46 Inconclusive CF diagnosis in Neonatal Screening

We started the neonatal screening for CF in 2003. Our protocol implies the RT-DNA determination. All samples with an IRT level higher than the cut-off value (70 ng/mL) are checked for mutation analysis using a multiplex MALDI-TOF MS assay developed by ourselves and adapted to our specific population (including all the INNO-LIPA mutations) screening simultaneously more than 180 mutations. So far, we have analyzed 128,465 newborns and we have diagnosed 16 cases of cystic fibrosis with a neonatal prevalence of 1/8,000. Other 7 cases were labelled as uncertain cystic fibrosis (one mutation associated with CF and other one with uncertain clinical significance), 63 cases of carriers and 7 cases with polymorphisms with not conclusively clinical significance.

The F508del was found in 14 of 16 cases of cystic fibrosis (6 cases of them were F508del homozygous). The allelic frequency was 20 with F508del; 2 with R1162X, 711→G→T, L206W; and one with V232D, E558V, 2176InsC, 2184insA, R117H, R334W. All of them presented high sweat chloride levels except one baby with F508del/R117H mutations.

In 7 cases we found two mutations but only one of them associated to cystic fibrosis in literature. All of them with inconclusive sweat test results or negative. Those cases were F508del/D1152H, F508del/V562I, F508del/Y1014C, D2170N/R74W, 2184insA/G576A-R668C, G576A/G1069R and G551D/Y1014C. We conclude that those cases must be followed to clarify the future possible clinical significance.

47 CF Diagnosis Announcement Practices following a neonatal screening in France
L.J. Guégan1, G. Mingue2, C. Langeard3, C. Faucher4, P. Carr4, P. Lombrañé5, G. Rault.1, National CF Reference Center, Nantes, France; 2 Ecole des Mines, Nantes, France; 3 Laboratory of social problems and collective action analysis, Bordeaux, France; 4University, Nantes, France; 5Medical Health, Evaluation and Public Health Pole, Nantes, France

In order to improve the quality of care, it was necessary to undertake an evaluation of the implementation of the CF diagnosis announcement recommendations published by the French CF Association.

Objectives: (1) establish an inventory of the declared practices with a questionnaire in all French concerned centers to collect practices in connection with recommendations, (2) check conflicts between practices and recommendations and check facilitating or limiting factors with discussions (focus group – all the team – and individual interviews – representative of every implied profession) in some centers according to a classification of practices.

Main perspectives: develop improvement actions and other works on announcement in CF, even in other pathologies.

Results: Today, we can expose the principal results of the questionnaires analysis (response rate: 34 of 37 centers, 92%), namely: the practices meeting the recommendations; the practices less conform to the recommendations and the themes requiring more investigations. Results also show that age of centers, annual number of announcements and internal organization are factors explaining differences in practices. So, 3 groups of centers could be identified: “historic” centers (screening practicing since the 80’s); “high practice” centers (practicing screening since few years, but for more than 4 years a year), “low practice” centers. Supported by: Fondation de France; Vaincre La Mucoviscidose.

48 Comparing six countries experience of newborn screening for CF
J. Coward1, S.B. Carr3, C.S. Pan3, 1Paediatric Respiratory Medicine, Barts and the London Children’s Hospital, London, United Kingdom

Introduction: London introduced newborn screening for CF in July 2007. Many countries now screen for CF but there is variation in care and no international pathway or standards of care.

Method: 8 Paediatric CF centres, in 6 countries were visited, looking at screening services, hospital & community professionals. All stages along the pathway from obtaining bloodspots to early management from diagnosis were examined.

Results: 8 centres were visited, each with 100–330 patients. 1–32 CFTR mutations are tested for at screening. Different health professionals are responsible for giving initial screening results to families; in 2 centres it is the CF CNS & HV, in 2 centres it is the Paediatrician and in the remaining 4 centres results are given by either HV alone, GP, Genetic Counselor or Lead Maternity Carer. For all centres, families are offered CF team review within 24 hours and first contact with the CF team is with CF CNS & Consultant. Pancreatic enzymes are started at the first contact in all centres. 4/6 countries offer outpatient CF education programmes to well infants and 2/6 offer inpatient programmes. 7/8 centres offer CF CNS home visits post diagnosis. Problems identified were CF information & informed consent at the heel prick test & repeat IRT, who should deliver the screening results, early post diagnosis management (surveillance, support, professionals involved). Innovative practices found were parent education DVDs, GP guides to CF and “new” CF baby book.

Conclusion: Due to differences between centres, there is probably no one ideal pathway. Local constraints include time, resources and for many geographical distance. It is difficult to establish exactly what “best care” is around screening & diagnosing CF. Our pathway will continue to be reviewed and revised as necessary and will involve parents in future planning.

A. Iron1,2, S. Bu1, M.P. Reboul2, P. Fergelot2, D. Lacombe2, M. Fayon1, 1CRCM pédiatrique, CHU, Bordeaux, France; 2Génétique Médicale, CHU, Bordeaux, France

In the French Aquitaine region, 207 174 newborns (nb) were screened for CF from 2003 to 2008. Day-3 (d3) immuno-reactive trypsin (IRT) was elevated in 174 nb in whom the most common CFTR gene mutation analysis was performed. At this stage, CF (2 CF-causing mutations) was diagnosed in 33 nb, 85 nb were heterozygotes (het) and 58 had no mutation. Five CF nb presented with meconium ileus (3 of whom were not screened due to normal IRT). Moreover 2 nb who presented with clinical signs of CF several months or years later, albeit without elevated IRT on d3, were considered as false negative CF cases of the screening. We focused on het nb on d3 with subnormal sweat test (ST) to test mild elevation of sweat chloride as an indicator for complete screening of CFTR gene in het nb. Sweat chloride (in duplicate) was measured in 83 het. The majority (n=69, i.e 83%) had low sweat chloride (mean: 9.3±3 mmol/l) and could definitely be considered as het. But 11 het nb (13% of het) had moderately but significantly increased ST (mean: 21.3±3 mmol/l, range 15–30) and often at the same time IRT > 100 µg/l. In 9 het nb a complete CFTR gene analysis was performed, and in 8 of these cases (89%) a second gene variation was detected. This additional variation was: a CF-causing mutation (n=4), a CFTR-RC-causing mutation (n=3), an apparently neutral nucleotide change (n=1).

The complete results of CF screening in the Aquitaine region (including those resulting from complete genotyping for d3 ‘het’ with a subnormal ST and the false negative CF cases of the screening) indicate an incidence of 1/4228 (n=49) for bearers of 2 CFTR gene variations and of 1/4603 (n=45) for CF children.