BPSU

22nd Annual Report 2007-2008

British Paediatric Surveillance Unit
Royal College of Paediatrics and Child Health

Supported by the Department of Health

DH Department of Health

Aims of the British Paediatric Surveillance Unit

To:

- Facilitate research into uncommon childhood infections and disorders for the advancement of knowledge and to effect practical improvement in prevention, treatment and service planning
- Allow paediatricians to participate in surveillance of uncommon disorders and to lessen the burden on reporting doctors of such requests arising from numerous different sources
- Increase awareness within the medical profession of the less common disorders studied and respond rapidly to public health emergencies.

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British Paediatric Surveillance Unit

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British Paediatric Surveillance Unit Annual Report 2007–2008

Contents

Foreword

Prof A Colver
Chair, BPSU Executive Committee

Once again with all your effort we have increased the compliance rate for the return of the orange card to 93.8%, with compliance to the questionnaires running at 90%. 21 years of achieving such high return rates is testament to the high esteem in which the unit is held by College members and to the dedicated work of the office staff. I am pleased to say there appears to have been no adverse affects on the reporting rate following the office move to Theobalds Road.

Each year, the environment in which BPSU operates becomes more complex and expectations increase. To maintain our high level of effectiveness it is important to look critically at our achievements and administrative processes. To do this we have undertaken an internal evaluation following the guidelines of the Communicable Disease Surveillance Centre Atlanta on evaluating surveillance systems. One element, was to survey a sample of orange card respondents and we are grateful to those who returned the questionnaire. One impressive finding is that 43% stated that they had changed their clinical practice following the publication of results from studies. Those of you who have been an investigator will also have received a questionnaire about what you thought of communications with BPSU. The findings of the evaluation have already informed the application we have made to the Department of Health for further funding; the full findings of the evaluation will be reported in due course.

Whilst I hope that the burden on paediatricians receiving the orange card has not increased, the burden on investigators has, in line with the need for better research governance and greater public involvement. I mentioned last year how we have negotiated with PIAG and research ethics committees to ensure arrangements are clear and processes as streamlined as possible. We now also expect investigators to indicate how they are working with the voluntary sector, how they expect to communicate the purpose of their study to the public and how they might consult with young people when appropriate. The aim is to increase awareness in the activities of the BPSU and to make information on the studies more accessible to the public.

One pleasing aspect of the BPSU is to see how its methodology has been developed and adapted by other specialties. We are working with the UK Obstetric Surveillance System on the feto-maternal alloimmune thrombocytopenia study. The successful involvement of child and adolescent psychiatrists in the study of early onset eating disorder led to the development of a child and adolescent psychiatric surveillance system (CAPSS). The study on intussusception is involving paediatric surgeons.

Internationally we still liaise with our counterparts around the world. Wherever possible we link researchers and encourage multi-national surveillance. Unfortunately our FP7 framework application to the EU was unsuccessful. However, we continue to maintain links through email, a newsletter, the web site and occasional face to face meetings. Our next such meeting takes place in Munich in September.

The press often takes us by surprise, picking up on reports which we had not expected them to be interested in. Understandably the Department of Health does not want to be taken unawares either. We usually know only the approximate date of publication of a BPSU study; and copyright prevents interested bodies seeing the article until one or two days before publication when it is released to the press with an embargo. We are working closely with Claire Brunert in the RCPCH press office to try to make this process run more smoothly. This year the BPSU report and accompanying editorial on complications of varicella attracted press interest – as did the study on early onset eating disorders.

Membership of the BPSU Executive Committee has changed. Donal Manning and Adam Finn stepped down due to other commitments. Chikwe Ihekweazu completed his secondment from the Health Protection Agency and was succeeded by Colin Campbell. The vice-president for research is an ex-officio member and so Terrence Stephenson has taken over from Neil McIntosh. Dr Claire Cameron has stepped down as Health Protection Scotland representative, to be replaced by Dr Katy Sinka. Ted Wozniak, seconded to the Department of Health, continues as an observer on the committee.

Jennifer Ellinghaus, our researcher facilitator, left for pastures new. I am very grateful to her and very pleased to welcome her successor, Helen Friend, who is already having a positive impact on the workings of the office.

Finally, the forthcoming year will be very important for the future of the BPSU, not least in financial terms; can I take this opportunity to thank for your continued support of the Unit, and please contact us if you have any comments or concerns about the Unit.

Allan Colver

Introduction

Rare diseases and infections are, paradoxically, a numerically important cause of morbidity and mortality in childhood. Individually uncommon, together they number thousands, and many result in severe sequelae. Many are characterised by chronicity, high rates of disability or death. These conditions pose a large financial and emotional burden for affected children, their families and health systems.

To address this problem in the UK and Ireland, in July 1986 the British Paediatric Surveillance Unit (BPSU) was set up, enabling paediatricians to participate in the surveillance and further study of rare disorders affecting children.

The BPSU's work primarily concerns epidemiological surveillance, defined as 'the collection, analysis and dissemination of high quality data relevant to the understanding, prevention and control of medical conditions of public health importance so as to satisfy the needs of health care professionals, science, government, voluntary organisations and the public at large'. (Adapted from: Bulletin of the World Health Organisation, 1994; 72).

Several agencies founded and continue collaborating to support the work of the BPSU: the Royal College of Paediatrics and Child Health (RCPCH), the Health Protection Agency (HPA), the Centre for Epidemiology and Biostatistics at the Institute of Child Health (London), Health Protection Scotland (HPS) and the Faculty of Paediatrics of the Royal College of Physicians of Ireland. As the BPSU monitors conditions of public health importance, an observer from the Department of Health attends the BPSU's Executive Committee, which meets every two months to consider individual applications and the progress of studies.

The aims and key challenges of the Unit are summarised on the inside front cover.

This report mainly focuses on activities undertaken during the year 2007. Reference is also made to studies and activities, which commenced in the year 2008.

2 How the Surveillance System Works

Selection of studies for inclusion in the scheme

A study is eligible for participation in the scheme if the subject is a rare childhood disorder (or rare complication of a commoner disease) of such low incidence or prevalence as to require cases to be ascertained nationally in order to generate sufficient numbers for study. All studies have to conform to high standards of scientific rigour and practicality. The system is open to any clinician or research group, but applicants are encouraged to approach the BPSU with, or through, a paediatrician or department of paediatrics/child health.

The number of conditions under surveillance is usually limited to 12 and there is keen competition for places on the BPSU card. The BPSU application procedure consists of two phases: a screening phase based on an outline of the study and a detailed consideration of the full application. Details about the BPSU application procedure can be downloaded from the website at http://bpsu.inopsu.com/methodol.htm or are available on request from the BPSU office.

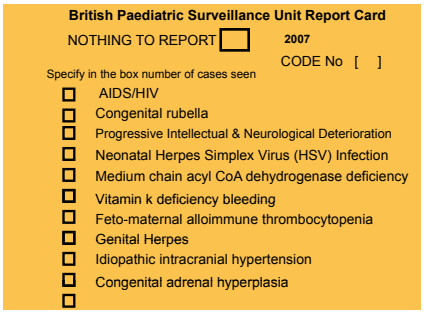

Figure 1:Orange Card Side A

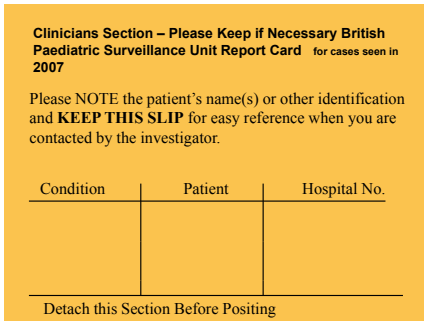

Figure 2: Orange Card Side B

Factors that increase the likelihood of a study being accepted include scientific importance, rarity of the condition, proposals with outcomes of clear importance to public health, clear achievable objectives and a clear and easily applied case definition. Once approved by the BPSU Executive, studies require Research Ethics Committee (REC) and Patient Information Advisory Group (PIAG) approval under Section 60 before commencement.

The reporting System

Those participating in the reporting system include consultant paediatricians who are either members of the RCPCH or the Faculty of Paediatrics of the Royal College of Physicians of Ireland.

Surveillance is 'active' as the BPSU Office actively sends out cards to clinicians asking for cases to be reported on the BPSU orange card (Figure 1) Each month, all clinicians participating in the surveillance scheme are sent the orange card listing the conditions currently under surveillance; follow-up reminders are sent to those who have not returned their card for two consecutive months.

A set of instructions for completing the card, including case definition of the conditions listed on the card is also circulated. When a new study begins, the mailing also includes a specially produced study protocol card and other information about the study.

When reporting a case, respondents are asked to make a note of the case (Figure 2) and keep the details for future reference as they will later be contacted by the study team with a questionnaire about each case.

Participants are also expected to return cards even if they have no cases to report - there is a 'nothing to report' box on the card for them to tick. This is an important feature of the surveillance scheme as it confirms whether other clinicians have seen cases but not reported them and ensures that the number of cases found reflects the true incidence in the population. The BPSU also regularly updates the list of consultant paediatricians who are eligible to participate and compliance rates are continually monitored, thus ensuring good coverage of the paediatric surveillance scheme across the whole of the UK and Ireland.

Follow-up and confirmation of case reports

On receiving a case report the BPSU informs the relevant study team. The study team then contacts the reporting clinician for further information about the case, usually through a short written questionnaire. Particular care is taken to ensure that questionnaires sent to reporting clinicians are as short as possible, clear, straightforward and not excessive in their demands. As the questionnaire cannot be fully anonymised, the amount of patient identifiable data collected is strictly limited to preserve patient confidentiality. The study investigators report back to the BPSU, indicating when cases have been confirmed or are duplicate case reports (Figure 3). Duplication of reporting is most likely to occur when the condition requires referral to another clinician, but this is encouraged, as it is better to receive duplicate reports than to miss a case.

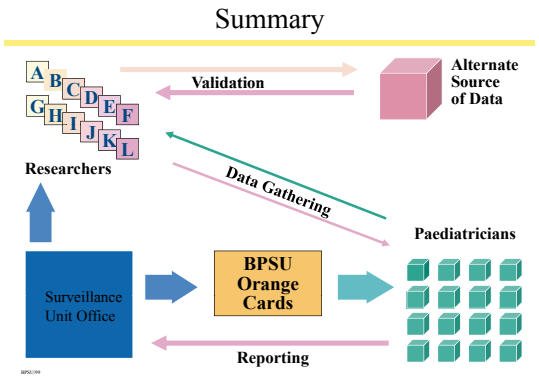

Figure 3: Surveillance mechanism

Table 2 (page 8) shows the number of cases reported to the BPSU from its inception until the end of year 2007 for conditions under surveillance at May 2008. The extent to which investigators receive survey data, identifying incorrect reports and duplicates and the speed in which this is done is known as the 'completion rate'. The number of cases which have so far been subsequently confirmed as meeting the case definition are also shown.

The time taken to follow-up a case report varies greatly between conditions and may be longer if microbiological or pathological details are required to confirm a case. The completion rate is high. For example, as of June 2008, only 549 (5%) of the 10,329 case reports had yet to be followed-up. The final completion rate normally averages average between 90-95% for a study undertaken through the BPSU.

Table 3 (page 9) summarises the outcome of the follow-up of all cases reported to the BPSU by the end of year 2007 and provides evidence for the level of accuracy of reporting by participating clinicians.

To improve case ascertainment for specific studies where a child may see specialist clinicians, consultants working in a number of other specialties have been invited to participate in the scheme. Pathologists have been included in the BPSU reporting scheme since 1992 and most studies of paediatric infections involve laboratory reporting by microbiologists. Apart from helping to improve ascertainment such complementary data sources help to validate the surveillance system (Figure 4).

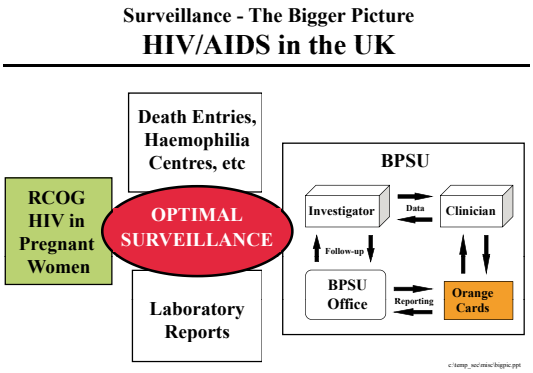

Figure 4: Surveillance - the bigger picture

Funding

The BPSU continues to be in receipt of a grant from the Department of Health to cover the majority of the running costs of the unit. In addition, the BPSU asks surveillance teams to contribute a sum to cover the administrative costs of coordinating their study. These funds also permit us to undertake additional activities such as holding workshops to support current and potential investigators, most recently in April 2007. The BPSU is also grateful for the ongoing support that it receives from the Royal College of Paediatrics and Child Health, the Institute of Child Health (London) and the Health Protection Agency.

3 Scientific Coodinator's Yearly Review of Activities

This past year has seen the commencement of three new BPSU studies. The first, genital herpes in children under the age of 11 years (investigator Dr Richard Reading) commenced in April 2007. The second is on idiopathic intracranial hypertension whose investigator Dr Yim, Yee Mathews, was the Sir Peter Tizard bursary 2005 recipient. The third study congenital adrenal hyperplasia, commenced in August 2007, investigator Dr Rachel Knowles.

Five studies had their period of surveillance extended for a further year: HIV, congenital rubella, progressive intellectual and neurological deterioration (PIND), medium chain acyl CoA dehydrogenase deficiency (MCADD) and feto-maternal alloimmune thrombocytopenia (FMAIT).

One study has so far commenced in 2008 – intussusception in children less than 12 months (March). This is the first BPSU study to ascertain cases using members of the British Association of Paediatric Surgeons (BAPS).

Since its inception in 1986 the BPSU has completed 68 studies (Appendix A). During 2007/2008, there were 16 publications and 21 presentations relating to BPSU studies (Appendices B and C).

The BPSU continues to disseminate information on its activities to clinicians and the public alike. This is achieved mainly through this report, the BPSU bulletin and BPSU website (http://www.bpsu.inopsu.com).

As liaison officer to the International Network of Paediatric Surveillance Units (INoPSU) it is my job to keep the units in contact, inform them of each other's work and put investigators in different countries in touch with each other in order to facilitate collaboration. In the past year, over 90 different conditions have been investigated across the 13 member surveillance units. The BPSU office continues to manage the INoPSU website (http://www.inopsu.com) where information on INoPSU's work is available.

Participation in the scheme during the year 2007

Following an audit of the College manpower census and membership list 334 consultants were placed on the mailing list whilst 111 were removed mainly following retirement or due to moving overseas. The BPSU mailing list also includes selected groups of consultants other than paediatricians such as cardiologists, clinical geneticists and pathologists.

(Photo by Joe Spinoza, aged 10)

Richard Lynn
Scientific coordinator

Reporting rates for returning the orange cards remain high - the overall card return compliance rate for the year 2007, calculated as a proportion of orange cards returned, was 93.8% (30,853/32,877), an increase of 0.1% from 2006. Monthly response rates ranged from 95.5% in March to 90.9% in December, with a median of 93.6%. To maintain this compliance rate respondents who have not returned cards for two consecutive months are now contacted by email, as much to verify postal address as to act as a reminder. This return rate remains higher than any equivalent UK scheme and ranks highly against other national paediatric surveillance units.

Wales continues to achieve the highest average yearly response rate – 97.7% - with North Scotland showing the highest move in the rankings up 12 to rank second with 97.0%.The Thames area showed a cumulative response rate of 91.8%, no change on 2006. North Western fell 12 places to rank 17. Full details of regional response rates are provided in Table 1. Overall the response rate is still exceptional and is a testament to the willingness of clinicians to support the BPSU reporting scheme.

