Prevention

Screening in cystic fibrosis

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Background

A)PRENATAL SCREENING

CFTR gene cloning has made prenatal diagnosis for CF possible. Prenatal diagnosis may be offered to CF carrier couples ("at risk") with selective pregnancy termination. Direct analysis of mutations by current methods (chorionic villi sampling) plays a key role in the prevention of cystic fibrosis. The non-invasive prenatal diagnosis for CF (Guissart C et al. 2017) may offer a new promising approach to couples with offspring at risk of CF. A low-cost next-generation sequencing method to facilitate the process of cell-based non-invasive prenatal testing (NIPT) has been proposed, including CF (Zhuo X et al. 2021). Cell-based NIPT could accurately state the fetal variant status and distinguish fetal trophoblasts from maternal cells. Anedoctal reports (Jeppesen LD et al. 2021) conferm that cell-based non-invasive prenatal diagnosis could provide a less invasive alternative to chorionic villous sampling.

B)NEWBORN SCREENING

The relevance of newborn screening (NS) for CF has been pointed out in a series of editorials/reviews (Massie J et al. 2016)(Farrell PM et al. 2016)(Castellani C et al. 2016)(De Boeck K et al. 2017)(Stephenson AL et al. 2017)(Farrell PM et al. 2017)(Farrell PM. et al 2020)(Farrell PM et al. 2020) (Shteinberg M et al.2021).

NS is feasible and recommended worldwide. Best practice guidelines of European Cystic Fibrosis Society Standards of Care updated in 2018 support the relevance of NS in CF.

However , while NS for CF has clearly improved the outcome for those with a 'classical' CF phenotype, understanding CFTR gene has become more complex and prognostication for some individuals that carry mutations that may result in minimal or no disease burden more challenging (Course CW,2019). In the last years NBS programs selected also carriers and babies who do not meet all the criteria for a CF diagnosis, having inconclusive diagnostic sweat chloride (SC) and/or DNA results.These infants are classified as CF screen positive, inconclusive diagnosis (CFSPID) in Europe (Munck A, 2015) and as CF transmembrane conductance regulator-related metabolic syndrome (CRMS) in the North-American nomenclature (Ren CL, 2017). The two terms have been harmonized through international communicationsi ntroducing the definition of CRMS/CFSPID, in an attempt to improve diagnostic appropriateness in the presence of unclear results, and analysis of clinical outcomes (Terlizzi V, 2019).

NS programs for CF represent a complex strategy involving laboratory quality control in specimen collection and analysis (IRT/DNA/sweat testing), genetic counseling and communication, and follow-up. Several critical points have been focused. First, defining the immunoreacive trypsinogen (IRT) cut-off value was previously discussed to identify key IRT testing issues (Therrell BL, 2012). Second, to date no "ideal" protocol has been challenged. Different stage protocols based on a second IRT test with or without subsequent genetic analyses have been developed in USA (Caggana M et al. 2017) and in Europe (Barben J et al. 2017) to reduce the false positive diagnoses associated with one stage IRT testing. A study from France suggests that NS programmes should have a centralized monitoring process to warrant adjustments for improving the performance in terms of early diagnosis and reducing pending diagnosis (Munck A et al . 2017). A new screening protocol (Sommerburg A et al. 2017) has been implemented in Germany using IRT as first tier and pancreatitis associated protein (PAP) as second tier. Gene analysis with a panel of 31 CFTR-mutations is used as third tier to increase the positive predictive value (PPV) which is known to be low in pure biochemical IRT/PAP protocols. Main results show that this protocol has a better performance and a decreasing number of false-positives, leading to less consultations including sweat tests, reducing anxiety in parents, and finally resulting in less costs after screening.

In general, advantages and disadvantages have been registered for each NS program worldwide (Turkey, Denmark, UK, France, Italy, Catalona, Ireland, Brazil, Cuba) in terms of specificity and sensitivity, costs, false-positive results, that may adversely affect the parents relationship with their baby, or false-negative screening tests, with false reassurance that may lead to delays in clinical diagnosis and loss of an opportunity to give genetic counseling at an appropriate time. In addition, there may be a risk of "labelling" as CF those patients with mild disease who might not have presented with clinical symptoms and exposing them to unnecessary treatments or interventions.

