



**TRUSTEES REPORT
EXTRACTS – 30 SEPTEMBER 1999**

Significant events

1. Studies in the role of aspirin in the pathogenesis of Reye's Syndrome

The results of the major study were published in *Biochimica et Biophysica Acta* in June 1999 under the title 'The mechanism of inhibition of beta-oxidation by aspirin metabolites in skin fibroblasts from Reye's syndrome patients and controls'. The authors were John FT Glasgow, Bruce Middleton, Raymond Moore, Alison Gray and Joanne Hill.

2. Epidemiological surveillance of Reye's Syndrome

The objectives of this project are to describe the epidemiological and clinical features of Reye's syndrome in children in the British Isles, to monitor long term trends, and to provide a database for detailed clinical, laboratory, and aetiological studies. The work is undertaken by Dr S Hall, consultant epidemiologist and honorary lecturer in the Department of Paediatrics, Sheffield University, and by Mr Richard Lynn, research officer at the Royal College of Paediatrics and Child Health (RCPCH)

Surveillance of Reye's syndrome began in August 1981 as a venture shared between the (then) British Paediatric Association and the Public Health Laboratory Service Communicable Disease Surveillance Centre (CDSC). Responsibility for case assessment was transferred to the British Paediatric Surveillance Unit (BPSU) of the RCPCH in June 1986 and from the CDSC to the Department of Paediatrics at Sheffield in 1995. From this point onwards the surveillance scheme has been supported entirely by the National Reye's Syndrome Foundation of the UK.

In addition to BPSU reporting, cases are also ascertained via death entries provided by the Office for National Statistics, the General Registry Office for Scotland, the Northern Ireland Statistics and Research Agency, and via laboratory reports to CDSC.

There is increasing recognition that a number of inherited metabolic disorders – most notably those affecting fat oxidation and ureagenesis may present a 'Reye-like' illness, clinically and pathologically indistinguishable from Reye's syndrome. The surveillance questionnaire, although currently in its simplest and shortest format since 1981, therefore seeks information on whether patients have been investigated for these disorders.

3. Publications and work in press October 1998 – September 1999

(a) Annual report

The report for the year 1 August 1997 – 31 July 1998 was published in the BPSU Annual Report in September 1999. Key findings were as follows.

Between August 1981 and July 1998 a total of 614 suspected cases of Reye's syndrome were reported to the surveillance unit but the diagnosis was subsequently revised in 156 (25%). Seventy six (49%) of the revisions were to one of the Reye-like inherited metabolic disorders. Two hundred and thirty five (53%) of the total 444 cases compatible with a diagnosis of Reye's syndrome died.



3. Publications and work in press October 1998 – September 1999 (continued)

(a) Annual Report (continued)

In the year to July 1998, 11 reports of new cases were received and further information was provided on all of them. Three of the 11 diagnoses had subsequently been revised, leaving eight patients whose clinical and pathological features were compatible with the case definition of Reye's syndrome. All the cases were first reported via the BPSU. Death entries were subsequently received for all five cases of Reye's syndrome who died.

The surveillance findings in 1997/98 were similar to those of the past five years – annual totals remained very low compared to those seen before 1986, the year when warnings about the association between aspirin and Reye's syndrome were first publicised by the Committee on Safety of Medicines. The trends mirrored those in the United States. It was apparent that the trend was continuing into 1999 – by the end of June a total of only seven reports had been received. The diagnosis was subsequently revised in two of these and a further case was highly atypical.

As was the case in the previous year, none of the 1997/98 patients with one possible exception, could be described as having classical "North American-type" Reye's syndrome. This was reflected in the relatively low median "Reye score". That Reye's syndrome was the final diagnosis reflects the fact that no alternative was found and that the case definition is non-specific. The most likely alternative diagnosis was one of the "Reye-like" inherited metabolic disorders, the detection of which may be extremely difficult. The design of the standard surveillance proforma, intended to be as short as possible for busy clinicians, meant that the extent to which each patient was investigated in detail for inherited metabolic disorders could not be determined. However, it appeared from volunteered information that the tendency was toward simply ruling out the commonest fat oxidation defect. For the third year in succession there was a case with a particularly high likelihood of having had an inherited metabolic disorder, who nevertheless was not investigated.