Workload of those reporting in the scheme

81% (2378) of participants reported no cases in 2007, 12% (354) reported a single case, 5% (159) reported between two and four cases and 1% (41) reported five or more cases. The greatest numbers of cases reported were by HIV/AIDS specialists, one of whom reported 121 cases and another 49. Specialties that had a particularly high level of reporting were paediatric neurologists (PIND), neonatologists and infectious disease specialists (AIDS/HIV, MRSA). Community paediatricians continue to make a significant contribution to the reporting, particularly to the PIND and HIV/AIDS studies and their continued involvement in the scheme is very much welcomed.

Table 1: Regional response rate 2006 and 2007

Region	Rank 2007	Rank 2006
Northern	4	11
Yorkshire	11	8
Trent	8	7
East Anglia	5	6
NWT	18	17
NET	20	20
SET	15	12
SWT	19	18
Wessex	3	10
Oxford	9	3
South Western	10	2
West Midlands	12	9
Mersey	16	19
North Western	17	5
Wales	1	1
North Scotland	2	14
South Scotland	14	16
West Scotland	7	13
Northern Ireland	6	4
Republic of Ireland	13	15

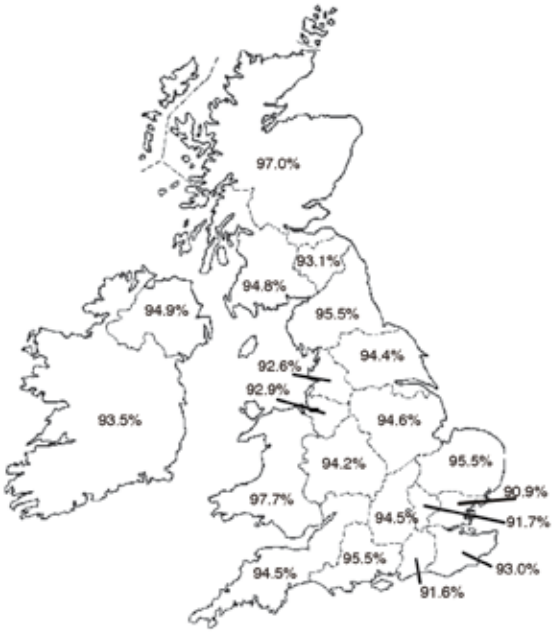

Figure 5: Average orange card return rate (%) by area, 2007

Table 2: Cases reported from June 1986 - December 2007 for conditions under surveillance at May 2008

Reports (confirmed cases)						
	Date when reporting began	June 1986-Dec-96	Jan-96 Dec-00	Jan-01 Dec-03	Jan-04 Dec-05	Jan-07 Dec-07
Conditions under serveillance						
HIV	Jun-86	991 (691)	1017(705)	1774 (1431)	2171(1829)	708(489)
Congenital rubella	Jun-91	72(39)	49 (25)	26 (6)	13 (4)	9(1)
PIND	May-97		1066 (630)	610(318)	503 (306)	208(111)
Neonatal Herpes Simplex	Feb-04				182 (102)	8 (0)
MCADD	Jun-04				267 (171)	67 (0)
EOED*	Mar-05				345 (133)	160 (75)
MRSA	Jun-05				125 (69)	39 (19)
Scleroderma	Jun-05				83 (46)	20(11)
FMAIT	Oct-06				17 (10)	85 (47)
VKDB	Oct-06				7 (1)	21 (4)
Genital Herpes	Apr-07					14 (5)
IIH	Jul-07					103 (23)
CAH	Aug-07					74 (22)
Total		**1063 (730)**	**2132 (1360)**	**2410 (1755)**	**3368 (2538)**	**1356 (732)**

Table 3: Outcome of follow-up of the cases reported in 2007 for conditions under surveillance at May 2008

	Date when reporting began	Valid reports	(%)	Duplication	Errors	Total (%)	Not yet known	(%)	Total
Condition under surveillance									
HIV/AIDS	Jun-86	5,145	77	626	19	255	299	4	6661
Congenital rubella	Jun-91	75	44	31	59	53	4	2	169
PIND	May-97	1365	57	296	677	41	49	2	2387
Neonatal Herpes Simplex	Feb-04	102	54	47	41	46	0	0	190
MCADD	Jun-04	171	51	47	31	23	85	25	334
EOED	Mar-05	208	41	103	144	505	51	10	505
MRSA	Jun-05	88	54	18	26	27	32	20	164
Scleroderma	Jun-05	57	55	12	27	38	7	7	103
FMAIT	Oct-06	57	56	7	13	20	25	25	102
VKDB	Nov-06	5	18	8	8	57	7	25	28
Genital Herpes	Jun-07	5	36	0	7	50	2	14	14
IIH	Jul-07	23	22	6	28	33	46	45	103
CAH	Aug-07	22	30	7	8	20	37	50	74
All		**7115**	**69**	**1105**	**1560**	**26**	**549**	**5**	**10329**

HIV Human immunodeficiency virus: reports of AIDS in June 1986 include cases previously seen; case definition extended to include HIV infection in January 1990
PIND Progressive Intellectual and Neurological Degeneration
MCADD Medium chain Acyl Co A dehydrogenase deficiency
MRSA Methicillin-resistant Staphylococcus aureus
FMAIT Feto-maternal alloimmune thrombocytopeania
VKDB Vitamin K deficiency bleeding
IIH Idiopathic intracranial hypertension
CAH Congenital adrenal hyperplasia

Table 4: Case report table

Valid reports:

Cases confirmed at follow-up as being both unique (i.e. not a duplicate) and satisfying the diagnostic criteria set out in the case definition. Confirmed cases reported to the BPSU but already known to the research worker from another source are included.

Invalid reports:

These include:

duplicate reports of cases already reported to the BPSU,

and

reporting errors arising as a result of a misdiagnosis, the wrong box on the orange card being ticked, the case not meeting the diagnostic criteria set out in the case definition or an inability to follow-up a case.

Outcome not yet known:

Outcome of follow-up not yet received by BPSU (by May 2008).

4 Main findings of studies undertaken in 2007

Commencing in July 2005 the two year study on **childhood scleroderma** (page 12) aimed to assess incidence, examine presenting features, and consider current management. In order to ascertain as many cases as possible, members of the British Society for Paediatric and Adolescent Rheumatology, the British Association of Dermatologists, and the UK Scleroderma Study Group are also being asked to report cases. There have been 79 confirmed and 11 suspected cases. Findings so far suggest that childhood scleroderma, at least linear scleroderma and Systemic Scleroderma, are even rarer than originally thought.

Principal investigators: Dr E Baildam, Liverpool Children's Hospital, Dr AL Herrick, Professor AJ Silman, University of Manchester, Dr Bhushan, Hope Hospital.

August 2007 saw the start of a DH funded study into **congenital adrenal hyperplasia (CAH)** (page 15). This studies aims to determine incidence, report clinical features at presentation and examine management, morbidity and mortality of CAH. In the first six months 26 children with newly confirmed CAH have been reported. Half were diagnosed under the age of one; though a significant number remained unrecognised until primary school age.

Principal Investigators: Dr R Knowles, Ms J Oerton, Ms M Khalid, Professor C Dezateux, Professor C Kelnar*, Professor P Hindmarsh – ICH London*, Univ. Edinburgh*

Surveillance for **congenital rubella** (page 18) has been underway in the UK continuously since 1971; the BPSU is the only source of surveillance for this condition in the UK. Among the 15 infants with congenital rubella born and reported in the UK or Ireland since 1997, ten had mothers who acquired their infection abroad. In almost all recent cases, maternal rubella infection was not diagnosed in pregnancy, and the diagnosis of congenital rubella infection in the newborn baby was unexpected

Principal Investigators: Dr P Tookey and Professor C Peckham, Dr E Miller – ICH London, HPA.

Undertaken in collaboration with the UK obstetric surveillance system a study on **feto-maternal alloimmune thrombocytopenia (FMAIT)** (page 21) commenced in October 2006. Data suggest that the incidence of clinically detected FMAIT is less than one third of that estimated from prospective screening studies. The information collected will be used to help reassess the case for antenatal screening.

Principal Investigator: Dr M Knight, National Perinatal Epidemiology Unit, University of Oxford.

Surveillance of **genital herpes in children** under 11 years of age (page 23) commenced in April 2007. In the first ten months of the study only five cases have been confirmed. This suggests the condition could be rarer than first thought. In view of the small number of case reports and the important implications of the study for child protection, we have applied for a study extension for a further year.

Principal Investigator: Dr Richard Reading - Norfolk and Norwich University Hospital.

The BPSU survey of **HIV infection in children** (page 25) is the cornerstone of paediatric HIV surveillance in the UK and Ireland. Findings from this study have had a substantial impact on current UK antenatal screening policy and clinical practice. Less than half of all new reports now come from the London area, and cases are being notified from all parts of the country. Reported births to HIV infected women have increased substantially year on year since 2000 but the proportion of infants who are actually infected has declined, thanks to greatly improved antenatal detection rates and high uptake of interventions to prevent transmission. Nevertheless, infected infants born to both diagnosed and undiagnosed women in the UK and Ireland are still being reported. Finally, the proportion of newly reported infected children who were born abroad has increased in recent years; these children tend to be older at diagnosis than those born in the UK and Ireland.

Principal Investigators: Dr P Tookey, Dr F Ncube, Professor D Goldberg – ICH London, HPA, HPS.

The third Sir Peter Tizard bursary study, on **idiopathic intracranial hypertension,** commenced in July 2007 (page 29). In the first six months 100 cases were reported of which 24

probable or confirmed. The low number of newly diagnosed cases suggests that IIH in children might be rarer than previously estimated. It is for this reason that an extension to the surveillance period has been approved.

Principal Investigator: Dr Yim Yee Mathews - Wrexham Maelor Hospital.

Surveillance of **medium chain acyl CoA dehydrogenase deficiency (MCADD)** (page 31) commenced in June 2004 and ended in June 2008. The study has shown that newborn screening reliably identifies affected children before they are likely to develop symptoms, enabling parents to use simple measures to avoid fasting and thereby reduce the chances of severe illness or death.

The Department of Health announced a ministerial decision to introduce universal screening for MCADD in England by April 2009 (Gateway number 7801).

Principal Investigators: Professor C Dezateux, Dr J Oerton, Ms P Phillips, Dr G Shortland – ICH London, University Hospital Wales.

Surveillance on **methicillin-resistant Staphylococcus aureus (MRSA)** (page 34) ended in June 2007 after 25 months. The study aimed to document the incidence in children and the clinical features and patterns of presentation. 116 confirmed cases have been notified to the BPSU, of which 70% were under the age of one. A further 245 confirmed cases have been reported through the HPA staphylococcal and voluntary reporting of isolates from hospital microbiologists to Labbase2.

Principal Investigators: Ms C Goodall, Dr A Johnson, Department of Healthcare Associated Infection & Antimicrobial Resistance, HPA Centre for Infections. Dr M Sharland, St George's Hospital.

Despite the complexity of the conditions involved in the survey of **progressive intellectual and neurological deterioration in children (PIND)** (page 38) has proved successful. A primary objective of the study is to identify new cases of variant Creutzfeldt-Jakob disease (vCJD) in UK children. Over 2300 cases of suspected PIND have been reported. Among them 1012 cases are confirmed diagnoses, comprising of 115 known degenerative conditions. Six cases of vCJD have been identified. Active surveillance will continue to 2010.

Principal Investigators: Dr C Verity, Mrs A-M Winstone, Mrs L Stellitano, Professor A Nicoll, Professor R Will – Addenbrooke's Hospital, ECDC, CJDSU.

October 2006 saw the commencement of the fourth BPSU survey of **vitamin K deficiency bleeding** (page 41). The reason for repeating this study is that since the withdrawal of Konakion Neonatal, the only product now licensed for intramuscular (IM) prophylaxis is Konakion MM. Published data about the long-term protection conferred by a single IM dose of this preparation, which has a completely different formulation from Konakion Neonatal, is very limited. This study will look for any change in incidence; assess the effectiveness of prophylactic regimens in use, particularly Konakion MM 1mg IM as a single dose at birth, to examine treatment and outcome. In the first 18 months of surveillance there have been four confirmed cases.

Principal Investigators: Dr A Busfield, Dr A McNinch, Dr J Tripp, Royal Devon & Exeter NHS Foundation Trust.

5 Surveillance Studies Undertaken in 2007

Childhood Scleroderma

Key points

- Seventy-nine children with confirmed and eleven with suspected childhood scleroderma were reported over a two year period
- Study enrolment is now closed, although information on any of the outstanding reports would still be welcome
- Follow up information to establish the health status of children 12 months after notification is being sought from paediatricians and is currently being collated

Background

Scleroderma may affect children as well as adults, and is associated with significant morbidity and mortality.[1-3] While some children with scleroderma have systemic sclerosis (SSc), more commonly scleroderma in children is localised and confined to the skin and underlying tissues. Two recent international studies have documented the clinical and immunological features of systemic sclerosis[4] and of localised scleroderma[5] in children.

Systemic Sclerosis: Systemic sclerosis is rare in children[6] but is an important condition because internal organ involvement can be life threatening (Figures 8, 9, 10).

Localised scleroderma: Although localised scleroderma is not a multisystem connective tissue disease, it can be severely debilitating and little is known about the epidemiology of localised scleroderma in children.[7] The early lesions of localised scleroderma are inflammatory, however, and a recent study has reported extracutaneous features in a significant proportion of children[8]. Therefore there is a rationale for early diagnosis and intervention (Figure 11).

Objectives

The study aims to:

- ascertain the incidence of childhood scleroderma in the UK and Ireland
- describe the usual presenting symptoms
- establish the delay between symptom onset and diagnosis

Dr A Herrick

- determine the pattern of care received by affected children before and after diagnosis
- ascertain the age at which most children are affected and the sex ratio
- describe regional and ethnic variations in incidence

Surveillance period

July 2005 – July 2007 (inclusive).

Methodology

Case definition

The reporting case definition was 'all cases of abnormal skin thickening (the skin will usually be difficult to pinch normally) first seen between July 2005 and July 2007 and suspected by the reporting clinician to be linear scleroderma or systemic scleroderma in children aged up to 16 years'. For confirmation of cases, the 12 month questionnaire asked if the diagnosis had been confirmed by a dermatologist or rheumatologist.

Additional sources of data

Some children with scleroderma are referred directly to adult rheumatologists or dermatologists with an interest in scleroderma. Members of the British Society for Paediatric and Adolescent Rheumatology (BPSAR), the British Association of Dermatologists (BAD), and the UK Scleroderma Study Group (UKSSG) were informed about the study and asked to notify cases. Members of the three organisations were mailed and asked to contact the University of Manchester directly if a case was identified. The questionnaires sent to BPSU respondents were also sent to clinicians from other sources who notified cases directly.

Figure 8: Limited cutaneous

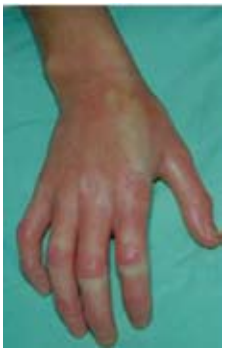

Figure 9: Diffuse cutaneous

Figure 10: Diffuse cutaneous

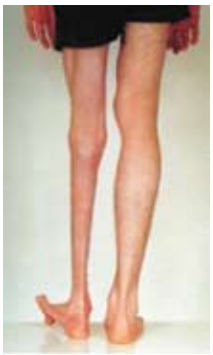

Figure 11: Localised

Expected number (per year)

Approximately 180 patients per year.

Funding

The Raynaud's and Scleroderma Association.

