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UPCOMING EVENTS

ECFS NSWG Annual Meeting
Lisbon, Portugal
12 June 2013

36th European Cystic Fibrosis
Conference Lisbon, Portugal
12 - 15 June 2013
<http://www.ecfs.eu/lisbon2013>



ECFS Neonatal Screening Working Group

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Introduction

Welcome to the third newsletter of the ECFS Neonatal Screening Working Group (NSWG). In this issue, Anne Munck and Sabine Renner report on Newborn Screening (NBS) in France and Austria. These are the two most established national programmes in Europe and there is a lot to learn from their experiences. Also in this issue we describe the forthcoming international survey which presents an exciting opportunity to carefully record the current status of NBS across Europe (and beyond). The programme for the 4th Annual Working Group meeting in Lisbon on Wednesday 12th June is at the end of the newsletter.

Kevin Southern

CF Newborn Screening in Austria, 15 years of experience

The nationwide CF-newborn screening in Austria was introduced in November 1997, together with the screening program for inherited metabolic diseases. All dried blood spot samples are analysed in the screening laboratory in Vienna.

Because of Austrian genetic law, a two-step IRT/IRT protocol was used initially.

The birth rate in Austria is about 78,000 per year. The protocol was a baseline IRT (IRT-1) in the first week after birth and a recall IRT (IRT-2) if required in the 4th week after birth with a written letter from the screening laboratory.

The cut-off for IRT-1 changed during the last 15 years from the 99.8th centile to the 97th centile because in the first years of the program some children were missed with an IRT on the 98th centile. Since 2010, the cut-off for IRT-1 is 60 mg/l. The cut-off for IRT-2 is 50 mg/l. If IRT-2 is elevated the family are informed in writing to go for a sweat test at the regional CF-centre, who then inform the screening lab the result of the diagnostic testing.

Data from Nov 1997 to Dec 2012 show an incidence of CF-diagnosis of 1/3,500 with a decrease of the incidence during the last 15 years from 1/3,400 (1997-2001) to 1/3,300 (2002-2006) and finally to 1/3,900 (2007-2012), consistent with other countries screening longer than 10 years.

From 1,114,215 births, 7,591 infants had a raised IRT-1 (0.68%). 1,936 (0.17%) had an elevated IRT-2 and CF was diagnosed in 318 (0.028%). The median age of diagnosis was 6.7 weeks. Excluding children with meconium ileus we missed about one child with CF per year (diagnosed



Sabine Renner

Austrian Report Continued....

by clinical symptoms or by performing the sweat test because of siblings with CF). 80% of the missed children had a false negative IRT-1 and 20% a false negative IRT-2.

Genetic testing is performed after the diagnostic sweat test. We have identified children with a rare mutation on both genes (15%) not included in a mutation kit with the most common 30 CFTR mutations reflecting the diversity of the Austrian population.

The main problem of the Austrian screening is the recall system, about 20 children do not have an IRT-2 sample taken and in most cases it is not clear why.

For that reason, in January 2013, we started a parallel project with IRT-1/ PAP followed by IRT-2. In a pilot study for 4 months in 2012, we found the same number of CF-diagnosis with a reduced number of recalls (60% less) and 90% less open diagnosis.

In summary the IRT/ IRT CF-newborn screening program in Austria is the oldest national NBS program in Europe. It has been working well for 15 years with an incidence of 1/3,500 and a median age of diagnosis of 6.7 weeks.

An ongoing project with IRT/PAP will determine the potential of this protocol, as DNA testing is not employed, initially because of Austrian law and also because of concerns about the genetic diversity of the Austrian population.

Sabine Renner



Anne Munck

Ten years of national CF Newborn Screening in France

All newborn infants in France and La Reunion Island and, more recently, Guadeloupe (2008) and French Guyana (2012), have been screened for CF since late 2002. The AFDPE (French association in charge of all NBS programmes) was mandated by its regulatory agencies (i.e. the Funding Agency for Social Insurance, Ministry of Health) in

agreement with the CF patient association, Vaincre La Mucoviscidose (VLM), to organise systematic screening for CF. An IRT-DNA protocol was employed following assessment of regional pilot programmes in France. Implementation was associated with reconfiguration of CF services in France, with the creation of 49 CF care centres (CRCM, 12 for adults, 37, paediatric or mixed) enabling a multidisciplinary approach with standardised follow-up protocol.

