).

Fifty one of the interviewed cases had had histological examinations all of which showed changes characteristic of Reye's syndrome. Of 56 survivors, 10 had sustained severe and two minor, neurological damage. There were two patients with juvenile chronic arthritis (an unexpectedly high prevalence) who were being treated with long term aspirin at onset of Reye's syndrome.

The physicians of 44 others were approached but these cases were not included for the following reasons: because of the parents' emotional state permission to interview was refused by the medical attendants of 13, and in one case the parents themselves refused; 26 were impossible to contact; in two the diagnosis was revised after the initial approach, and in two others the study ended before the interview could be arranged.

In the remaining 114 cases the medical attendants were not approached for various, mainly administrative reasons—for example, the family doctor's name or parental address were unavailable (n=43); the report was received after data collection had ceased (n=17); the geographic location was incompatible with the approaching end of the study (n=13); diagnostic revision was already established (n=22); and diagnostic uncertainty (n=19).

Table 1 Characteristics of 264 cases of Reye's syndrome reported to the British Reye's syndrome surveillance scheme

	Included in risk factor study	Omitted from risk factor study	
		Approached	Not approached
No of children	106	44	114
Median age (months)	23	14	11
Year of onset (%):			
1981	7	5	19
1982	14	31	32
1983	34	38	19
1984	34	18	31
1985	11	8	0
Country (%):			
England	74	75	57
Northern Ireland	13	6	22
Scotland	6	6	7
Wales	4	9	3
Republic of Ireland	4	3	11
Mortality (%):	47	64	48

Those interviewed were slightly older and had a more recent onset than those excluded (table 1). Mortality was higher in those not included after the initial approach and there were more cases not approached in Ireland.

COMPARISON PATIENTS

Of the comparison patients 100 were interviewed in London and 85 in Belfast; the median admission to interview interval was two days (range 24 hours–13 days). One hundred and thirty three interviews took place in 1985, April to December, and 52 (all Belfast) in 1986, January to mid April.

COMPARABILITY OF CASES AND COMPARISON PATIENTS

Cases of Reye's syndrome were older (table 2), but social class distribution was similar. There were significantly more white children among the cases (97% compared with 84%, $p=0.0006$). The figure shows preadmission symptomatology: cases were

significantly more likely to report headache, anorexia, vomiting, abdominal pain, drowsiness, altered behaviour, and unconsciousness, while more comparison patients had fever, rhinorrhoea, cough, and sneezing.

Mean (SD) length of preadmission illness was 8.4 (8.6) days in the cases of Reye's syndrome and 10.4 (10.7) days in comparison patients. The family doctor, consulted for 92% of cases and 81% of comparison patients ($p=0.01$), prescribed one or more drugs for 84% and 81% of these, respectively. In the three weeks before admission, the mean number of drugs (prescribed and over the counter) received by the two groups was 2.2 and 1.9 per patient. Forty four (19%) of 230 drugs given to the cases were available for inspection, in contrast with four out of 344 (1%) given to comparison patients (all confirmed parents' statements). Antibiotics accounted for 47 (20%) and 86 (25%) of all drugs given to the cases and comparison patients, respectively ($p=0.24$).

Table 2 Age distribution of Reye's syndrome cases and comparison patients

Age*	Cases	Comparison patients		
		London	Belfast	Total
	No (%)	No (%)	No (%)	No (%)
12 months	39 (37)	45 (45)	43 (51)	88 (48)
13–60 months	29 (27)	43 (43)	40 (47)	83 (45)
5–10 years	23 (22)	10 (10)	2 (2)	12 (7)
11–15 years	15 (14)	2 (2)	—	2 (1)
Total	106	100	85	185

*Median age of cases was 23 months; median age of comparison patients was 13 months.