Although it was apparent that primary prevention of Reye's syndrome in children was continuing effectively, the concern expressed the previous year remained, that aspirin-associated cases were continuing to occur in children over 12, the upper age limit on the warning. The one aspirin-associated case in 1997/98, a child who died, was over 12 as were two of three such cases reported in 1998/99 (they all survived). This brought the total aspirin-associated cases since the 1986 warning to 17, 10 of whom were over 12.

(b) Letter in the New England Journal of Medicine

In mid 1999, an important paper from the Centers for Disease Control (CDC) in Atlanta, describing trends in Reye's syndrome in the USA was published in the New England Journal of Medicine (NEJM). The authors demonstrated a sharp decline in reported Reye's syndrome in the USA from a peak of over 500 cases in 1980, the year when the aspirin-Reye's syndrome association was first reported, to not more than 2 cases annually between 1994 and 1997. They also emphasised the increasing importance of the Reye-like metabolic disorders now that "classic" Reye's syndrome has become so very rare. There was an accompanying editorial entitled "The Disappearance of Reye's Syndrome – a Public Health Triumph" which, inter alia, highlighted the vital role that parents' groups in the USA had played in the public education campaign about the dangers of aspirin.



3. Publications and work in press October 1998 – September 1999 (continued)

(b) Letter in the New England Journal of Medicine (continued)

These papers provided the opportunity for Dr Hall and Richard Lynn to publicise the British Reye's syndrome surveillance scheme in this widely read and highly prestigious journal. Accordingly, a letter was submitted which was subsequently accepted for publication. They also took this opportunity to highlight the important contribution of the Foundation to Reye's syndrome research in the UK.

The NEJM letter generated media interest in the UK with features about Reye's syndrome and aspirin (particularly focussing on the issue of the age limit on the warning) in the *Pharmaceutical Journal*, the *Yorkshire Post*, the *Sunday Mirror* and the *Daily Mail*.

(c) Chapter

This was commissioned from Dr Hall and Dr John Glasgow by Professor Kim Rainsford of Sheffield Hallam University, editor of a book to be called "Aspirin and Related Drugs (A Century of Aspirin)" and published by Taylor and Francis. It has a total of 15 chapters, most devoted to the history and pharmacology and therapeutic uses of salicylates. The headings of the chapter on Reye's syndrome include a clinical features, diagnosis, management and outcome and the authors also provided a detailed literature review of the "Aspirin Story". The book was to be published in 2000. A pre-publication copy of the chapter was sent to the Foundation's Honorary Administrator. The authors believe that this work will publicise all aspects of Reye's syndrome to a wider audience than that which usually reads mainly paediatric and epidemiological texts.

d). Work with the Medicines Control Agency (MCA)

Epidemiological surveillance is not just an academic exercise – its purpose is to detect trends in the occurrence of a disease which require action. This is usually some form of public health intervention aimed at preventing the disease in question. In the case of Reye's syndrome, this action is labelling on all medications containing aspirin, which warns against their use in children. Currently, the upper age limit on the British warning is 12 years. The surveillance data, however, indicate that over half of the aspirin associated cases since the 1986 warning, have been in children over 12 (see above). Dr Hall and Mr Lynn began drawing this observation to the attention of the MCA in May 1997. After an initially slow response from the Agency, continued correspondence from Dr Hall and from the Foundation eventually led them to prepare a paper for the Committee on Safety of Medicines (CSM) to deliberate whether the age limit should be changed to include teenagers, as is the case in the USA.

Assistance with the preparation of the MCA's paper involved considerable additional work in 1998/99 providing them with both non-routine aggregated analyses and anonymised clinical data on individual cases. The CSM meeting at which the paper was discussed was to be held in November 1999.

4. Advisory support for the National Reye's Syndrome Foundation

Over the period under review, Dr Hall has advised the Honorary Administrator (Mr Gordon Denney) on a number of issues arising from correspondence received by him, as well as on the layout and content of the revised leaflets produced by the Foundation one for the public and one for professionals. She has also maintained literature searches, provided the Foundation with copies and has obtained copies of relevant original papers.



5. Register of Inherited Metabolic Disorders

In 1998 a grant, the application for which was prepared by Dr S. Hall and Professor D Hall, was awarded to the Research Unit of the RCPCH jointly by the Research Trust for Metabolic Diseases (RTMDC) and the NRSF UK. This was a feasibility study of a surveillance scheme to monitor the effectiveness of tandem mass spectrometry (TMS) screening for inherited metabolic disorders (IMD's) when this is initiated as a national programme. The study was to be conducted by a senior researcher who was in part advised and supervised by Dr Hall. The grant did not include an element for Dr Hall's time because the work was relevant to the future of Reye's syndrome surveillance. This is because of the potential importance of ascertaining all unexplained childhood encephalopathies, including those which are Reye-like, in order to detect cases missed by screening. It was possible that the study would find support for a long-term "home" for Reye's syndrome surveillance under the auspices of an IMD monitoring programme.

