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UPCOMING EVENTS

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

Neonatal Screening
Working Group Meeting
2013 ECFC
Congress Centre
Lisbon, Portugal
12th June 2013

<http://www.ecfs.eu/lisbon2013>



ECFS Neonatal Screening Working Group

ISSUE 2

NOVEMBER 2012

Introduction

Welcome to the second newsletter of the ECFS Neonatal Screening Working Group (NSWG). In this issue, Kevin reports from the North American CF Conference, where he was asked to represent the Working Group on the CFF Quality Improvement Consortium (QIC). He also reports back from the ISNS Conference in Budapest Hungary, where a number of presentations were related to CF newborn screening. Finally we have the answers to an interesting question posed by Bert Elvers, who co-ordinates the Dutch NBS programme.

International Society of Neonatal Screening

European Regional Meeting - Budapest 4-6th November 2012

Brief Summary of CF Presentations

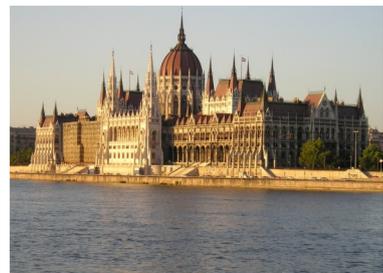
There was considerable interest in CF newborn screening (NBS) at the 8th ISNS meeting in Budapest, highlighted by the plenary lecture, given by Sabina Gallati from Switzerland, which reflected on genotype/phenotype relationships in CF and raised the interesting consideration that IRT concentration in the first week of life may be a useful predictor of subsequent phenotype.

For the session on NBS for CF, I gave an introductory talk on the challenges of establishing NBS for CF across Europe, which was followed by four talks from emerging programmes. In my

talk I highlighted the potential negative impact of NBS for CF namely,

- The recognition of infants with an equivocal or unclear diagnosis
- The acute stress associated with the assessment and sweat testing of infants who do not have CF (false positive NBS results)
- The consequences of incorporating DNA analysis into a NBS protocol (recognition of healthy carriers and non-paternity)

Peter Schielen, who co-ordinates the screening programme in the Netherlands with Bert Elvers and Gerard Loeber, presented the results of the Dutch programme, which was established following a clinical trial. The programme reduces the number of samples referred for mutation analysis through analysis of Pancreatitis Associated Protein (PAP) in samples with a raised IRT-I. Samples with one mutation identified on a 38 mutation panel are sent for more extensive gene sequencing and if that is negative, infants are considered carriers and the families



ISNS Continued....

counselled appropriately. At present, the programme incorporates a “failsafe” stage, where infants with high IRT levels but no mutations are also referred for sequencing. After one year, this strategy has resulted in 120 samples analysed, but no CF referrals have resulted from this extended gene sequencing. The “failsafe” strategy will continue for another year and, if it does not identify any infants with CF, may be abandoned after that time period. Overall the Dutch programme appears to be performing adequately and achieving the goal of reducing the number of sweat tests required, however this appears to be at the expense of some sensitivity with three false negatives presented (one with meconium ileus, not considered a true false negative in the Dutch programme).

Geraldine Roche, representing the Irish Screening Programme, presented the results of the first year of NBS for CF in Ireland. The programme employs an IRT/DNA protocol



and data from the first year suggest it is performing very well, possibly as a reflection of the screened population with a high incidence of phe508del and gly551asp. The programme does not incorporate a safety net or “failsafe” strategy for infants with a high IRT-I and no mutations, but no false negative results have been reported at this early stage through missing infants with unusual severe mutations. Geraldine highlighted some issues with sweat testing and how these were being addressed. She also described preliminary data from an ongoing project suggesting that in this population PAP may have a role in reducing the referrals for sweat

testing without impacting on sensitivity. We await the full presentation of these data by the investigator, Ingrid Borovickova and her colleagues.

The Polish NBS programme has been running for over 5 years and Agnieszka Sobczyska-Tomaszewska presented the most recent data from that programme. The Polish programme was the first in Europe to incorporate extended gene analysis for samples with a high IRT but only one mutation identified on the initial panel. This strategy has resulted in the recognition of some novel mutations and mutations not seen in Poland before. Agnieszka presented some data suggesting that the disease incidence from the NBS programme was approximately 1 in 5300, similar to previously reported Polish Registry data. We await clinical details from the Polish programme before we can assess the performance of this protocol.

