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Trends in the incidence of Reye's syndrome and the use of aspirin

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Abstract

In 1986 there was a public warning in the United Kingdom about a link between the consumption of aspirin and Reye's syndrome. To find out if the use of aspirin and paracetamol in children had altered, and whether the incidence of Reye's syndrome had changed since a previous study, parents were interviewed in Belfast and London, and the British Reye's Syndrome Surveillence System data were reviewed. Children with febrile illnesses were 17 times more likely to have received aspirin before admission to hospital in 1985/6 compared with 1988/9. Only 21 Belfast parents (40%) and 13 London parents (27%) had heard of Reye's syndrome and only 12 in Belfast (23%) and seven in London (15%) knew of its association with aspirin, suggesting a continuing need for public education. Cases of Reye's syndrome declined both in numbers (from a peak of 79 in 1983/4 to 19 in 1988/9) and in median age. Of the 418 reported cases, the diagnosis was subsequently revised in 89, most often (in 31 of 89, 36%) to 'inborn errors of metabolism'.

The precise aetiology of Reye's syndrome, a severe encephalopathy of childhood that is complicated by selective hepatic dysfunction,[1] is unknown but believed to be multifactorial.[2] Six case-control studies conducted in the United States between 1978 and 1989 showed that there was an association between Reye's syndrome and taking aspirin.[3–8] Consequently, the public health authorities required warning labels to be placed on aspirin products and introduced a public education campaign throughout the United States in 1985. A study in the United Kingdom in 1986 also demonstrated an association between taking aspirin and cases of Reye's syndrome.[9] In June 1986, the Committee on Safety of Medicines recommended that aspirin should not be prescribed for children under 12 years of age except for rheumatic diseases. The aspirin products were withdrawn from sale and a public education campaign was initiated in the United Kingdom.[10]

The present study was conduced in 1988/9, firstly to find out what drugs were being used to treat fever among children admitted to hospital with acute febrile illnesses; secondly, to compare this use with that among similar children whose parents were interviewed in the earlier study conducted before the warning by the Committee on Safety of Medicines in mid 1986[9]; thirdly, to find out whether (two to three years after the publicity) parents had heard of Reye's syndrome and, if so, whether this influenced their choice of drug; and finally, to find out from the British Reye's Syndrome Surveillance Scheme (BRSSS), what changes had taken place since 1986.

Methods

SURVEY OF DRUG TREATMENT

Parents of children admitted to hospital with acute febrile illnesses were interviewed on the wards using a standard structured questionnaire. The two hospitals, one in Belfast and the other in London, were the same as those used for ascertainment of a comparison group in the earlier British study.[9] In Belfast the interviews took place between January and November 1988, and were conducted by a paediatrician. In London, subjects were interviewed between January 1988 and March 1989 either by an epidemiologist or by one of two medical students.

Demographic data were collected and the occupation of the parent (or head of the household) was used to judge social class.[11] Information about symptoms before admission, consultations with the general practitioner, and what drugs had been taken (both prescribed and given by parents) was collected using the same format as in the earlier study.[9] In addition, parents were asked whether they had changed the drugs they used to treat childhood febrile illness during the previous two years and if so for what reasons; whether they had heard of a disease called Reye's syndrome; and whether they knew if aspirin was associated with bleeding from the stomach, ringing in the ears, diarrhoea, or Reye's syndrome.

Coded data from the questionnaires from both centres were analysed at the Public Health Laboratory Service (PHLS) Communicable Disease Surveillance Centre (CDSC). Odds ratios were calculated and χ^2 or Fisher's exact test of probability were applied where appropriate.

Ethical approval for the two surveys was obtained from relevant research ethics committees. The study data were compared with those obtained from comparison patients in the earlier British study of risk factors in Reye's syndrome to assess the comparability of the two groups, and to see if there had been any significant changes in which drugs were used before admission.[9] The following symptoms were assessed: being generally unwell, or having a runny nose, earache, cough, fever, anorexia, vomiting, abdominal pain, irritability, drowsiness, and loss of conciousness.

