National Reyes Syndrome Foundation UK

TRUSTEES REPORT
EXTRACT – 30 SEPTEMBER 1998

Significant events

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

The following is a report of Dr John Glasgow:-

The Research Team based at the Department of Child Health, The Queen's University of Belfast has concluded it's major project carried out in collaboration with Dr Bruce Middleton, Department of Biochemistry, University of Nottingham. The final year of this study was able to confirm previous findings of demonstrable, inhibition of mitochondrial B-oxidation in intact, skin fibroblasts from two groups of children – those who have recovered from Reye's syndrome (RS) and controls.

There is very significant (50%) concentration related inhibition of the pathway by two of the aspirin metabolites – salicylic acid (SA) and hydroxy-hippurate acid (HHA). These findings and precise details confirm for the first time that these metabolites have a very significant inhibitory effect on this important pathway. There was a general effect both in control and RS cells. However the fibroblasts of RS patients were peculiarly sensitive to inhibition by salicylates even at low concentration (<5 mmol/1) i.e. at levels well within the therapeutic range. This sensitivity, if widely expressed in body tissues, could explain the reaction of certain individuals to aspirin which might thus contribute to the syndrome of encephalopathy.

Precise details of the kinetic reactions that take place in relation to the intra-mitochondrial enzyme systems have been explored and further refined.

We have confirmed that the site of inhibition is the long chain acyl CoA dehydrogenase (LCHAD) enzyme system, in that the cells of individuals with known deficiency of LCHAD fail to show demonstrable inhibition.

These novel findings will be reported in an international, peer reviewed scientific journal. It is our joint intention to build upon this work, and shortly to put further proposals to the trustees for future funding. For the first time in human material we have demonstrated a specific link between the epidemiological findings and a plausible biological mechanism.

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The following is a report of Dr Susan Hall:-

2. Epidemiological surveillance of Reye's Syndrome (RS)

Epidemiological surveillance of RS is an ongoing survey whose principal aims are to monitor trends in the occurrence of the disease, to heighten and maintain diagnostic awareness among clinicians and to provide a resource for further research.

3. Paediatric Reye's Syndrome Surveillance Activities

This work is undertaken by Mr Richard Lynn, scientific co-ordinator of the British Paediatric-Surveillance Unit (BPSU) of the Royal College of Paediatrics and Child Health (RCPCH) and by Dr Susan Hall, consultant epidemiologist and honorary lecturer, Department of Paediatrics, Sheffield Children's Hospital.

Towards the middle of each year, preparations for production of the BPSU's Annual Report begin. This has become an important, highly professional produced publication, which is circulated to all RCPCH members as well as to outside bodies, such as the UK Departments of Health, other Royal Colleges, the public and professional media (it is announced via a press release) and overseas paediatric organisations. Its main content consists of contributions from each investigator whose study is on the BPSU report card. This of course includes Reye's Syndrome.

In his capacity as scientific co-ordinator, Mr Lynn is responsible for the overall production of the BPSU Annual Report and Dr Hall prepares the contribution from the Reye's Syndrome Surveillance Scheme, in close collaboration with him. The report includes an acknowledgement to the National Reye's Syndrome Foundation of the UK. In the year under review, the 1996/97 report was prepared (the 16th since surveillance began in 1981) and published in the *12th BPSU Annual Report (September 1998)*.

The Report notes, inter alia, that between August 1981 and July 1997 a total of 604 suspected cases of Reye's syndrome were reported to the surveillance unit (Table), but the diagnosis was subsequently revised in 151 (25%). Nearly half (48%) of the revisions were to one of the 'Reye-like' inherited metabolic disorders. In the year to July 1997, seven reports of new cases were received and further information was provided on all of them. Two of the seven diagnoses had subsequently been revised, leaving five cases whose clinical and pathological features were compatible with the case definition of Reye's syndrome. All cases except two were reported via the BPSU. Two patients were ascertained via death entries alone; both had died suddenly and unexpectedly at home.

The authors comment that the total reports received in 1996/97 was the lowest since the surveillance scheme began in 1981. Moreover, not one of the 'non-revised' cases resembled 'classic' Reye's syndrome, even though they all satisfied the basic case definition. In keeping with trends, observed in recent years, of increasing diagnostic awareness of the inherited metabolic disorders that mimic Reye's syndrome, six of the seven patients were investigated for these conditions. It was of concern that again, as observed among reports received in 1995/96, there was a case in whom Reye's syndrome was diagnosed at autopsy, but no metabolic investigations undertaken.

In contrast to the previous year, no case in 1996/97 was reported to have had pre-admission aspirin, an observation consistent with the atypical clinical and epidemiological features of all patients. The surveillance data demonstrated, therefore, that primary prevention of 'classic' aspirin-associated Reye's syndrome is continuing. Nevertheless, the authors stress that there is no cause for complacency because at least one such case had been reported in 1997/98 and because of the spectre of an influenza pandemic raised by the 1997 Hong Kong avian influenza outbreak, the index case of which was complicated by Reye's syndrome following medication with aspirin.

