ECFS Neonatal Screening Working Group

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UPCOMING EVENTS

ECFS Diagnostics Network Working Group Meeting,
Jerusalem, Israel
13-16 February 2013

2013 ECFS Conference
Congress Centre
Lisbon, Portugal
12-15 June 2013
http://www.ecfs.eu/lisbon2013

Introduction

Welcome to the first newsletter of the Neonatal Screening Working Group (NSWG). These newsletters will help keep everyone up-to-date with what is happening in the world of CF screening. It has been a busy and interesting five years. Much has been achieved but it is important we monitor developments and provide our patients with the best strategy for early identification of this condition.

The newsletter will include commentary on difficult issues (philosophical and practical) and reports from countries on progress of their NBS programmes. The first newsletter includes reports from Spain and Switzerland. Reports from countries not beginning with the letter S will feature in subsequent newsletters!

The NSWG aims to be inclusive with a membership from various professions. The specific aims of the group are stated below, but our objective is to work in as open a way as possible. If you have any suggestions or want to become a member then please contact Vicki Winters (v.winters@liv.ac.uk).

We are looking for a key worker from each country. Key workers will be links for meetings and provide updates on status in their country. Key NBS workers will be invited to join the Core Committee, which is responsible for co-ordination of the WG. If you would like to apply for this important role for your country, please contact Vicky or myself (kwsouth@liv.ac.uk).

Kevin Southern on behalf of the ECFS NSWG

AIMS OF THE NSWG

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

Switzerland

Dr Jurg Barben (President of the Swiss Working Group for Cystic Fibrosis (SWGCF)) reports the progress of newborn screening programme in Switzerland. The pilot study organised by Barben and his colleagues has been a good example of careful implementation of a national NBS programme and the Swiss team now are awaiting final ratification from their Government. The programme utilises a limited panel of seven mutations, targeted at the Swiss population. Because of this fairly limited panel they have opted for a second IRT measurement at 2-3 weeks in infants with an initial raised IRT and no CFTR mutation identified, in order that infants with less common CFTR mutations are not missed. At the moment, the threshold for organising a second IRT measurement is 60 ng/ml (equates to the 99.5th centile). Results of the pilot study suggest that the threshold may be raised without any significant impact on performance. This appears a sensible and successful strategy for the Swiss population, which has a diverse cultural mix.

"The pilot study organised by Barben and his colleagues has been a good example of careful implementation of a national NBS programme"

Successful implementation of CF-newborn screening in Switzerland

Newborn screening (NBS) for CF was introduced in Switzerland as a pilot study for two years on January 1st, 2011. Screening is based on a two-step IRT/DNA algorithm. Infants with raised IRT-1 are tested for the 7 most common Swiss CFTR mutations. The biggest challenge was to implement CF screening without compromising the current NBS program, as in 2007, Switzerland introduced a strict new law for genetic testing. For NBS, oral consent was considered sufficient, whereas for other genetic testing written informed consent is mandatory.

In 2011, 83,198 newborns were tested and in 647 (0.76%) the IRT was above the cut-off value. Sixty-five of them had a positive DNA screening (1 or 2 CFTR mutations). 456 infants with a raised IRT-1 but no mutation recognized, had a 2nd IRT test (recall rate = 0.55%), and of these 19 still had elevated IRT values. In total, 84 children (65+19) were referred to a CF centre for further investigations (referral rate = 13%). In 30 children, CF was confirmed (PPV = 35.7%), an additional child was clinically diagnosed having meconium ileus with a normal IRT (incidence, 1:2683).

In the pilot phase, we also compared the performance of two sweat test methods (Macroduct® collection system and chloride determination versus Nanoduct® sweat test analysing system measuring conductivity) for feasibility and the results will be presented at the next ECFC.

After 4 months, the IRT-1 cut-off was increased (from the 99th to the 99.2nd percentile) resulting in significantly less recalls (from 0.85% to 0.41%) without any child with CF being missed in the first year of screening. For children with an IRT < 60ng/ml without one of the 7 CFTR mutations recall proved unnecessary. Evaluation of the second year will show if we can further reduce the threshold for undertaking IRT -2. Overall, the implementation of newborn screening for CF was very successful, and the large majority of parents (91%) were glad that their child had been screened, independent of the final CF diagnosis.

Jürg Barben

Spain

Establishing newborn screening across Spain has been hindered by the regional nature of health care provision in that country. Following a number of meetings (some supported by the NSWG) and a lot of hard work from our Spanish colleagues, progress is being made. Dr Silvia Gartner from Barcelona updates us with the report below.

Spain has settled into its present structure with 17 autonomous communities. Each community decides independently which diseases to include in its newborn screening (NBS) programme. In 1999, Cataluña and Castilla-León, started NBS programmes for Cystic Fibrosis. A few years later the Balearic islands and Galicia began NBS. In the last 3 years, implementation has spread more rapidly and 14 autonomous communities now offer NBS for CF; the remaining communities will soon follow.

Spain has a population of approximately 47 million people with nearly 500,000 births annually. Up to 2010, these programmes had screened more than 1,500,000 infants for CF and detected over 250 affected babies. Because of the heterogeneous ethnic mix in the south compared to the north, there are many different NBS strategies across Spain. Although all protocols begin with IRT measurement, combined IRT + DNA testing + sweat test are used. Some strategies measure the IRT level on a second blood spot from newborns with raised IRT at birth. Babies with persistently elevated IRT levels are tested for *CFTR* mutations. Others protocols are based on a high IRT with analysis for a selected panel of CFTR mutations or *CFTR* gene scanning. Infants with one or two mutations are referred for sweat testing in the CF Units.

In Cataluña, the NBS programme was based on determination of IRT in blood spot collected at 3-5 days. Infants with higher than cut-off were recalled for a second measurement, IRT-2, at 20-30 days. If the level remained high they were referred to a CF Unit for sweat testing and submitted for *CFTR* mutation analysis (50 common mutations). Extended DNA analysis (sequencing) is undertaken on infants with a positive or inconclusive sweat test and one mutation. During 11 years more than one million newborns were screened with an incidence of positive cases of 1/6496, lower than expected (incidence elsewhere; Castilla-León 1/4339, Galicia 1/4430, Murcia 1/5376 and Balearic islands 1/6602).

Each strategy has different advantages in terms of CF prevalence, *CFTR* mutation distribution and financial aspects. Our current aim is to harmonize protocols in order to ensure that all babies born in Spain receive equitable access to an early diagnosis and appropriate management.

Silvia Gartner

Progress to date

The NSWG was established by Dr Carlo Castellani in 2006. The early work of the Group involved collecting data on current practice and developing a consensus on best practice. The WG was divided into 4 themes, exploring technical issues, the use of genetics, information and management pathways. Four peer-reviewed papers have been published in the Journal of CF, which summarise the results of these efforts

Outputs (peer reviewed papers with Pubmed ID numbers)

- A survey of NBS for CF in Europe, JCF (PMID number, 16870510)
- A European consensus for the evaluation and management of infants with an equivocal diagnosis following NBS for CF, JCF (18957277)
- European best practice guidelines for neonatal screening for CF, JCF (19246252)
- Guidelines on the early management of infants diagnosed with CF following NBS, JCF (20605539)

Summaries of these papers and future directions will be included in newsletters. The direction of the NSWG has changed somewhat over the past five years. The main focus is now on supporting emerging programmes throughout the world. However the NSWG is still enthusiastic to ensure best practice and this will be achieved by rigorous comparison of programme performance. There are a bewildering number of different strategies for screening newborns for CF and it is imperative that we do all we can to ensure that those employed provide the best available service for children and families.