The study has now been completed and the report will be published in 2000. Two points emerged which are relevant to the future of Reye's syndrome surveillance.

First, it was clear both from the study and from other informal discussions, that the possibility of securing the long-term future of Reye's syndrome surveillance, with central funding, is unlikely to occur as part of setting up and maintaining a national register of IMD's in association with the proposed screening programme. This was disappointing but not entirely unexpected.

Second, it was also clear from the study and from discussions with colleagues, that clinicians perceive Reye's syndrome as more or less a condition of the past which has satisfactorily been dealt with by the public health action on aspirin. The emphasis has now shifted to the early diagnosis, optimum management and research into "Reye-like" IMDs with specific enzyme defects such as medium chain acyl CoA dehydrogenase deficiency. It is likely that clinical awareness of these IMDs will receive a major boost if, as seems likely, a national TMS screening programme for newborns gets underway. Thus this particular role of the Reye's surveillance scheme will be well catered for in the future.

6. Surveillance of Reye's Syndrome in Adults

It was noted in the previous report that attempts to ascertain cases of adult Reye's syndrome in a manner appropriate for epidemiological surveillance has so far met with only qualified success. Potential sources were neurologists, the Intensive Care National Audit and Research Centre (ICNARC), Hospital Episodes Statistics (HES), microbiology laboratory reports and death entries. The work referred to in the preceding sections meant that little time was available in the period under review to pursue ICNARC and HES. However, it is planned that these should be taken up again next year although there may be difficulties. For example, use of HES has recently become more complex. The main constraint is the requirement for patient confidentiality – this has been strengthened by the 1998 Data Protection Act. This means that any data which might lead to identification of individuals, such as date of birth, or health authority of residence, have to have detailed justification. The dilemma currently facing many epidemiologists studying rare diseases like Reye's syndrome, is that deductive disclosure of individuals' identities is more likely with rare conditions, but at the same time some identifying data are necessary to rule out duplicates.



APPENDIX

BRITISH PAEDIATRIC SURVEILLANCE UNIT EXTRACT FROM 13th ANNUAL REPORT 1998/99

Reye's syndrome

Background

Surveillance of Reye's syndrome began in August 1981 as a venture shared between the (then) British Paediatric Association and the Public Health Laboratory Service Communicable Disease Surveillance Centre (CDSC). Responsibility for case ascertainment was transferred to the Surveillance Unit in June 1986 and from CDSC to the Department of Paediatrics at Sheffield in 1995. In the early years, the results of surveillance showed that the incidence of Reye's syndrome in the British Isles was similar to that in the USA but cases occurred at a younger mean age, there was no clear seasonal (winter) peak, no striking association with influenza and chickenpox (although such cases did occur), and a higher case fatality rate.

In 1984/85 a study of risk factors mounted on to the surveillance database showed an association between Reye's syndrome and consumption of aspirin. In response to this and similar findings in the USA, the Committee on Safety of Medicines issued public and professional warnings in 1986 about the use of aspirin in children under 12 years. Since then, products that contain aspirin have been required to carry warning labels.

There is increasing recognition that a number of inherited metabolic disorders – most notably those affecting fat oxidation and ureagenesis, may present as a Reye-like illness, clinically and pathologically indistinguishable from Reye's syndrome. The surveillance questionnaire, although currently in its simplest and shortest format since 1981, therefore seeks information on whether patients have been investigated for these disorders.

In addition to BPSU reporting, cases are also ascertained via death entries provided by the Office for National Statistics and by the Northern Ireland Statistics and Research Agency, and via laboratory reports to CDSC.

Objectives

To describe the epidemiological and clinical features of Reye's syndrome in the British Isles, to monitor long term trends, and to provide a database for detailed clinical, laboratory, and aetiological studies.

Case definition

A child under 16 years old with unexplained non-inflammatory encephalopathy, and one or more of:

- * serum hepatic transaminases elevated to at least three times the upper limit of normal;
- * blood ammonia elevated to at least three times the upper limit of normal;
- * characteristic fatty infiltration of liver (biopsy or autopsy).



