



Royal College of Paediatrics and Child Health

The British Paediatric Surveillance Unit (BPSU) is part of the Research Division of the Royal College of Paediatrics and Child Health

Contact

Richard Lynn MSc
Scientific Coordinator

Tel: 020 7307 5671
Fax: 020 7307 5694
Email: bpsu@rcpch.ac.uk
Website: <http://bpsu.inopsu.com>

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Surveillance of Medium Chain Acyl CoA Dehydrogenase Deficiency (MCADD) commences in June 2004

The Department of Health (DH) are piloting the introduction of a newborn screening service for MCADD in areas served by six English newborn screening laboratories which between them screen about half of all babies born in the UK. Concurrently, a DH funded research programme to evaluate this service has commenced, led by researchers at the Institute of Child Health. This is being carried out in collaboration with researchers at the University of Oxford, the BIMDG, UKNSLN and CLIMB – the parent support group. As part of this research programme, surveillance of MCADD through the BPSU will commence in June 2004 for a 25-month period.

Ascertainment of cases through the BPSU will allow

- Assessment of test performance in a UK setting, notably false negative rate.
- Evaluation of clinical outcome to 2 years of age in those diagnosed through clinical presentation, family history or through screening.

This research will add to evidence from an earlier BPSU surveillance study¹ and a subsequent retrospective study² and will contribute to the National Screening Committee review of future screening policy.

MCADD is one of the most common of the fatty acid oxidation defects. These are disorders of intermediary metabolism that may cause hypoglycaemia, acute encephalopathy and sudden death. Children with MCADD usually present clinically before the age of two. MCADD is recessively inherited and between 1 in 40 and 1 in 80 of the UK population are unaffected carriers. Approximately 80-90% of affected individuals have the same genetic mutation and from this it is predicted that the birth prevalence is about 1 in 10,000.

The diagnosis of MCADD can be made through clinical presentation, through investigation of children with an affected family member or through newborn screening.

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

- Elevated octanoyl carnitine in the presence of normal free carnitine levels on blood test using tandem mass spectrometry

AND/OR

- Characteristic urine profile of organic acids with hexanoyl, suberyl and phenylpropionyl glycine.

WITH OR WITHOUT one or both of the following:

- Molecular genetic studies confirming presence of the common mutation G985A on one or both alleles
- Enzyme studies based on skin fibroblasts showing reduced activity of MCAD.

Paediatricians are asked to notify any confirmed or suspected cases on the orange card in the normal way. The co-ordinating centre will then send a case notification questionnaire to the notifying paediatrician. If necessary, this may be followed-up at four months with a brief questionnaire to confirm diagnosis. Follow-up questionnaires will be sent at one and two years after initial notification to establish clinical outcome following diagnosis

The study has GOS-MREC approval and is funded by the DH. The protocol card is enclosed with the June orange card but if you need any further information or advice please contact

Professor Carol Dezateux (Tel: 020 7905 2362, E-mail: c.dezateux@ich.ucl.ac.uk),
Juliet Oerton (Tel: 020 7905 2241, E-mail: j.oerton@ich.ucl.ac.uk)

References

1. Pollitt RJ, Leonard JV. Prospective surveillance study of medium chain acyl-CoA dehydrogenase deficiency in the UK. *Archives of Disease in Childhood* 1998; **79**:116-119
2. Pourfarzam, M., Morris, A., Appleton, M., Craft, A., Bartlett, K. Neonatal screening for medium-chain acyl-CoA dehydrogenase deficiency. *The Lancet* Sept 29, 2001; **358**:1063-1064

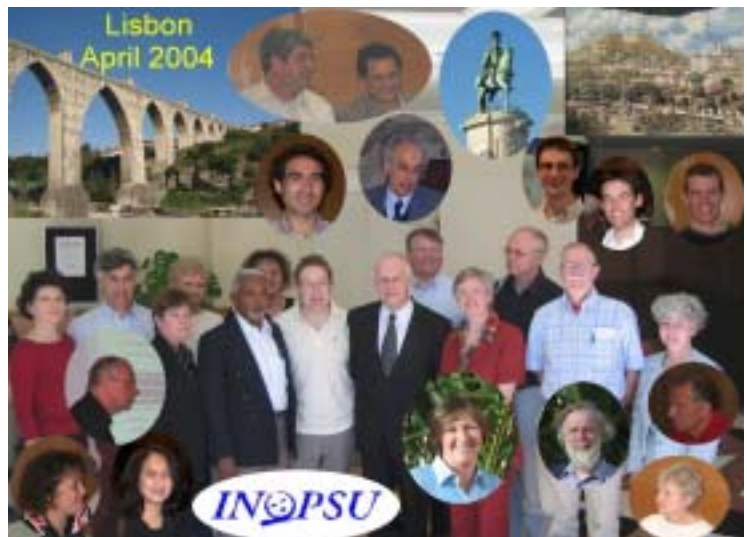
International Activities

3rd International Network of Paediatric Surveillance Units (INoPSU) conference: Following similar meetings in Ottawa in 2000 and York in 2002, the Portuguese Paediatric Surveillance Unit hosted the third INoPSU conference. This conference was held over three days during April in Lisbon.

