National Reyes Syndrome Foundation UK

TRUSTEES REPORT
EXTRACTS FROM – 30 SEPTEMBER 1996

Significant events

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

The following is a report of Dr. John Glasgow

Mr. Raymond Moore and Dr John Glasgow report that "this phase of the work has been both rewarding and exciting and has stimulated the enthusiasm of ourselves and our collaborators – Dr Bruce Middleton – as well as our two research laboratory assistants.

Following the primary phase of the project which was completed in December 1994, we focused on two aspects of beta-oxidation, one of the major biochemical pathways present within the mitochondrion which is responsible for intracellular energy production. Attention has been directed at this particular organelle because it has long been recognised that in Reye's Syndrome both structure and function of mitochondria are seriously compromised. Studies have been carried out using purified enzymes. Some, such as short chain hydroxyl acyl CoA dehydrogenase, were purchased commercially others, eg the long chain equivalent enzyme known as trifunctional enzyme (TFE) were prepared in the laboratory of Dr Bruce Middleton. The work has shown that both enzymes are rapidly and maximally inhibited by three metabolites of aspirin – especially hydroxy hippuric acid (HHA), but also by salicylic acid (SA) and gentisic acid (although for technical reasons it was not possible to pursue work with this inhibitor). Interestingly, acetylsalicylic acid (aspirin) itself is without inhibitory effect. In an attempt to confirm the above work, metabolism of the entire beta-oxidation pathway in intact fibroblasts has been studied using previously described radioenzymatic methodology. We confirmed that in RS and controls the entire pathway is rapidly impaired by the addition to the medium of inhibitors at >5mM(SA and HHA). At lower concentrations (<5mM) of SA there was a striking difference in that controls showed an increase in palmitate oxidation, an effect which was absent from RS cells. Further work currently being completed should confirm whether this is a consistent effect seen with each of the inhibitors.

We have further confirmed that the inhibition did not occur at the step of fatty acid activation at the mitochondrial membrane (ie upon entry to the organelle), but has pinpointed to the long chain hydroxyl acyl CoA dehydrogenase (LCHAD) component of the trifunctional enzyme system. Kinetic analysis has demonstrated that the inhibition is competitive (ie the inhibitor competes with normal metabolites for a binding site within the LCHAD enzyme) and reversible. This is consistent with our original hypothesis. Additional work is being completed to work out binding constants (see above), but it is already clear that HHA is a particularly potent inhibitor.

This work has been presented to the April 1997 Meeting of the Royal College of Paediatrics & Child Health and will be given at the annual meeting of The Society for the Study of Inborn Errors of Metabolism at Gotenburg, Sweden in September. At the request of the British Paediatric Surveillance Unit it will be published as a resume in its Quarterly Bulletin in the summer of 1997.

Definitive publications for a peer reviewed journal are in preparation.

2. Adult Reye's Syndrome Surveillance

The following is a report of Dr Susan Hall:

A surveillance scheme for Adult Reye's Syndrome (ARS) was developed further during its second year. Initially, cases were ascertained via the British Neurological Surveillance Unit (BNSU) an 'active' reporting scheme for rare neurological disorders run by the Association of British Neurologists. However, because of concern that not all cases of ARS might be seen by neurologists and because only 3 case reports were received during the first year, it was decided to expand the ascertainment method. Since all patients with severe ARS will be admitted to an intensive care unit, a collaboration was set up with the Intensive Care National Audit and Research Centre (ICNARC). ICNARC itself is still in the development phase but the joint project means that in due course all patients admitted to an ICU in the UK with ARS will automatically be reported centrally to the study base via computer.

Additionally, a collaboration with the Department of Health's Hospital Episode Statistics (HES) is under way. Since 1995, HES are using the International Classification of Disease edition 10 (ICD-10) to code the diagnosis of all patients discharged from or dying in, hospitals in England and Wales. Unlike previous editions, ICD-10 has a code specific for RS thus enabling cases to be identified for surveillance purposes. HES anticipate the first data will be available in mid 1997.

Pathologists are another potential source of 'reporters' of ARS. Unfortunately they have no scheme like the BNSU or BPSU (see below). However an article to raise awareness and invite case reports was published in their Royal College Bulletin during the year.

