National Reyes Syndrome Foundation UK

TRUSTEES REPORT
EXTRACTS YEAR TO 30 SEPTEMBER 2000

The significant events in the year ended 30 September 2000 were as follows:

(I) 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 Susan Hall, consultant epidemiologist and honorary lecturer in the Department of Paediatrics, Sheffield University; and by Mr. Richard Lynn, research officer of 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 ascertainment 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. The grant holder is Professor David Hall, Sheffield Centre of Health and Related Research, Sheffield University.

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 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.

Annual Report

The report for the year 1 August 1998 - 31 July 1999 was published in the BPSU Annual Report in September 2000.
(http://bpsu.rcpch.ac.uk)

(ii) Work with the Medicines Control Agency

During 1999 anonymised data from surveillance scheme were requested by the Medicines Control Agency for a paper to be put before the Committee on Safety of Medicines. This paper reviewed the case for increasing the age limit on the UK aspirin warning to include teenagers (as it does in the USA) and was partly prompted by the observation that, of 17 aspirin-associated cases reported since June 1986, 10 have been aged over 12. The Committee on Safety of Medicines reached its decision in November 2000; it "was of the opinion that there is currently insufficient evidence of a causal association in these children, and therefore advised that extension of the existing advice to include children aged 12 years and above could not presently be justified."

This was a disappointing decision, especially in view of the two aspirin associated cases over 12 in the year under review and the decision has been challenged by Dr. Hall. However, the Committee went on to advise that: "monitoring of the incidence of Reye's syndrome should continue, as clearer trends may emerge in the future". They further noted that "a review of this issue might well be appropriate when additional information is available". (See also www.bmj.com June 30th 2001, MC McGovern et al: Reye's syndrome and aspirin: "lest we forget" for further information on Reye's syndrome in children over 12).

(iii) Advisory Support for the National Reye's Syndrome Foundation (NRSF/UK)

Over the period under review, Dr Hall has advised the Honorary Administrator of the Foundation on a number of issues arising from correspondence received by him. These included a grant application from the Department of Clinical Chemistry at Sheffield Children's Hospital, which was awarded after minor modifications to the protocol. She has also maintained literature searches, provided the Foundation with copies and has obtained copies of relevant original papers.

European Aspirin Foundation (EAF)

Towards the end of 1999, the Honorary Administrator was invited to meet the Executive Director of the EAF in order to discuss issues raised at a scientific meeting hosted by the EAF in Edinburgh in September 1999. There had been two presentations by statisticians who sought to demonstrate that the evidence linking aspirin and Reye's syndrome was seriously flawed. There were also unpublished data from France, made available to the EAF but not presented at Edinburgh, which allegedly threw further doubt on the link. The EAF was now proposing a further meeting involving both the MCA and scientists nominated by both it and the NRSF/UK, to attempt to establish "the scientific truth". There was also a suggestion of possible collaborative research.

This approach clearly required a considerable response by the NRSF/UK and Dr Hall undertook to prepare this by both formally consulting members of its Medical and Scientific Advisory Board and seeking independent statistical advice. She also contacted the author of the French work. The responses were collated into a report which was forwarded to the EAF.

This report concluded that, while the approach from the EAF had raised some most interesting issues and provided the stimulus to revisit the evidence linking aspirin and Reye's syndrome, it was the EAF who had a case to make, not the NRSF/UK. How they would do this was up to them, but one would expect to see both the statistical critiques, presented at Edinburgh, and the French data, published in peer review journals. Once these had undergone scrutiny and acceptance by the scientific community, for example in journal correspondence or in accompanying commentary, then there might be a case for the EAF to commission someone to design a protocol to answer whatever research questions they thought appropriate. This might then be submitted as a grant application to the NRSF/UK and it would have to undergo the same peer review process expected of other applications.

If that research (whether funded by the NRSF/UK or elsewhere) demonstrates that there is substantial cause to doubt the Reye's syndrome-aspirin association, then clearly it would be important for the two organisations to meet, with Medicines Control Agency involvement, to try to establish agreement on the scientific truth. Until that time comes,

such a meeting would not serve any useful purpose. By September 2000 no response to the Foundation's report had been received from the EAF.

