



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



Royal College of Paediatrics and Child Health

Editor

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FMAIT Surveillance Commences

A 13 month study of fetomaternal alloimmune thrombocytopenia (FMAIT) commences in October 2006, funded by the charity Wellbeing of Women. FMAIT, also known as neonatal alloimmune thrombocytopenia or NAIT, is the most common cause of severe neonatal thrombocytopenia in otherwise well term infants, and is analogous to the fetal/neonatal anaemia caused by haemolytic disease of the newborn (HDN). 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. In contrast to HDN, infants of first pregnancies are often severely affected and the diagnosis is usually made with the birth of a first affected infant. There is therefore a current debate about the utility of antenatal screening for the condition. 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 screening¹. This study aims to address three of these deficiencies: (1) to determine the true incidence of severe haemorrhage associated with FMAIT, (2) to describe the clinical outcome of affected cases and (3) to identify prognostic factors.



Dr Marian Knight,
Principal Investigator

This is the first study to be undertaken simultaneously through the BPSU and the UK Obstetric Surveillance System (UKOSS) and is being run by the National Perinatal Epidemiology Unit, University of Oxford, in collaboration with the National Blood Service and the John Radcliffe Hospital, Oxford. The combined use of both obstetric and paediatric reporting systems will help to ensure identification of cases is as complete as possible and will allow collection of comprehensive antenatal and postnatal information. The study results will be used to inform ongoing review of the case for antenatal screening for this condition. PIAG and MREC approval are currently being sought.

The **case definition** includes all infants 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 $<50 \times 10^9/l$
- 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.

Please report all cases of FMAIT that you see, irrespective of whether the condition was diagnosed before or after birth or whether the case has also been reported to UKOSS through your hospital obstetrician or midwife. If you would like any advice regarding the eligibility of a particular case for inclusion in the study, or any other information about the study please contact: Dr Marian Knight, National Perinatal Epidemiology Unit, University of Oxford. Tel: 01865 289700, E-mail: marian.knight@npeu.ox.ac.uk

1. Murphy MF, Williamson LM, Urbaniak SJ. Antenatal screening for fetomaternal alloimmune thrombocytopenia: should we be doing it? *Vox Sang* 2002; 83 Suppl 1:409-16.

Study News – VKDB Surveillance Resumes

Vitamin K Deficiency Bleeding (VKDB) is rare; it can cause severe handicap or death but is preventable by the appropriate use of either oral or intramuscular vitamin K (VK) prophylaxis together with surveillance for liver disease. It has been the subject of three previous BPSU studies, the data from which have undoubtedly influenced practice; the principle of VK prophylaxis is now accepted by all UK units (although the route of administration remains controversial) and there is far greater awareness of the importance of investigating any 'warning bleed' or prolonged jaundice.

The third BPSU study (2000-02) found the rate of VKDB in the UK to be at its lowest recorded, comparing favourably with published rates from other countries. During this study there was no death or long-term morbidity from VKDB. At the time of this study Konakion Neonatal was used by most of the 60% of units recommending intramuscular (IM) prophylaxis. With exceedingly rare exceptions, a single 1mg dose of this preparation IM at birth is known to protect against VKDB for several months. Konakion Neonatal has now been withdrawn leaving only Konakion MM licensed for IM use.

Konakion MM's novel formulation enhances bioavailability after oral administration; however there are few data about the long-term protection conferred by a single IM dose and it cannot be assumed to be the same as that after 1mg of the differently-formulated Konakion Neonatal. The Medicines and Healthcare Product Regulatory Agency have advised a surveillance study to monitor the effects of withdrawal of the cremophore preparation. This fourth BPSU study of VKDB, with data from a contemporaneous survey of VK prophylaxis policies used in the same population, will provide the efficacy data required and not available elsewhere.

Surveillance will commence shortly. The protocol card will be included with the first mailing.

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. This is the same case definition as used in the 3 previous BPSU studies of VKDB, to allow comparison.