3. Paediatric Reye's Syndrome Surveillance Activities (continued)

Reminders warning parents to avoid giving aspirin to children under 12 are included in the UK Departments of Healths' multiphase contingency plan for pandemic influenza, but the surveillance scheme data suggest these may be too restrictive. Of the total 13 aspirin-associated cases reported since the 1986 warnings about aspirin and institution of product labelling, seven have been aged over 12 years. An analysis of the entire database going back to 1981 showed that 15/34 (44%) cases aged over 12 had reported aspirin exposure compared to 51/400(13%) aged under 12 years.

Of course surveillance data must be treated with caution as they are not as rigorous as those collected in an analytic study. Nevertheless, this observation is compatible with the hypothesis that the younger the case of "Reye", the more likely it is that the patient has one of the Reye-like inherited metabolic disorders. Detailed review of the 15 aspirin-associated cases over 12 shows that, in contrast to the 1996/97 cases, all resembled 'classic' Reye's syndrome and were clinically and epidemiologically a homogeneous group with a mean Reye score of 18. Furthermore, the mean score of cases occurring before and after mid-1986 were similar, underlining their homogeneity. This is in contrast to reported cases as a whole, among whom the score dropped significantly after 1986.

These surveillance scheme data were provided, at their request, to the relevant central policy making bodies; they are of considerable public health significance.

4. Other Activities

Dr Hall was also involved in providing detailed (but anonymised) information on all aspirin-associated cases of Reye's syndrome over 12 years ever reported to the surveillance scheme, at the request of the Medicines Control Agency. They subsequently informed her that they were planning formally to review the age limit. This collaboration was time-consuming and is likely to be so until the matter is resolved, but it has been a most worthwhile exercise, which will hopefully publicise Reye's syndrome and possibly lead to prevention of older cases if the age limit is changed.

Dr Hall also wrote to the Medicines Control Agency to express disappointment about the content of the new product information leaflet which is required by *EC Regulations* to accompany aspirin-containing products. It is too late to change it now, but hopefully expert advice from the surveillance scheme will be sought when drafting future editions.

The publication in the British Medical Journal (BMJ) in February 1998 of a Leader about the avian influenza outbreak in Hong Kong, the index case of which was complicated by Reye's syndrome, provided Dr Susan Hall and Mr Richard Lynn with the opportunity to submit a letter to the Editor. This was accepted for publication in the correspondence columns of the BMJ and appeared in July 1998. It is hoped that this will not only publicise Reye's syndrome but lead to Departmental action regarding plans for pandemic influenza. Clearly, any such action would be influenced by the outcome of the Medicines Control Agency's deliberations.

5. Adult Reye's Syndrome Surveillance

There are two main elements in the work of the project, which is undertaken by Dr S. Hall. *First*, discovering feasible methods of ascertaining cases of Adult Reye's syndrome, since adults and teenagers with this condition, unlike children, may be admitted under a variety of specialists. With the exception of the British Neurological Surveillance Unit (BNSU) there are no BPSU equivalents among relevant adult specialities.

The *second* aspect has been to attempt to raise diagnostic awareness of Adult Reye's syndrome, because adult physicians are probably less likely than paediatricians to consider Reye's syndrome in patients with unexplained encephalopathy (even teenagers), since Reye's syndrome may be perceived as mainly a disorder of young childhood.

Case ascertainment sources:

a) *The British Neurological Surveillance (BNSU)*

The study was completed in July1997 and during the period currently under review, Dr Hall prepared a report for publication in the Unit's Newsletter. It was disappointing that none of the three cases reported were likely to have had Adult Reye's syndrome – this may have reflected a truly negligible incidence of Adult Reye's syndrome between 1995 and 1997 or under diagnosis or both. The Newsletter article provided an opportunity to remind neurologists about Adult Reye's syndrome – both 'classic' and 'Reye-like' and to invite them to continue to report cases directly to the study.

b) *Intensive Care National Audit and Research Centre (ICNARC)*

Progress in this collaboration was slow in the period under review, mainly because of problems at ICNARC in setting up their national database. However, there was some progress: in May 1998, ICNARC conducted the first Adult Reye's syndrome analysis on data submitted by the first 30 ICU's recruited to their system – this represents 8,057 admissions in 1996. Of these 59 cases fell within the study code criteria and it was then planned to follow them up to test the specificity of the codes. No case was in the Reye/Reye-like category. This will be a useful exercise to pilot the methodology in preparation for the time when all units are on stream and the database is up and running.