Since this definition is relatively non-specific, cases reported from surveillance year 1994/95 onwards, whose diagnosis has not been revised, have been allocated a 'Reye-score'. Because of the non-specificity of the case definition and because there may still be 'Reye-like' inherited metabolic disorders as yet undiscovered, a case of Reye's syndrome can rarely, if ever, be described as confirmed; it is better designated as '*compatible with*' the diagnosis.

Study duration

The BPSU involvement with this study began in June 1986; it has been granted a further one year extension to July 2000.

Analysis

Between August 1981 and July 1998 a total of 614 suspected cases of Reye's syndrome were reported to the surveillance unit (Table 18), but the diagnosis was subsequently revised in 156 (25%). Seventy-six (49%) of the revisions were to one of the 'Reye-like' inherited metabolic disorders. Two hundred and thirty-five (53%) of the total 444 cases compatible with a diagnosis of Reye's syndrome died.

In the year to July 1998, eleven reports of new cases were received and further information was provided on all of them. Three of the 11 diagnoses had subsequently been revised, leaving eight cases whose clinical and pathological features were compatible with the case definition of Reye's syndrome. All the cases were first reported via the BPSU. Death entries were subsequently received for all five of the cases of Reye's syndrome who died.

Cases compatible with a diagnosis of Reye's syndrome (N=8): year to July 1998.

There were four males and four females; the ages ranged between 10 months and 13 years with a median of 4 years and 9 months. Six lived in England, one in Wales and one in Northern Ireland. Two were ill in August; five, between September and March; and one in June.

Only two children survived normal, outcome was unclear at the time of reporting in the other survivor. Among the five patients who succumbed, there were two sudden unexpected deaths (these children were aged four and a half years and 10 months) and in these cases the diagnosis was first made at post mortem. A third child who died had a pre-existing chronic neurodegenerative disorder of unknown cause, but was reported to have had the characteristic hepatic histological appearance of Reye's syndrome as well as the biochemical features. Two cases had had no pre-admission medications; four had received paracetamol, one, the patient with a neurological disorder, was on long term benzhexol; the eighth, a child aged 12 years seven months, had been given aspirin.

Seven of the eight patients had had a pre-encephalopathic viral type prodrome – flu like in three; gastroenteritis in three, and varicella in one. This last case was confirmed serologically and influenza A was isolated from one other patient; in none of the others was there a confirmed microbiological diagnosis.

Five patients were reported to have had a range of investigations for inherited metabolic disorders, although in two the reporting paediatrician referred only to those for medium chain acyl coA dehydrogenase deficiency (MCADD). In two cases this information was unavailable; the other patient was not investigated. This was the 10 month old infant who had died suddenly and unexpectedly.



The 'Reye Score' (*possible range 1-25*) ranged between 11 and 16 with a mean and median of 13. The median compares with 12, 12 and 13 in the previous three years respectively. One patient, the child who had received aspirin, could not be scored because of missing information; however she was described as a 'classic' case of Reye's syndrome associated with an influenza-like prodrome.

Revised diagnosis cases (N=3)

One patient was a two year old male who survived the encephalopathic episode and was subsequently found to have a carnitine transport defect. Another, a four year old boy, had two episodes of a Reye-like encephalopathy within a short interval; detailed investigations suggested the presence of a metabolic disorder, the precise nature of which is as yet undetermined. The third case was a 10 year old female with cerebral palsy associated with birth asphyxia. She developed an acute encephalopathy and Reye's syndrome was a provisional diagnosis made at autopsy, because of the histological changes in the liver. However, these were not typical of classical Reye's syndrome, no cerebral oedema was noted and hepatic transaminases were not raised antemortem, so although no obvious alternative diagnosis was reported, this case did not satisfy the criteria for inclusion.

Comment

The surveillance findings in 1997/98 were similar to those of the past five years – annual totals remain very low compared to those seen before 1986, the year when warnings about the association between aspirin and Reye's syndrome were first publicised by the Committee on Safety of Medicines. The trends also mirror those in the USA described earlier this year². It appears that the trend is continuing into 1999 – by the end of June a total of only seven reports had been received. The diagnosis was subsequently revised in two of these and a further case was highly atypical.