Regard carefullness of genetic analysis included in NS programmes previous data from California (Currier RJ et al. 2017) showed that using third-tier CFTR gene sequencing may improve CF detection following an initial elevated IRT associated to detection of only one mutation on a second-tier panel, improving the utility of this approach in states that have diverse multiethnic populations.

Recently (Rispoli T et al. 2020) mini-sequencing for the simultaneous 25 CFTR gene variants were included in the NBS programe in Brazil, able to increase identification rates of two alleles from 33 to 52.43% in CF patients and consequentlly to increase detection rate to 93.01% of all mutated alleled registered in the Brazilian Registry.

Regarding the still unresolved problem whether the marked increase in the life expectancy of people with CF registered over the past 30 years could be attributed to improvements in therapy and/or to early treatment in asymptomatic children with CF diagnosed by NS further evidence on based studies should be implemented. The Baby Observational and Nutrition Study (BONUS), a multicenter, longitudinal, observational cohort study, conducted at 28 US Cystic Fibrosis Foundation-accredited Care Centers from January 2012, through May 2015, including 231 infants younger than 3.5 months who underwent NS with confirmed CF, and followed up the first 12 months of life showed a significant improvement in nutritional status, with normalization of weight, but not height in the first year of life (Leung DH, 2017). A recent review (Davies D, 2020) confirmed that at present there is insufficient evidence to draw firm conclusions

about the effect of NBS on early lung function.

A multicenter study showed differences in height, weight, and BMI between NBS children and LD children at diagnosis in a cohort of subject followed for several years. Even though these differences were not statistically significant at median level, LD children were found to have reduced weight, height, and BMI values compared to NBS children, confirming that the LD children were at a disadvantage compared to the NBS group at diagnosis. During longitudinal observation this discrepancy was not registered (Pagani S et al, 2019).

Generally, given that NS not only saves lives, but can also yield net societal economic benefit, several studies have been performed calculating the net economic benefit from NS also including the monetary equivalent of avoided deaths, reduction in costs of care for complications associated with late-diagnosed individuals minus the additional costs of screening, diagnosis, and treatment associated with prompt diagnosis. The experience of the Washington State Department of Health has been previously published including data on newborn screening for CF (Grosse SD, 2016).

C)CARRIER SCREENING

A paucity of experience-database is available to assess what proportion of pregnant women are likely to be offered carrier screening for CF and what proportion are likely to accept the test if it is offered free by their own physician. Women found to be carriers generally followed through with partner testing and, if they were found to be at risk, through with prenatal diagnosis. Women who would not consider pregnancy termination for CF generally decline screening.

Further advantages can lead to testing of parents and family members as carriers, and possible affected future siblings.

On the contrary, potential disadvantages of screening at individual and population levels can inadvertently identify newborn infants as 'carriers' that could provide unjustified anxiety about the health of the baby for the parents and ethical problems concerning the child's future reproductive choices. In several cases screening can reveal that the putative father is not the biological father.

So there is an urgent need to develop a clear guidance as how to respond.

Issues

PRENATAL SCREENING

- To define what are future technological changes to adopt for prenatal CF diagnosis.

NEWBORN SCREENING

-To advance in technology enhancing the expansion of newborn blood spot screening

-To address whether NS for CF:

1. improves survival;
2. reduces the number of respiratory exacerbations and improves overall respiratory status;
3. improves nutritional status;
4. reduces long-term complications such as CF–related diabetes and liver cirrhosis;
5. is associated with significant adverse effects in the CF group diagnosed by NS (including delay in clinical diagnosis of 'missed' cases because of false-negative tests and 'labelling' of those with mild disease, as well as early colonization by gram-negative bacteria);
6. is associated with significant adverse effects in the screened population (including psychological damage following false-positive tests, interference with developing family relationships and misconceptions and miscommunication of results, as well as the effect that an early diagnosis has on the quality of life of the child and the parents (cost–utility analysis);
7. is a more economic way of achieving a diagnosis of CF than through signs or symptoms.

❍ CARRIER SCREENING

- To identify acceptable ways of disclosing carrier status depending on the condition for which screening is offered.
- To identify acceptable ways of not disclosing carrier status depending on the condition for which screening is offered.