6. Hospital Episode Statistics (HES)

This is a potentially exciting source of cases of Reye's syndrome at all ages because from 1995/96 (HES) use financial years onwards, they are using the International Classification of Diseases, 10th edition (ICD-10) *to code the diagnoses of all discharges and deaths from hospitals in England and Wales*. In ICD-10, unlike all previous editions, Reye's syndrome has its own specific code, which vastly simplifies the task of identifying cases within this huge dataset.

For 1995/96 the Adult Reye's syndrome study asked for the following variables to be supplied for each case: date of admission source of admission, date of discharge; method of discharge (this includes deaths); speciality of consultant; minor operations; hospital of admission; district health authority of residence; sex; age.

6. Hospital Episode Statistics (HES) (continued)

HES data are anonymous which is of some, but limited, value to the surveillance scheme. However, the variables provided enable detection of duplicates within the HES data themselves and also between HES and Reye's syndrome surveillance scheme reported cases. Progress with this collaboration was unfortunately also slow, because the HES system itself suffered delays in processing its first year ICD-10 data. However, in March 1998, the printout for 1.4.95 – 31-3-96 was received.

There were nine records of patients discharged with a diagnosis of Reye's syndrome. Three were duplicates within HES; of the other six, three were already known through BPSU reports; one was a child aged 2 years not previously reported; one was a 2 year old being electively admitted for endoscopy and

biopsy of the upper gastrointestinal tract (i.e. unlikely to be a new case of Reye's syndrome, therefore possibly miscoded); the third was an adult – a 19 year old female admitted under a general physician via accident and emergency. However, there is another possibility of miscoding since the patient was discharged the same day and there is no record of a transfer to another centre; clearly this is incompatible with Reye's syndrome.

HES was asked to expand the inquiry into the 1995/96 dataset; initially, the search was restricted to cases where Reye's syndrome was coded as the principle reason for admission. This was to avoid ascertaining cases who had had Reye's syndrome in the past and were now being re-admitted for management of some complication – eg neurological handicap. However, because HES was clearly under-ascertaining paediatric Reye's syndrome (from the BPSU data there were a further six in the relevant time period which should have appeared in the HES data), the study asked for all cases where Reye's syndrome was coded as the secondary diagnosis. This yielded a further 19 records; a review of their <u>main</u> reasons for admission revealed some that might have been compatible with the case being a new one.

Potentially HES is a very powerful and efficient means of case ascertainment for conditions like Reye's syndrome which are uncommon and have a specific ICD code. However its value depends on the accuracy of coding by HES clerks at individual hospitals and the preliminary data demonstrate significant problems here.

Office for National Statistics, General Register Office, Scotland and General Register Office, Belfast

In addition to the 11 Adult Reye's syndrome deaths ascertained retrospectively between 1981 and 1995, the study has been notified of only two further adult deaths since the project began – one in 1996 and one in 1997. Neither in fact had classic Reye's syndrome and the information supported the conclusion from the paediatric cases ascertained by death entry only – that there is substantial misunderstanding and under investigation of Reye's syndrome and Reye-like conditions among pathologists.

Public Health Laboratory Service – CDSC (Microbiology Laboratory reports)

There were no reported cases of Reye's syndrome at any age from this source in the year under review.

National Reyes Syndrome Foundation UK

APPENDIX

BRITISH PAEDIATRIC SURVEILLANCE UNIT
EXTRACT FROM 12th ANNUAL REPORT
1997-1998

Reye's syndrome

Background

Surveillance of Reye 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 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 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 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 epidemiology and clinical features of Reye 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 <u>one or more of</u>***

* ***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-specifity of the case definition and because there may still be "Reye-like" inherited metabolic disorders as yet undiscovered, a case of Reye syndrome can rarely, if ever, be descrbed 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 1999.

Analysis

Between August 1981 and July 1997 a total of 604 suspected cases of Reye syndrome were reported to the surveillance unit (table 9), but the diagnosis was subsequently revised in 151 (25%). Nearly half (48%) of the revisions were to one of the Reye-like inherited metabolic disorders. In the year to July 1997, seven reports of new cases were received and further information was provided on all of them. Two of the seven diagnoses had subsequently been revised, leaving five cases whose clinical and pathological features were compatible with the case definition of Reye syndrome. All cases except two were reported via the BPSU. Two patients were ascertained via death Entries alone; both had died suddenly and unexpectedly at home.

Cases compatible with a diagnosis of Reye syndrome (N=5): year to July 1997

All were males; the ages ranged between five months and 5 years with a median of 14 months. Three lived in England, and two in the Republic of Ireland. Three were ill between November and January and two in June.

Only one child survived normal, three died during their acute illness; one died four months later of a gastrointestinal haemorrhage. Two cases had had no pre admission medications, three had been given paracetamol. All five patients had had a pre encephalopathic viral-type prodrome – flu-like in three, gastroenteritis in two, one of whom, the five year old, also had a sore throat and high fever. In no patient was there microbiological confirmation of viral infection although one had a lymphocytic lung infiltrate at autopsy.

