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UPCOMING EVENTS

ECFS NSWG
Annual Meeting
Gothenburg, Sweden,
June 2014 (Date TBC)

37th European
Cystic Fibrosis Conference,
Gothenburg, Sweden,
11 - 14 June 2014
www.ecfs.eu/gothenburg2014



ECFS Neonatal Screening Working Group

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Report on the Annual Meeting of the Neonatal Screening Working Group

For a fourth year, the Working Group (WG) held a satellite meeting the day before the European CF Conference. This year the conference was in Lisbon and we were pleased that colleagues from Portugal were able to join us. Laura Vilarinho and others have made good progress in moving towards a national programme in Portugal. They are helped by a centralized newborn screening (NBS) service and hopefully will be able to implement their programme within the next 12 months.



Lisbon June 2013

The meeting was an educational event and we were fortunate to have a series of excellent speakers. At the start of the meeting, I thanked those who had contributed to the WG survey and presented some early findings. We have a much clearer picture of the global situation, with reports from all the national and regional NBS programmes. We also have data on emerging programmes. Over 13,000,000 babies are screened for CF every year. What is evident from the survey is the tremendous amount of variability that exists with respect to screening methodology and ongoing data analysis will try to examine the impact of protocol design on performance, in particular with regard to sensitivity, specificity and the recognition of infants with an unclear diagnosis.

Ian Balfour-Lynn, Royal Brompton Hospital, London, presented data from the first four years of screening in London and the South East of England. This metropolis has a unique demographic and contributes to a significant proportion of the UK births each year. Since 2007, over one million babies have been screened in this area. The UK protocol obtains IRT-I at day 5-8 of life and examines infants with a raised IRT-I (>99.5 centile) for a limited panel of 4 CFTR mutations. The protocol has a safety net for infants with no mutations but a very high IRT-I (>99.9th centile). The results suggest that the incidence of CF in this region (approximately 1 in 4000) is less compared to elsewhere in the UK. This may reflect the ethnically diverse nature of the population. Ten false negative cases that resulted in a delayed diagnosis were reviewed.

Dr Balfour-Lynn concluded that the UK protocol had performed well on this population during this period.

Richard Parad, Harvard Medical School, discussed the issue of diagnostic designation following newborn screening. He highlighted differences between US practice and other programmes, notably those in Europe. The main difference relates to the designation of infants with an unclear diagnosis following NBS. In the US this situation is called CFTR-related metabolic syndrome (CRMS) and Professor Parad reinforced that this was not an uncommon outcome with CRMS infants accounting for approximately 1 in 10 registrations on the US CF registry. The term CRMS has been adopted by some other programmes outside the US, but most countries in Europe and elsewhere have opted to avoid a designation for these infants, describing them as an equivocal diagnosis following NBS. Professor Parad reviewed the rationale behind these terms and concluded that both systems have their advantages and disadvantages, that it is a situation that is confusing for families and physicians, and that this lack of consistency makes comparing international datasets a challenge. There are some strong opinions on this situation, but all agreed that international groups should try to work together for more consistent criteria for designation. In addition, Professor Parad recommended that robust algorithms should be explored as a tool for establishing a diagnostic designation, removing the variability in interpretation that currently exists.

Professor Parad was also able to provide a detailed account of the challenges of screening infants born prematurely and some of the perinatal issues associated with a diagnosis of CF. He concluded that IRT was a valid undertaking but with reduced positive predictive value in the pre-term population. He also described the issues around performing a sweat test in this population. He highlighted the use of DNA analysis in the diagnosis of CF in this age group.



NSWG Annual Meeting 2013. Left to right - Olaf Sommerburg, Richard Parad, Fiona Ulph, Kevin Southern, Veronika Krulisova, and Philip Farrell.

Veronika Krulisova, University Hospital Motol Prague, described the nationwide screening programme in the Czech Republic. This protocol, IRT-DNA-IRT, includes a safety net, where infants with no mutations but a high IRT-I have a repeat IRT measurement and a sweat test if this value is raised. In the time period assessed the programme identified 52 infants with CF. Five children with false negative NBS result were subsequently identified, giving an approximate incidence of 1 in 6500. Dr Krulisova described some unfortunate consequences of NBS, firstly the recognition of non-paternity and secondly, two families who, when given the result placed their child for adoption. The group have been investigating the use of PAP to reduce referrals for DNA analysis. These data were discussed later by Dr Sommerburg.

Fiona Ulph, University of Manchester, presented her work examining the impact of reporting NBS results and how to reduce negative impact. An important component was identified as prior knowledge and Dr Ulph highlighted the lack of understanding of young adults with respect to screened conditions and the challenges in providing this information in valid and constructive manner; one that makes the information personally relevant to the parents. Communication processes significantly affect the impact of receiving a result on parents. She highlighted the responsibility of programmes to provide clear and correct information. Programmes need to minimise the time between receiving a result and referral to appropriate specialists/support. Research is needed to establish best practice and ensure that unnecessary distress is avoided.

Philip Farrell, University of Wisconsin-Madison, described the last ten years of NBS for CF in the US, moving from four States offering screening in 2004 to total coverage by 2009. Each State organizes their own programme, leading to some variability across the country, however there are essentially three types of protocol. The majority of States use an IRT-DNA protocol. In six States a second dried blood sample is routinely collected at 2-3 weeks and DNA analysis only undertaken with persistent raised IRT. Finally eleven States (including Alaska and Hawaii) use an IRT-IRT protocol with no DNA analysis. One State (California) employs extended DNA analysis if one mutation is identified on the initial limited panel. With successful implementation of NBS across the US, the emphasis has now turned to quality improvement and Professor

Farrell described a programme of activities (supported by CFF grants) that have already had a positive impact on performance. This initiative has been facilitated by a Quality Improvement Consortium (previously Special Interest Group), with representation from each State. The consortium has set tough targets, for example aiming for a sensitivity of over 99%. Professor Farrell reported early programmes, which have focused primarily on improving sweat test services and information for families. Subsequent funding will examine clinical outcomes in CRMS patients, nutritional outcomes, improving diagnostic pathways, educational strategies and genetic counseling. Outcomes from these projects will provide useful guidance for all programmes.

Finally **Olaf Sommerburg, University Children's Hospital Heidelberg**, presented a comprehensive review of the use of Pancreatitis Associated Protein (PAP) as a biochemical biomarker for CF NBS. A number of programmes in Europe have explored PAP as a screening tool and several now employ PAP in their screening protocol. Dr Sommerburg reviewed all available data, with the conclusion that IRT-PAP is a valid protocol, even when a single cut-off for PAP is employed, but does reduce the specificity of the protocol, with the an increased number of infants referred for sweat testing compared to IRT-DNA protocols. He described third tier strategies such as extended DNA analysis or repeat IRT measurement to reduce the number of false positives. More work is required on the performance of those strategies. A clearer conclusion is that IRT-PAP protocols should employ a safety net strategy to improve sensitivity. The advantages of an IRT-PAP protocol are the lack of recognition of carriers and possibly a reduction in the number of infants with an equivocal diagnosis. For programmes that do not wish, for whatever reason, to use DNA analysis, IRT-PAP may offer an alternative protocol albeit with a significant reduction in specificity.

Overall this was a very high quality meeting and the Working Group thanks all the speakers for their contribution. Next year the ECFC is in Gothenburg and the WG will hold another satellite meeting on the day before the conference; organized with our co-host Dr Isabelle de Monestrol.

Kevin Southern

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

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.