ECFS Neonatal Screening Working Group

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UPCOMING EVENTS

ECFS Diagnostic Network Group Meeting
Berlin, Germany
13-15 February 2014

ECFS NSWG Annual Meeting
Gothenburg, Sweden
11 June 2013

The 37th ECFS Conference
Gothenburg, Sweden
11-14 June 2014

Introduction

In this newsletter, we have reports from Poland and the Russian Federation on the national CF screening programmes in those countries. We are very grateful to Dorota, Katarzyna and Mariusz from Poland and Nataliya and Victoria from Russia for these detailed reports. It is fascinating to see how each country has tackled the challenges of NBS in quite distinct ways and the impact this healthcare strategy has had on their countries. An objective of our working group is to critically evaluate protocol performance and reflect on which strategies provide best performance. We are hoping to complete analysis of data sent through to us early in the New Year and we thank all those who have taken the time to provide those data to us.

Finally, on behalf of Anne, Sarah, Jürg and all members of the Core Committee we would like to thank those who have contributed to the "Equivocal Diagnosis" project. This project is undertaking a second round of comments and responses have been interesting and varied. For the second round we had helpful input from Richard Parad, representing the US Quality Improvement Consortium for CF NBS and Nico Derichs, representing the ECFS Diagnostic Network. The Core Committee have worked hard to assimilate everyone's comments and we are hoping that consensus statements will be agreed in the New Year.

Kevin Southern

CF Newborn Screening in the Russian Federation


Nataliya Kashirskaya

The Russian Federation has a population of approximately 143, 371 million (2013) with nearly 1.9 million infants born each year. A national newborn screening (NBS) programme for CF was introduced in January 2007 following a pilot study from June 2006. CF was included in the NBS Programme alongside adrenogenital syndrome, congenital thyroid deficiency, phenylketonuria and galactosaemia, as part of a national project called "Health".

A two-step IRT/IRT protocol was employed for CF screening (see figure 1). Infants with a raised second IRT measurement (IRT-2 greater than 40 mg/L) at day 21-28 are referred for sweat testing at the local Neonatal Screening Laboratory or Regional CF Centre. Infants with a normal sweat test are monitored by their local doctor for one year. Infants with an equivocal sweat test result are offered DNA analysis for common CF causing mutations, but funding is currently an issue and families must pay for this investigation. Infants with a positive sweat test are referred to one of 57 regional CF Centres in Russia.

The cut-off for IRT-1 changed during those years from the 98.5th centile to the 98th centile (65 mg/L) because in the first year of the program some children were missed. Data from the whole country are not available, but at least one child from Moscow, with an IRT-1 of 67, was missed. Data from 2007 to 2012 show an incidence of CF in Russia as 1:10,000 (median 1: 9,854) (Figure 2) with significant difference in geographical regions, from 1:7,000 in Central, South and Far East regions to 1:17,000 in the North-West.

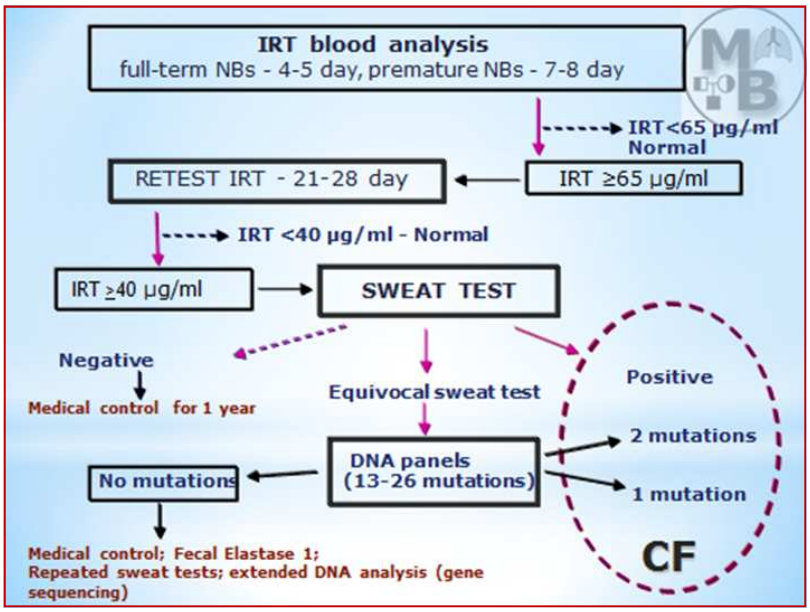

Figure 1

This incidence of CF is likely to be an underestimate as up to 20% of infants with positive IRT-2 do not come for the sweat test in some regions. In most cases it is not clear why.