EXPOSURE TO ASPIRIN AND PARACETAMOL

Although similar overall proportions (72% compared with 68%, $p=0.64$) of cases and comparisons had received antipyretics, 63 (59%) cases and 48 (26%) comparison patients had had aspirin ($p<0.000001$); five cases but none of the comparison group had been given two proprietary forms. Twenty seven (25%) cases had been given paracetamol compared with 91 (49%) comparison patients ($p=0.00015$). Fourteen (13%) cases and 16 (9%) comparisons had received both antipyretics. Fifty (79%) of the cases given aspirin had had this medication with no ill effects in the past.

Six cases of Reye's syndrome each of whom had

Figure Preadmission symptoms in cases of Reye's syndrome and in comparison patients expressed, for each symptom, as proportion of total subjects for whom information available (49–100% cases and 37–100% comparisons, depending on symptom).

also had aspirin had been given non-aspirin salicylate, compared with nine comparison patients, five of whom had had aspirin; the most frequent preparation was a teething gel containing choline salicylate.

Analysis of antipyretic exposure by age (those less than 5 years compared with those 5 or more) showed that an excess of the cases of Reye's syndrome had been given aspirin in each group, although in the older cases this difference just failed to reach significance (table 3). Conversely, among comparison patients in both age groups there was excess exposure to paracetamol but in the younger group significance was not achieved.

Among London comparison patients, there was no difference in aspirin use when comparing white children with other ethnic groups as a whole.

An analysis of aspirin use in England and Northern Ireland separately was undertaken. In Northern Ireland all 14 children with Reye's syndrome had received aspirin compared with 32 (38%) of the comparison patients ($p=0.00002$). In England, by contrast, 38 (49%) of the 78 cases had had aspirin compared with 16 (16%) London comparison patients ($p=0.000004$). Belfast comparison patients had received aspirin significantly more frequently than those in London ($p=0.0014$). All six cases of Reye's syndrome in Scotland, three of the four in

Table 3 Antipyretic exposure in relation to age in Reye's syndrome cases and comparison patients

Antipyretic	Aged <5 years		p Value	Aged 5 years and over		p Value
	Cases No (%)	Comparisons No (%)		Cases No (%)	Comparisons No (%)	
Aspirin	33 (49)*	41 (24)*	0.0005	30 (79)	7 (50)	0.07
Paracetamol	24 (35)	84 (49)	0.07	3 (8)	7 (50)	0.004
Total in age group	68	171		38	14	

*Includes 18/39 cases v 13/85 comparison patients who were <1 year old, $p=0.0008$.

the Republic of Ireland, and two of the four in Wales had been given aspirin.

REYE SCORE

There was a strong association between this score and the likelihood of receiving an antipyretic (table 4). Analysis by type of medication showed a highly significant correlation between aspirin exposure and Reye score (trend $p=0.00001$), in contrast with that with paracetamol ($p=0.07$). Eleven out of the 12 cases with scores of 15–16 had had aspirin, compared with none of the four with scores of 0–4. Further analysis suggested that this link between the Reye score and aspirin use was age independent.

In the following analyses we attempted to estimate the presence and effect of certain biases (for example, recall, prior knowledge, protopathic bias, and different case-comparison illness dates) which might have influenced case-comparison differences in antipyretic exposure. In the cases with Reye's syndrome there was no relation between admission to interview interval and the use of aspirin, paracetamol, or neither antipyretic. Parents could recall the aspirin brand name in a similar proportion of case (59/68, 87%) and comparison patient (44/48, 92%) aspirin exposures. Among these a higher proportion of cases had received an adult preparation (37/59, 63%) compared with comparison patients (11/44, 25%) ($p=0.00002$).

Reported preadmission aspirin usage among the 57 (54%) parents of cases who volunteered prior knowledge of a Reye's syndrome-aspirin association was compared with that among the 49 parents who did not volunteer such knowledge. The proportions were 45 (79%) and 18 (37%), respectively ($p=0.0002$). An analysis of Reye score and antipyretic exposure within the 'no prior knowledge' group, however, still showed a highly significant correlation between this score and aspirin (but not paracetamol) exposure.