(iv) 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 Royal College of Paediatrics and Child Health (RCPCH) jointly by the Research Trust for Metabolic Diseases in Childhood (now called "Climb") and the NRSF/UK. This was for a feasibility study of a surveillance scheme to monitor the effectiveness of tandem mass spectrometry (TMS) screening for inherited metabolic disorders (IMDs) 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 work was relevant to Reye's syndrome surveillance 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.

The study was completed and the report was published by the RCPCH in August 2000. It was also submitted to the National Screening Committee of the Department of Health, who wished to consider the implications of implementing its recommendations.

(v) Professional Education

Concerns about "Classic" RS

Some clinicians have dismissed classic Reye's syndrome as being no longer of any clinical importance because of the action on aspirin which has reduced the incidence of this condition. However, for a disease with the capability of re-emergence during a major influenza epidemic or pandemic, especially if aspirin warnings are disregarded or else ignored because the child is aged over 12 years, this is a dangerously complacent view. The decline of Reye's syndrome means that a new generation of paediatricians in training and young consultants will certainly never have seen or heard about a case and are unlikely to have read about it or had it included in educational materials. Furthermore, it is very likely to be unknown to/under-recognised by, physicians caring for teenagers and older adults. Thus, if there is a resurgence, we shall return to the "old days" of late diagnosis, late or inappropriate treatment and poor outcome in terms of mortality and brain damaged survivors.

Concerns about Reye-like disorders

The findings of the British Reye's syndrome surveillance scheme (BRSSS) have recently prompted concern that some infants and children are sub-optimally investigated for IMDs when they present with a Reye-like encephalopathy or when they die suddenly and unexpectedly. In the latter situation the diagnosis of "Reye's syndrome" is made at autopsy, usually on the basis of fatty change in the liver and (but not always) cerebral oedema. Of 54 cases reported between 1992/93 and 1999/00 in whom the diagnosis of Reye's syndrome was not revised, 24 fell in this second category. It is depressing that this state of affairs continues in 1999/2000 in spite of publications in 1992 and 1996, based on the BRSSS, which emphasised the importance of investigating such cases for IMDs.

National Reyes Syndrome Foundation UK

Although numbers of cases are relatively small, patients and parents still deserve accurate diagnoses, not least because of the implications for specific treatment, pre-natal diagnosis of future siblings and investigation of existing siblings. In these days of heightened public expectations and of availability of information about medical conditions on the Internet, clinicians and pathologists will be under increasing pressure from parents to provide specific diagnostic labels to account for a child's unexplained illness or death. The frustration, grief and anger of unfulfilled expectations may eventually result in litigation in some cases.

In recent years, the children of parents who approach the NRSF/UK for support have increasingly been likely to have had a Reye-like illness rather than classic Reye's syndrome. Some of these children have been reported to the BRSSS as having had Reye's syndrome, but have been inadequately investigated for IMDs or not at all, and therefore the Foundation has become interested in widening its educational initiatives to address methods of improving the diagnosis of these disorders.

In August 2000 a meeting between the Foundation's Honorary Administrator and Professor and Dr Hall was held at which, inter alia, possible educational strategies were discussed. It was agreed that Professor and Dr Hall should approach the chairman of the British Inherited Metabolic Disease Group with a view to organising a workshop in 2001. The principal goal of this workshop would be to set up an educational initiative to optimise the diagnosis and management of Reye-like childhood encephalopathies and of classic Reye's syndrome in the UK. There would be three specific objectives to achieve:

a) Determining the content of the educational package
b) Determining the optimum methods of its dissemination
c) Implementation

The content of the package would consist of consensus evidence-based guidelines devised by experts in the field. Methods of dissemination might include publication in a journal; publication on the RCPCH and RCPath websites; a dedicated website; a CD; a poster, a proforma for insertion in medical records; other media recommended by experts in medical education. It would also be important to include the guidelines in paediatric and pathologist training curricula and to include them in Membership examination questions.

It was further agreed that, in principle, the Foundation would be willing to consider a grant application from the steering group which would be convened to organise the workshop. (About the National Reye's Syndrome Foundation).