Finally the study collaborates with the Office for National Statistics in ascertaining both ARS and paediatric RS cases (see below) where RS is mentioned as a cause of death on the death entry. A retrospective sweep to 1982 yielded 11 ARS cases and they are currently being followed up.

3. Paediatric Reye's Syndrome Surveillance:

The surveillance of paediatric Reye's syndrome is now undertaken by Dr Susan Hall and Mr Richard Lynn, British Paediatric Surveillance Unit (BPSU), Royal College of Paediatrics and Child Health and funded by the National Reye's Syndrome Foundation. In their annual report to the BPSU they provided a table headed "Reye's syndrome surveillance 1981/82 – 1994/95" for a fourteen year period (August through to July) which contained inter-alia the following information:

Total reports from the British Isles	**579**	
Revised diagnosis	**145**	**(69 inherited metabolic disorder)**
Cases of Reye's syndrome	**417**	
Number of deaths (of cases)	**219**	

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

The narrative states inter-alia that in the year to July 1995, 17 reports were received and follow up was complete on 14 at the time of writing. Three of the 14 diagnoses had subsequently been revised leaving 11 cases whose clinical and pathological features were compatible with Reye's syndrome. Among the three cases on whom further information is pending there were two ascertained via death entries alone. They were aged 10 months and 23 months and both died at home. Full details are contained in the BPSU 10th Annual Report published by the Royal College of Paediatrics and Child Health. (see Appendix below)

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4. Medical and Scientific Advisory Board (MSAB)

During the year Dr. Susan Hall, MB, BS, MSc, FRCP, FFPHM was appointed Chairman of the Medical & Scientific Advisory Board following the untimely death of Professor Alex Mowat. The Board has been further strengthened by the following appointments viz:-

Dr. Jim R. Bonham **BSc, MSc, PHD, MRCPath**	**Consultant Biochemist** **Dep. of Paediatric Chemical Pathology** **Sheffield Children's Hospital NHS Trust**
Dr. Colin Kennedy **MD, FRCP**	**Consultant Paediatric Neurologist** **Child Health Directorate** **Southampton General Hospital**
Professor M. Stuart Tanner **MS, BS, MSc, FRCP**	**Professor of Paediatrics** **University of Sheffield** **The Sheffield Children's Hospital**

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APPENDIX

BRITISH PAEDIATRIC SURVEILLANCE UNIT
EXTRACT FROM 10th ANNUAL REPORT

Reye's Syndrome

Background

Surveillance of Reye's syndrome began in August 1981 as a venture shared between the BPA and the CDSC. Responsibility for case ascertainment was transferred to the Surveillance Unit in June 1986. 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 United States although cases occurred at a younger mean age, there was no clear seasonal (winter) peak, no obvious association with influenza and chickenpox, and there was a higher case fatality rate.

In 1984/85 a study of risk factors mounted on the surveillance database showed an association between Reye's syndrome and consumption of aspirin. In response to this and similar findings in the United States, 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, 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 SU reporting, cases were also ascertained via death entries provided by the Office for National Statistics and the Northern Ireland Statistics and Research Agency, and via laboratory reports to the PHLS, Communicable Disease Surveillance Centre.

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 the liver (biopsy or autopsy).**

Since this case definition is relatively non-specific, cases reported from surveillance year (19945/95 onwards have been allocated a 'Reye-score' (Reference 1 below).

Study duration

The SU involvement with this study began in June 1986; it has been granted a further one year extension to July 1997.

Analysis

Between August 1981 and July 1995 a total of 579 suspected cases of Reye's syndrome were reported. In 145 cases (25% of the total) the diagnosis has subsequently been revised. Nearly half (48%) of the revisions were to one of the 'Reye-like' inherited metabolic disorders. In the year to July 1995, 17 reports were received and follow up was complete on 14 at the time of writing. Three of the 14 diagnoses had subsequently been revised leaving 11 cases whose clinical and pathological features were compatible with Reye's syndrome. Among the three cases on whom further information is pending there were two ascertained via death entries alone. They were aged 10 months and 23 months and both died at home.