Parents' reports of aspirin use were compared with the original reports to BRSSS from the

notifying clinician. Because of an alteration in the surveillance questionnaire, comparable data were available for only 33 cases. There was agreement in 28 (85%). Of the remaining five, the BRSSS indicated that four had not been given aspirin, whereas the risk factor study response was that it had; the reverse was the case in one other.

BRSSS data were also used to compare aspirin use in the cases whose parents were excluded from interview, with that in cases whose parents were interviewed. Limited data on antipyretic use were available for 65 excluded cases and suggested that four out of 17 (24%) of those approached and 25 out of 48 (52%) of those not approached had received aspirin. This compared with 63 out of 106 (59%) in those interviewed.

An attempt was made to exclude protopathic bias by repeating the case-comparison analysis of aspirin exposure after exclusion of cases of Reye's syndrome given aspirin on the day of 'onset' or thereafter. 'Onset' was arbitrarily defined as the first day on which anorexia, vomiting, drowsiness, or behavioural change occurred, except where the latter was reported within 24 hours of prodrome onset. Thus defined 17 cases were excluded: 10 out of 33 who were less than 5 years of age and seven out of 30 who were 5 or older. A significant difference remained between the two groups as a whole ($p=0.004$), although this disappeared in cases less than 5 years of age taken separately ($p=0.38$).

There was no significant difference between aspirin exposure rates among Belfast comparison patients interviewed in 1986 and those interviewed in 1985. Exclusion of the former from case-comparison analyses did not reduce the levels of significance of the differences in aspirin exposure.

If the analysis was restricted to those cases and comparisons with onsets in 1985, the difference in aspirin exposure (10/12 (83%) compared with 32/133 (24%) respectively) was even more striking than among the two groups as a whole.

Table 4 *Reye score in relation to antipyretic exposure*

Score*	No of patients	Aspirin No (%)†	Paracetamol No (%)‡	No antipyretic No (%)§	Total No (%)
0–8	22	5 (21)	7 (29)	12 (50)	24 (100)
9–10	29	13 (38)	11 (32)	10 (29)	34 (100)
11–13	30	23 (68)	5 (15)	6 (18)	34 (100)
14–16	25	22 (79)	4 (14)	2 (7)	28 (100)
Total	106	63	27	30	120

*Groups divided into (approximate) quartiles for statistical efficiency.

Trend p values: †0.00001; ‡0.07; §0.003.

Row totals do not add up as some subjects had each antipyretic.

Discussion

The findings of this study suggest that there is an epidemiological association between the development of Reye's syndrome and use of aspirin during the viral prodrome. Significant differences were shown between the cases of Reye's syndrome and comparison patients as a whole, for those under 5 years of age, and for the English and Northern Ireland groups separately. Cases of Reye's syndrome were more likely than comparison patients to have been given two or more aspirin preparations. There was also a strong relation between diagnostic precision of Reye's syndrome, as measured by the Reye score, and the likelihood of prior aspirin medication.

When interpreting these findings, several important methodological issues must be addressed. These exemplify the inherent difficulties in an epidemiological study of medication risk factors in a condition such as Reye's syndrome.¹³

(1) DATA COLLECTION BIASES

(a) *Emotional background to interview*

All the parents of children with Reye's syndrome had lived through a major life event after which they had had varying lengths of time to adjust. For many this interview was their first opportunity to ventilate concerns and anger about possible causes and avoidability. In contrast with the studies in the United States, which were mainly conducted while the index case was still in hospital⁴⁻⁸ (and which make no reference to parental emotional state) our case interviews were carried out in the home and when outcome was known. Our comparison parents, interviewed in hospital, may have been in a somewhat more stressful setting, although none of these patients required intensive care. The effect of these differences on comparability of recall accuracy between the two groups is difficult to assess.