Submitted by
Dr Susan Hall, MSc, FRCP, FFPHM, FRCPCH
9.2.01

National Reyes Syndrome Foundation UK

APPENDIX

BRITISH PAEDIATRIC SURVEILLANCE UNIT
EXTRACT FROM THE 14th ANNUAL REPORT
1999-2000

Reye's syndrome

Key Points

* **The incidence of "classic" Reye's syndrome has dropped dramatically since June 1986.**

* **Occasional aspirin associated cases continue to occur, predominately in children aged 12 years and over.**

* **Continued monitoring of Reye's syndrome is essential to determine whether current advice on aspirin for children requires modification.**

* **Most cases now reported, although satisfying the diagnostic criteria, are atypical.**

* **It is essential to investigate fully, patients presenting with a Reye-like illness or with sudden death associated with cerebral oedema and fatty liver, for the relevant inherited metabolic disorders.**

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 BPSU in June 1986. The administration of the scheme was transferred from CDSC to the Department of Paediatrics at Sheffield in 1995.

In the early years, the surveillance data demonstrated that the incidence of Reye's syndrome in the British Isles was similar to that in the USA, where national surveillance of this condition has been in place since the mid-seventies. However, British and Irish 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 risk factor study, mounted on to the surveillance database, showed an association between Reye's syndrome and consumption of aspirin. In response both to this and to 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. Since then, products that contain aspirin have been required to carry warning labels which state "Do not give to children under 12 except on the advice of a doctor". From April 1998, aspirin-containing medications are additionally required to state on patient information leaflets: "There is a possible association between aspirin and Reye's syndrome when given to children with a fever".

There has been increasing recognition that a number of inherited metabolic disorders – most notably those affecting fat oxidation, amino acid metabolism and ureagenesis, may

present as a 'Reye-like' illness, *which is 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, the General Register Office for Scotland, 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 the study began in June 1986 and is reviewed annually

Analysis

Between August 1981 and July 1999 a total of 625 suspected cases of Reye's syndrome were reported (Table 15), but the diagnosis was subsequently revised in 161 (26%). Seventy-nine (49%) of the revisions were to one of the 'Reye-like' inherited metabolic disorders. Two hundred and thirty seven (53%) of the total 447 cases compatible with a diagnosis of Reye's syndrome died. The figures for 1997/98 in the Table differ slightly from those in last year's report because of a late ascertainment of a diagnostic revision – a five year old boy who had anicteric hepatitis A with hyperammonaemia and hypoglycaemia.

***In the year to July 1999,* 11 reports of new cases were received and further information was provided on all of them. Four of the 11 diagnoses were later revised, leaving seven patients whose clinical and pathological features were compatible with the case definition of Reye's syndrome. Nine of the cases were first reported via the BPSU, two were ascertained only via death entries. In addition to these 11 cases, two further death entries were received: one was for a child first reported to the BPSU in 1993, who died**

from the neurological sequelae of Reye's syndrome aged six years; the other was a 23 year old woman whose main cause of death was pneumonia, with Reye's syndrome recorded as the underlying cause. This case had not previously been reported and further enquiry revealed that Reye's syndrome had been diagnosed at the age of 4 months in 1976 before the surveillance began.

Cases compatible with a diagnosis of Reye's syndrome (N=7). There were six males and one female; the ages ranged between 2 months and 13 years with a median of 2 years 5 months. Five lived in England, and two in Northern Ireland. There were no reports from the Republic of Ireland, Wales or Scotland. One patient was ill in June, the remainder had their onsets between September and March.

Five children recovered completely. Of the two who died, one was a five year old who had also had congenital cytomegalovirus infection with spastic quadriplegia and epilepsy. The other was a two year old in whom the diagnosis was made at autopsy on the basis of cerebral oedema and a fatty liver. The child had died suddenly during an episode of gastroenteritis. Investigation of post mortem urine and liver for disorders of fat oxidation and amino acid metabolism did not reveal an inherited metabolic disorder.

Three cases had had no pre-admission medications other than oral electrolyte solutions for gastroenteritis; one, the patient with congenital cytomegalovirus infection, was taking sodium valproate; none had received paracetamol. Three patients had taken aspirin, of whom two were aged over 12 years and one was nine months old.

Six of the seven patients had had a pre-encephalopathic viral-type prodrome –flu like in three, and gastroenteritis in three. Virological investigation confirmed influenza B infection in one of the older cases who had taken aspirin; 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. In one case this information was unavailable; the other patient, a two month-old infant, was not investigated.