France has a population of approximately 65 million, with an annual birth rate of over 800 000.

Screening strategy: Screening was based on three steps: IRT-1 (at day 3)/DNA (CF 30 Elucigene kit, covering 80% of allele detection and including mutations specific to the tested population, (i.e., Y122X, 3120+1G>A) when the IRT value was above the fixed cut-off level (aimed at 0.5% positive)/IRT safety net. To fulfil requirements of French bioethical legislation for genetic testing, informed written parental consent was mandatory. If DNA consent was not obtained or if no mutation was detected, a second IRT sample (IRT-2) was performed at 3 weeks of age. Infants with 1 or 2 identified mutations and those with a second IRT value above the cut-off were referred directly to a CRCM for sweat testing (ST) and clinical evaluation.

Programme surveillance: Data were centralised by AFDPE. Distribution of IRT values and molecular biology tests were collected from screening laboratories/regional associations and analysed every 3 months. CRCM Physicians provided data on ST,

symptoms and false-negative cases (annual questionnaire). Analysis of early data led to protocol changes to reduce the number of infants referred for ST without CF (false-positive cases). Firstly IRT-1 and IRT-2 cut-offs were increased; secondly, the safety net IRT-2 was performed for infants with no detected mutation only if IRT-1 was greater than 100 µg/L.

Results: 7,606,887 newborns were screened between 2002 and January 1, 2012 and 42,316 (0.55%) had elevated IRT values; 4,825 of them had positive DNA screening (1 or 2 mutations). A total of 15,050 infants without identified mutations or no DNA testing had a second IRT test (0.2%) and from these, 1,793 underwent ST related to persistent elevated IRT. A total of 6,512 infants were referred for ST (referral rate=15.3%) and CF diagnosed in 1,631 infants (PPV=25 %). 14% of these infants had an equivocal CF diagnosis (as defined by a high IRT level with a ST<60 mmol/L and 2 CFTR mutations with at least one not falling into the severe mutation panel) with 50% carrying the R117H mutation. Median age at initial visit was 35 days [29-45]. 54% were symptomatic, mainly showing poor growth, digestive symptoms and pulmonary symptoms. The incidence of CF through NBS, including equivocal diagnoses, was 1/4,664 [1/4,902-1/4,448]. Overall, including cases with meconium ileus or antenatal diagnosis and IRT below the cut-off, false-negative CF diagnosed based on symptoms was 1/4,312 [1/4,523-1/4,120].

Discussion: Two major points are subject to discussion. First, for infants with an equivocal CF diagnosis, it is impossible to inform parents as to whether or not their child will develop signs and symptoms of CF, and such ambiguity may have harmful effects. An on-going prospective national phenotypic evaluation (DPAM study) starting at 6 years of age, of an atypical cohort matched with classical CF, will attempt to provide answers. Among these infants, R117H represented over 50% of cases, and the possibility of modifying the mutation panel to exclude R117H is under discussion. Second, use of a multiple CFTR mutation panel increases detection of healthy carriers. Recently, the National Ethical Committee issued a negative opinion, N° 57 01/2007, since only families with one child and elevated IRT-1 (1/2,000 instead of 1/33 in the general population) have the opportunity of being detected; thus, an alternative strategy that does not identify carrier status should be considered. In 2010, a study comparing current strategy with IRT/pancreatic-associated protein (PAP) was conducted on 500,000 births. Data demonstrated non-inferiority in terms of sensitivity and a decreased rate of detected equivocal cases, but a rate of ST multiplied by 2.5 that represented a barrier to implementing this strategy. The financial estimate of the two strategies was slightly cheaper with IRT/PAP because of the absence of DNA testing and genetic counseling and an underestimate of ST cost in France. According to the Dutch experience, IRT/PAP/DNA protocol can significantly reduce the number of ST, at a cost probably close to IRT/DNA; thus, despite a residual number of detected carriers, this protocol will soon be submitted to French authorities.