The National CF NBS programme has resulted in earlier detection of infants with CF and a clearer picture of the incidence of this condition in our population. The NBS programme has driven an improvement in the provision of CF care across Russia.

The incidence of CF in Russian Federation (2007-2012)

Year	Newborns	CF	Incidence
2007	1 297 676	129	1: 10 059
2008	1 417 722	142	1: 9 983
2009	1 444 623	145	1: 9 962
2010	1 742 728	166	1: 10 498
2011	1 654 229	193	1: 8 571
2012	1 863 679	181	1: 10 296

Data from Russian Ministry of Health

Figure 2

The main problems have a lack of central funding for DNA analysis, lack of CF centres and specialists in some regions and absence of a National CF Registry.

A study undertaken in the Moscow population from 2006-11 compared the national IRT/IRT protocol to one in which DNA analysis was undertaken on infants with a high IRT-1 (IRT/DNA). The results demonstrated an improved sensitivity (to 100%) with the IRT/DNA protocol with the potential for earlier diagnosis. The DNA panel was restricted to 11 CFTR mutations (CFTRdele2,3 (21kb), F508del, Idel507, 1677delTA, 2184insA, 2143delT, 2183AA>G, 2184delA, 394delTT, 3821delT, L138ins) which represent about 70 % of CFTR mutations in this population. Hopefully these results will enable an IRT/DNA protocol to be adopted across the Federation. The Russian programme has now screened over 10 million infants for CF with the recognition of over 1000 cases. This has had a significant impact on the well-being and outlook for children with this condition in the Russian Federation.

Victoria Sherman

Reference

1. Kusova ZA, Kashirskaya NY and Kapranov NI. Cystic Fibrosis Newborn Screening protocols (IRT/IRT and IRT/DNA) in the Russian Federation. *J Cyst Fibros* 2012; vol 11 (suppl 1) : S.47.

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Newborn Screening for Cystic Fibrosis in Poland


Dorota Sands

The strategy for CF NBS has evolved over time in Poland. At first, an IRT/IRT protocol was implemented, but the number of newborns called to CF Centre for sweat testing was high for the number of positive cases identified (PPV; 0.08 (7.6%)). For the next protocol DNA analysis was undertaken on infants with a raised IRT-1 to improve the specificity. Over time the number of mutations on the DNA panel has expanded and extended gene analysis (EGA) has been undertaken on infants with only one mutation recognized on the panel. With these changes specificity has improved (PPV; 0.27 (27.3%)), although this has been associated with an increase in carrier recognition and cases with an inconclusive diagnosis.

A pilot study in four Polish regions was undertaken from 1999 to 2003, with 444,063 infants screened and 71 cases of CF diagnosed. In 2006 CF NBS started again and was gradually extended across the country. 582,693 newborns were screened from September 2006 to December 2011 in four regions and 100 children were diagnosed with CF. Newborns with positive results of CF NBS were called to the CF Centre, and sweat tests were performed. Children with mutations in both alleles of the *CFTR* gene (even if one of them has undefined pathogenicity) were referred to a CF Centre for their Care. Their height, weight, clinical manifestation and microbiological culture were assessed as well as their chest radiographs.

Currently the IRT/DNA/EGA protocol is applied across the whole country. A variable floating cut off is used to identify children with an IRT-1 value > 99.4 centile. These samples are sent for initial DNA analysis (640 mutation panel). In newborns with only one mutation recognized, first step sequencing of the full *CFTR* gene is performed.

The most frequent mutation in all patients was F508del occurring in 66% of cases. In Pilot NBS group frequency of F508del was 77%. With the current NBS protocol a higher incidence of 3849+10kcC>T has occurred (infants with this mutation have lower sweat tests values than those with other CF causing mutations). The programme appears to be sensitive (99.9%) with few false negative cases and an average time to diagnosis of 34 days.

In conclusion, the IRT/DNA/EGA strategy provides opportunity for earlier CF diagnosis even in children with normal sweat test values. However this model caused frequent carrier detection and inconclusive diagnosis in comparison to IRT/IRT or IRT/DNA with a limited number of mutations. The conductivity sweat test was useful for confirmation of CF as well as the iontophoresis method. Early diagnosis made by the introduction of NBS for CF provides an opportunity for taking preventive measures and providing treatment before the development of irreversible changes in the respiratory tract and other complications.

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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:
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