What is known

PRENATAL SCREENING

Despite a still high cost-effective ratio a national In vitro-Fertilization (IVF)-Preimplantation-Genetic –Diagnosis (PGD) program could be a novel preventive medicine tool in alternative to conventional current methods and would avoid most births of individuals affected with CF (Reprod Biomed Online, 2010), taking into account that reproductive decisions are complicated by the diversity of disease-causing variants in the CFTR gene and by the complexity of correlations between genotypes and associated phenotypes. Several years ago (Girardet A, 2016), on behalf of the EuroGentest Network, eighteen experts in PGD and/or molecular diagnosis of CF from seven countries published the best practice guidelines for amplification-based PGD established by ESHRE (European Society of Human Reproduction and Embryology), in order to contribute to a better harmonization of practices across Europe. Different topics were covered including variant nomenclature, inclusion criteria for accessing to test, genetic counseling, PGD strategy and reporting of results.

One CDSR (Hussein N, 2021) found no RCTs of preconception genetic risk assessment for thalassaemia, sickle cell disease, cystic fibrosis, or Tay?Sachs disease included in either the earlier or current versions of this review; the authors recommend considering potential non?RCTs studies (for example prospective cohorts or before?and?after studies) for future reviews. While RCTs are desirable to inform evidence?based practice and robust recommendations, the ethical, legal and social implications associated with using the trial design in order to evaluate the implementation of preconception genetic risk assessment involving carrier testing and reproductive autonomy must also be considered. In addition, rather than focusing on single gene?by?gene carrier testing preconception expanded genetic screening should also be included in future searches as a more pragmatic strategy. The research evidence for current international policy recommendations is limited to non?randomised studies.

NEWBORN SCREENING

Several years ago a Cochrane Database Systematic Review (CDSR) on NS was update at 2009 in order to evaluate whether NS improves clinical outcomes, quality of life and survival. Searches of this CDSR identified six trials. Two trials involving 1.124.483 screened neonates (210 with CF) with a maximum follow up of 17 years were eligible for inclusion. 552.354 (49.1%) were allocated to the screened group and 572.129 (50.9%) to the control group. A total of 210 CF participants were included in the analysis. The participants ranged from 0 to 16 years of age. Length of follow up reported ranged from one year to 16 years. Varying study designs, outcomes reported and summary measures precluded calculation of pooled estimates and only data from one study were analyzed.

Main results pointed out that:

- severe malnutrition was less common among screened participants. Compared with screened participants, the odds ratio of weight below the 10th percentile was 4.12 (95% CI 1.64; 10.38) and for height was 4.62 (95% CI 1.69; 12.61) in the control group.
- at age seven, 88% of screened participants and 75% of controls had lung function parameters within normal limits of at least 89% predicted. At diagnosis chest radiograph scores were significantly better among screened participants: 33% of screened versus 50% of control participants, but over time chest radiograph scores were worse in the screened group. Results were no longer significant after adjustment for genotype, pancreatic status, and Pseudomonas aeruginosa (PA) culture results. In screened participants colonization with PA occurred earlier (but this result was related to minimal prevention measures for segregation).

For issues 1,4,5,6 previously raised collected data of CDSR are not conclusive. In particular, results on long-term pulmonary prognosis are biased by confounding factors such as infection and pancreatic status and make difficult analysis of results.

Overall these results suggested that, even within the context of modern care at specialized centres for patients with CF, the early diagnosis by NS appears to offer global advantages. Regarding the pulmonary outcomes described in both trials, screened participants at the time of diagnosis had better chest radiograph scores and more participants in the screened group had lung function tests within the normal limits at 7 years of age, although differences in lung function parameters were not statistically significant between groups. However, differences between screened and control participants regarding the several lung function parameters in the longitudinal analyses were not specified. Over time chest radiographs were worse in the screened groups and long-term differences in lung function were statistically not significant between groups.

Data collected by an overview (Salvatore D, 2010) in order to define the role of NS on better prognosis and survival over 30,000 people with CF were evaluated from registries, including very heterogeneous clinical trials. Taking into account that comparison between screened and not screened subjects could be influenced by different plan of care for subjects diagnosed by NS in recent years, despite of adjusting the analysis for possible confounding factors, the main results of this review are as follow:

- no data are conclusive related to the impact of early diagnosis on respiratory function;
- NS is effective in promoting better nutritional status and lowering morbidity;
- early diagnosis by NS could positively impact on a lower number of adverse events as growth failure, delayed culture positive for PA, and hospitalization rate, although inclusion of mild forms of CF could overestimate these results.