Ethics approval

South Manchester Research Ethics Committee.

Support group

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Analysis

Description of reported cases: During 25 months of surveillance, 103 reports were received from 69 clinicians (Table 5). These reports yielded 51 (50%) confirmed cases. In addition to BPSU notifications, we have also received reports of a further 76 cases from BSPAR, BAD and the UKSSG. These have yielded 28 confirmed cases. Although the total number of confirmed cases is expected to rise above the current level of 79, its does appear that childhood scleroderma is even rarer than initially expected.

Stratification of confirmed cases by specialty indicated that children with scleroderma are referred to a range of different specialists. Paediatric rheumatologists and adult dermatologists reported the majority of cases of childhood scleroderma.

Localised vs diffuse: Of the confirmed cases, 73 (92%) were localised scleroderma, predominantly the linear subtype, and six (8%) were SSc. While the overall number of cases is small, preliminary analysis suggests that dermatologists and paediatric dermatologists tend to see a greater proportion of cases of morphoea and En Coup de Sabre than other specialists, while cases of linear scleroderma and systemic sclerosis were predominantly seen by paediatricians and paediatric rheumatologists.

Clinical characteristics of case: As anticipated, the majority of confirmed cases were female (62%). The proportion of all subtypes of scleroderma was significantly higher in females than males with the exception of the one reported (male) case of Parry-Romberg syndrome. Sixty-five (82%) of confirmed cases were described as white British. The median age at the onset of symptoms was estimated to be 10 years of age with the median age at diagnosis 11 years. The median delay between the onset of symptoms and diagnosis was 12 months.

Data from 12 month questionnaires: By March 2008, 65 of the 12 month follow-up questionnaires had been sent out and 47 of these returned. Of the 47 follow-ups received, 25 cases reported an overall improvement, five were static or stable, 10 deteriorated and one case had resolved. In one case the diagnosis changed from localised scleroderma to angioma serpiginosum and in another case from SSc to localised scleroderma. In four instances, cases were lost to follow up.

Table 5: Status of reported cases by reporting source

Organisation	Confirmed	Duplicates or Errors	Outstanding	Total
BPSU	51	35	17	103
BAD	26	16	31	73
BSPAR	1	0	0	1
UKSSG	1	1	0	2

Discussion

Findings so far suggest that childhood scleroderma, at least linear scleroderma and SSc, are even rarer than originally thought.

The main conclusions so far are as follows:

1. Childhood linear scleroderma and SSc are rare

2. BPSU notifications are higher in number than those from other clinical specialist groups, which may reflect the longer experience of paediatricians in surveillance and the active surveillance methods used by the BPSU

3. Analysis of the study will be completed shortly after July 2008 when the last of the 12 month follow-up questionnaires is returned.

Please note the data presented are provisional, not peer reviewed and definitive conclusions should not be drawn from them.

Further research: The study will provide data that should be of value in defining the need for supra-regional referral services and in the design of future clinical trials.

Acknowledgements

We are extremely grateful to all paediatricians, dermatologists and rheumatologists who notified cases and completed forms. We are also indebted to the Raynaud's and Scleroderma Association for funding this study.

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Congenital Adrenal Hyperplasia (CAH)

Dr R Knowles

Key points

- Congenital adrenal hyperplasia (CAH) is a recessively inherited deficiency of cortisol production which may present in newborns with an acute life threatening adrenal crisis or with excess androgen production, resulting in girls being incorrectly assigned as boys at birth. It may also present in later childhood with early puberty, accelerated growth and/or short stature.
- Newborn screening is undertaken in some countries but is not offered in the UK; the findings of this study will inform future UK newborn screening policy.
- In the first six months of surveillance, 26 children with confirmed CAH were reported through the BPSU and 25 children were notified through UK laboratories participating in the Biochemical surveillance scheme for CAH.

Background

Congenital adrenal hyperplasia (CAH) is a recessively inherited deficiency of cortisol production with an estimated birth prevalence of 1 in 10,000 to 20,000. Just over half of those affected have a salt wasting form which can present in newborns with an acute life threatening adrenal crisis.[1] CAH is also often associated with accelerated growth and excess androgen production, which may result in girls being incorrectly assigned as boys at birth. Early detection by newborn screening combined with cortisol and mineralocorticoid replacement can prevent life-threatening episodes, and ensure normal growth and sexual development. Newborn screening for CAH is undertaken in most US states and many European countries, but has not been introduced in the UK[3] reflecting inconsistent information about disease burden. It is now timely to obtain better epidemiological data on CAH in the UK. The BPSU study of CAH will estimate incidence and short term outcome to inform future UK newborn screening policy.

Objectives

The objectives of this study are to:

- determine the incidence of clinically presenting CAH in children under the age of 16 years in the UK (excluding Northern Ireland), and to report its distribution by age, sex and ethnic group
- report the clinical features at presentation
- report the proportion of cases who become clinically unwell by 5-8 days of life
- report early clinical management and morbidity and mortality to one year post diagnosis, including the proportion of girls with initially incorrect sex or sex reassignment

Surveillance period

August 2007 – August 2008 (inclusive).

Coverage

UK excluding Northern Ireland and the Republic of Ireland.

Methodology

Case definition

A child will be considered to have a diagnosis of CAH:

IF AT LEAST ONE of the following clinical features is found:

- Adrenal crisis or adrenal insufficiency
- Virilisation of female genitalia
- Precocious puberty
- Accelerated skeletal age
- Short stature
- Hypertension
- Incomplete masculinisation of male genitalia
- Positive family history in first degree relative

AND AT LEAST ONE of the following criteria are met:

- Elevated 17 OHP in blood test
- Positive synacthen stimulation test
- Test result diagnostic of rarer form of CAH, e.g. 3ß-hydroxysteroid dehydrogenase (3ß-HSD) deficiency or 11ß-hydroxylase (11ß-OH) deficiency

The diagnosis of CAH may be made following clinical presentation, investigation of a sudden unexpected death, or diagnosis in a sibling or other affected family member.

All notifications will be reviewed by an independent diagnostic review panel.

Additional sources of data

A Biochemical Surveillance System for CAH (BioCAHSS) has been set up through 16 UK laboratories providing diagnostic testing for CAH. Participating laboratories report new cases directly to the investigators using the BioCAHSS monthly reporting card.

Expected number (per year)

The expected number of cases (all forms of CAH) is estimated to be between 79 and 162 per year.

Analysis

BPSU case notifications: During the first six completed months of surveillance there were 82 case notifications through the BPSU, of which eight were duplicate notifications and eight were excluded as the diagnosis was made before August 2007.

Questionnaires were received for 26 children; these were reviewed by an independent clinical review panel which met in February 2008 and confirmed the diagnosis of CAH in all cases. The ratio of boys to girls was 10:16. Half of these children with CAH were aged under one year at the time of diagnosis, whilst the remainder ranged from two to 14 years old (Figure 6).

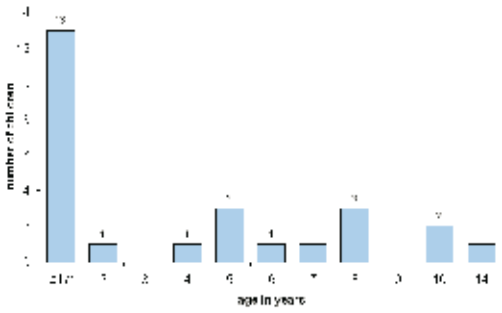

Figure 6: Age at time of diagnosis for 26 confirmed cases in the first 6 months of surveillance

The majority (73%) of children were of white British ethnicity. There were 12 children with the 21-hydroxylase deficiency form of CAH and 14 who had rarer forms, including 3ß-hydroxysteroid dehydrogenase and 11ß-hydroxylase deficiency. Adrenal insufficiency was reported in nine children, however only seven had experienced a salt-wasting crisis. Virilisation of the genitalia was present in 14 (87%) girls. Outcome data are not yet available.

Biochemical surveillance system (BioCAHSS) case notifications: Sixteen UK laboratories which routinely test for CAH, have agreed to participate in the laboratory reporting system (BioCAHSS) (Figure 7). Monthly card mailings began in January 2008 with a look-back over the six months from August 2007 until January 2008. In the first six months of surveillance, laboratories have notified 25 cases. Further data are not yet available.

Figure 7: Distribution of laboratories participating in the BioCAHSS system

Discussion

In the first six months of surveillance in the UK (excluding Northern Ireland), 26 children with newly diagnosed confirmed CAH have been reported to the study. Less than half of these children were reported to have the 21-hydroxylase deficiency form of CAH. The relatively high proportion of children with rarer forms of CAH will be explored in more detail in later analyses. There were more girls than boys in keeping with previous studies. Half of all children with CAH were diagnosed under the age of one year; however a significant number remained unrecognised until primary school age.

Please note that the data presented here are provisional not peer reviewed and limited to the first six months of surveillance so conclusions should not be drawn from them.

Funding

Department of Health.

Ethics approval

Thames Valley MREC (Ref: 07/MRE12/25); PIAG Section 60 Support (Ref: PIAG/BPSU 1-05(FT4)/2007).

Support group

CLIMB-CAH UK Support Group is a sub-group of Climb (Children Living with Inherited Metabolic Disorders) Registered Charity No. 1089588
Web: www.livingwithcah.com (previous web address www.cah.org.uk also links into this site).

CAH study website - www.ucl.ac.uk/paediatric-epidemiology/cahss/cahss.html

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We are very grateful to all paediatricians who have completed monthly cards, particularly those who have notified cases and returned their completed questionnaires to us. We would also like to thank Dr Jonathan Middle (NEQAS) and Dr Jim Bonham (Sheffield Children's Hospital) for their help in setting up the laboratory surveillance scheme, as well as staff in participating laboratories for their continuing support.

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Congenital Rubella

Key Points

- Congenital rubella continues to be extremely rare in the UK and Ireland, with only one confirmed case reported in 2007.
- Among the 15 infants with congenital rubella born and reported in the UK or Ireland since 1997, ten (67%) had mothers who acquired their infection abroad.
- In almost all recent cases, maternal rubella infection was not diagnosed in pregnancy, and the diagnosis of congenital rubella infection in the newborn baby was unexpected.

Background

The National Congenital Rubella Surveillance Programme was established in 1971 to monitor congenital rubella births in England, Scotland and Wales. Active surveillance through the BPSU started in 1990, and since then reports have also been received from The Republic of Ireland and Northern Ireland. Diagnosed rubella infection in pregnancy is monitored through laboratory reports to the Health Protection Agency (HPA) or Health Protection Scotland (HPS), and has remained at a very low level in recent years (<10 a year). Women with diagnosed first trimester infection usually opt for termination of pregnancy in the UK; most mothers of congenitally infected infants are unaware of their infection until their baby is diagnosed.

The World Health Organisation Regional Office for Europe set a target for the elimination of measles and rubella, and prevention of congenital rubella infection (<1 case of congenital rubella syndrome per 100,000 births) by 2010. Long-standing vaccination programmes have already led to the virtual elimination of congenital rubella in the UK and Ireland.[1,2] Nevertheless, sub-optimal MMR coverage, and migration within Europe present major challenges to reaching this target, and maintaining control in the long term. As a result of over 10 years of inadequate vaccine uptake with no wild virus circulating, there are likely to be substantial pockets of susceptible children in parts of the UK and Ireland. In addition, inward migration from countries without long-standing high uptake rubella vaccination programmes will have lead to greater concentrations of susceptible individuals in some areas, often the very places where MMR uptake has been low (e.g. parts of London). Under these circumstances it is possible that rubella could once again start to circulate in the British Isles, as it still does in many parts of the world.

Dr P Tookey

Comprehensive national surveillance through the BPSU therefore remains extremely valuable. Timely reporting by paediatricians will help us to recognise any resurgence in numbers at an early stage, and will also assist in the implementation of appropriate control measures. Congenitally infected infants excrete rubella virus for an extended period of time, and it is important that they are diagnosed and managed appropriately to avoid the risk of further community transmission.

Objectives

To monitor the effectiveness of the rubella immunisation programme by determining the incidence of congenital rubella and investigating the circumstances surrounding any new cases.

Surveillance period

Surveillance through the BPSU began in January 1990 and is reviewed annually.

Methodology

Case definition

Any infant (live or still born) or child up to 16 years of age who, in the opinion of the notifying paediatrician, has suspected or confirmed congenital rubella with or without defects, based on history, clinical, and/or laboratory findings. This includes “imported cases”, i.e. children born in the British Isles where the maternal infection occurred abroad, AND children who were born abroad, as well as British-born infants whose mothers acquired infection in the British Isles.

CDC-Public Health Image Library

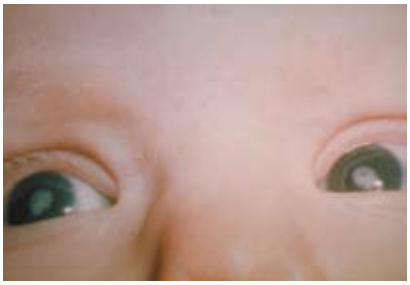

Figure 12: Cataracts due to congenital rubella syndrome

Reporting instructions: Any live or still born infant, or child, seen for the first time in the past month who meets the case definition, regardless of country of birth. The reporting instructions were extended in 2005 to include reports of children born abroad: this has been instituted as part of the enhanced surveillance necessary to monitor progress towards the European elimination target.

Additional sources of data

No active additional sources, but reports are occasionally made direct to the investigator (e.g. from virologists, audiologists), and there is close liaison with the HPA, HPS and the Health Protection Surveillance Centre in Ireland.

Expected number

Currently fewer than five births a year in the UK and Ireland, but this number could increase if there were renewed circulation of rubella infection in the community. Rubella-associated terminations of pregnancy are monitored through reports to the Office for National Statistics, but the annual number is not currently published because there are so few cases.

Analysis

Only one confirmed birth was reported in the UK in 2007. The infant's mother was born abroad, had lived in the UK for several years, but was probably infected while visiting her country of origin in early pregnancy. There were nine BPSU reports in 2007, three of which related to the confirmed case; one report was of an older child (>10 years) who was born abroad, and the other five were made in error.

The number of reported congenital rubella births and rubella associated terminations declined from, on average, 50 births and 740 terminations a year in 1971-75 to 22 births and 54 terminations a year in 1986-90.

Since the beginning of active surveillance in 1990, 165 reports have been made through the BPSU (Table 6). Of the 144 reports from England, Scotland and Wales, 51 are confirmed or compatible, previously unreported cases of congenital rubella, four are possible cases, and 13 had already been reported from another source; the remaining reports were: duplicates (25), reporting errors (46), and five where further information could not be obtained. Sixteen reports were from Northern Ireland or Ireland, and included four children with confirmed congenital rubella (one born in 1989, two in 1996 and one in 2004), and a fifth possible case (born in 1983); the other eleven Irish reports were duplicates, errors or previously reported.

Since the reporting definition was extended in 2005, five reports have related to four children who were born abroad. In previous years reports of foreign-born children were not requested, and any such reports were categorised as errors. These four children are not included in Table 6 since the main aim of the surveillance is to monitor births in the UK or Ireland. However, the data are useful at a European level, and we appreciate these reports.