The morning of day one saw presentations from various disease surveillance registries, including the Portuguese birth defect registry, the registry for primary immunodeficiencies and the Spanish epidemiological network on rare disease research. Presentations from Orphanet (www.orpha.net) a web based database of rare disease and orphan drugs and the newly established network of public health institutions on rare disease were also received. The afternoon session concentrated on discussions in areas of concern to the surveillance units. Firstly there was a discussion on how to appropriately recognise the work of the reporting physicians and how they should be acknowledged. Following this discussion it was agreed that INoPSU should prepare an addendum to the Vancouver protocol on authorship of scientific papers, aimed at national studies of rare disease. The second discussion of the afternoon centred on the completeness of ascertainment of case reports. The use and fallibilities of capture-recapture techniques were reviewed. The BPSU also presented their analysis of the effectiveness of using different sources for case ascertainment e.g. adult specialty groups, laboratory data and patient support organisations.

Day two saw papers presented on conversion disorder in Australian children, invasive fungal infection in very low birth weight children in the UK and Group b *streptococcal* infection in Portugal. Of particular interest was the six country international collaborative paper on surveillance of haemolytic uraemic syndrome, comparing and contrasting the disorder across nations. An important paper for all surveillance units was that outlining the extensive evaluation of the Canadian paediatric surveillance program was received. This evaluation, based on the Communicable Disease Centre, Atlanta guidelines on evaluating surveillance systems, measured the effectiveness of the Canadian surveillance program which we were pleased to hear scored very highly.

The final day brought together 21 representatives from 10 of the 15 national surveillance units and the British Ophthalmology Surveillance Unit for the business meeting (Figure 1). Professor Mike Preece and the BPSU Scientific Co-ordinator, Richard Lynn represented the UK. Countries represented at the meeting included the hosts Portugal, Germany, Netherlands, Australia, New Zealand, Republic of Ireland, Switzerland and Canada. The aims of INoPSU were reiterated, to facilitate communication between existing units; encourage the sharing of information between researchers and to assist in the development of new units. With the final aim in mind the Greece/Cyprus surveillance unit was accepted as a full member of INoPSU whilst the Trinidad and Tobago Unit was accepted as an affiliate until such time as it has fulfilled the requirements for entry. The meeting also heard that Argentina, the Czech republic and Poland were interested in setting up similar units.



Topics discussed included how INoPSU should secure funding to fulfil its aims and the difficulties surrounding consent, confidentiality, data collection and handling. Ways in which communications can be improved by national research teams were also proposed and it is hoped that this will stimulate the use of multi-national surveillance protocols.

The meeting was considered a great success and it will be repeated in 2006. Copies of the abstracts are available via the BPSU office or online at <<http://bpsu.inopsu.com/Whatsnew.htm>>. A free copy of the first INoPSU progress report is available from the BPSU office (E-mail bpsu@rcpch.ac.uk). Further information on INoPSU is also available online at <<http://www.inopsu.com>>.

Irish Paediatric Surveillance Unit: Professor Denis Gill reports, “As you are probably aware there is a parallel surveillance system being run in Ireland. Though the Irish paediatricians receive the BPSU orange card they also receive a “green card. Set up in 1996 by the Faculty of Paediatrics of the Royal College of Physicians (Ireland) in cooperation with the Ulster Paediatric Society the IPSU complements the work of the BPSU by surveying more common childhood disorders in Ireland. Covering a child population of around 1.3 million, surveillance is achieved through a monthly-prepaid postcard circulated to around 150 members of the Irish Paediatric Society. The response rate is around 80% Studies undertaken in 2003 include; Autism under 5 years; Type I Insulin Dependent Diabetes Mellitus; Alcohol and Children; Type II Non-insulin diabetes mellitus and Fragile X. New studies for 2004 include: Opsoclonus Myoclonus syndrome; Congenital Toxoplasmosis and Immune Thrombocytopenic Purpura.

The Type I insulin dependent diabetes study is going into its second year and will compare current insulin figures to the previous survey in 1997. A large number of reports have been seen and the impression prior to analysis is that there is a continuing increase in new onset Type I diabetes in children as in other countries. The last survey put the Republic of Ireland and Northern Ireland into the moderate to high group of countries concerning diabetes mellitus and the results of the 2003/2004 study are awaited with interest.

International Activities, contd.