Finally, Emma Lundman presented data from the newly established Norwegian programme after screening 26,000 infants. The programme uses a IRT/DNA protocol. Samples with a high IRT-I and one mutation are analysed in a third tier test that uses gene sequencing to identify certain mutations known to occur in the Norwegian population. From 16 samples, this strategy had resulted in recognition of one additional patient. The remaining infants were considered carriers with no further assessment. Emma reported that a reduction in the IRT had been undertaken during the summer from 65 to 60 mg/L to achieve a 0.5% capture of samples. Seasonal variations in IRT levels have been reported by other programmes (lower in warm weather). At this early stage, this programme appears to be performing well. Similar to the Irish programme, the Norwegians have not formally adopted a safety net (or “failsafe”) strategy, but are considering this and we will await the longer term data to assess the impact of this on performance.

ISNS continued....

These four presentations highlight the variance that occurs in CF newborn screening across the world. There are a number of interesting themes that the Working Group will continue to examine,

1. The consideration of PAP as an addition to the early sample analysis
2. The need for incorporation of a safety net strategy
3. The use of extended gene sequencing and the impact of recognition of infants with an equivocal diagnosis

Kevin Southern

Report on the US CFF Quality Improvement Consortium

Orlando Conference Centre 10th October 2012

The CFF Newborn Screening Quality Improvement Consortium (QIC) evolved from the Special Interest Group (SIG) established by Phil Farrell and colleagues in 2006. The SIG identified and enrolled a key worker from each of the United States to monitor the implementation and standards of newborn screening for CF. Most key workers in the SIG were CF physicians, some Screening Laboratory Directors. We are trying to establish a similar system in European countries.

Newborn screening for CF is now well established in all States and the initial purpose of the SIG, to establish protocols across the US, has been achieved. The CFF were impressed with the work of the Group and asked them to continue, but in a different format, the Quality Improvement Consortium. The QIC meet once a year just before the NACFC and have focused on projects to improve standards.



It is interesting that current NBS projects funded by the CFF are focused on 1) improving the performance of sweat testing laboratories and 2) improving the communication with families (the interface between the result and the family). To some degree this reflects the US Health Care system and the issues around processing a positive result, however it is a credit to the QIC that so many good projects are exploring these challenges. The abstracts from this meeting and eventual results of these projects will be published on the CFF website.

Clement Ren presented the early results from inclusion of infants with an equivocal diagnosis on the CFF Registry. In the US, the term CFTR-related metabolic syndrome (CRMS) has been adopted for these infants. It is very important that these infants are recorded on a database to monitor their progress and this remains a challenge for Europe. Clement made the point that infants were regularly mislabeled, although the common entry point for infants with CF and CRMS can over-ride incorrect determination (for example, CRMS is restricted to infants identified through NBS). Richard Parad further highlighted the importance of correct diagnostic determination and described a Health Resources and Services Administration (HRSA) project being undertaken to clarify diagnosis after NBS. Richard will be discussing this topic at the NSWG meeting in Lisbon next year. Probably the most surprising aspect of the CRMS registry is the number of CRMS infants being entered (in the order of one infant with CRMS for every ten with a classical diagnosis of CF). This is not a completely reliable estimate of incidence (as it depends on submission of data), but it does highlight the extent of this issue. The long-term follow-up of these infants is critical and the CFF should be congratulated on establishing the CRMS registry.

The QIC projects have progressed well and the CFF are planning to release further funding calls, which research teams can apply for to improve standards of NBS.

Question from Bert Elvers to the ECFS NSWG

Bert Elvers, who runs the NBS programme in The Netherlands, has asked if we would approach members and enquire at what age you would not screen for CF?

We have had the following responses to date,

Italy - "Up to and Including 60 days, however the cut-off to use after the first 2 weeks is a moot point."

Poland - "8 weeks , but we have different cut off values for babies elder than 10 days."

Serbia - "We would not screen samples from babies over 30 days of life (for IRT/IRT screening protocol). If screening uncompleted, we perform sweat test."

Slovakia - "We would not screen for CF after 35 days, because IRT in this age of newborns is not suitable for CF screening. Our algorithm is IRT/1 = 4. days of life, IRT/2 = 14. - 21. day of life (the last days for suitable second sample is 35 days of life, if we cannot get sample for any reason on 14. - 21. day of life)."

Spain - "Our NBS programme (Cataluña) does not screen for CF over 30 days. So all babies more than 30 days go to sweat test.. Most of the rest in Spain does not screen for CF after 35 days and one centre after 40 days."

Switzerland - "We usually get the heel prick samples within one week, and so far we haven't had any tests after 4 weeks."

United Kingdom - "8 weeks of age (56 days). Samples from babies over 56 days are not analysed for IRT in the UK, so they miss the CF programme."

Uruguay - "We perform IRT up 30 days of life"

In summary, these responses suggest that there is varied practice across Europe. We do not have reliable data on which to base assessment of an IRT result after 60 days and this appears to be the maximum age at which infants are incorporated into a NBS protocol, however in some countries this is much younger.

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.