Anne Munck^{1,2}, Michel Roussey^{1,3}

¹AFDPHE, Paris; ²University Hôpital Robert Debré, Paris; ³University Hôpital Mère-Enfant, Rennes, France



Michel Roussey

An International Survey of Newborn Screening for CF

The Working Group are repeating the European survey undertaken by Carlo Castellani and colleagues in 2006⁴. That widely cited survey provided us with valuable information that has informed the implementation of NBS across the globe. It is an appropriate time to repeat the survey and gain a clearer understanding of progress across Europe and beyond. The survey will enable us to better assess the performance of NBS globally and help us to determine optimal protocols and best practice. We are indebted to the volunteers who have stepped forward to be key contacts in each country. If you feel you can help the key contact from your country, email myself or Vicki and we will put you in touch. It is a difficult task to collect these data and we are pleased that countries and states outside of Europe have expressed an interest in supplying data. We hope to achieve as much coverage as possible with this survey, even countries without NBS have been asked to participate to record their current position and any plans for NBS in the future.

Thank you again to everyone who is helping with this project.

Vicki Winters and Kevin Southern

⁴Southern KW et al. A survey of newborn screening for CF in Europe. *J Cyst Fibros* 2007;6:57-65

The ECFS NSWG Annual Meeting

The ECFS NSWG annual meeting will be held in Lisbon on Wednesday 12th June, the day before the ECFS Conference. We are pleased that colleagues in Portugal will be attending and we hope this meeting helps with their plans to implement a national NBS programme for CF.

NSWG Annual Meeting Programme 2013

Morning session starts at 10.00 with teas and coffees served from 09.30.

Chaired by Kevin Southern, University of Liverpool, UK.

- 10.00 Welcome to Lisbon
Laura Vilarinho, National Institute of Health INSA, Porto, Portugal
- 10.10 Aims of the meeting
Kevin Southern, University of Liverpool, UK
- 10.15 Update on progress in Europe
Kevin Southern, University of Liverpool, UK
- 10.40 How do we manage infants with an equivocal diagnosis after NBS, an ethics based approach
John Massie (TBC), The Royal Children's Hospital, Melbourne, Australia
- 11.05 Consistency in designation (avoiding inappropriate labels)
Richard Parad, Harvard Medical School, Boston, USA
- 11.30 Lessons from the Czech Republic Newborn Screening Programme
Veronika Krulisova, University Hospital Motol, Prague, Czech Republic
- 11.55 Reducing the negative impact of NBS results to families
Fiona Ulph, University of Manchester, UK
- 12.30 Break for lunch sponsored by PerkinElmer

Afternoon session starts at 13.15.

Chaired by Anne Munk, AFDPHE and CF Centre Director, Hôpital Robert Debré, Paris, France.

- 13.15 The Challenges of Screening Premature infants for CF
Richard Parad, Harvard Medical School, Boston, USA
- 13.35 Improving the performance of NBS programmes: US QI Project
Phil Farrell, University of Wisconsin, Madison, USA
- 14.05 Update on the development of IRT PAP protocols across Europe
Olaf Sommerberg, Heidelberg University, Germany
- 14.30 Discussion including a debate on safety net (failsafe) strategy

If you would like to attend the meeting, please register with Vicki Winters v.winters@liv.ac.uk before March 22nd. There is no registration fee for the meeting, thanks to kind sponsorship from industry partners. Please be aware that membership of the WG is also free, but we do, however, strongly encourage membership of the ECFS.

Kevin Southern

Aims of the NSWG

To support the implementation of newborn screening (NBS) for CF

1. To monitor performance and compare protocols to optimise effectiveness, whilst reducing negative impact
2. To encourage enrolment of all infants identified through NBS in clinical trials
3. To determine the optimal management of infants with an equivocal diagnosis following newborn screening

If you have anything you wish to add to the next ECFS NSWG Newsletter please email v.winters@liv.ac.uk or kwsouth@liv.ac.uk.