Congenital rubella births in the UK or Ireland 1990-2007: Fifty-nine children and three stillborn infants with confirmed or compatible congenital rubella have been born and reported since the beginning of active surveillance in 1990; 47 (77%) of these were first reported through the BPSU (Table 7). Fifteen of these infants were born in the last 10 years, including one born in Ireland, and one stillborn infant. Although 10 were imported cases with maternal infection acquired abroad (five in Southern or South Eastern Asia, five in Africa), five infants were born to women whose infection occurred in the UK. Five maternal infections were acquired in England or Scotland, two by British-born women, and three by women who were born abroad, but who had all been resident in the UK for several years.[2] There were over 80 terminations for rubella disease or contact in pregnancy recorded by the Office for National Statistics in England

Table 6. Congenital rubella reports to BPSU 1990-2007 (includes births occurring in earlier years)

	Confirmed or compatible	Possible cases	Cases already reported	Duplicate, error or lost	Total
Place of birth					
Engalnd, Scotland and Wales	51	4	13	76	144
NI and Ireland	4	1	2	9	16
Born abroad (reports 2005-2007 only)	2	2	0	1	5
Total	**57**	**7**	**15**	**86**	**165**

Table 7. Confirmed and compatible congenital rubella births repoted in the UK and Ireland 1990-2006

	Primary source of notification		
year of birth	BPSU	Other	Total
1990-94*^	22	10	32
1995-99	12	4	16
2000-04*	10	1	11
2005-07	3	0	3
Total	**47**	**15**	**62**

and Wales since 1990, but annual data are no longer published since the numbers are so low.

Discussion

The number of reported cases of congenital rubella has remained at a very low level over the last ten years, but virtually all reports concern infants with serious rubella-associated defects present at birth (Figure 12). It is possible that some infants with less obvious signs of congenital rubella, or those with later onset, are not diagnosed and reported.

Rubella susceptibility in pregnant women in the UK varies by ethnic group, with women from many parts of Asia and Africa having particularly high susceptibility rates especially if they are having their first baby.[3] Women originating from countries without comprehensive and long-standing vaccination programmes are likely to be at higher risk if there is renewed circulation of rubella here. Even while rubella infection is rare in the British Isles, susceptible women who travel abroad during early pregnancy may come into contact with infection. Awareness of rubella infection and congenital rubella among paediatricians and other health professionals must be maintained.

Please continue to look out for and notify all infants with suspected congenital rubella, whether or not they have the associated typical defects, and regardless of country of birth.

Pease note the data presented are provisional, not peer reviewed and definitive conclusions should not be drawn from them.

Funding

The Health Protection Agency makes a contribution towards the costs of the surveillance. Additional support is received from Sense and from the Centre for Paediatric Epidemiology and Biostatistics at the UCL Institute of Child Health.

Ethics approval

The London Multicentre Research Ethics Committee reaffirmed approval in 2005 (Ref: 05/MRE02/2). Surveillance of congenital rubella through the BPSU also has PIAG approval (PIAG/BPSU 2-10(f)/2005).

Support Group

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Feto-maternal Alloimmune Thrombocytopenia (FMAIT)

Dr M Knight

Key points

- FMAIT is associated with significant fetal and infant morbidity and mortality; first pregnancies are often severely affected and the diagnosis is usually made with the birth of a first affected infant.
- Parallel descriptive studies using the UK Obstetric Surveillance System (UKOSS) and the National Blood Service database as well as the BPSU, suggest that the incidence of clinically detected FMAIT is less than one third of that estimated from prospective screening studies.
- There is a debate about the utility of antenatal screening for the condition and this information will be used to help reassess the case for antenatal screening.

Background

Fetomaternal Alloimmune Thrombocytopenia (FMAIT), also known as neonatal alloimmune thrombocytopenia or NAIT, is the most common cause of severe neonatal thrombocytopenia in otherwise well term infants.[1] The condition results from a fetomaternal incompatibility in platelet alloantigen, most commonly HPA-1a, and can lead to serious bleeding, intracranial haemorrhage and sometimes death of the fetus or infant.[2] First pregnancies are often severely affected and the diagnosis is usually made with the birth of a first affected infant. A recent evaluation against the National Screening Committee criteria for appraising a screening programme has identified a number of deficiencies in basic epidemiological information needed to assess the utility of antenatal screening[3], which this study aims to address. Additionally, there are considerable controversies in the optimal management of FMAIT-affected pregnancies.[3]

This is the first study to be conducted simultaneously through the BPSU and the UK Obstetric Surveillance System (UKOSS); this will ensure identification of cases is as complete as possible and allow comprehensive collection of antenatal and postnatal information.

Objectives

The aims of the study are to:

- combine the use of existing obstetric, paediatric and National Blood Service reporting systems to assess the incidence of Fetomaternal Alloimmune Thrombocytopenia (FMAIT) in the UK
- describe the current obstetric and paediatric management of FMAIT in the UK
- describe the outcomes of affected infants
- use the information gained to inform ongoing review of the case for antenatal screening for this condition.

Surveillance period

October 2006-October 2008 (extended for one further year of surveillance).

Methodology

Case definition

Any infant live born during the study period with a documented maternal/fetal platelet antigen incompatibility, usually in the presence of maternal antibodies, AND at least one of the following:

i. Cord platelet count at birth <50 x 10^9/l
ii. Haemorrhagic complications before or after birth (e.g. intraventricular haemorrhage, GI bleed, bruising or petechiae)
iii. Antenatal therapy with either maternal steroids, IVIg or fetal platelet transfusion.

Additional sources of data

Cases are also being sought in a parallel study involving UK obstetric centres, conducted through UKOSS. Cases reported through the surveillance studies will be compared with cases referred for investigation to the National Blood Service or Welsh Blood Service.

Expected number (per year)

Severely affected infants: approximately 50 cases per year in the UK. All clinically detected infants (including mild cases): approximately 250 cases per year in the UK.[2]

Table 8: Management of antenatally diagnosed cases of FMAIT

Antenatal treatment	Number of infants (%)
Steroids, intravenous immunoglobulin (IVIg) + intrauterine platelet transfusion (IUT)	9 (41)
IVIg alone	8 (36)
Steroids + IVIg	2 (9)
IVIg + IUT	2 (9)
IUT alone	1 (5)

Analysis

There were 79 cases reported through the three reporting systems over the period October 2006 to September 2007, in an estimated 726,517 births, representing an estimated incidence of 1.1 cases per 10,000 total births (95% CI 0.9-1.4). Capture-recapture analysis suggests there are unlikely to be any missed cases. Further information on 77 confirmed cases, including 17 infants born before 01/10/06, or after 30/09/07, have been received. Fifty-five cases (71%) were identified postnatally and 22 (29%) antenatally. The management of the 22 antenatal cases is illustrated in Table 8. There were two intrauterine deaths, one infant death and seven infants had an intracranial haemorrhage. Seven of these ten cases with serious clinical problems occurred in women without a history of FMAIT.

Discussion

The incidence of clinically detected FMAIT estimated from this national study is less than one third of that estimated from prospective screening studies.[2] More than two thirds of cases with serious clinical problems were diagnosed postnatally, highlighting the importance of appropriate assessment of the case for antenatal screening.

Please note the data presented are provisional, not peer reviewed and definitive conclusions should not be drawn from them.

Funding

Wellbeing of Women.

Ethics approval

London MREC (06/MRE02/53); Patient Information Advisory Group (BPSU PIAG 03-04(FT4)/2006).

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Genital Herpes in children under 11 years of age

Dr R Reading

Key points

- This condition is even rarer than expected in young children
- When a case is suspected, virological confirmation is essential to aid further management

Background

Genital herpes in prepubertal children is rare, and when it occurs, raises the question of possible sexual abuse. Paediatricians currently have very little evidence on which to base an opinion on possible mode of transmission, yet their advice is key to whether or not a child protection investigation proceeds. A recently published literature review highlights both the inconsistency in current guidelines and the weakness of epidemiological data on this condition (Reading and Ranaan-Eliya, 2007).

This study will provide data on the incidence of genital herpes in young children in the UK, and describe clinical, social and other features which might point to possible modes of transmission (sexual and non-sexual). It will not be able to confirm the mode of transmission because there is no way of definitively ascertaining whether sexual abuse has occurred or not. However, indicative data on anything more than a handful of cases are currently not available.

A national surveillance study is necessary to provide such data because of the rarity of the condition, the need to collect true population based data to eliminate referral bias, and because most cases will be referred to a paediatrician at some stage in the initial presentation because of the child protection implications.

Objectives

The study aims to:

- estimate the incidence of genital herpes in children under 11 years old in the UK and Ireland by age and sex
- describe the clinical presentation of cases
- describe clinical, developmental and social features which might indicate possible modes of transmission
- describe the extent and outcome of child protection enquiries consequent on a diagnosis of genital herpes

Surveillance period

April 2007 - April 2009 (extended from 13 to 25 months of surveillance).

Methodology

Case definition

Children aged one month to ten years inclusive with typical herpetic vesicular lesions in genital or perineal area presenting as new cases to secondary care (includes recurrent cases seen for the first time in secondary care).

- Proven cases: Herpes simplex isolated by viral culture, or PCR in association with typical lesions.
- Suspected cases: Supportive evidence in addition to typical clinical lesions, e.g. rising paired antibody titres, viral culture from lesions elsewhere (such as oral lesions), giant multinuclear cells on cytology or positive viral culture in a physical contact.

Excluded cases: Recurrent lesions previously identified and seen in secondary care. No viral isolation and no supportive clinical or virological evidence.

Additional sources of data

Reported cases will be cross-referenced with laboratory reports from the Health Protection Agency to ensure cases are not being missed. Members of the British Association for Sexual Health and HIV/AIDS, and of the British Paediatric Dermatology Society have been circulated with details of the study and updated through their newsletters asking for notification of any cases known to them.

Expected number (per year)

20 – 30 cases per year.

Analysis

There have been 13 reports to the end of February 2008 (10 months reporting), of which five are valid cases, seven are either errors, not confirmed, or other diagnoses, and questionnaire information is awaited on one case. No duplicates have been reported. Ages of valid cases range from 10 months to seven years, with three boys and two girls. No other analysis has been performed at this stage.

Discussion

20 to 30 valid case reports a year were expected – the actual number is an order of magnitude lower. We have no evidence that cases are not being reported, nor that other secondary care specialists are seeing cases without paediatric involvement. Some of the case reports which were not confirmed ultimately had a range of unusual diagnoses, which emphasise the need for formal virological identification in all cases. This may avoid child protection enquiries, many of which will remain unresolved. In view of the small number of case reports and the important implications of the study for child protection, this study has been extended for a further year.

Please note the data presented are provisional, not peer reviewed and definitive conclusions should not be drawn from them.

Funding

Birmingham Children's Hospital Research Fund.

Support group

The Herpes Viruses Association, 41 North Road, London N7 9DP.
Telephone helpline: 0845 1233205
Web: www.herpes.org.uk

Ethics approval

London MREC (Ref: 07/MRE02/9); PIAG Section 60 Support (Ref: 4-06(FT6)/2006).

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HIV infection in childhood

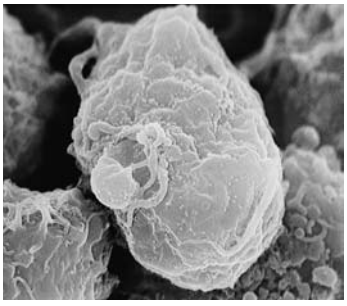
Key points

- Over 80% of reports to the study have been made since 2000 and the majority are of children exposed to maternal infection.
- Between 2000 and 2006 the overall mother to child transmission rate from diagnosed women was 1.2%.
- Three quarters of infected children accessing paediatric services are now aged seven years or older, including a quarter who are 14 years or older.

Background

National surveillance of paediatric HIV infection and AIDS began in 1986 and is based on complementary paediatric, obstetric and laboratory reporting schemes. Reporting is voluntary and confidential and data from all sources are combined as the National Study of HIV in Pregnancy and Childhood (NSHPC) at the UCL Institute of Child Health (www.nshpc.ucl.ac.uk).

Most children currently living with HIV in the UK and Ireland, whether born here or abroad, acquired their infection through mother-to-child transmission. Combining NSHPC with unlinked anonymous survey data shows that in the UK the number of exposed infants increased substantially from about 300 in 1997 to about 1200 in 2006 (www.hpa.org.uk). Antiretroviral treatment, delivery by elective caesarean section and the avoidance of breastfeeding reduce transmission rates from diagnosed women to around 1% in comparison with a likely transmission rate of about 25% without interventions. Women must be diagnosed in time to be able to access these interventions, and antenatal HIV testing is now routinely recommended to all pregnant women throughout the UK and Ireland. The proportion of HIV positive women diagnosed before delivery



C. Goldsmith

Figure 13: Scanning EM of HIV, grown in cultured lymphocytes. Virions are seen as small spheres on the surface of the cell

Dr P Tookey and team

increased from an estimated 32% in 1997 in the UK to over 90% since 2004.

Children with confirmed HIV (Figure 13) infection who were either born abroad or were born to undiagnosed women in the UK/Ireland are generally diagnosed when they present with symptoms or because a member of their family is diagnosed with HIV infection.

Objectives

The surveillance of paediatric HIV infection and AIDS in the United Kingdom and Ireland.

Surveillance period

Surveillance began in June 1986 and is reviewed annually.

Methodology

Case definition

Any child less than 16 years of age who has AIDS, or has been diagnosed with HIV infection. Any child born to a woman known to be HIV infected at the time of delivery regardless of the child's infection status.

Additional sources of data

Paediatric reports made directly to the NSHPC; reports of pregnancy in HIV positive women made through a parallel active reporting scheme run under the auspices of the Royal College of Obstetricians and Gynaecologists; laboratory reports to the Health Protection Agency (HPA) Centre for Infections and Health Protection Scotland (HPS); and in earlier years cases reported through the UK Haemophilia Centre. Direct reporting arrangements have been established with some centres in order to simplify reporting and reduce the burden on individual paediatricians.

Expected number (per year)

The number of infants born to HIV infected women in the UK and Ireland has exceeded 1000 each year since 2003. Over 100 infected children, the majority of whom were born abroad, are currently being diagnosed each year.

Analysis

Number and geographical distribution of reports: By the end of December 2007 there had been 6455 BPSU reports, of which 4838 were confirmed cases of HIV infection or exposed infants at risk of vertical transmission, 675 were duplicates and 602 reporting errors; the remaining 340 reports were still being investigated. A further 5573 confirmed cases were reported through other sources (see methods). Table 9 shows the likely source of infection or exposure risk for all confirmed cases.

Overall the majority of reports (81%) were made between 2000 and 2007 and this pattern was similar for all regions except Scotland (Table 10). In England before 2000, only 29% of reports were received from outside London compared with 44% of reports made between 2000 and 2007.

Children born to infected women: Most reported children (9971/10363 - 96%) were born to infected women. By the end of 2007, 1659 (16%) of these children were known to be infected, and 6923 (67%) uninfected; infection status for the remaining 1389 (13%) had not been reported. While only 8% were born abroad, they accounted for 47% of confirmed mother-to-child infections.

Between 2000 and 2006 there were over 6000 births to diagnosed women in the UK and Ireland and since 2003 there have been over 1000 births each year (Table 11). Although the infection status of some of these children has yet to be reported, most will be uninfected. The overall transmission rate for births between 2000 and 2006 was 1.2% (61/5151, 95% CI: 0.9-1.5%), and 0.8% (40/4864) for women who received at least two weeks of antiretroviral therapy prior to delivery.

Infected children: Since surveillance started in 1986, 2050 infected children have been reported to the NSHPC, about half of whom were born outside the UK and Ireland. A total of 333 (16%) are known to have died, 84 (4%) to have gone abroad and 116 (6%) to have transferred to adult services: a further 208 (10%) are either reported as lost to follow up or have had no follow up information reported since 2005.

Over 1000 infected children and young people reported as paediatric cases were known to be alive and accessing paediatric services in the UK or Ireland at last follow up in 2006 or 2007: median age at the end of 2007 was 11 years (IQR 7-14 years).