(b) *Interviewer bias*

Limited resources meant that the same person was concerned both with the preparation for, and the conduct of, the risk factor study. The principal interviewer was, therefore, fully aware of published aetiological hypotheses about Reye's syndrome. On the other hand, because of striking epidemiological differences in Reye's syndrome between the British Isles and the United States,¹¹ there seemed no cogent reason why the same risk factors might apply. From the outset our approach was, therefore, to study a wide range of risks, rather than concentrate on the narrower field of prodromal medication.

As in the studies in the United States, it was impossible for the principal interviewer to be unaware of the group (case/comparison) to which

parents belonged, and difficult to see, given the serious nature of Reye's syndrome (47% of the cases we studied died) how this bias could have been avoided.

(c) *Product identification*

In contrast with the studies in the United States, this was more possible in the children with Reye's syndrome whose parents were interviewed at home than in the comparison groups seen in hospital. Although direct sighting always confirmed parents' statements, the numbers concerned were small. The value of this method of verification is questionable, however, as it takes no account of other unrevealed drugs in the home.

(2) SELECTION BIAS

(a) *Excluded cases*

There were minor demographic and clinical differences between these and the included cases, but it is not felt that their omission introduced any systematic bias. We attempted to measure antipyretic exposure in these patients from BRSSS data. Although the proportions reported as receiving aspirin were lower in the two groups of excluded cases than in the group interviewed, the value of these data was hampered by small numbers and the non-standardised manner of collection.

It could be suggested that some clinicians might only make a diagnosis of Reye's syndrome whenever a patient had actually received aspirin. This issue was a major criticism¹⁰ of the pilot study in the United States, which took place during a time of heightened public debate concerning the role of aspirin.⁷ Although there had been some publicity in the United Kingdom before this study, there was little media attention until the Committee on Safety of Medicines announcement in June 1986. Furthermore, the only clinical series published in the United Kingdom at the time of the study had found no evidence to support the then strongly disputed Reye's syndrome-aspirin association.¹⁴ Thus although there could have been some selection bias because of an unrepresentative case sample, this seems unlikely in the study period concerned.

(b) *Subject classification*

The epidemiological case definition of Reye's syndrome is sensitive but non-specific. A precise diagnosis remains problematical, depending upon an amalgam of clinical and biochemical features, supported by histopathological and ultrastructural data. Not all of our cases, however, conformed to this exacting standard. Similar criticisms may be levelled at the case-control studies from the United States that used broadly similar criteria. While it is a

straightforward matter to diagnose salicylate intoxication, certain inborn errors of metabolism which mimic Reye's syndrome have proved much more difficult to exclude with certainty.¹² Using the current standard case definitions, it seems likely that any series of 'Reye's syndrome' cases will contain some patients in whom, on more sophisticated investigation, specific metabolic disorders will be discovered. Unless it is postulated that aspirin has a role in such conditions it is not easy to explain the high proportion of cases given this medication in studies in the United States (93–100%). In contrast, only 59% of our cases were similarly exposed and it was this which made our novel method of analysis using the Reye score both valid and essential.

Although clinical scoring is arbitrary and can easily be criticised, this exercise was carried out 'blind' to medication usage. The strong correlation between Reye score and aspirin medication in contrast with that with paracetamol was therefore both striking and surprising and may help balance a degree of diagnostic imprecision.

(c) Comparability of case and comparison patients

Although this was not conceived as a formal case-control study, if inferences are to be drawn from differences in antipyretic use the characteristics of the two groups should be compared. The comparison patients were slightly younger than the cases. Comparison of age specific aspirin exposure rates, however, still showed a significant excess among the cases of Reye's syndrome who were less than 5 years of age (as well as in those less than 12 months of age). In the older group the small numbers of comparison patients may have prevented detection of a true difference. We cannot therefore conclude that aspirin does not have a role in these older patients.

There were geographical differences in the use of aspirin, possibly reflecting different parental and professional attitudes to choice of antipyretic. All of the cases in Northern Ireland and Scotland were so treated and the rates of aspirin ingestion were also significantly higher in Belfast than in London comparison patients. Geography alone, however, was not a major confounding variable, as there were still significant case-comparison differences in aspirin exposure within Northern Ireland and England when analysed separately.