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BRSSS DATA REVIEW

Surveillance of Reye's syndrome in the British Isles began in August 1981 and is maintained by the reporting of cases that conform to a standard case definition.[12] Reporting is undertaken by paediatricians and data are collated by CDSC. Clinicians are asked to inform the scheme if patients, initially reported as satisfying the diagnostic criteria, subsequently have the diagnosis revised.

The BRSS began with passive reporting, but active ascertainment was introduced in July 1986 with the inception of the British Paediatric Surveillance Unit (BPSU).[13] For this study, annual totals, age distributions, and final diagnoses were reviewed for the period 1 August 1981 to 31 July 1989.

Results

SURVEY OF DRUG TREATMENT 1988–9

One hundred and one parents were interviewed, 53 in Belfast and 48 in London. The ages of the children ranged from 6 weeks to 11 years, 49 being girls and 52 boys. The age range, mean age, sex distribution, parental occupation, and social class were similar in the two study populations but ethnic distribution was different, reflecting the larger non-white population in London (table 1).

Medical advice about symptoms before admission was sought by more of the parents in Belfast compared with those in London (table 2), but no differences in prescribing practices by general practitioners was observed. There was five times as much use of the parents' choice of drug in Belfast as in London, which was accounted for by paracetamol being given more often in the three weeks before admission (table 2). Only one parent in Belfast and one in London had given their children aspirin during the three weeks before admission to hospital.

During the two years before the interview, 10 families in Belfast (19%) and 12 in London (25%) had stopped using aspirin for treating their children's febrile illnesses. Eight Belfast families (80%) changed drugs as a result of information in the media about aspirin and Reye's syndrome, compared with one in London. In contrast, 11 London families changed drugs after advice from medical services (pharmacists, nurses, or doctors) compared with one family in Belfast. More parents in Belfast had heard of Reye's syndrome than in London and only 12 in Belfast (23%) and seven in London (15%) knew of its association with aspirin (table 2).

Symptoms of illness before admission were similar in patients in Belfast and London. Only sneezing and loss of consciousness were recorded more often in Belfast than in London ($p<0.05$). Symptoms were similar between the patients in the current survey and the combined comparison group from the earlier risk factor study.[9] Higher proportions of the latter, however, had complained of headache, sore throat, sneezing, diarrhoea, and rashes ($p<0.05$).

The comparison children in the study of risk factors were twice as likely to have been given a drug to reduce fever by their parents during the three weeks before admission to hospital compared with those admitted in 1988/9 (table 3). Furthermore, they were 17 times more likely to have received aspirin in the three weeks before admission to hospital in 1985/6 compared with 1988/9. The difference in the use of aspirin between the two time periods was particularly striking among the Belfast patients; 32 of 85 in 1985/6 (38%) compared with one of 53 in 1988/9 (2%). In London the numbers fell from 16 of 100 in 1985 (16%) to one of 48 in 1988/9 (2%).

Table 1 Demography of the populations studied in the Belfast and London survey of drug treatment 1988–9

	Belfast (n=53)	*London (n=48)*	*Odds ratio*	*95% confidence intervals*
Age range	6 weeks–11 years	4 months–9 years		
Mean age (years)	1·9	2·2		NS
Male:female ratio	26:27	26:22		NS
Ethnic groups:				
No (%) white	50 (94)	24 (50)		
No (%) non-white	3 (6)	24 (50)	16·7	4·3 to 92·1
Social groups:				
No (%) I–II	12 (23)	17 (35)		
No (%) III–V	34 (64)	22 (46)		
No (%) unknown	7 (13)	9 (19)		NS

BRSSS DATA REVIEW

Four hundred and fifty initial reports of Reye's syndrome were received in the period 1 August 1981 to 31 July 1989. Detailed information was provided for 418 of these patients (93%), of whom 89 (21%) subsequently had the diagnosis revised (table 4). The most common revision of diagnosis was an 'inborn error of metabolism' (31 of 89, 36%), typically a disorder of fatty acid oxidation or of the urea cycle.