Of the 854 children known to have acquired infection from their mothers in the UK or Ireland, most (79%) were born to women who were not diagnosed by the time of delivery; 164 infants born since 2002 (110 to undiagnosed and 54 to diagnosed women) were confirmed infected by the end of 2007. Eighty-seven of these cases (born in England 2002-2005 and reported by the end of March 2006) were the subject of an audit of perinatal transmission carried out in 2006: these infants were born in hospitals throughout England: a third to diagnosed and two-thirds to undiagnosed women.

Possible factors contributing to transmission of infection in the 33 infants born to diagnosed women included: late diagnosis and/or premature delivery, concurrent infections, lack of communication within or between hospitals or between healthcare staff and women, and delay in antenatal testing, reporting of results or initiation of treatment. No cases were identified following optimal care where the maternal viral load at delivery was undetectable and there were no concurrent maternal infections.

Table 9: HIV infection and infants born to HIV infected women *(all reporting sources)*
Source of report and exposure/likely source of infection *(notified by 31 December 2007)*

Exposure / likely source of infection	BPSU reports	Reports from other sources	Total
Children born to HIV infected women	4728	5243	9972*
Likely source of infection for other infected children			
Haemophilia treatment	48	219	267
Blood transfusion/products	37	20	57
Other/not yet established	24	43	67
Total	4838	5525	10363

*1659 known to be infected

Table 10: HIV infection and infants born to HIV infected women (all reporting sources) Region and time period report *(notified by 31 December 2007)*

Region of first report	1986-1999	2000-2007	Total
England Total	1575	7169	8744
London	1122	4001	5123
North	181	933	1114
Midlands & East	128	1381	1509
South	144	854	998
Wales	26	90	116
Northern Ireland	4	29	33
Scotland	232	241	473
Ireland	170	827	997
Total	2007	8356	10363

At least one third of the 54 undiagnosed women had declined antenatal testing and at least 20% seroconverted during pregnancy; in a few cases antenatal testing was not offered or hospital procedures failed. Many of the mothers in both groups had serious immigration and/or housing problems or other major social or mental health problems.

Discussion

The number of births to HIV infected women in the UK and Ireland has increased substantially each year since 2000, and since 2003 there have been more than 1000 births each year.[1] Most of these infants were born to diagnosed women who were able to take advantage of interventions to reduce the risk of transmission and are themselves uninfected. Overall mother-to-child transmission rates in the UK and Ireland are now at around 1% with even lower rates among women who received appropriate treatment according to the British HIV Association guidelines (www.bhiva.org.uk).[2] However, despite high uptake of antenatal testing and interventions, some infants are still acquiring HIV infection from their mothers. An audit of cases occurring in England between 2002 and 2005 was carried out in 2006 in association with the Audit and Analysis Unit for Specialized Services and the Children's HIV Association. The resulting report with recommendations was published in 2007 (executive summary and recommendations available at (www.nshpc.ucl.ac.uk). The audit revealed that in many cases adverse social circumstances mitigated against the delivery of optimal care, but even so, opportunities for intervention were missed.

Table 11: Year of birth and infection status of children born in the UK and Ireland to HIV diagnosed women

Year of Birth	Infected	Indeterminate	Not infected	Total
1984-1999	110	147	895	1152
2000-2004	43	296	3432	3771
2005	13	97	1101	1211
2006	8	242	970	1220
2007*	3	532	303	838
Total	177	1314	6701	8192

*reports for 2007 expected to rise substantially

Changing trends in the demographic profile of HIV infected children and young people living in the UK and Ireland have implications for current and future health and social service provision. The introduction of highly active antiretroviral therapy (HAART) in 1997 has substantially improved the prognosis for HIV infected children, with most surviving into their teens and some now reaching adulthood. There are now several hundred young teenagers living with HIV, and currently being seen in paediatric clinics, who will need appropriate and specialised services to support their transition into adult care.[3]

Reports to the NSHPC from all areas of the UK and Ireland have increased in recent years.[1] The wide geographical distribution of the newly reported cases highlights the important role of the BPSU in identifying infected children diagnosed outside the specialist paediatric HIV centres, as well as exposed infants born to infected women in lower prevalence areas.

Please note the data presented are provisional, not peer reviewed and definitive conclusions should not be drawn from them.

Funding

This study is funded by the HPA; additional support has come from the collaborating institutions and the Medical Research Council.

Ethics approval

The London Multicentre Research Ethics Committee reviewed and approved the NSHPC and the associated CHIPS study on 28 January 2004 (Refs: London MREC/04/2/009; MREC/04/2/010). Paediatric surveillance of HIV through the BPSU also has PIAG approval (ref PIAG/BPSU 2-10(a/2005).

Support groups

Barnardos Positive Options, William Morris Hall, 6 Somers Road, London, E17 6RX.
Web: http://www.barnardos.org.uk

Positively Women, 347-349 City Road, London, EC1V 1LR.
Web: http://www.positivelywomen.org.uk

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Idiopathic Intracranial Hypertension (IIH)

Key points

- Among the 100 cases reported in the first six months (July to December 2007) of surveillance, only 11 confirmed and 13 probable cases of idiopathic intracranial hypertension have been identified.
- The low number of newly diagnosed cases suggests that IIH in children might be rarer than previously estimated.
- Follow up data collection at one-year post diagnosis will be commenced from July 2008.

Background

Idiopathic intracranial hypertension (IIH), previously known as pseudotumour cerebri or benign intracranial hypertension is a rare condition of increased intracranial pressure without any identifiable pathology. In adulthood, IIH is most common in obese young women, however, in childhood both genders are equally affected.[1] The clinical definition and association of this unique condition have evolved with time and the advances in neuroimaging making both the diagnosis and management challenging. Despite intervention, the clinical course of IIH is often prolonged and recurring with potential complications of distressing headache and blindness.[2-4] The overall (including children and adult) annual incidence of IIH is estimated to be 1-3 per 100,000 population[5,6], however the epidemiological data on childhood IIH to date are sparse and limited to hospital based retrospective case series.[7,8]

Objectives

The study aims to determine the:

- annual incidence of IIH in children aged 1 to 16 years in the UK and Ireland
- spectrum of clinical presentation of IIH in children across various age groups
- national incidence of various established associations of IIH in children in particularly with obesity at presentation
- frequency and spectrum of visual disturbances in children presenting with IIH
- current clinical management of children with IIH

Dr YY Mathews

- clinical course of headache and spectrum of the visual outcome in this national cohort one-year post diagnosis following various treatment modalities. A follow-up questionnaire will facilitate this prospective review.

Surveillance period

July 2007 – July 2009 (inclusive).

Methodology

Case definition

Any **newly presenting** child aged 1 to 16 years (not including 17th birthday) seen in the past month who fulfils at least two of the key features and all of the three essential criteria.

At least TWO Key Features:

- Symptoms of raised intracranial pressure (such as headache, nausea, vomiting or irritability) and/or visual symptoms of diplopia, blurring vision or transient visual loss
- Papilloedema, unilateral or bilateral
- Raised opening cerebrospinal fluid pressure above 20 cm by lumbar puncture

AND all THREE Essential Criteria:

- Normal level of consciousness
- Cranial imaging (including CT or MRI and MR or CT venography) does not reveal a structural cause such as ventricular dilatation, cerebral mass, vascular lesion or sinus venous thrombosis*, to explain the presenting symptoms or signs of raised intracranial pressure
- Normal cerebrospinal fluid contents (for atraumatic tap, white cell count < 6 x 10^6 /L, protein < 0.4 g/L, ratio of cerebrospinal fluid glucose to blood glucose > 0.5 or cerebrospinal fluid glucose > 2.1 mmol/l).

Table 12: Regional distributions of the first six months, 100 IIH notifications

	Confirmed/ Probable	Positive duplicate	Error	Necative duplicate	Excluded	Unable to follow up	Outstanding	Reply awaiting
England	20	6	14	2	4	4	20	14
Scotland	1	0	2	0	0	0	0	1
Wales	2	0	1	1	0	0	2	1
NI & ROI	1	1	3	0	0	0	0	0
Total	24	7	20	3	4	4	22	16

Excluding

* Sinus venous thrombosis whose neuroimaging appearances can be difficult to distinguish from venous obstruction related to raised intracranial pressure. Reporters were asked to report if they had any doubt or if case was excluded due to sinus venous thrombosis

Caution: Optic nerve head Drusen (a degenerative condition consists of hyaline deposits within the optic nerve head which results in an apparent elevation or swelling of the optic disc) can mimic papilloedema. However, papilloedema and optic nerve head Drusen can occur concurrently, their differentiation can be made by optic ultrasound and/or orbital CT scan. Reports are encouraged if a case is suspected.

Expected number (per year)

390 cases were expected nationally.

Analysis

A total of 100 BPSU notifications were received between July and December 2007 and their regional distributions are as shown in Table 12. Among these 11 were confirmed and 13 were probable (without MR/CT venography) IIH cases. There were 10 duplicates, 20 cases were reported in error (either historic cases or not IIH), four cases were excluded for not meeting the case definition, four cases could not be followed up, 22 outstanding cases are awaiting case ascertainment by the investigators team and the remaining 16 cases are pending return of the questionnaire.

The distribution of the numbers of the total, error, confirmed or probable notifications from July to November 2007 are shown in Figure 14.

Of the 24 included cases, 18 cases (75%) were female. The median age at diagnosis was 12.1 years in female (range 5.6 to 15.6) and 12.8 years in male (range 3.7 to 16.3).

Discussion

It is not possible to draw any conclusions with the preliminary data at this early stage in the study. However, a large discrepancy is noted between the expected and the actual number of newly diagnosed IIH cases. Following confirmation of the even geographical spread of all notifications and the above findings, this interim low number of confirmed or probable cases suggests that the incidence of IIH in children may be lower than that estimated from the previous local retrospective survey in Coventry in 2003-2005.

Please note the data presented are provisional, not peer reviewed and definitive conclusions should not be drawn from them.

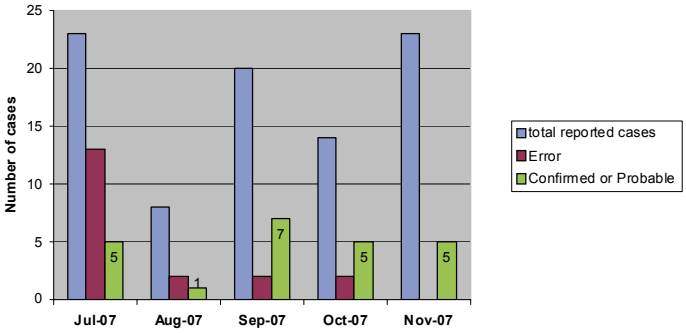

Figure 14: Monthly number of total, error, confirmed/ probable IIH notifications from July – November 2007

Funding

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Ethics approval

East London and the City Research Ethics Committee (Ref: 07/Q0603/47); PIAG Section 60 Support (PIAG/BPSU 1-05(FT3)/2007).

Support group

Association for Spinal Bifida and Hydrocephalus (www.asbah.org).

Acknowledgements

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Medium chain acyl CoA dehydrogenase deficiency (MCADD)

Key points

- Medium chain acyl CoA dehydrogenase deficiency (MCADD) is an autosomal recessive disorder of fatty acid oxidation that may cause hypoglycaemia, encephalopathy, hepatic dysfunction and sudden death.

- Since 2004, well over one million babies have been screened for MCADD in England. The study has shown that newborn screening reliably identifies affected children before they are likely to develop symptoms, enabling parents to use simple measures to avoid fasting and thereby reduce the chances of severe illness or death.

Dr C Dezateux

- Interim results from this study together with international evidence led to the ministerial announcement on Feb 7th 2007, that newborn screening for MCADD would be implemented throughout England by April 2009 (Gateway reference number: 7801). Implementation of the MCADD screening programme is being managed by the UK Newborn Screening Programme Centre. Details are available at www.newbornbloodspot.screening.nhs.uk.

Background

Medium chain acyl CoA dehydrogenase deficiency (MCADD) is a recessively inherited metabolic disorder that may cause hypoglycaemia, encephalopathy, hepatic dysfunction and sudden death[1] and which has been identified as a candidate for newborn screening through three systematic reviews commissioned by the Health Technology Assessment Programme concluded that more information was needed on test performance and clinical outcomes in a UK setting. Subsequently the Department of Health and the National Screening Committee have funded a pilot newborn screening service for MCADD. They have also commissioned a concurrent research study to evaluate the service. Although primary studies of MCADD screening in other countries have been carried out, important questions remain unanswered.[2, 3] Specifically, uncertainty remains over the clinical outcome following detection through newborn screening. Furthermore, the findings of these studies may not be generalisable to a UK setting; screening is carried out several days later in the UK and the population is ethnically more diverse than countries that have previously reported MCADD screening.

Objectives

The study aims to:

- ascertain all cases of MCADD diagnosed during the study period in order to determine clinical outcomes up to two years of age
- estimate test performance, predictive value, specificity and detection rate of screening for MCADD.

Surveillance period

April 2004 – May 2008 (inclusive).

Methodology

Case definition

MCADD is an inherited fatty acid oxidation disorder resulting from the lack of an enzyme required to convert fat stores into energy. During an intercurrent illness, such as gastroenteritis, there may be progressive encephalopathy with drowsiness, lethargy and hypotonia progressing to coma. Severely ill children may be hypoglycaemic. Without screening, children with MCADD usually present clinically before the age of two. It is predicted that the birth prevalence is about 1 in 10,000.[1]

Diagnosis of MCADD will be accepted if one or more of the following criteria are met:

- Elevated octanoyl carnitine in the presence of normal free carnitine levels on blood test using tandem mass spectrometry.
- Characteristic urine profile of organic acids with hexanoyl, suberyl and phenylpropionyl glycine.
- Molecular genetic studies confirming the presence of a mutation characteristic of MCADD.
- Enzyme studies based on skin fibroblasts showing reduced activity of MCAD.

All valid notifications reported up to February 2006 were reviewed by an independent diagnostic review panel.

Additional sources of data

A Biochemical Surveillance Scheme for MCADD (BioSS–MCADD) has been set up through UK laboratories providing diagnostic testing for MCADD, in order to increase ascertainment of cases. Cases are also notified to the study through the six laboratories currently undertaking MCADD screening.

Expected number (per year)

Approximately 65 cases are expected per year.

Analysis

Numbers of cases notified to the BPSU: Between April 2004 and the end of December 2007, 322 notifications of MCADD had been received by the BPSU. Of these, 116 were duplicate notifications representing 55 cases. 13 notifications were made in error (not MCADD or diagnosed outside surveillance period) bringing the case total to 248 cases of MCADD reported. 70 were confirmed clinically diagnosed cases of MCADD, 146 were detected by newborn screening, and 32 are as yet unknown, pending return of follow-up questionnaires.

Of the 70 diagnosed clinically, 41 presented with clinical symptoms (of whom five (12 %) died), one was investigated due to behavioural problems, and 23 were investigated because of affected siblings and five due to other causes.

Of those who presented with clinical symptoms, 15 (37%) were female, with a median age at diagnosis of 14.1 months (range 0 to 173). Of the 23 who were confirmed as having MCADD following diagnosis of an affected sibling, 13 (57%) were female, with a median age at diagnosis of 4.9 months (range 0 to 132).

152 follow-up forms have been sent to clinicians to ascertain clinical outcome in infants diagnosed over one year ago. 148 of these have been returned. No deaths or major encephalopathic events were reported in the year following diagnosis.

80 two year follow-up forms have been sent to clinicians. Of these 75 have been returned. No deaths or major encephalopathic events have been reported through this follow-up.

