ECFS Neonatal Screening Working Group

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UPCOMING EVENTS

ECFS NSWG Annual Meeting
Brussels, Belgium
10 June 2015

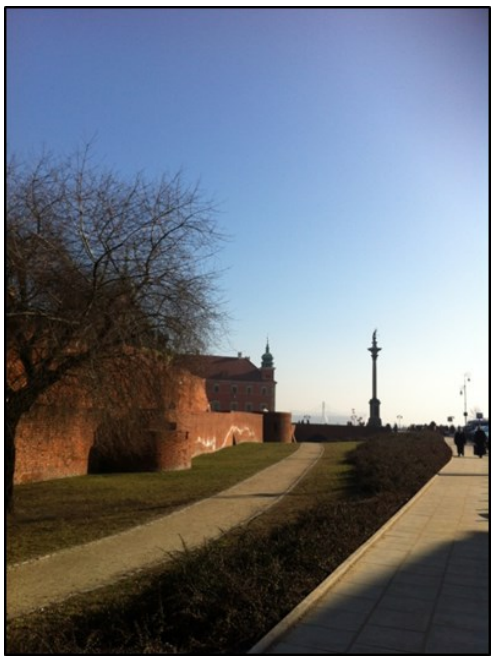
The 38th ECFS Conference
Brussels, Belgium
10-13 June 2015

Annual Meeting of the Diagnostic Network Working Group

Warsaw, Poland

As has been the case for the past few years, a section of the DNWG meeting was devoted to issues associated with newborn screening. This is a good illustration of the close partnership working between these two groups, although the groups do have clear differences in aims and objectives.

A brief summary of the main discussion points is presented below.



The Old Town in Warsaw

CF Screen Positive, Inconclusive Diagnosis (CFSPID)

The exercise to provide a designation for infants with an unclear diagnosis following NBS is now complete and is about to be published in the Journal of CF. This paper represents the outcome of an international Delphi consensus process and provides recommendations for the management of these infants, which include the use of the term CFSPID to designate these infants. There was majority support for the use of the "Screen Positive" in the term, in order to highlight that this is not a clinical presentation. The word inconclusive was felt to better represent the situation, and be more easily understood in countries where English is not the first language, in contrast to alternatives such as equivocal and unclear. There remain issues with the translation of this term, particularly in countries where the term "mucoviscidosis" is used. However we are hopeful that this term will be widely adopted, will improve the consistency of care that families in this situation receive and facilitate accurate collection of data on these infants. The CFSPID initiative demonstrates excellent partnership working between the Neonatal Screening and Diagnostic Network Working Groups.

Newborn screening in Poland

There is a long history of NBS for CF in Poland (pilot programme started in 1999). The Head of Screening Department, Dr Oltarzewski described the evolution of the NBS protocols used in Poland. Early CF protocols had limited positive predictive value (PPV), with the outcome that many families were exposed to a sweat test in order to recognise a small number of infants with CF. In an effort to improve the PPV of the programme the Polish team developed a protocol that involves more extensive gene analysis as a second tier of testing. At present, the initial gene panel includes sequencing of major exons and some intronic regions, recognising the main 16 Polish mutations but also many others (>500). When one mutation is recognised the sample is exposed to further extensive sequencing of the CFTR gene, with the resulting recognition of a second mutation or reassurance of carrier status (although these infants still have a sweat test). The Polish team have discontinued the safety net for infants with a very high IRT and no mutations as they did not find this contributed significant recognition of infants with CF in their population with this protocol. Although the PPV of the programme has improved considerably, this has been at the expense of recognition of a significant number of infants with CFSPID and the Polish team are currently considering whether they can adapt the protocol to reduce this.

Sweat testing and newborn screening

A number of presentations highlighted the challenges that newborn screening places on sweat testing services. Undertaking the measurement on infants less than four weeks of age is associated with increased difficulty in obtaining enough sweat for sweat chloride analysis. Jürg Barben showed data from Switzerland that suggest that this is not always associated with size of CF centre, with smaller units with dedicated staff sometimes achieving much better success rates than larger centres. Data presented from Switzerland and Poland support previous reports that the nanoduct technique may provide a more successful technique with respect to collecting adequate sweat volume for analysis in these challenging infants. It was agreed that this test has potential in this unique situation for the exclusion of a diagnosis of CF if a low conductivity is recorded. High or intermediate sweat conductivity results would need confirming with a definitive sweat chloride measurement, but this strategy may provide a solution to the problem of maintaining a valid sweat test service in the face of reducing requests for this test from general paediatricians after NBS is established in a country. Natalia Cirilli (natalia.cirilli@ospedaliriuniti.marche.it) is leading an initiative to better define the current situation with respect to sweat testing across Europe and develop ECFS guidelines for this test. She plans to undertake a Europe-wide survey in the next month.

Removal of R117H from the French NBS panel

Anne Munck presented an update on the situation in France. The first national NBS programme has been refined over the past 12 years to improve performance. This programme has maintained good performance but has consistently resulted in the recognition of a significant number of infants with R117H, often with a normal sweat test. In the French population, all these screen positive infants are compound heterozygotes for R117H and another mutation (CFTR kit 30) or are homozygous for R117H. They predominately have R117H on the background of a 7T poly T region, the normal splicing of which reduces the significance of this class 4 mutation, in contrast to R117H occurring with a 5T variant, which does affect splicing. The cause of the high prevalence of this specific mutation on a T7 background in the French population is unclear. The National French NBS organisation, after consultation with the Geneticist Board and CF Paediatricians across France, has decided to remove R117H from the initial DNA panel undertaken on samples from infants with a high IRT. This change in protocol was instigated in January 2015 and the French team will monitor the impact on performance.

Advances in molecular genetics

Milan Macek presented an update on advances in molecular genetics, highlighting the opportunities for newborn screening, but also the potential challenges from these developments. Professor Macek will be presenting a "state of the art" lecture at the next WG meeting on 10th June in Brussels and we will provide a full report after that.

News of the CF EVE application

In the summer of 2014, we applied to the Horizon 2020 funding stream. The application was to support a project examining the validity and effectiveness of screening for CF, and many of you contributed to this application.

The CF EVE project scored well but unfortunately was not automatically funded. The application has been placed on a reserve list and if funds become available, the EU is keen to fund it. We will let you know the outcome in Brussels.

We would like to thank CF EUROPE for campaigning on our behalf, increasing the profile of CF and NBS in the European Parliament. Of the three applications examining NBS, we were the most successful, but it is unfortunate that no NBS application has been automatically supported by this funding round at this point.

Many of us have been very busy with the CF EVE application and we apologise for the lack of newsletters over this time. Normal service will now be resumed. Don't hesitate to contact Vicki if you have any news or would like to contribute an update on your NBS programme.

The Annual Meeting of the Working Group in Brussels (10th June 2015)

You will have received a "save the date" notification from Vicki for this meeting. It promises to be a very interesting day. Phil Farrell will report on the work he has completed updating the CLSI guidance on CF NBS. Although based in the US, the CLSI document has been a valuable resource for all and Phil has taken efforts to ensure that the update, which includes topics such as PAP and CFTR2, is relevant globally. We have many other very good speakers, including Milan Macek, who will present on the advances in the field of molecular genetics and the impact of this on CF NBS and Nick Simmonds, who will reflect on CFSPID, from an adult physician's perspective!

Aims of the NSWG

1. To support the implementation of newborn screening 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

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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.