The study on alcohol and children concluded acute, severe alcohol ingestion by children resulting in hospital admission and has produced a worrying number of high adolescents particularly girls presenting to children's units in an intoxicated state. The result of this study will be presented at the Spring meeting of the Irish Paediatric Association and have already generated some media interest and concern. We have put congenital toxoplasmosis on the IPSU card, knowing that it is already on the BPSU card as we are anxious to ascertain as completely as possible the frequency of this condition in Ireland."

For more information contact Professor Denis Gill, Children's Hospital, Temple Street, Dublin 1, Republic of Ireland. E-mail: gilld@iol.ie

Welsh Paediatric Surveillance Unit (WPSU): The WPSU biannual report has recently been published highlighting the work of the Unit. Like the Irish unit the WPSU looks at conditions, which are considered too common for a UK study or too uncommon for a local hospital to perform. Funding for the unit is through the Welsh Office for Research and Development and latterly the National Assembly for Wales and the Welsh Paediatric Society. Studies highlighted in the report include childhood tuberculosis, facial nerve palsy, newly diagnosed diabetes, palliative care, physical child abuse, splenectomy and hyposplenism in childhood, neonatal abstinence syndrome and subdural haemorrhage. Current studies on the card include hypernatraemia in infancy, subdural haemorrhage, septo-optic dysplasia, juvenile idiopathic arthritis, adverse events from complementary and alternative medicine and complicated pneumonia including empyema.

For more information on the WPSU or for a copy of the report please contact Dr John Morgan, Royal Glamorgan Hospital, Llantisant, South Glamorgan CF72 8XR. E-mail: oconnellhi@cardiff.ac.uk

Study News

Study extensions: Several studies have recently had their surveillance period extended for a further 12 months. The study on **severe hyperbilirubinaemia in the newborn** (principal investigator Dr Donal Manning, Arrowse Park Hospital) will continue to June 2005. To date 47 reports have been received of these 23 have met the case definition, with two deaths. The survey of **Langerhans cell histiocytosis (LCH)** (principal investigator Professor Louise Parker, RVI Newcastle), which also commenced in June 2003, has also had its request for a second year of surveillance approved. Funded by the Histiocytosis Association the LCH study aims to describe the epidemiology in children. To date 26 cases have been confirmed. Cases ascertainment is being supplemented through an additional mailing to pathologists, oncologists, dermatologists, orthopaedic surgeons and other clinician's who may also see children with this condition. Further information on these reports was published in the Spring bulletin (vol 12 no 1). Finally the **Progressive Intellectual and Neurological Deterioration (PIND)** study (investigator Dr Chris Verity, Addnebrookes Hospital) continues into its eighth year, 1234 cases have been discussed by an expert neurological advisory group of six paediatric neurologists. 716 have a definite diagnosis, which is not vCJD, and these comprise 114 known degenerative conditions. To date only six cases of variant CJD (four confirmed, two probable) have been identified.

Study ends: The survey of **congenital toxoplasmosis** (principal investigator Dr Ruth Gilbert, ICH London), which commenced in July 2002, comes to an end this July after 25 months. By April 2004, 148 reports of suspected toxoplasmosis had been made. 33 were notified through BPSU, 54 through BOSU, 48 through the reference laboratories, three through individual clinicians reporting direct to the study, and 10 through secondary sources who were clinicians approached for further information after an initial report by a laboratory, paediatrician or ophthalmologist. To date a total of 93 children (105, excluding 12 duplicate reports) with suspected symptomatic toxoplasma infection have been reported, of which 51 presented within the surveillance period of the study. Provisional classification, based on the clinical and laboratory findings and the clinician's opinion, 27 were classified as definite or probable toxoplasma retinitis and/or congenital toxoplasmosis. Further information from clinicians and, in some cases, from retrospective testing for specific IgM of stored neonatal Guthrie card blood spots, may modify these classifications. Just over half of the children were considered to have congenital toxoplasmosis (14/27), and 22 had toxoplasma retinitis. Five had no information on ocular findings. As expected, most children with congenital toxoplasmosis (10/14) presented in the first year of life, but two presented with ocular symptoms in adolescence and were considered to have congenital toxoplasmosis due to the presence of intracranial pathology. In the 22 children with toxoplasma retinitis 13 (59%) did not have evidence of congenital toxoplasmosis, and were more likely to have acquired infection after birth. Apart from the 27 cases with toxoplasmosis, all of which were live births, a further six miscarriages or stillbirths were reported, five classified as possible, and one as definite, congenital toxoplasmosis.

On behalf of the investigators we thank you for your time in completing the proforma and for those who have yet to return their proforma can we encourage you to do so.