Please report any infant presenting with a bleeding disorder in the first six months of life where no alternative firm diagnosis (e.g. haemophilia, septicemia with DIC) has been established. If there is serious suspicion of VKDB, please report the case and allow us to decide.

For advice about the eligibility of a case for inclusion, please contact: Alison Busfield Tel: 01392 411611(bleep) E-mail: Alison.Busfield@rdehc-tr.swest.nhs.uk; John Tripp Tel: 01392 403148 E-mail: John.Tripp@pms.ac.uk; Andrew McNinch Tel: 01392 402676 E-mail: Andrew.McNinch@rdehc-tr.swest.nhs.uk



Dr Alison Busfield,
Principal Investigator

2nd Sir Peter Tizard Research Bursary Update – Malaria in Children

Background and Aims of the study: Imported malaria is a preventable disease. The United Kingdom currently has one of the highest reported incidences of imported malaria cases among industrialised countries, with over 2000 cases reported every year, of which, children account for around 10-15%. The on-going BPSU study aims to (i) Estimate the incidence of imported childhood malaria in the United Kingdom and Ireland; (ii) Describe clinical and laboratory features, management, complications and outcome at discharge; and, (iii) Identify risk factors for imported cases of severe malaria.

Case definition: Any child less than 16 years of age who is diagnosed with malaria through either microscopic examination of thick and thin blood smears or malaria antigen detection in the blood using commercially-available assays.

Progress so far: Imported malaria was added to the BPSU orange card in January 2006. So far, 59 cases have been reported in the first 6 months of the study. There were 50 cases reported from the UK (18 cases from London) and 9 from Ireland. For the UK, the number of cases reported is significantly lower than expected. Between 1999 and 2003, an average of almost 100 cases were reported to the Malaria Reference Laboratory during the first 6 months of each year. Completed questionnaires have been returned for only 29 cases. Of these, 26 have been confirmed as malaria (22 cases of *P. falciparum*), while two were duplicates and one was a false positive malaria antigen test case.

Difficulties encountered so far: We have been informed that a number of paediatric malaria cases are being treated directly in the Emergency Department by paediatric senior house officers and registrars, who currently do not receive the BPSU orange card. These patients are not being admitted to the paediatric ward and are, therefore, not seen by a paediatric consultant. In addition, most children with malaria are admitted to the paediatric ward for only a short period of time. As a result, consultants may not be aware of these cases. We, therefore, urge all junior paediatric trainees to inform their consultants of all confirmed cases of paediatric malaria. They can also contact the study-coordinator directly by telephone or email (details given below) to notify the case. In addition, consultants are urged to liaise with their haematology department to identify and report any paediatric malaria cases that might have been missed in the first 6 months of this year.

It is important that we identify all cases of imported malaria in children in order to obtain an accurate estimate of incidence, complications and outcome. This study will continue until February 2007. For further information, please contact:

Dr Shamez Ladhani. Tel: 020 7882 2615. E-mail: s.ladhani@qmul.ac.uk

Study Extensions

Progressive Intellectual and Neurological Deterioration

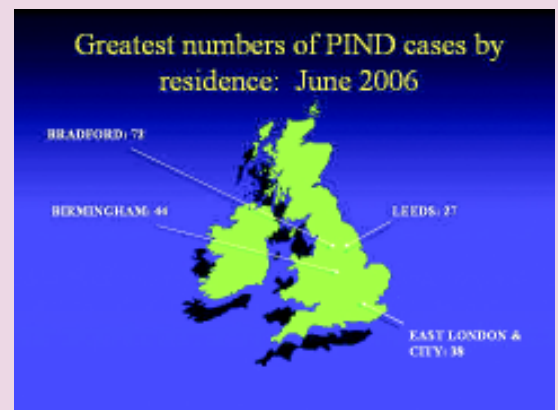
Since May 1997 we have used the BPSU's "Orange Monthly Report Card" so that UK Paediatricians can notify all childhood cases of progressive intellectual and neurological deterioration (PIND) to us. The aim of the PIND study is to identify cases of variant Creutzfeldt-Jakob disease (vCJD) occurring in children in the UK. As the clinical presentation of vCJD is not typical of classical CJD and could be different in children, suspected cases are detected by looking at a broader group of conditions. This group needs to be large enough to include all possible cases of CJD (including any novel variant) hence the need to perform surveillance for all children with PIND.