Table 2 Comparison of drugs used and knowledge of Reye's syndrome in London and Belfast

	No (%) in Belfast (n=53)	*No (%) in London (n=48)*	*Odds ratio*	*95% confidence intervals*
Medical advice sought	41 (77)	32 (67)	1·7	0·7 to 4·5
Parents' use of drugs:				
Parent gave drug to child	35 (66)	13 (27)	5·2	2·1 to 13·5
Aspirin given in previous three weeks	1 (2)	1 (2)	0·9	0·1 to 72·4
Paracetamol given in previous three weeks	34 (64)	12 (25)	5·4	2·1 to 14·1
Change in use of drugs:				
Change of drug for treatment of fever from aspirin during the previous two years	10 (19)	12 (25)	0·7	0·2 to 2·0
Reason for change in drugs used for treatment of fever:				
Media	8 (80)	1 (8)	0·02	0·0 to 0·4
Medical advice	2 (20)	11 (92)	44·0	2·5 to 1847·0
Knowledge of Reye's syndrome and aspirin:				
Knew of any side effects of aspirin	27 (51)	25 (52)	1·0	0·4 to 2·3
Heard of Reye's syndrome	21 (40)	13 (27)	1·8	0·7 to 4·5

Table 4 shows trends in annual totals of cases of Reye's syndrome, with a peak in 1983/4 followed by a consistent gradual decline, which became pronounced in 1988/9. This trend was not seen in the revised diagnosis group.

Reports from Northern Ireland are shown separately in table 4 because case ascertainment from the province has been complete and consistent since the inception of the reporting scheme because of the special interest of one of us (JFTG) in Reye's syndrome. The sharp decline in incidence since 1984 (in contrast to the previous excess incidence compared to the rest of the British Isles shown in the table, has also been reported elsewhere.[14]

There was also a change in the age distribution of the non-revised cases of Reye's syndrome: the annual mean age between 1981/2 and 1987/8 ranged between 33 and 54 months, but fell to 16 months in 1988/9. The median age between 1981/2 and 1987/8 ranged from 13 to 19 months; it was 8 months in 1988/9.

Discussion

There were two principal findings in the survey of drug use: firstly, a fall in the number of children given aspirin before admission to hospital with febrile illnesses in 1988/9 compared with 1985/6, and secondly a lack of parental knowledge about Reye's syndrome. The decline in the use of aspirin is probably a result of the withdrawal of children's aspirin preparations and the warning labelling on all preparations containing aspirin in the United Kingdom, and supports the findings of an earlier study that also showed a fall in the use of aspirin after the publicity campaign organised by the Aspirin Foundation in June 1986.[15] Labelling has been compulsory since 1987 and recommends that children under 12 years of age should not be given aspirin unless prescribed by a doctor; Reye's syndrome is not mentioned. The lack of knowledge about Reye's syndrome, and its association with aspirin, suggests that the effects of the 1986 publicity campaign have not been sustained. Despite the influences of media pressure or medical advice, only 19 parents knew that aspirin had been associated with Reye's syndrome and only 27% in London and 40% in Belfast had heard of Reye's syndrome. This emphasises the continuing importance of labelling products and public education.

Surveillance of Reye's syndrome began in the British Isles in 1981, and in the United States in 1974. In the United States the annual number of reported cases declined from a peak of 550 in 1980, to 20 in 1988.[16] The speed of decline increased in 1985 when there was a national publicity campaign about the association with aspirin and labelling of products was started.[17 18]

Trends in the British incidence of Reye's syndrome are more difficult to interpret because the surveillance programme began more recently and because the annual numbers are small. Furthermore, two confounding influences on reported incidence need to be considered. Firstly, the method of case ascertainment of Reye's syndrome was changed in July 1986 from passive reporting to active reporting through the BPSU,[13] and this could be expected to increase reporting. Annual totals of Kawasaki disease, previously ascertained by the same method as Reye's syndrome, increased nearly fourfold when the BPSU started work.[13] This improved surveillance might tend to be counterbalanced by any decline in case numbers as a result of the Committee on the Safety of Medicines publicity about the association with aspirin in 1986. It is therefore especially encouraging to note the continued slow decline since 1986/7 in cases reported annually.