The variables that influence the choice of an antipyretic in an acute febrile childhood illness are largely unknown. American parents may be more likely to use aspirin than paracetamol for more severe illness as judged by the height of fever.⁹ The effect of this variable was difficult to compare in our

case and comparison groups because, although fever was reported by parents to be the most severe preadmission symptom in comparison patients' parents (in contrast with cases among whom it was vomiting), the majority in each group assessed its presence and degree by touch rather than by thermometer measurement. The very slight difference in prodrome duration might, if anything, have led to cases of Reye's syndrome receiving fewer antipyretics, but in fact the overall proportions receiving these drugs in each group were similar. Whether the qualitative differences between the two groups in the range of symptoms influenced the choice of antipyretic is speculative. Parents of cases tended to report symptoms that might have reflected rising intracranial pressure, while those of comparison patients described those suggestive of a viral upper respiratory infection (figure). Although family doctors were consulted significantly more often by the cases, there was no difference in the proportions of total medications given to each group that were antibiotics, which suggests a degree of comparability in severity.

(3) RECALL AND REPORTING BIAS

In contrast with the parents of children with Reye's syndrome, parents of comparison patients were interviewed within a few days of onset and this may have helped minimise recall bias associated with less severe illnesses compared with that of the cases. Whether the seriousness of the illness of the cases improved recall by their parents and balanced the influence of the longer admission to interview intervals is speculative. It did not appear to affect antipyretic reporting rates, brand name recall ability, or to result in significant disparity with BRSSS medication data.

The apparent association between 'prior knowledge' of aspirin as a risk factor and likelihood of reporting preadmission aspirin may reflect a serious reporting bias. This bias, whose detection and prevention would be extremely difficult, was not addressed in the studies in the United States where parents were likely to have been more informed because of both national and local publicity campaigns. In our study it is hard to see how reporting bias could have influenced the Reye score findings, which still showed a significant association with aspirin within the group with 'no prior knowledge'.

(4) PROTOPATHIC BIAS

It is arbitrary, and, if aspirin has an exacerbatory rather than an initiator aetiological role, possibly irrelevant, to identify the point of onset of Reye's syndrome. After excluding cases in whom the day of onset (on our definition) coincided with aspirin

exposure, there still remained a significant case-comparison difference in the overall proportions given aspirin.

(5) OTHER ISSUES

Demonstration of a dose-response relation is one of the classic criteria of causality. Although a significant excess of cases exposed to aspirin had been given adult preparations, we made no formal attempt to study dose-response for several reasons: (a) indices of response, such as coma stage on admission or outcome that have been used in earlier studies,^{4 15} are subject to many confounding variables linked to the wide range of treatments used; (b) aspirin pharmacokinetics in the Reye's syndrome prodrome may differ from those in normal children with a trivial febrile illness;^{3 16 17} and (c) if the role of aspirin is idiosyncratic or adjuvant, dosage may be irrelevant.

The finding that almost four fifths of cases given aspirin, had been so exposed in the past, without ill effects, shows the complexity of the aetiopathogenesis of Reye's syndrome. If aspirin has an aetiological role there must be an exceptional unpredictable combination of circumstances that act as a trigger.

Three of the studies in the United States gave data on the types of salicylate to which cases had been exposed.^{4 7 9} Although some of those patients, as in this series, had been exposed to non-aspirin salicylates, only three patients out of all four studies had not also taken aspirin. Non-aspirin salicylate exposure in our study may have been incompletely ascertained, however, because some parents may not have perceived such preparations as medications. The possibility of a role for these agents in Reye's syndrome remains unknown.

