26 Cystic fibrosis transmembrane conductance regulator (CFTR) gene sequence variation in Portuguese infertile males

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Objectives: Obstructive azoospermia is present in the greatest majority of male patients with Cystic Fibrosis (CF), mainly because of congenital bilateral absence of the vas deferens (CBAVD). The aim of this study was to identify the presence of CFTR gene mutations in Portuguese adult infertile males, clinically diagnosed with CBAVD, CUAVD, azoospermia and other clinical reasons of infertility.
Methods: The CFTR gene analysis was performed in 105 patients, using ARMS-Amplification Refractory Mutation System, RDB-Reverse Dot-Blot (INNO-LiPA CFTR19 and 17+Tn update), DGGE-Denaturing Gradient Gel Electrophoresis) and DNA sequencing, detecting about 93% of the mutations associated to CF in the Portuguese population.
Conclusion: In the group of patients clinically diagnosed with CBAVD/CUAVD/ Azoospermia (82/105): CFTR mutations were found in 60% (2 mutations in 33% and 1 mutation in 27%).
The most frequent CF mutation was c.1521_1523delCTT (F508del) in 32% of the patients and the poly-T variation c.1210–12T[5] (IVS8–6(5T)) was found in 40%. The most frequent genotype was c.[1521_1523delCTT];[1210–12T[5]] (F508del/IVS8–6(5T)) present in 23% of the patients.
In the remaining infertile patients (23/105) the frequency of CFTR mutations was similar to the general population. Although the clinical diagnosis is not very specific, we were able to detect a high frequency of CF carriers. It's important to analyze these men in assisted reproduction programs to prevent new cases of CF.

27 Diagnosing cystic fibrosis: Neonatal screening versus clinical diagnosis. A national registration

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Introduction: From July 1, 2007 to January 1, 2012 all newly diagnosed CF patients in the Netherlands were registered by the Dutch Pediatric Surveillance Unit (DPSU). Newborn screening for CF (NBSCF) was performed from January 2008 during a study of two new screening strategies in 4 provinces. From May 1, 2011 NBSCF was added to the Dutch routine newborn screening program.
Objectives: To assess influence of NBSCF on state of disease at the time of diagnosis.
Methods: All children diagnosed with CF and reported to the DPSU between July 2007 and January 2012 were included in the study. State of disease was assessed by questionnaires sent to the attending paediatricians.
Results: In total there were 204 reports of CF. In 179 CF was confirmed. 133 questionnaires were returned. 90 patients were diagnosed clinically, 34 by neonatal screening, 3 otherwise. In 6 the way of diagnosis was unclear. Median age at diagnosis was 31.5 weeks (IQR 8.25–106.75) for a clinical diagnosis resp. 3.6 weeks (IQR 3.0–4.0) for neonatal screening. Children diagnosed clinically had significantly more growth retardation for height and weight ($p < 0.05$), steatorrhoea ($p < 0.001$) or recurrent pulmonary problems (42.5%) at the time of diagnosis than children diagnosed by screening (0%).
Conclusion: Growth retardation is present in most children diagnosed clinically and many have chronic pulmonary problems at the time of diagnosis. Newborn screening offers the opportunity to start treatment before growth retardation or pulmonary problems have arisen.

28 Performance of a novel newborn screening strategy in the Dutch routine heel prick program

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Objectives: Since May 2011 newborn screening for CF (NBSCF) has been added to the Dutch routine screening program. Aim of study: to evaluate performance and effectivity of NBSCF in the Netherlands.
Methods: All newborns included in the Dutch routine heel prick program were screened for CF by a 4-step screening strategy, IRT/PAP/DNA/extended gene analysis (EGA). NBSCF was positive only when 2 CF mutations were identified. As fail-safe procedure EGA was performed on all samples with IRT >100 μg/l without CF-mutations.
From May 2011 to October 2012 256,008 newborns were screened for CF. PAP concentrations >cut-off point were found in 345 of 2969 samples (1.25%) with IRT >60 μg/l. Subsequent DNA-analysis found 2 CF-mutations in 47, and one mutation in 29 samples. In these 29 samples, EGA revealed a second mutation in 10, resulting in 57 babies with a positive screen for CF (1: 4491), and 14 carriers of one clinically relevant CF-mutation (1:18285). CF was confirmed in 47 newborns, 10 babies had non-classical CF with equivocal (n = 4) or normal sweat tests; this resulted in a PPV of 85% for classical CF. Nine babies had meconium-ileus (MI), of which 1 was missed by screening. The failsafe procedure identified no CF-patients. So far, 2 babies without MI were missed by screening, resulting in a sensitivity of the program of 95%. In 2011 treatment in a CF centre was started within the first month of life in 85% of the identified patients.
Conclusion: The IRT/PAP/DNA/EGA strategy applied in a large birth cohort leads to an early CF diagnosis and treatment, shows a high PPV of 85% and an acceptable sensitivity of 95%, confirming earlier findings (Thorax 2012;67,289–95).

29 A review of the management of infants with an equivocal diagnosis of cystic fibrosis (CF) following newborn screening in a UK CF regional network

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Newborn Screening programmes will identify infants with an equivocal diagnosis of CF. The absence of guidelines for management of these infants presents CF teams with the challenge of monitoring their progress without medicalisation of the child. Since 2007 we have screened 29,000 infants p.a. with an IRT-DNA-IRT protocol. Of 109 positive referrals 86 have a diagnosis of CF with 11 having an equivocal diagnosis [1] and are 14–52 months post diagnosis. We reviewed the genotype, pancreatic function, nutritional parameters, treatment, clinic attendances, microbiology, radiology, hospital admissions and compliance with the guidance from the European consensus on the management of these infants [1]. 10/11 had 2 CF genes at referral. All had normal pancreatic function and are thriving. All have had a prophylactic antibiotic and were given standard advice on smoking and flu vaccination. They have been seen routinely in a multidisciplinary CF clinic, had CF Annual Review and been reviewed yearly by the regional specialist CF team. Staph. aureus was isolated in 3/11 and pseud.aeruginosa in 4/11 and treated routinely (2/4 had IV therapy). Chest x-rays are normal. The parents have agreed to data entry on the UK CF registry. Compliance with the guidance from the European consensus has been variable. These infants account for >10% of those diagnosed following NBS in our network and their clinical management has not differed from other CF patients. Parent's perception of the value of routine follow up in this group should be sought. A national review of the management of these children could inform a UK management protocol supporting CF teams in their delivery of care.

Reference(s)

[1] PMID: 18957277.