Four patients had been investigated for inherited metabolic disorders. The patient not investigated was the five year old. He had died suddenly and unexpectedly at home and "Reye-like syndrome" was diagnosed on the basis of cerebral oedema and microvesicular fat in the liver (and in renal tubular epithelium) identified at post-mortem.

***The 'Reye Score' (possible range 1-25)* ranged between 10 and 14 with a median of 12 and mean of 11.8.**

Revised diagnosis cases (N=2)

One, who survived but with neurological damage, was a nine month old male found subsequently to have medium chain acyl-CoA dehydrogenase deficiency (MCAD). The other, a previously healthy 23 month old female, was found unconscious at home and died soon after. The preliminary post-mortem findings suggested Reye syndrome, but subsequent biochemical and genetic investigations revealed MCAD.

Comment

The total reports received in 1996/97, seven, was the lowest since the surveillance scheme began in 1981. Moreover, not one of the 'non-revised' cases resembled 'classic' Reye syndrome, even though they all satisfied the basic case definition and this is reflected in their relatively low scores[1], and in their young median age, which was almost one third that of the cases reported in 1995/96 (age is not included in the score). In keeping with trends, observed in recent years, of increasing diagnostic awareness of the inherited metabolic disorders that mimic Reye syndrome, six of the seven patients were investigated for these conditions and two had the commonest fatty acid oxidation defect, MCAD. Three others had been intensively investigated by laboratories with extensive experience in these conditions but, despite the fact that two had previous histories of unexplained severe life threatening illness, and one had widespread fatty disposition in many tissues not a feature of classic Reye syndrome, no inherited metabolic disorder was found. The other patient was less comprehensively investigated. It was of concern that again, as observed among reports received in 1995/96, there was a case in whom Reye syndrome was diagnosed at autopsy, but no metabolic investigations undertaken.

In contrast to last year, no case in 1996/97 was reported to have had pre-admission aspirin, an observation consistent with the atypical clinical and epidemiological features of all the patients. The surveillance data demonstrate, therefore, that primary prevention of 'classic' aspirin-associated Reye-syndrome is continuing. Nevertheless, there is no cause for complacency because at least one such case has been reported in 1997/98 and because of the spectre of an influenza pandemic raised by the 1997 Hong Kong avian influenza outbreak, the index case of which was complicated by Reye syndrome[2].

Reminders warning parents to avoid giving aspirin to children under 12 are included in the UK Department of Health's multiphase contingency plan for pandemic influenza, but the surveillance scheme data suggest these may be too restrictive. Of the total 13 aspirin associated cases reported since the 1986 warnings about aspirin and institution of product labelling, seven have been aged over 12 years. An analysis of the entire database going back to 1981 showed that 15/34 (44%) cases aged over 12 had reported aspirin exposure compared to 51/400 (13%) aged under 12 years. Of course surveillance data must be treated with caution as they are not as rigorous as those collected in an analytical study. Nevertheless, this observation is compatible with the hypothesis that the younger the case of "Reye", the more likely it is that the patient has one of the Reye-like inherited metabolic disorders. Detailed review of the 15 aspirin-associated cases over 12 shows that, in contrast to the 1996/97 cases, all resembled 'classic' Reye syndrome and were clinically and epidemiologically a homogeneous group with a mean Reye score of 18. Furthermore, the mean scores of cases occurring before and after mid-1986 were similar, underlining their homogeneity. This is in contrast to reported cases as a whole, among whom the score dropped significantly after 1986[1].
These surveillance scheme data have been provided, at their request, to the relevant central policy making bodies; they are of considerable public health significance and the investigators are indebted to BPSU respondents for their time and trouble in contributing to the scheme by reporting cases and providing detailed information.

Funding

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

Table 9 ***Reye Syndrome Surveillance 1981/82 – 1996/97***

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	70	10	(6)	59	34
1983/84	93	12	(3)	81	36
1984/85	64	8	(2)	56	32
1985/86	53	13	(4)	40	22
1986/87	47	21	(11)	26	13
1987/88	44	12	(3)	32	19
1988/89	31[1]	12	(6)	18	9
1989/90	24[1]	8	(5)	15	7
1990/91	25	12	(7)	13	5
1991/92	24[2]	6	(5)	16	6
1992/93	21[3]	10	(6)	7	4
1993/94	20[4]	12	(6)	3	3
1994/95	17[5]	3	(2)	11	3
1995/96	18[1]	2	(1)	15	7
1996/97	7	2	(2)	5	4
TOTAL	604	151	(72)	434	230

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*

* *Compatible with the diagnosis (see text)*

References

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2. Walker E, Christie P. Chinese avian influenza. BMJ 1998; 316:325.

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