Cases compatible with a diagnosis of Reye's syndrome year (12 months) to July 1995

There were five males and six females, the ages ranged between two months and thirteen years with a median of fourteen months. Nine lived in England, one in Wales and one in the Republic of Ireland. Two were ill in Autumn; four had their onsets between December and March, two in April and three in July. Of the nine survivors, six were normal, two had neurological sequelae and the outcome was unclear in one. Five patients had received no preadmission medication, three had received paracetamol plus an antibiotic, one had been given paracetamol and aspirin, one had been given penicillin and one had been on antiepileptic treatment.

Four patients were reported to have had no prodromal illness, five had had upper respiratory tract infections and two had had non-specific pre-admission symptoms such as lethargy and feeling cold. An enterovirus was recovered from faeces in one patient and campylobacter jejuni from a rectal swab in another; none of the others had microbiological confirmation of infection. Eight patients were reported to have been investigated for inherited metabolic disorders; three (aged 11 weeks, 14 months and eight years) had not. The 'Reye-Score' (possible range: 1-25) ranged between 6 and 21 with a median of 13.

Revised diagnosis cases

Of the three cases, one female aged six months had a confirmed inherited metabolic disorder, medium chain acyl-CoA dehydrogenase deficiency; she had had previous 'Reye-like' illnesses and a sibling had died during a similar episode. In another, a male aged 18 months, an inherited metabolic disorder was considered by the clinician to be more likely than Reye's syndrome because of pre-existing developmental delay and spasticity, although a definite diagnosis had not yet been made. In the third, aged five months, the revised diagnosis was haemorrhagic shock encephalopathy syndrome, associated with cytomegalovirus infection.

Comment

Surveillance year 1994/95 saw the lowest annual total reports to the Reye's syndrome surveillance scheme since it began in August 1981. The annual totals for 1992/93 and 1993/94 reported previously were spuriously low because of the delay in obtaining death entry data. This also accounts for most of the cases awaiting further information. It is noteworthy that, between 1992/93 and 1994/95, ten of the total 58 reports were death entries of patients not ascertained via the SU. These are currently the subject of a follow up study.

The continuing problem with surveillance of Reye's syndrome is the non-specificity of the case definition. Thus, unlike many other disorders surveyed by the SU, a case of Reye's syndrome can rarely, if ever, be described as 'confirmed'. Confirmation requires ultrastructural examination of the liver cells during the acute state of the illness. However, this investigation has been undertaken in only a handful of reported cases since surveillance began. This probably reflects a combination of caution in undertaking liver biopsy in patients with disordered clotting and restricted availability of electron microscopy.

In 1994/95 the number (3) and proportion (21%) of revised diagnosis cases was lower than in any year since 1984/85; the same applies to those with a definite or suspected inherited metabolic disorder. As knowledge of these conditions increases this trend is to be expected. Nearly 75% of the non-revised cases were reported to have been investigated for inherited metabolic disorders. However, it is not known how complete the investigations were as the proforma does not seek this information. The lack of seasonality, young median age and atypical features such as absent or non-specific prodrome and absent or minimal vomiting, suggests that some may have had unrecognised inherited metabolic or other Reye-like disorders, especially those with low Reye scores. Two of these 11 patients whose diagnosis was not revised by the clinician nevertheless may not have satisfied that part of the case definition which requires the encephalopathy and disordered liver function to be 'unexplained'. One did have unexplained encephalopathy but had had a cardiac arrest before the liver function tests were performed; the other, a child with pre-existing cerebral palsy and epilepsy, had been treated with sodium valproate, although there was uncertainty as to whether it had been given prior to the onset of the Reye-like illness.

Just under half the patients had received pre-admission medication for prodromal symptoms but only one, a 13 year old, had received aspirin. This patient, who was extensively investigated for an inherited metabolic disorder, also had the highest Reye score (21) which is in keeping with recent observations on the relationship between the score and aspirin exposure (Reference 1 below)

Reference

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

Dr S Hall, c/o PHLS Communicable Disease Surveillance Centre

Mr R Lynn, Surveillance Unit, College of Paediatrics and Child Health