The second possible influence on these trends is increased awareness that inborn errors of metabolism can mimic Reye's syndrome. These include disorders of ureagenesis and of branched chain amino acid catabolism that have been known for some time, and defects of ketogenesis that have been recognised more recently.[19] The proportions of cases of Reye's syndrome for which there was subsequent diagnostic revision reached a peak in 1986/7, but subsequently declined (table 4). It is possible that some patients are now being more extensively investigated in the first place, so that the true diagnosis is made before the case is reported to the BPSU.

Table 3 Changes in the use of drugs for the treament of fever between 1985 and 1989

	No (%) in 1985/6 (n=185)	*No (%) in 1988/9 (n=101)*	*Odds ratio*	*95% confidence intervals*
Child given drug to reduce fever during three weeks before hospital admission	126 (68)	47 (47)	2·5	1·5 to 4·2
Child given aspirin during three weeks before admission	48 (26)	2 (2)	17·3	4·3 to 149·8
Child given paracetamol during three weeks before admission	91 (49)	45 (45)	1·2	0·7 to 2·0

Table 4 Reye's syndrome in the British Isles: cases with follow up reported between 1 August 1981 and 31 July 1989

	Total reports in British Isles	*Classified as Reye's syndrome*		*No (%) in whom diagnosis revised*	*Northern Ireland reports (Reye's syndrome only)*	
		No	*Rate/100 000 <16 years old*		*No*	*Rate/100 000 <16 years old*
1981/2	39	32	0·25	7 (18)	5	1·2
1982/3	60	50	0·39	10 (17)	10	2·3
1983/4	90	79	0·61	11 (12)	16	3·7
1984/5	61	53	0·41	8 (13)	8	1·9
1985/6	50	37	0·29	13 (26)	3	0·7
1986/7	47	26	0·20	21 (45)	2	0·5
1987/8	44	32	0·25	12 (27)	1	0·2
1988/9	27	19	0·16	8 (29)	0	—
Total	418	329	0·32	89 (21)	45	1·5

On the other hand, from the reports of unrevised diagnoses of Reye's syndrome in young infants—sometimes with a suggestive family history—it seems that awareness of these metabolic disorders is still low.

These two confounding influences do not apply to reporting from Northern Ireland, where numbers have declined since the peak in 1983/4. Furthermore, there has been no concomitant increase in children with 'Reye-like' disorders, nor of inborn errors of metabolism subsequently, who would have fulfilled the Reye's syndrome criteria in spite of continuing efforts by a research team actively monitoring this area (JFT Glasgow, unpublished observations).

It has been suggested that Reye's 'syndrome' is a heterogeneous group of disorders, some with identifiable causes such as inborn errors of metabolism, some with an as yet undefined cause (primary or idiopathic Reye's syndrome), and others—for example as a result of the combined effects of a viral infection and aspirin treatment.[19] Inborn errors that mimic Reye's syndrome are more likely to present in early life, whereas primary Reye's syndrome is more likely to appear later when infection with influenza or varicella are at a peak. The 'Reye score' of patients in the risk factor study[9] was related to age: more cases aged over 10 years had a score of 12 or more compared with those aged under 5 years (11 of 16, 69%, compared with 23 of 70, 33%) (S M Hall, unpublished observations). The mean age of cases reported to the BRSSS (excluding revised diagnoses) fell to 16 months in 1988/9. This trend could be associated with a reduction in older cases (primary and aspirin associated Reye's syndrome), resulting therefore in a relative increase in the proportion of younger patients with Reye's syndrome likely to have an unrecognised inborn error of metabolism.

In conclusion, this study shows that between 1986 and 1988 there has been a reduction in the use of aspirin for children with febrile illnesses admitted to a hospital in both Belfast and in London. The young age group of cases currently reported to the BPSU may suggest that in some patients alternative diagnoses—for example, inborn errors of metabolism—are being missed. Finally, despite the decline in Reye's syndrome and the use of aspirin, many parents are still unaware of the Reye's syndrome-aspirin association, and therefore warning labels on products containing aspirin, and public education, continue to be important in prevention.

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