Number of cases by source of data

The three sources of data are:

- British Paediatric Surveillance Unit
- Newborn screening laboratories currently undertaking MCADD screening, which notify screened cases
- Biochemical Surveillance Scheme for MCADD (BioSS – MCADD)

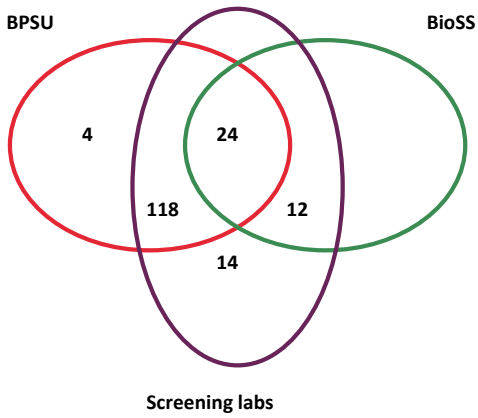

Figure 15: Number of confirmed cases by source of data
Screened (presumptive) positives, N=172

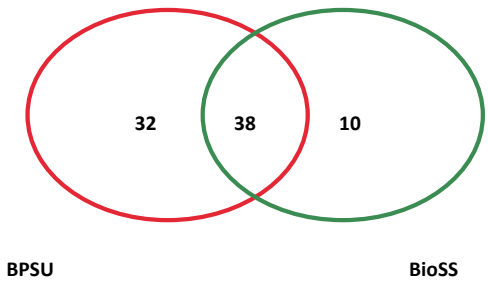

Figure 16: Confirmed cases clinical. Clinically diagnosed, N=80

Discussion

From preliminary data comparing screened and unscreened populations in the UK, the estimated prevalence of MCADD identified after clinical diagnosis appears to be a half to two-thirds of that after newborn screening. This suggests under-diagnosis and/or variable penetrance – similar to that reported in other countries and screening programmes. Of those presenting clinically, over 80% are homozygous for common mutation 985A>G, whereas this falls to 55% for those diagnosed through newborn screening.

Since 2004, this study has been one of the largest studies of newborn screening carried out worldwide, with well over one million babies having been screened for MCADD in England. The study has shown that newborn screening reliably identifies affected children before they are likely to develop symptoms, enabling parents to use simple measures to avoid fasting and thereby reduce the chances of severe illness or death.

Further research: Interim results from this study together with international evidence from other screening programmes were reviewed by the National Screening Committee in May 2006. This led to the ministerial announcement on Feb 7th 2007, that newborn screening for MCADD would be implemented throughout England by April 2009 (Gateway reference number: 7801).

Implementation of screening for MCADD in England is being managed by the UK Newborn Screening Programme Centre. Details are available at www.newbornbloodspot.screening.nhs.uk.

Further research on the panel of mutations identified through extended mutation screening is underway.

Please note the data presented are provisional, not peer reviewed and definitive conclusions should not be drawn from them.

Funding

The Department of Health and the National Screening Committee.

Ethics approval

This study was approved in April 2004 by the London GOS MREC (04/Q0508/2 with no local investigator status); it also has approval from the Patient Information Advisory Group (PIAG/BPSU 2-10(e)/2005).

Support group

Children Living with Inherited Metabolic Disease (CLIMB). Climb Building, 176 Nantwich Road, Crewe, CW2 6BG. Tel: 0800 652 3181.
Web:http://www.climb.org.uk/Climb

Acknowledgements

We are very grateful to the BPSU and all members of the RCPCH, particularly those paediatricians who have reported cases and completed questionnaires, for their support. We are also grateful to Professor Anne Green, Birmingham Children's Hospital and Dr Jim Bonham, Sheffield Children's Hospital, collaborators in the UKCSNS MCADD, who also helped set up the Biochemical Surveillance Scheme for MCADD. We also thank Professor James Leonard (Chair), Dr Jacqui Calvin, Dr Morteza Pourfarzam, Dr Johannes Zschocke and Dr Graham Shortland, members of the international expert Diagnostic Review Panel.

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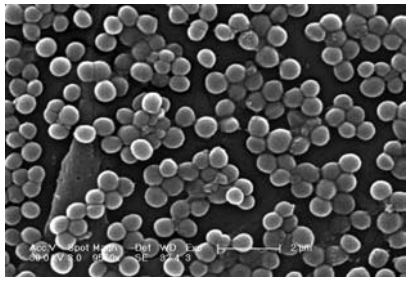
Methicillin-Resistant Staphylococcus aureus (MRSA)

Key points

- 265 cases of MRSA bacteraemia were reported from five countries via four sources over a two year period.
- Cases were concentrated in very young children; 42% under one month and 57% were aged under one year.
- Strain characterisation of isolates indicates that the majority were representatives of EMRSA-15, the most prevalent healthcare-associated MRSA currently seen in the UK.



Janice Carr

Figure 17: Scanning EM numerous clumps of MRSA: x9560.

Dr A Johnson

Ms C Goodall

- Data collection finished on 31st May 2007, laboratory tests on submitted isolates are ongoing.
- Results currently being written up for peer-review publication.

Background

Analysis of data obtained through routine national surveillance identified a potentially worrying increase in Methicillin-Resistant Staphylococcus aureus (MRSA) bacteraemia in children, with the number of reported cases rising from four in 1990 to 77 in 2000.[1] Fifty three per cent of the 376 cases reported between 1990 and 2001 involved infants less than 12 months of age, although substantial numbers of infected infants aged one to four years were also reported. As these data were derived from voluntary reporting of cases, they were thought likely to reflect an under-estimate of the true incidence of infection.

The aims of this study were to obtain a robust estimate of the incidence of MRSA bacteraemia in children, and to define the demographic and clinical features of the patient population in order to identify those children at high risk. Isolates of MRSA from children were characterised in terms of their antibiotic resistance pattern, strain type and biological properties (particularly virulence traits). Possible associations between organism type and clinical features of infection were investigated. This study has indicated that in the UK the majority of isolates were hospital strains in contrast to the changing epidemiological picture seen in other countries, particularly the USA where high levels of community-associated infections have emerged.[2-5] These findings have significant relevance for the management and control of severe paediatric infections due to S. aureus.

Objectives

The study aims to determine

- the incidence of MRSA bacteraemia in children aged <16 years
- whether the incidence of MRSA bacteraemia varies between children of different ages
- the spectrum of clinical features and patterns of presentation of MRSA bacteraemia in children
- whether MRSA bacteraemia in children is mainly due to healthcare- or community-associated MRSA and whether acquired nosocomially or in the community
- whether cases of MRSA bacteraemia in children tend to occur in particular hospital units or specialties
- whether strains of MRSA that cause bacteraemia in children have particular biological characteristics. In particular:
  - (i) Are the isolates similar to those found in hospitalised adults?
  - (ii) Are the isolates representative of true community-associated MRSA reported in the UK and other countries?
  - (iii) Do the strains possess particular virulence traits, such as Panton-Valentine leukocidin?

Surveillance period

June 2005 – June 2007 (inclusive).

Methodology

Case definition

Isolation of methicillin-resistant Staphylococcus aureus (MRSA) from blood culture(s) of children less than 16 years of age.

Reporting instructions

Clinicians are asked to report any cases seen within the last month that meet the case definition. However, this surveillance does not replace other forms of routine S. aureus reporting to the HPA.

Additional sources of data

In addition to cases ascertained through the BPSU, cases were also sought using the following sources:

1. Reports of MRSA bacteraemia submitted on a voluntary basis to the Health Protection Agency (HPA) from hospitals in England, Wales and Northern Ireland.

2. Cases of MRSA bacteraemia in children reported to the HPA, Health Protection Scotland or the National Disease Surveillance Centre (Dublin) by hospitals participating in the European Antimicrobial Resistance Surveillance System (EARSS), a pan-European surveillance programme looking at antimicrobial resistance in a number of pathogenic bacteria including S. aureus. About 30 hospitals in England and Wales, and all hospitals in Scotland and Northern Ireland participate in EARSS.

3. Cases identified following referral of blood culture isolates of MRSA from children to reference laboratories including the HPA Laboratory of Healthcare Associated Infection or the HPA Antimicrobial Resistance Monitoring and Reference Laboratory (based on the same site in London), the Scottish MRSA Reference Laboratory (Glasgow) or the National MRSA Reference Laboratory (Dublin).

4. Since October 2005, cases were identified in England through national surveillance based on enhanced mandatory surveillance of MRSA bacteraemia in patients of all age groups.

Data from these sources were pooled and reconciled to identify a unique set of cases.

Expected number

Approximately 100-120 each year.

Table 13: Patient's age at the date the specimen was taken *(all countries)*

	<1 year	1-4 years	5-9 years	10-15 years	unknown	Total
Confirmed BPSU Cases	80 (68.97%)	24 (20.69%)	4 (3.45%)	8 (6.90%)	0 (0.00%)	116
Reference Laboratory Isolates	55 (58.51%)	15 (15.96%)	4 (4.26%)	9 (9.57%)	11 (11.70%)	94
LabBase 2 reports	92 (60.93%)	34 (22.52%)	10 (6.62%)	14 (9.72%)	1 (0.66%)	151
Mandatory enhanced surveillance	82 (56.94%)	37 (25.69%)	9 (6.25%)	16 (11.11%)	0 (0.00%)	144
Total cases reported	151 (56.98%)	57 (21.51%)	17 (6.42%)	28 (10.57%)	12 (4.53%)	265

Analysis

Two hundred and sixty five cases were identified over the two year reporting period in the five countries stated above. Due to differences in geographical coverage of the data sources, voluntary reporting of isolates from hospital microbiologists to LabBase 2 covered England, Wales and Northern Ireland whilst the mandatory enhanced surveillance of MRSA only included NHS trusts in England. The mandatory enhanced surveillance commenced in October 2005, hence data were only available for 20 of the 24 months of the reporting period.

Irrespective of the notification source, reports of MRSA bacteraemia were concentrated in very young children with the majority (57%) of cases occurring in children less than one year old although a substantial proportion of cases (21%) were reported in infants aged 1-4 years (Table 13).

Table 14: Strain characterisation of isolates submitted to the HPA Staphylococcal Reference Laboratory

(all countries)

MRSA Strain type	Total
EMRSA-15	64
EMRSA-16	11
Distinct strain	17
Awaiting strain typing	2
Total	94

Characterisation of the referred isolates in the Reference Laboratory indicated that the majority were representatives of EMRSA-15, the most prevalent healthcare-associated MRSA seen in the UK (Table 14).

Discussion

Results are currently being subject to more in-depth analysis with a view to submitting results for publication in the peer reviewed scientific literature. Interim results suggest that

1. MRSA bacteraemia in children remains rare in contrast to the situation in adults (where more than six thousand eight hundred cases were reported via the mandatory enhanced MRSA surveillance scheme in 2006).[6]

2. MRSA bacteraemia in children primarily involves healthcare-associated strains. This has implications for potential control measures aimed at reducing further the frequency of infection.

3. Ascertainment of cases via the BPSU Orange card reporting route was lower than had previously been expected (44% of the total number of cases). This may reflect the fact that there were several routes of reporting cases by microbiologists.

Further research: In addition to MRSA, the large increase in the incidence of methicillin-susceptible *Staphylococcus aureus* (MSSA) warrants further investigation in the paediatric population.[7]

Please note the data presented are provisional, not yet peer reviewed and so definitive conclusions should not be drawn from them.

Funding

The Department of Health.

Ethics approval

This study has been approved by the Eastern MREC (05/MRE05/28). This study has Patient Information Advisory Group approval through the HPA (PIAG 03-c)/2001.

Support Group

MRSA Action UK. Tel: 01606 559748
E-mail:info@mrsaactionuk.net
Web: http://www.mrsaactionuk.net/

Website details
http://www.hpa.org.uk/infections/topics_az/staphylo/default.htm
http://bpsu.inopsu.com/studies/mrsa/index.html

Acknowledgements

We are very grateful to the BPSU and all participating paediatricians and microbiologists for their continued support, especially those who have notified cases and completed questionnaires.

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Progressive Intellectual and Neurological Deterioration

Key points:

- After completing almost eleven years of surveillance 2391 children have been notified. 1692 cases have been discussed by the Expert Group of six paediatric neurologists. There have been 1012 children with a known diagnosis other than vCJD, and in the diagnosed group there are 115 different neurodegenerative disorders.

- Six cases of variant Creutzfeldt-Jakob disease have been reported to the study since December 1998. Of these four have been classified as "definite" and two "probable" according to the National Creutzfeldt-Jakob Disease Surveillance Unit criteria. All have now died.

- Further active surveillance is planned until April 2010.

- Even if you have made a diagnosis we still want to hear about all children with progressive intellectual and neurological deterioration.

Background

Active prospective surveillance of UK children with progressive intellectual and neurological deterioration (PIND) commenced in May 1997. Funded by the Department of Health, it is being carried out via the British Paediatric Surveillance Unit (BPSU) in conjunction with the National Creutzfeldt-Jakob Disease Surveillance Unit in Edinburgh (NCJDSU) and the Health Protection Agency (HPA).

The main aim is to determine whether or not any children in the UK have developed variant Creutzfeldt-Jakob disease (vCJD). This new disease was first described by Will et al in 1996. vCJD (Figure 18) has been described in patients as young as 12 years of age[1] and it could occur in younger children. It is possible that the clinical presentation of vCJD in young children might differ from that described in adults. The strategy is to detect suspected vCJD cases by looking at a broader group of conditions causing progressive intellectual and neurological deterioration in children. It is only by carefully examining the clinical details in all these PIND cases that we can be reasonably sure that vCJD is not being missed among the numerous rare neurodegenerative

The PIND Expert Group

disorders that affect children. An Expert Group of six paediatric neurologists independently reviews the anonymised clinical details for all the PIND cases. This unique dataset provides the opportunity to detect vCJD cases and highlight the variety of PIND conditions in the UK.[2]

The surveillance team uses a detailed questionnaire to gather information via a telephone interview or site visit to review the case notes; alternatively the notifying paediatrician may wish to complete the questionnaire. There is further follow up of undiagnosed cases via the local paediatricians.

Objectives

The study aims to:

- carry out active prospective surveillance of UK children with paediatric neurological conditions (including those with specific diagnoses) defined by their common presentation – progressive intellectual and neurological deterioration (PIND) - to determine the incidence and distribution of PIND.

- evaluate cases presenting with PIND in order to classify them and investigate the possibility that vCJD is occurring in children.

Surveillance period

Surveillance commenced in May 1997 and continues until 2010.

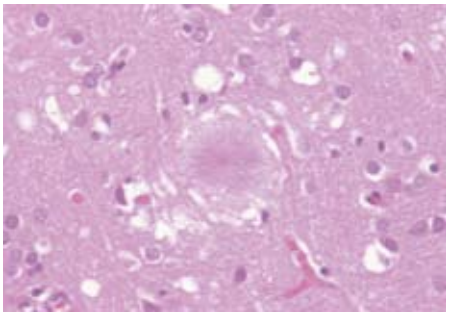

Figure 18: Florid plaque in vCJD x 400 haematoxylin/ eosin stain

Methodology

Case definition

Any child under 16 years of age at onset of symptoms who fulfils all of the following three criteria:

- Progressive deterioration for more than three months

With

- Loss of already attained intellectual/ developmental abilities

And

- Development of abnormal neurological signs.

Excluding: Static intellectual loss, e.g. after encephalitis, head injury or near drowning.

Including:

- Children who meet the case definition even if specific neurological diagnoses have been made.
- Metabolic disorders leading to neurological deterioration.
- Seizure disorders if associated with progressive deterioration.
- Children that have been diagnosed as having neurodegenerative conditions but who have not yet developed symptoms.

Expected number

Approximately 200 suspected cases per year.