The case definition is any child under 16 years at onset of symptoms who fulfils all of the following 3 criteria:- Progressive deterioration for more than 3 months **with** loss of already attained intellectual/developmental abilities. **And** development of abnormal neurological signs.

We include children who meet the case definition even if specific neurological diagnoses have been made!

Anonymised data are discussed and classified by an Expert Neurological Advisory Group of seven paediatric neurologists. PIND cases are thoroughly reviewed (especially our group of "Undiagnosed" PIND Cases) to ensure no possible vCJD case is missed and no novel variant of CJD is emerging. Collaboration with the National Creutzfeldt-Jakob Disease Surveillance Unit increases the likelihood of detection via dual ascertainment.

After nine years of surveillance, 2108 children with suspected PIND have been reported. Of the 902 cases of definite PIND, six have a diagnosis of vCJD and all have been reported since December 1998. One was a girl aged 12 years at onset – the youngest UK case of vCJD. All share common psychiatric, cognitive and neurological symptoms and common diagnostic features.



The study is also producing unique population-based data on the causes of PIND. The majority of children with PIND have a known degenerative disease or a likely underlying diagnosis that is not vCJD. Our top diagnostic conditions include the Neuronal Ceroid Lipofuscinoses (e.g. Late Infantile NCL 46 cases); Mitochondrial Cytopathies (e.g. Leigh's 22, Unspecified cases 20); Mucopolysaccharidoses (e.g. San Filippo 60 cases).

Since commencement in 1997 we have received notifications from as far afield as Elgin and Truro. There is a wide variation in the number of PIND cases reported according to place of residence with the highest numbers residing in Bradford (72), Birmingham (44), East London & City (38) and Leeds (27) (fig 1). We are very pleased to still receive an average of 19 notifications per month and note that the general paediatricians are just ahead of the paediatric neurologists in our analysis of study notifications. We have provided clinical feedback to those notifying paediatricians who have requested it, as we very much appreciate the time taken in providing us with such data. The local clinicians can then make the decision as to whether or not they use this feedback.

We therefore conclude that the BPSU's "Orange Card" reporting system has been invaluable in our obtaining the necessary data for the success of our study. Apart from Canada, no other similar study has been carried out elsewhere in the world. So we would like to thank all the paediatricians who have ensured the success of our study by notifying to us – we trust you will continue for a little while longer! Active surveillance is planned until April 2008.

C Verity A-M Winstone & L Stellitano L Addenbrookes Hospital, Hills Road, Cambridge, CB2 2QQ. A Nicoll, Health Protection Agency, Colindale. R Will, National Creutzfeldt-Jakob Disease Surveillance Unit, Edinburgh.

As you will have read in the BPSU's Summer Quarterly Bulletin, surveillance of **congenital rubella**, which commenced in 1990, has been extended for a further year. Professor Adam Finn of the University of Bristol and a recent addition to the BPSU Executive Committee, provides his thoughts on the importance of longer term surveillance of rare conditions such as these. For further information please contact Mrs Lesley Stellitano, Tel: 01223 216 299, Email: lesley.stellitano@addenbrookes.nhs.uk.

Congenital Rubella Surveillance – Why Bother?

"Apart from those resident on the dark side of the moon, all will be aware that there has been a significant drop in uptake rates of both the first and second doses of MMR vaccine in children in the UK since the hypothesis, for which evidence is still totally lacking, that the vaccine might cause inflammatory bowel disease and/or autism started to receive publicity in the mid to late 1990s. The result, inevitably, has been a rise in the numbers of cases and outbreaks of measles. Large outbreaks of mumps have also been occurring especially in young adults primarily because those individuals where born before 1988 when MMR was introduced and, unlike measles and rubella, there was no mumps catch up programme in schools in the mid-1990s.