Study approvals: The survey on **thyrotoxicosis** from the Sir Peter Tizard bursary applicant Dr Scott Williamson with commence once MREC approval has been received. Two further studies have recently been approved by the BPSU Executive, these being **non-type 1 diabetes** (principal investigators Linda Haines, Dr Julian Shield, Dr Tim Barrett, Richard Lynn) and **early onset eating disorders (5-13 years)** (principal investigators Richard Lynn, Dr Dasha Nicolls, Dr Russell Viner). Currently both these studies are seeking funding and MREC approval.

Recent Publications

1. Variations in neurodegenerative disease across the UK; findings from the national study of Progressive Intellectual and Neurological Deterioration (PIND). Devereux G, Stellitano L., Verity CM, Nicoll A, Rogers P. Arch Dis Child 2004; **89**:8-12.
2. Is variant Creutzfeldt-Jakob disease in young children misdiagnosed as Alpers' syndrome? An analysis of a national surveillance study. te Water Naude J, Verity CM, Will RG, Devereux G, Stellitano L. JNNP June 2004 Vol75 No 5.
3. Group B streptococcal disease in UK and Irish infants < 90days of age. Heath PT, Balfour G, Weisner AM, Efstratiou A, Lamagni TL, Tighe H, O'Connell LAF, Cafferkey M, Verlander NQ, Nicoll A, AC McCartney. Lancet 2004;**363**:292-4.
4. Characterisation of Group B Streptococci from Infants with Invasive Disease in England and Wales. Weisner AM, Johnson AP, Lamagni TL, Arnold E, Warner M, Heath PT, Efstratiou A. Clinical Infectious Disease 2004; **38**:1203-8.
5. HPA. COVER programme: October to December 2003. Vaccination coverage statistics for children up to five years of age in the United Kingdom. Commun Dis Rep CDR Wkly [serial online] 2004 [cited 4 May 2004]; 14 (13): immunisation. Available from <<http://www.hpa.org.uk/cdr/PDFfiles/2004/cdr1304.pdf>>.
6. Invasive fungal infections in very low birthweight infants: United Kingdom national surveillance study. Clerihew, Lamagni T, Brocklehurst P, Balfour A, McGuire W. York 2004. Arch Dis Child 2004; **89** (Suppl 1). A1-A7
7. Hankin CD, Tookey PA, Lyall EGH, Peckham CS. Follow up of children exposed to antiretroviral therapy in pregnancy (CHART). York 2004. Arch Dis Child 2004; **89** (Suppl 1): A76.

Copies are available from the BPSU office.

Monthly Analysis

TABLE 1 - % RESPONSE RATE

Aug – Jan 04	% retd	Rank (Aug – Jan 04)
North	91.0	5 (12)
Yorks	92.7	2 (4)
Trent	90.5	7 (11)
EAnagl	88.5	14 (15)
NWT	87.0	16 (9)
NET	81.4	20 (20)
SET	87.4	15 (14)
SWT	85.7	19 (19)
Wessex	89.7	11 (10)
Oxford	88.7	13 (3)
SWest	90.5	8 (8)
WMids	91.1	4 (7)
Mersey	90.6	6 (13)
NWest	89.9	10 (6)
Welsh	93.6	1 (1)
NScot	89.6	12 (17)
SScot	86.9	17 (16)
WScot	90.3	9 (6)
NIre	92.4	3 (2)
RIre	86.4	18 (18)
Total	89.0	

TABLE 2 - ALL CASES REPORTED AND FOLLOW-UPS TO 16/05/2004

		I VALID	II INVALID		NYK		as % of total		
Condition	Started	I	Ia	Ib	III	Ttl	I	II	III
HIV/AIDS	1986	2747	419	503	235	3904	70	24	6
CR	1990	70	25	50	1	146	48	51	1
PIND	1997	1041	194	436	49	1720	61	37	3
Con Toxo	2002	6	2	18	9	35	17	57	26
Varicella	2002	103	21	28	36	188	55	26	19
IFInfect	2003	83	18	21	21	143	58	27	15
Se. Hyperbil	2003	34	3	20	8	65	52	35	12
LCH	2003	15	9	21	23	68	22	44	34
Tuberculosis	2003	58	13	20	70	161	36	20	43
NNH	2004	3	1	4	13	21	14	24	62
Total		3920	705	1121	465	6451	64	28	8

I = confirmed/already known

Ib = reporting error or revised diagnosis

Ia = duplicate

III = status not yet reported to BPSU by investigator

AIDS/HIV - Acquired Immunodeficiency Syndrome / Human Immunodeficiency Virus

CR - Congenital Rubella

PIND - Progressive Intellectual Neurological Degeneration

Con Toxo - Congenital Toxoplasmosis

Varicella - Severe complications of varicella

IFInfect - Invasive fungal infections in VLBW infants

Se. Hyperbil - Severe hyperbilirubinaemia in the newborn

LCH - Langerhans cell histiocytosis

NNH - neonatal herpes simplex virus infection

ALL DATA IS PROVISIONAL & CONTINUALLY BEING UPDATED