Analysis

By the beginning of March 2008, a total of 2391 children had been notified (Figure 19). Six paediatric neurologists and a representative from the NCJDSU meet quarterly in London to classify the anonymised clinical information. Six cases have been categorised as probable/definite vCJD, 1012 have a clear diagnosis of PIND, 145 have idiopathic PIND, 140 are still under investigation, 998 are "No Cases" (not meeting PIND definition, duplicate notifications, reported in error, no traceable clinical information) and for 90 cases data are outstanding.

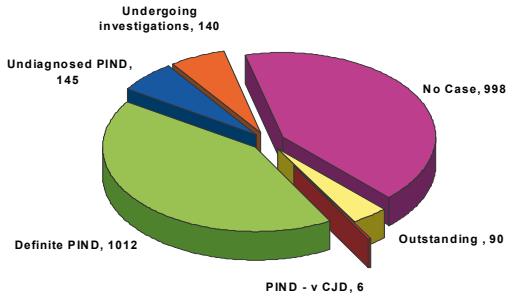

Figure 19: PIND study – current status

Definite/probable cases of vCJD: Six cases of vCJD (four definite and two probable) have been notified - the youngest was a girl aged 12 years at onset. The other five were three girls (two aged 14 years and one aged 13 years at age of onset) and two boys aged 15 years at onset. The last child to present with vCJD developed symptoms in 2000. All have now died and neuropathology has confirmed vCJD in four cases; a post mortem was not carried out on the remaining two cases.

Children with PIND who have definite diagnoses other than vCJD: The majority of children with PIND have a confirmed or likely underlying diagnosis that is not vCJD. In the 1012 children with a confirmed diagnosis there were 115 different neurodegenerative conditions.

The five most commonly occurring diagnostic groups are the neuronal ceroid lipofuscinoses (128 cases), the mitochondrial cytopathies (105 cases), the mucopolysaccharidoses (97 cases), the gangliosidoses (93 cases), and peroxisomal disorders (62 cases) (Figure 20).

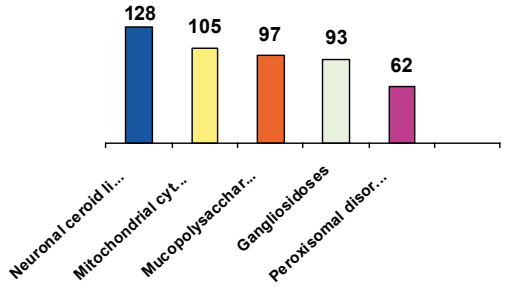

Figure 20: Five most commonly reported PIND diagnostic groups

Discussion

PIND surveillance has been running for almost eleven years now. Six cases of vCJD in children under 16 years of age at first presentation have been notified to the study. There were four cases of definite vCJD and two cases of probable vCJD. One girl was age 12 years at onset, the youngest ever reported case of vCJD. There have been no other children with the clinical features of vCJD, however, there is concern that more childhood cases may appear. Eleven years is a short time to

perform surveillance for a disease about which there are still many unanswered questions - for example, the number of children who may be incubating vCJD, the length of the incubation period and the exact nature of transmission. In 2004 Peden et al reported a case of preclinical vCJD discovered at autopsy. The patient had received blood from a donor who later developed vCJD.[3] This preclinical case had a methionine/valine genotype at codon 129 of the prion protein gene. All previously confirmed cases of vCJD have been methionine homozygous at this site. Methionine/valine genotypes make up 51% of the general population. It is possible that methionine/valine genotypes might develop vCJD with a longer incubation period than the methionine homozygotes resulting in a "second wave" of vCJD cases.

"It is important to note that although a peak has been passed, it is possible that there will be future peaks, possibly in other genetic groups. There is also the possibility of ongoing person to person spread as seen with four cases of transfusion association vCJD infection to date, who received blood from earlier cases".
(NJ Andrews,Senior Statistician, HPA, Dec 2006)

Please note the data presented are provisional, not peer reviewed and definitive conclusions should not be drawn from them.

Funding

Department of Health (ref 121-6443).

Ethics approval

Initial approval in 1997 was given by the Local Research Ethics Committee, Addenbrooke's Hospital (ref: 97/010) and the Public Health Laboratory Service Ethics Committee and the Patient Information Advisory Group (PIAG/BPSU 2-10(c)2005).

Support groups

1. Creutzfeldt-Jakob Disease Support Network, PO Box 346, Market Drayton, Shropshire TF9 4WN. Web: http://www.cjdsupport.net

2. Batten Disease Family Association, c/o Heather House,Heather Drive, Tadley, Hampshire, RG26 4QR. Web: http://www.bdfa-uk.org.uk

3. The Society for Mucopolysaccharide Diseases, MPS House, Repton Place, White Lion Road, Amersham, Buckinghamshire, HP7 9LP. Tel: 0845 389 9901

4. Climb National Information and Advice Centre for Metabolic Diseases. 176 Nantwich Road, Crewe, CW2 6BG. Tel: 0800 652 3181 Freephone Family Service Helpline, 0870 770 0326. E-mail:info@climb.org.uk. Web: http://www.climb.org.uk

5. Adrenoleukodystrophy (ALD) Ald Family Support Trust, 30-32 Morely House, 320 Regent Street, London W1R 5AB.

Acknowledgements

Many thanks to the UK paediatricians who are still responding enthusiastically with a median number of 17 notifications per month. The PIND surveillance team is very grateful to the members of the paediatric neurology Expert Group (Prof J. Aicardi, Dr P. Baxter, Dr. J. Livingston, Dr. M. Pike, Prof. R. Robinson, and Dr J. Wilson) for all their work in classifying cases.

We were deeply saddened by the sudden and untimely death of Professor Robert Surtees who had given his time generously in support of the study. He will be greatly missed by us all.

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Vitamin K Deficiency Bleeding

Key points

- In each of the BPSU studies of Vitamin K Deficiency Bleeding we have encouraged the reporting of all possible cases as well as the unequivocal ones. We remain grateful to all paediatricians who notify; the condition being very rare, every case is important.

- Measurement of PIVKA-II levels can help document vitamin K deficiency; because of the half-life of about 60 hours, levels remain elevated for days (even weeks) after vitamin K supplementation (and are unaffected by blood products) so samples collected after treatment can give useful information. Ideally, however, serum should be collected (and protected from light in storage) before treatment for later documentation of both PIVKA-II and vitamin K levels. [See 'Measurement of PIVKA-II and vitamin K levels' below].

Background

Vitamin K Deficiency Bleeding (VKDB) is a rare, potentially-handicapping or fatal condition (Figure 21), preventable by a combination of vitamin K prophylaxis and surveillance for predisposing conditions, particularly liver disease.[1,2] Three previous BPSU studies of VKDB have certainly informed practice. All UK units now offer prophylaxis[2] and there is greater awareness of the importance of investigating 'warning bleeds' and prolonged jaundice.

The third BPSU study (2000-02) found the incidence of VKDB in the UK and Ireland to be the lowest recorded with no death or long-term morbidity. Following 42 notifications there were only seven confirmed cases of VKDB; four had received no prophylaxis (in each case because parents refused consent for recommended IM vitamin K and, probably, for an alternative oral regimen), one had received IM prophylaxis and two had received oral prophylaxis.[2]

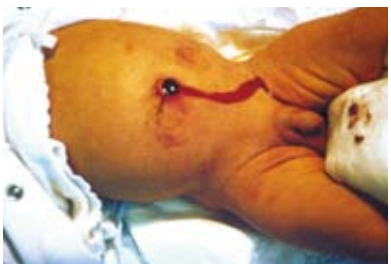

Figure 21: Bleeding from umbillicus due to VKDB

Dr A Busfield

At the time of the third study Konakion Neonatal was used by most of the 60% of units recommending IM prophylaxis. With exceedingly rare exceptions, a single 1mg IM dose of that preparation at birth was known to protect against VKDB for several months. Since then, however, there have been two important developments: first, Konakion Neonatal has been withdrawn (leaving Konakion MM as the only licensed preparation for IM or oral prophylaxis); second, guidelines from the National Institute for Health and Clinical Excellence have recommended IM in preference to oral prophylaxis. It is inevitable that the use of IM prophylaxis with Konakion MM will increase (there being no alternative preparation for IM administration) despite the paucity of published data about the duration of protection it confers.[3] The Medicines and Healthcare Product Regulatory Agency have therefore advised surveillance following withdrawal of Konakion Neonatal. This fourth BPSU study, with data from a contemporaneous survey of VK prophylaxis practices in the same population, will provide the efficacy data required and not available elsewhere.

Objectives

The study aims to document:

- incidence of VKDB following the withdrawal of Konakion Neonatal
- effectiveness of current prophylactic regimens, particularly Konakion MM 1mg IM as a single dose at birth
- whether alternative routes of administration were offered to parents who withheld consent for Vitamin K
- clinical presentation and management of bleeding
- risk factors
- outcomes following VKDB

Surveillance period

October 2006 – October 2008 (inclusive).

Methodology

Case definition

Any infant under six months of age with spontaneous bruising, bleeding or intracranial haemorrhage associated with prolonged clotting (prothrombin time at least twice control value) and normal or raised platelet count, NOT due to an inherited coagulopathy or disseminated intravascular coagulation.

Cases will be classified as 'confirmed', 'possible' or 'no case' by the criteria used in the previous studies.

To allow international comparison, cases of late VKDB will also be classified in accordance with more stringent internationally-agreed criteria, which are:

Infants older than seven days with spontaneous bruising, bleeding or intracranial haemorrhage NOT due to an inherited coagulopathy or disseminated intravascular coagulation but associated with prothrombin time at least four times the control value AND at least one of the following:

- Platelet count normal or raised AND normal fibrinogen and/or absent fibrin degradation products.
- Normal prothrombin time after vitamin K administration.
- Concentration of under-carboxylated prothrombin (i.e. PIVKA-II) above normal controls.

Expected number (per year)

0 -70 confirmed cases per year.

Analysis

During the first 18 months of surveillance (up to March 2008) there have been 34 notifications, 32 via the BPSU and two reported directly to the investigators.

Five cases fell outside the study period and were therefore excluded. There have been four confirmed cases of VKDB, seven cases were considered not to be VKDB, eight were duplicate reports and further information is still awaited on ten cases.

Of the four confirmed cases, three received no vitamin K (VK) prophylaxis because the parents withheld consent. In each case, IM VK was the recommended prophylaxis: in one case both oral and IM VK were declined, in one the parents were not offered oral VK and in the third case it is not known whether oral VK was offered. The fourth case probably received one dose of oral VK (Orakay 1mg).

All infants were greater than 37 weeks gestation and weighed more than 2.5 kg. Three were solely breast fed and the other predominantly breast fed. No infant had underlying liver disease or other identified predisposing condition.

There was one case of early VKDB presenting at 15 hours of age, one case of classical VKDB presenting on day five and two cases of late VKDB presenting at 20 and 35 days. The baby with early VKDB presented with gastrointestinal bleeding and prolonged bleeding after heel prick; no maternal medications were implicated. The baby with classical VKDB had a delayed presentation, presenting on day five after birth and three days after the onset of bleeding, (oozing after heel prick and bruising). Both cases of late VKDB suffered intracranial haemorrhage confirmed by CT imaging; both also had concurrent bruising and gastrointestinal bleeding of less than 24 hours duration; one is expected to have permanent long-term sequelae.

Discussion

No firm conclusions can yet be drawn as the incidence of the condition is so low and full details are lacking for one-third of reported cases.

Further research: To provide denominator data a survey of current practices of prophylactic vitamin K in the UK has begun. Questionnaires were sent to all consultant-led maternity units in February 2008.

Please note the data presented are provisional and are not peer reviewed; definitive conclusions should not be drawn from them.

Measurement of PIVKA-II and vitamin K levels

Measurement of serum PIVKA-II can give retrospective confirmation of recent vitamin K deficiency using blood taken days, even weeks, after treatment and normalisation of clotting. In VKDB intravenous vitamin K alone may improve clotting sufficiently to stop bleeding in just 20-30 minutes, but the raised serum PIVKA-II levels are unaffected by vitamin K (or blood products) and

decline slowly. Both vitamin K and PIVKA-II levels can be measured in just 0.5ml of serum/plasma, or PIVKA-II alone in only 10 microlitres of serum/plasma – samples should be protected from light from immediately after collection (light degrades vitamin K). Dr Martin Shearer is happy to carry out the assays; contact details are:

Dr Martin J Shearer, Consultant Clinical Scientist & Honorary Senior Lecturer, Centre for Haemostasis and Thrombosis, 1st Floor North Wing, St Thomas' Hospital, London SE1 7EH.
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E-mail: martin.shearer@gstt.nhs.uk
Website: http://keqas.com

Funding

Roche Pharmaceuticals Ltd.

Ethics approval

Cornwall Research Ethics Committee (ref. 06/Q2101/74); Patient Information Advisory Group approval (ref. BPSU PIAG 03-04(FT5)/2006).

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6 New Studies 2008

Intussusception in children under 12 months

Background

Availability of high quality intussusception (IS) epidemiological data at a national level is becoming a high priority due to the availability of new rotavirus vaccines. A previous oral rotavirus vaccine (RotaShield®; Wyeth Vaccines) was withdrawn from the United States in 1998, shortly after its introduction due to evidence for a causal association with IS. At present, two new rotavirus vaccines, have received European approval (Rotarix®; GSK Vaccines and Rotateq®, Sanofi Pasteur). However, the UK Joint Committee on Vaccination and Immunisation has yet to consider recommendations for their use.

Throughout the development of the new rotavirus vaccines, the risk of IS has been a prime consideration. Large clinical trials have been able to exclude any significant association with relatively high power,[8-9] but nevertheless many countries are implementing high quality IS surveillance studies to gain data on background incidence. This is in order to provide clear statements to the public and health professionals about the incidence of IS pre-vaccination, and have a baseline against which to rapidly evaluate any post-vaccination adverse event reports that may be submitted. It is considered a high possibility that safety concerns will be raised, potentially causing controversy and adversely affecting uptake.

Objectives

The study aims to

- estimate the incidence of IS in children aged less than 12 months.
- describe the epidemiology of IS, including:
  - age, gender and ethnicity
  - risk factor prevalence
  - variation in management strategies (enema, surgical reduction, surgical resection, spontaneous recovery)
  - Short-term outcomes (recovery, death).

Surveillance period

March 2008 - March 2009 (13 months).

Prof B Taylor

Methodology

Case definition

Any child under 12 months of age who is in the opinion of the notifying paediatrician / surgeon, have suspected or confirmed intussusception based on clinical, radiological and or surgical findings. Reported cases will then be classified by the investigators as definite, probable, possible, or suspected intussusception cases according to internationally agreed and validated Brighton Collaboration criteria.[7]

Reporting instructions

Please report any child aged less than 12 months who has suspected or confirmed intussusception based on clinical, radiological and or surgical findings.

Expected numbers (per year)

300 cases are expected during the surveillance period.

Funding

Educational fund of GlaxoSmithKline Biologicals.

Ethics approval

This study has been approved by the Wandsworth Research Ethics Committee, reference 07/Q0803/62 and is exempt from site-specific assessment. Copies of the REC application, the REC approval letter and the study protocol will be sent to each notifying paediatrician with a request to kindly forward them to their R&D department if requested. The study also has PIAG approval (PIAG/BPSU 2-05(FT1)/2007).

References

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7 International Network of Paediatric Surveillance Units (INoPSU)

Figure 29: International Network of Paediatric Surveillance Units (INoPSU)

Background

Following the success of the BPSU, the same methodology was adopted and adapted in the 1990s to other countries who wished to set up active paediatric surveillance systems. In 1992, surveillance units were established in the Netherlands and Germany and, in 1994, in Switzerland. The European initiative was also the stimulus for the development in 1992 of an Australian unit and later the Malaysian unit (1994) to be followed by units in Canada (1996), Papua New Guinea (1996), New Zealand and Latvia (1997), Portugal (2001) and Greece/Cyprus (2003). Wales (1994) and Republic of Ireland (1996) developed surveillance units using a similar methodology to the BPSU, but are including on more common disorders in their surveillance. Unfortunately the Malaysian and Papua New Guinea units are currently not active. However, Argentina, Italy and Poland have shown an interest in developing similar such units.