Conclusions

We have emphasised the complexities of conducting an epidemiological risk factor study to assess the role of preadmission aspirin in Reye's syndrome. This was not a prospectively designed formal case-control study, and, as in the studies in the United States, some inherent biases were present whose influences were unmeasurable. Nevertheless our findings suggest that an association between Reye's syndrome and preadmission aspirin may exist, which together with the finding of a reverse association with paracetamol confirms published results.⁴⁻⁸

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Appendix

'REYE SCORE'

- (a) *Clearly defined prodrome*: yes=2; no=0; not recorded=1.
- (b) *Vomiting*: moderate-severe=2; minimal=1; no=0; not recorded=1.
- (c) *Serum alanine/aspartate transaminase*: raised three or more times normal concentration=3; raised less than three times normal concentration or concentration not specified=2; not raised=0; not measured/not recorded=1.
- (d) *Plasma ammonia*: as (c).
- (e) *Cerebrospinal fluid*: white cell count $\leq 8 \times 10^9/l$ =2; white cell count $> 8 \times 10^9/l$ =0; not examined, or bloody tap, or not recorded=1.
- (f) *Hepatic pathology*: macroscopically fatty but no histological examination=1; histological description: panlobular microvesicular fatty infiltration=3; histological description: 'typical or suggestive of Reye syndrome'=2; histology not recorded or not undertaken=0.
- (g) *Investigations to exclude alternative diagnoses*: done=2; not done or not recorded=0.
- (h) *One or more atypical features* (for example, family history, history of recurrent episodes, unusual presentation such as sudden death)=-2.

Highest possible score=17.

If patient initially met case definition but subsequently had the diagnosis revised (for example, as a result of histological findings at postmortem examination or of investigations for metabolic disorders) a score of 0 was allotted.

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Commentary

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The decision to severely restrict the use of aspirin in children in the United Kingdom was probably influenced by components of the carefully analysed study by Hall and her colleagues. Please note that 40% of the cases in the study were not thought to have taken aspirin before or during their illness. Note that four out of five of the cases who had taken aspirin had taken it in the past without ill effects. Note too that the authors conclude that 'If aspirin has an aetiological role there must be an exceptional unpredictable combination of circumstances that act as a trigger.' Reye's syndrome 25 years after it was first defined still presents many challenges.^{1 2}

For the clinician the first is early consideration of the diagnosis in any child with encephalopathy and vomiting so that steps can be taken to prevent a further increase in intracranial pressure and so that glucose may be given intravenously in sufficient concentration to provide energy for cells deprived because of disordered mitochondrial function. The second challenge is to arrange appropriate investigations to identify genetically determined metabolic disorders which may present as Reye's syndrome. At least 23 have been reported to date. Defects of fatty acid oxidation and urea synthesis can cause particular difficulties in diagnosis. While most of these disorders present before 3 years of age, presentation in the second and third decade has been reported.

Accurate diagnosis may only be possible if samples of serum or urine have been collected in the acute stage and stored at -70°C for subsequent

analysis. It is not clear how many of these disorders have been rigorously excluded in any of the epidemiological studies. We should be very cautious about diagnosing cryptogenic Reye's syndrome in the first three years of life. Accurate diagnosis of alternative genetic disorders is essential for genetic counselling and to prevent relapse with the risk of brain damage or death in the proband. Siblings may be at risk, not only of Reye's syndrome but of 'cot death'.

In cryptogenic Reye's syndrome there are two characteristic but *unexplained* pathogenic phenomena.

(1) An unusual disturbance of mitochondrial structure associated with a decreased activity of all mitochondrial enzymes, best documented in liver tissue. These abnormalities are most severe in the first 48 hours after onset, progressively returning to normal within five to nine days. Other subcellular organelles show only minor changes.

(2) An intense catabolic state, the duration of which seems to be similar to the mitochondrial abnormality.

At least 19 different viruses, including examples from major groups of RNA and DNA containing viruses, have been implicated in the viral prodroma. Viruses are rarely recovered from the liver or brain. Just why such viral infection could cause a specific mitochondrial lesion in between 1:20 000 to 1:500 000 of children infected is quite unknown. In laboratory studies it has been shown that hepatic