As was the case last year, none of the 1997/98 patients, with one possible exception, could be described as having classical 'North American-type' Reye's syndrome¹. This is reflected in the relatively low median 'Reye score'. That Reye's syndrome was the final diagnosis reflects the fact that no alternative was found and that the case definition is non-specific. The most likely alternative diagnosis is one of the 'Reye-like' inherited metabolic disorders, the detection of which may be extremely difficult. The design of our standard surveillance proforma, which is intended to be as short as possible for busy clinicians, means that we cannot determine the extent to which each patient is investigated in detail for inherited metabolic disorders. However, it is our impression from volunteered information that the tendency is toward simply ruling out the relatively common fat oxidation defect, MCADD. For the third year in succession there was a case with a particularly high likelihood of having had an inherited metabolic disorder, who nevertheless was not investigated.

Although it is apparent that primary prevention of Reye's syndrome in children is continuing effectively, we reiterate our concern expressed last year, that aspirin-associated cases are continuing to occur in children over 12, the upper age limit on the warning. The one aspirin-associated case in 1997/98, a child who died, was over 12 as were two or three such cases reported to date in 1998/99 (they all survived). This brings the total aspirin-associated cases since the 1986 warning to 17, 10 of whom were over 12. In the USA series, 8% of cases were aged 15 and over and we suspect that we under-ascertain Reye's syndrome in this age group in the UK as they may be



admitted to adult intensive care units, where Reye's syndrome is unlikely to be as high on the agenda as it is in the paediatric setting.

We are grateful to all the paediatricians who report cases and who provide further information.

Key points

- * Children presenting with Reye-like encephalopathy may not always be receiving optimum investigation for inherited metabolic disorders:
- * The age limit on the aspirin warning may need amending upwards.

Funding

The Reye's syndrome surveillance scheme is funded by the National Reye's Syndrome Foundation of the UK, to whom the investigators are most grateful.

Table 18 *Reye's syndrome surveillance 1981/82 – 1997/98*

| Reporting period (August-July) | Total reports from the British Isles | Revised diagnosis (inherited metabolic disorder in brackets) | | Cases of Reye syndrome* | Number of deaths (of cases) |
|-----------------------------------|--|--|-------------|----------------------------|-----------------------------------|
| 1981/82 | 47 | 7 | (3) | 40 | 26 |
| 1982/83 | 69 | 10 | (6) | 59 | 34 |
| 1983/84 | 93 | 12 | (3) | 81 | 36 |
| 1984/85 | 64 | 8 | (2) | 56 | 32 |
| 1985/86 | 53 | 13 | (4) | 39 | 22 |
| 1986/87 | 47 | 21 | (11) | 26 | 13 |
| 1987/88 | 44 | 12 | (3) | 32 | 19 |
| 1988/89 | 31 ¹ | 13 | (6) | 18 | 9 |
| 1989/90 | 24 ¹ | 8 | (5) | 15 | 7 |
| 1990/91 | 25 | 13 | (8) | 12 | 5 |
| 1991/92 | 23 ² | 6 | (5) | 15 | 6 |
| 1992/93 | 21 ³ | 10 | (6) | 5 | 4 |
| 1993/94 | 20 ⁴ | 13 | (7) | 3 | 3 |
| 1994/95 | 17 ⁵ | 3 | (2) | 12 | 3 |
| 1995/96 | 18 ¹ | 2 | (1) | 15 | 7 |
| 1996/97 | 7 | 2 | (2) | 5 | 4 |
| 1997/98 | 11 | 3 | (2) | 8 | 5 |
| TOTAL | 614 | 156 | (76) | 444 | 235 |

- * *Compatible with the diagnosis (see text)*
- 1 *Follow-up not received for one case*
- 2 *Follow-up not received for two cases*
- 3 *Follow-up not received for five cases and one case did not meet the case definition*
- 4 *Follow-up not received for five cases*

Note numbers may differ from previous versions of this table because of late ascertainment of cases and revised diagnosis



**National Reyes Syndrome
Foundation UK**

References

1. Hardie RM, Newton LH, Bruce JC, Glasgow JFT, Mowat AP, Stephenson JBP, Hall SM. The Changing Clinical Pattern of Reye's Syndrome 1982-1990. *Arch.Dis.Child.* 1996; 74: 400-405
2. Belay ED, Bresee JS, Holman RC, Khan AS, Shahriari A, Schonberger LB. Reye's syndrome in the United States from 1981 through 1997. *N Engl J Med*; 340: 1377-1382
3. Walker E, Christie P. Chinese avian influenza. *BMJ* 1998; 316:325

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