The mission of INoPSU is the advancement of knowledge of rare and uncommon childhood infections and disorders and the participation of paediatricians in surveillance on a national and international basis so as to achieve a series of benefits to clinical practice and health policy. A document, known as the Amsterdam-Ottawa Note, details the functions and structure of the network and has been posted on the INoPSU website (www.inopsu.com).

Through the use of active ascertainment, the aforementioned units provide an efficient, effective framework for case finding for investigators who wish to study rare conditions in children using similar research protocols. In doing so this has allowed national comparative analysis to be undertaken. Leading, in this past year, to the national comparative presentation on hyperbilirubinaemia, congenital herpes and early onset eating disorders.

2007 also saw the establishment of an administrative post within the BPSU to take forward the objectives of INoPSU. This post is being funded by contributions from each individual national unit. This has allowed INoPSU to submit an application for EU funding, unfortunately not successful, the update of the website, the development of an E-newsletter and assist in the preparation for the 5TH INoPSU conference in Munich, Germany. It also led in June 2007 to the publication of a joint paper entitled - Beyond counting cases: public health impacts of national paediatric surveillance units in ADC vol. 92 pg. 527-533.

Over the past two years, INoPSU countries have facilitated the surveillance of 70 different rare conditions (and have now undertaken over 180 studies), covering a child population of over 50 million and involving over 10,000 clinicians. Details on all the activities of each surveillance unit is available form their respective websites and also from the INoPSU website, where the 2006-07 annual report can be found.

APPENDIX A - Completed Studies 1986-2007

By mid-2008 the BPSU had completed 68 studies. Information about these studies has been included in previous annual reports of the BPSU, which are available from the BPSU office and are also listed on the BPSU website (http://bpsu.inopsu.com/studies/completed.html). Information on studies completed from 2005, principal investigators and definitive papers are listed overleaf.

X-linked anhydrotic ectodermal dysplasia

Haemolytic uraemic syndrome I

Lowe syndrome

Insulin dependent diabetes in under fifteens

Haemorrhagic disease of the newborn

Congenital toxoplasmosis

Acute rheumatic fever

Measles, mumps, rubella-meningococcal meningitis

Acute flaccid paralysis

Long term parenteral nutrition

Juvenile dermatomyositis

Haemophagocytic lymphohistiocytosis

Neonatal necrotising enterocolitis

Biliary atresia

Adverse neonatal outcomes of delivery or labour in water

Congenital cataract

Pyroxidine dependent seizures

Cerebral oedema and death following diabetic ketoacidosis

Congenital brachial palsy

Inflammatory bowel disease in under 20 year olds

Invasive *Haemophilus influenzae* infection

Haemolytic uraemic syndrome II

Reye's syndrome

Encephalitis in early childhood (2 months – 3 years)

Vitamin K deficiency bleeding III

Thrombosis in childhood

Suspected fatal adverse drug reaction in children

Invasive fungal infections in VLBW infants

Haemorrhagic shock encephalopathy syndrome

Kawasaki disease

Neonatal herpes

Drowning and near drowning

Galactosaemia

Higher order births

Rett syndrome

Chemistry set poisoning

Androgen insensitivity syndrome

Insulin dependent diabetes in under fives

Congenital dislocation of the hip

Non-accidental poisoning/ Munchausen syndrome by proxy

Vitamin K deficiency bleeding II

Transient and permanent neonatal diabetes

Congenital syphilis

Medium chain acyl-CoA dehydrogenase

Neonatal meningitis

Hepatitis C virus infection

Subdural haematoma and effusion

Fatal/Severe allergic reactions to food ingestion

Severe visual impairment /Blindness

Group B Streptococcal disease

Subacute sclerosing panencephalitis

Cerebrovascular disease, stroke and like illness

Congenital cytomegalovirus

Internal abdominal injury due to child abuse

Severe complications of varicella (chickenpox) in hospitalised children

Langerhans cell histiocytosis

Studies completed since 2005

Severe hyperbilirubinaemia
Surveillance Period: May 2003 – May 2005
Investigator: Dr Donal Manning
Published Paper: Prospective surveillance study of severe hyperbilirubinaemia in the newborn in the United Kingdom and Ireland. Manning DJ, Maxwell MJ, Todd PJ, Platt MJ. *Arch Dis Child. Fetal Neonatal Ed. 2007;* ***92****: F342-F346*

Thyrotoxicosis in children
Surveillance Period: September 2004 – September 2005
Investigator: Dr Scott Williamson
Published Paper: Thyrotoxicosis in childhood. 20th BPSU Annual Report 2005/06. BPSU London 2006

Non-type 1 diabetes in children under 17 years
Surveillance Period: October 2004 – October 2005
Investigator: Ms Linda Haines, Dr Kay C Wan, Mr Richard Lynn, Dr Tim Barrett, Dr Julian H Shields
Published Paper: Rising incidence of type 2 diabetes in children in the United Kingdom. Haines L, Wan KC, Lynn R, Barrett TG, Shield JP. *Diabetes Care*. 2007; **30(5)**: 1097-1101

Early onset eating disorders in children under 13 years
Surveillance Period: March 2005 – March 2006
Investigator: Dr Dasha Nicholls, Mr Richard Lynn, Dr Russell Viner
Published Paper: 21th BPSU Annual Report 2006/07. BPSU London 2007

Neonatal herpes simplex virus (HSV)
Surveillance Period: January 2004 – January 2007
Investigator: Dr Pat Tookey, Mr Richard Lynn, Professor Catherine Peckham
Published Paper: 21th BPSU Annual Report 2006/07. BPSU London 2007

Malaria
Surveillance Period: January 2006 – January 2007
Investigator: Dr Shamez Ladhani
Published Paper: 21th BPSU Annual Report 2006/07. BPSU London 2007

Methicillin-Resistant Staphylococcus (MRSA)
Surveillance Period: June 2005 – June 2007
Investigator: Dr Alan Johnson, Dr Catherine Goodall, Dr Mike Sharland
Published Paper: 21th BPSU Annual Report 2006/07. BPSU London 2007

APPENDIX B - Published Papers 2007-2008

1. Townsend CL, Cortina-Borja M, Peckham CS, Tookey PA. Low rates of mother-to-child transmission of HIV following effective pregnancy interventions in the United Kingdom and Ireland, 2000-2006. *AIDS* 2008; **22(8)**: 973-81

2. Townsend CL, Cortina-Borja M, Peckham CS, Tookey PA. Trends in management and outcome of pregnancies in HIV infected women in the United Kingdom and Ireland, 1990-2006. *BJOG* 2008, *in press*

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7. Cameron C, Allen G, Johnstone F, Finn A, Heath PT, Booy R. Severe complications of chickenpox in hospitalised children in UK and Ireland. *Arch Dis Child.* Dec 2007; 92:1062-1066

8. Lynn R, Ross E. The British Paediatric Surveillance Unit: the first 20 years *Arch Dis Child,* Sep 2007; **92**: 744 - 745.

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10. McNinch A, Busfield A, Tripp J. Vitamin K deficiency bleeding in Great Britain and Ireland: British Paediatric Surveillance Unit Surveys, 1993–94 and 2001–02 *Arch Dis Child,* Sep 2007; **92**: 759 – 766.

11. Busfield A, McNinch A, and Tripp J. Neonatal vitamin K prophylaxis in Great Britain and Ireland: the impact of perceived risk and product licensing on effectiveness *Arch Dis Child*, Sep 2007; **92**: 754 - 758.

12. Cheng K, Masters S, Stephenson T, Cooke R, Ferner R, Ashworth M, Nunn T. Identification of suspected fatal adverse drug reactions by paediatricians: a UK surveillance study. *Arch Dis Child,* Jul 2008; **93**: 609 - 64.

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14. Ladhani S, Aibara RJ, Riordan FA, Shingadia D. Imported malaria in children: a review of clinical studies. *Lancet Infect Dis.* 2007 May;7(5):349-57. Review.

15. Manning D, Todd P, Maxwell M, Platt M J. Prospective surveillance study of severe hyperbilirubinaemia in the newborn in the UK and Ireland. *Arch Dis Child* Fetal Neonatal Ed. 2007; **92**: F342-F346

16. Rising incidence of type 2 diabetes in children in the United Kingdom. Haines L. Wan KC, Lynn R, Barrett TG, Shield JP. *Diabetes Care*. 2007; **30(5)**: 1097-1101.

APPENDIX C - Presentations 2007-2008

RCPCH Annual Scientific Meetings 2007 and 2008

1. A spectrum of neurodegenerative disease in UK children. Findings of a prospective national study after almost ten years of surveillance. Verity C, *Arch Dis Child;* 2008; **93** (Suppl 1): A41-42.

2. Very low risk of mother to child transmission of HIV in women on HAART achieving viral suppression in the UK and Ireland. Townsend C, Cortina-Borja M, Peckham C, de Ruiter A, Lyall H, Tookey P. *Arch Dis Child;* 2008; **93** (Suppl 1):A3-4.

3. Congenital abnormalities and in-utero exposure to antiretroviral therapy in the UK and Ireland. Wiley B, Townsend C, Cortina-Borja M, Peckham C, Tookey P. *Arch Dis Child;* 2008; **93** (Suppl 1):A83.

4. The burden of imported childhood malaria in the UK and Ireland. Ladhani S, Garbash M, Riordan A, Chiodini P, Whitty C, Shingadia D *Arch Dis Child;* 2008; **93** (Suppl 1):A83.

5. Long-term follow-up study of children with *Haemophilus influenzae* serotype B vaccine failure to determine long term complications and the risk of serious infections. Ladhani S, Heath P, Aibara, Ramsay M, Slack M, Hibberd M, Pollard A, Moxon R, Booy R. *Arch Dis Child;* 2008; **93** (Suppl 1):A80.

6. The BPSU study of Biliary Atresia: Outcome 13 years. McKiernan, Baker A, Lloy C, Mieli-Vergani G, Kelly D. *Arch Dis Child 2007; **92** (Suppl):A4-A5.*

7. Enhanced surveillance of Meticillin-Ressistant Staphylociccus aureus bacteraemia in children less than 16 years in the UK and Ireland. June 2006 – November 2007. Goodall C, Johnston A, Sharland M. *Arch Dis Child* 2007; **92** (Suppl 1): A75-79.

8. Morbidity, mortality and response to treatment in perinatally HIV-infected children in the UK and Ireland, 1996-2006: A prospective cohort study. Doerholt K, Judd A, Sharland M, Tookey P et al *Arch Dis Child* 2007; **92** (Suppl 1): A80-87.

9. Vertically acquired HIV infection in the UK and Ireland in the era of routine antenatal testing (2000-5) Townsend J, Masters C, Peckham C, Tookey P. *Arch Dis Child* 2007; **92** (Suppl 1): A80-87.

10. Active surveillance of early onset eating disorders: potential for a child psychiatric surveillance system. Lynn R, Nicholls D, Viner R. *Arch Dis Child* 2007; **92** (Suppl 1): A50-A52.

11. Eating disorders in children under 13: clinical profiles from a British national surveillance scheme. Nicholls D, Lynn R, Viner R. *Arch Dis Child* 2007; **92** (Suppl 1): A50-A52.

Other Conferences & Meetings

12. A national prospective population-based study of children with mitochondrial disease: clinical presentation and method of diagnosis in 101 cases. Krishnakumar D. British Paediatric Neurology Association Annual Meeting, Leeds, January 2008.

13. The causes of progressive intellectual and neurological deterioration (PIND) in UK children. Findings of a prospective national study after almost 10 years of surveillance. Verity C. American Academy for Cerebral Palsy and Developmental Medicine, Annual Scientific Meeting. October 2007.

14. Study of Newborn Screening for MCADD. Ethnic-specific birth prevalence of 985A>G homozygous Medium-Chain Acyl-CoA Dehydrogenase Deficiency (MCADD): results from screening ~ 1.1 million newborn infants. Khalid JM, Oerton J, Cortina-Borja M, Andresen BS, Besley G, Dalton N, Downing M, Foo Y, Green A, Henderson M, Dezateux C. On behalf of the Clinical Scientific Group of the UK Collaborative. ISNS 5th Annual European Congress in Screening. Reykjavik, Iceland. June 2007.

15. An audit of laboratory diagnosis of HIV-1 infection in infants. Tosswill J, Pillay D, Zuckermann M, Masters J, Tookey P, Parry J. BHIVA 2007.

16. Mother-to-child transmission of HIV in the UK and Ireland: 1990-2004. Townsend CL, Cortina-Borja M, Peckham CS, Tookey PA. CROI, Los Angeles, February 2007.

17. International comparison of severe neonatal hyperbillirubinaenia and neonatal herpes simplex infection. Grenier D, Sgro M, Wong T, Manning D, Tookey PA, Jones CA. Canadian Paedeatric Society, Montreal, June 2007.

18. Poster – Making the diagnosis in leucoencephalopathy: key features in a cohort of children with Pelizaeus-Merzbacher disease A Maw. British Paediatric Neurology Association Annual Meeting, Leeds, January 2008.

19. Poster - Early Clinical Outcomes of Medium Chain Acyl-CoA Dehydrogenase Deficiency (MCADD): Experience from the UK Collaborative Study. Oerton J, Khalid JM, Chakrapani A, Champion M, Cleary M, Sharrard M, Walter JH, Dezateux C on behalf of the UK Collaborative Study of Newborn Screening for MCADD. ISNS 5th Annual European Congress in Screening Reykjavik, Iceland. June 2007.

20. Poster -, A Green on behalf of the Laboratory Scientific Working Group of the UK Collaborative Study of Newborn Screening for MCADD. How can we improve phenylalanine measurement? – data from the UK Collaborative MCADD Study Quality Assurance sub-group. Goddard P, Stanford B, Khalid JM, Pollitt R, Loeber G, Dezateux C. ISNS 5th Annual European Congress in Screening Reykjavik, Iceland. June 2007.

21. Poster – "How useful is a clinical scoring system in diagnosing mitochondrial cytopathies? Findings from a large national case series." D. Krishnakumar British Paediatric Neurology Association Annual Meeting, Edinburgh. January 2007.

APPENDIX D - Membership of Executive Committee 2007-2008

Professor Allan Colver	Chair
Mrs Sue Banton	Patient and Carers Advisory Group
Dr Claire Cameron*	Health Protection Scotland
Dr Colin Campbell	Medical Adviser (infectious disease)
Professor Carol Dezateux	Institute of Child Health (London)
Professor Adam Finn*	Co-opted
Dr Shankar Kanumukala	Co-opted
Ms Linda Haines	Royal College of Paediatrics and Child Health Research Division
Dr Sue Hobbins	Royal College of Paediatrics and Child Health Treasurer
Dr Chikwe Ihekweazu*	Medical Adviser (infectious disease)
Dr Rachel Knowles	Medical Adviser (non-infectious disease)
Mr Richard Lynn	Scientific Coordinator
Dr Donal Manning*	Co-opted
Dr Colin Michie	Co-opted
Dr Simon Mitchell	Co-opted
Dr Richard Pebody	Health Protection Agency
Dr Richard Reading	Co-opted
Professor Terence Stephenson	Royal College of Paediatrics and Child Health Vice President for Science and Research
Mrs Anne Seymour	Patient and Carers Advisory Group
Dr Ted Wozniak	Department of Health (observer)
Dr Sandra Williams	Department of Health (observer)

* Stepped down in 2008


BPSU
1986-2008


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