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Professor Adam Finn,
BPSU Executive

Study Extensions continued . . .

So far, thank goodness, there is no sign of an upturn in cases of congenital rubella. However, there is a very real concern that this could soon happen and there is a very real need for continued surveillance at present. Paediatricians of a certain age will need no reminder of the horrors of this entirely preventable congenital infection, younger colleagues may not have seen it. Experience with Hib disease in 2000-2 reminded us that bad diseases eliminated by immunisation could come back if we drop our guard. Congenital rubella is another example of an avoidable disaster waiting to happen."

Please continue to report any cases of **suspected or confirmed** congenital rubella in infants (live or still born) or children up to 16 years of age to the BPSU. For further information about this study please contact Dr Pat Tookey: E-mail: p.tookey@ich.ucl.ac.uk

In-house

The BPSU *20th Anniversary Special Edition Annual Report 2005-2006* has recently been published. College members will receive their copies with the Autumn College Newsletter. The report contains feedback on the current projects underway, includes a detailed section on international activities and the yearly unit analysis. To celebrate 20 years of surveillance, the 20th edition also includes a pull out section which reflects upon the BPSU's achievements since its inception. A limited number of additional copies of the 20th Anniversary Annual Report are available from the BPSU office. Alternatively the report can be viewed on the BPSU website at <http://bpsu.inopsu.com>. To increase circulation of the report we encourage you to place this link on your hospital website.

Analysis: As you can see from **Table 1** the card response rate for 2006 is now running at 90.7%. In 2005 we saw an increase of 1.6% on 2004 to 93.6%. This is an amazingly high compliance rate and given the system is now 20 years old shows that reporting fatigue has not set in. Over 1800 cases were reported in 2005, one of the highest for the BPSU in a single year. The BPSU and its associated researchers extend their thanks to all paediatricians.



TABLE 1 - % RESPONSE RATE
January – June 2006

Region	% rtd	Rank (Jan-Dec 05)
North	89.0	17
Yorks	91.4	8
Trent	92.0	6
EAngl	93.4	3
NWT	87.4	19
NET	86.3	20
SET	91.2	10
SWT	90.3	13
Wessex	91.5	7
Oxford	92.6	4
SWest	93.9	2
WMids	90.5	12
Mersey	89.2	15
NWest	90.7	11
Wales	94.3	1
NScot	90.0	14
SScot	89.1	16
WScot	91.4	9
Nlre	92.4	5
Rlre	87.8	18
Total	90.7	

TABLE 2 – ALL CASES REPORTED AND FOLLOW-UPS TO 05/09/2006

Condition	Started	VALID				NYK	Total	as % of total		
		C/R	D	E	X			C&R	D&E	X
HIV	1986	4052	534	561	462	5609	72	20	8	
CR	1990	71	28	52	6	157	45	51	4	
PIND	1997	1243	246	583	48	2120	59	39	2	
NNH	2004	75	24	21	30	150	50	30	20	
MCADD	2004	152	44	11	28	235	65	23	12	
EOED*	2005	230	88	100	85	503	46	37	17	
MRSA	2005	49	5	19	24	97	51	25	25	
Scleroderma	2005	25	2	18	24	69	36	29	35	
Malaria	2006	25	2	1	60	88	28	3	68	
Total		5922	973	1366	767	9028	65	26	8	

C/R = confirmed/already known

E = reporting error or revised diagnosis

HIV – Human Immunodeficiency Virus – In Childhood

CR – Congenital Rubella

PIND – Progressive Intellectual Neurological Degeneration

NNH – Neonatal Herpes Simplex Virus infection

*includes case reports from the child psychiatrists

D = duplicate

X = status not yet reported to BPSU by investigator

MCADD – Medium chain Acyl CoA dehydrogenase deficiency

EOED – Early onset eating disorders in children less than 13 years of age

MRSA – methicillin-resistant Staphylococcus aureus.

All data presented in this quarterly bulletin is preliminary and is continuously updated. Please note data has yet to be peer reviewed.