The 'Reye-Score' (*possible range 1-25*) ranged between 8 and 20 with a mean of 15 and median of 16. The median compares with 12, 12, 13 and 13 in the previous four years respectively.

Revised diagnosis cases (N=4)

One patient was a 25 month old boy, who developed an influenza-like illness and pneumococcal bacteraemia and who died. A fatty acid oxidation defect, probably long chain hydroxyacyl dehydrogenase deficiency, was reported. Another, a 13 month old boy, had an influenza-like illness preceding encephalopathy; he survived and cytochrome oxidase deficiency was the revised diagnosis. The third was a nine month old male with a two day history of gastroenteritis who died suddenly. Reye's syndrome was initially diagnosed on the basis of the autopsy findings, but further investigation revealed medium chain acyl coA dehydrogenase deficiency. Details were unavailable on the final case, but the child survived and the diagnosis was reported as still uncertain.

Comment

The findings for 1998/99 differed little from those in the previous five years: the annual total Reye's syndrome cases remained under 10, compared to a peak of 81 during the years before the 1986 aspirin warning; the number of deaths, two, was the lowest yet recorded; two other deaths were ascertained, but they were both the consequence of

serious brain injury from Reye's syndrome acquired some years ago. These trends are continuing in the current surveillance year: by June 2000 only three reports had been received, compared with seven in the same period last year.

Only two of the seven non-revised cases could be described as having "classic" or North American-type Reye's syndrome[1,2], both were over 12 and both had received aspirin. The two who died were both atypical; one child had pre-existing neurological damage and was taking sodium valproate which is, rarely, associated with a Reye-like syndrome; the other died suddenly during an episode of gastroenteritis. These patients illustrate the low specificity of the standard case definition and in fact the former could equally be allocated to the revised diagnosis category, as her encephalopathy might have been "explained" by the valproate. The ages of the other three patients ranged from two to 19 months, again, atypical[2] and it is possible that they had unrecognised inherited metabolic disorders, although none were found in the two who were investigated (one of these latter was the infant who had been given aspirin and it is of concern that the warning label was not heeded in this case).

This year, as in the previous four years, there was a winter predominance in onsets which is an epidemiological feature of "classic" Reye's syndrome; however, it is also compatible with that of the presentation of Reye-like inherited metabolic disorders since encephalopathic episodes in these too, are likely to be precipitated by common childhood viral infections, which are more prevalent in winter.

During 1999 anonymised data from the surveillance scheme were requested by the Medicines Control Agency for a paper to be put before the Committee on Safety of Medicines. This paper reviewed the case for increasing the age limit on the UK aspirin warning to include teenagers (as it does in the USA) and was partly prompted by the observation that, of 17 aspirin-associated cases reported since June 1986, 10 have been over the age of 12[3]. The Committee on Safety of Medicines reached its decision last November: it "was of the opinion that there is currently insufficient evidence of a causal association in these children, and therefore advised that extension of the existing advice to include children aged 12 years and above could not presently be justified". This was a disappointing decision, especially in view of the two aspirin associated cases over 12 in the year under review. However, the Committee went on to advise that: "monitoring of the incidence of Reye's syndrome should continue, as clearer trends may emerge in the future". They further noted that "a review of this issue might well be appropriate when additional information is available". As a result of this, the Medicines Control Agency have informed us that it is "essential to continue monitoring the incidence of Reye's syndrome in the UK".

The investigators are most grateful to all the paediatricians who report cases and who provide further information.

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.

National Reyes Syndrome Foundation UK

Table 15 Reye's syndrome surveillance 1981/82 – 1998/99

Reporting period (August-July)	Total reports from the British Isles	Revised diagnosis (Inherited metabolic disorder in brackets)	Cases of Reye's 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	4 (2)	7	5
1998/99	11	4 (3)	7	2
TOTAL	625	161 (79)	447	237

** 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

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 1999; 340: 1377-1382

3. Hall SM and Lynn R. Reye's syndrome. New Engl. J Med 1999; 341:845-846.

Dr S M Hall Department of Paediatrics Sheffield Children's Hospital, Sheffield
Mr R Lynn BPSU, RCPCH, London