Recently (Barreda CB, 2021) a retrospective analysis of the RCT cohort derived from the Wisconsin Cystic Fibrosis Neonatal Screening Project was performed to assess whether early diagnosis of CF via newborn screening may impact on long-term pulmonary and mortality outcomes. The analysis showed that NBS alone does not improve pulmonary outcomes in CF. Among the 145 subjects who consented to the original study, 104 subjects met inclusion criteria and had adequate data in the CFFPR. The rates of ppFEV$_1$ decline were 1.76%/year (95% CI 1.62 to 1.91%) and 1.43%/year (95% CI 1.26 to 1.60%), respectively ($p<0.0002$) in the screened group (n= 57) and in the control group (n=47). Pseudomonas aeruginosa acquired before 2 years was partially responsible. There was no difference in mortality rate between the two groups.

Furthermore other papers report that

- the cost of care of patients diagnosed by NS is significantly lower than the cost of treatment of patients diagnosed by symptoms requiring fewer therapeutic interventions and, overall, less intensive therapy (Sanders DB, 2012);
- the IRT/IRT screening algorithm reduces the costs to laboratories and insurance companies but has more system failures. IRT/DNA offers other advantages, including fewer delayed diagnoses and lower out-of-pocket costs to families (Wells J, 2012);
- a purely biochemical IRT/PAP protocol obtained in a large cohort of ?330,000 newborns in Germany has been obtained as an acceptable alternative to genetic CF-NS (Sommerburg O, 2015);
- in 2012 a Health Technology Assessment report reviewed clinical and cost-effectiveness of NS for CF with the aim to estimate the accuracy of eight different NS protocols and to compare costs of IRT/IRT protocol to IRT/DNA protocol. Despite the review documented a lower cost of the first protocol, decision of which NS panel to use should be made considering the benefits of an early treatment related to accuracy of early diagnosis;
- an historical cohort study (Zhang Z, 2016) assessed pubertal height growth and adult height after newborn screening. Early linear growth benefits of NS were sustained through puberty, leading to better adult height in CF.
- A systematic review (Schmidt M, 2018) revealed that all screening strategies are cost-effective compared with no-screening option; the IRT/PAP seems to be the most cost-effective screening strategy.

CARRIER SCREENING

No controlled trials about disclosing carrier status have been found.

1 CDSR was updated to 2008 for assessing whether psychological interventions for CF provide significant psychosocial and physical benefits in addition to standard care: only one paper reported gene pre-test education counseling within a screening program for relatives of individuals diagnosed with CF. The primary outcome indicator was level of knowledge retained about genetic aspects of CF.

Population-based screening programs are encouraged rather than selective screening tests for individuals already known to be at high risk. The information for carriers may be of no immediate benefit to their health or treatment.

Prenatal CF carrier screening engages for widely medical, social, and ethical perspectives (Castellani C, 2016). A cost-effectiveness of preconceptional carrier screening for CF was detected in Australia to evaluate benefit of information from pregnancy to pregnancy, including both initial and subsequent pregnancies (Norman R, 2012). Beyond reduced annual incidence of CF births, results reported a reduced incidence of CF in subsequent pregnancies at lower additional costs. Routine prenatal CF carrier screening might increase the spread of carrier screening and ultimately increase competition among laboratories, reducing the cost of testing. Furthermore, increasing efficient screening for large numbers of mutations may reduce costs.

In a paper reporting the experience of an Italian Prenatal Diagnosis Center for beta-thalassemia (BT), CF and other rare genetic disorders (Maruotti GM et al, 2013) all the couples referred to the center from January 1993 to May 2013 were analyzed retrospectively for the indication for prenatal diagnosis. 1269 prenatal diagnosis were performed for genetic disorders. The majority of the people were screened for CF carrier status after the birth of an affected child in the same family or through the cascade screening if they had a positive familial history for CF.

The preconception carrier screening test for CF is usually performed using ethnically targeted panels of selected mutations. Expanded, ethnically indifferent, pan-population panels for preconception carrier screening testing might achieve higher preconception detection rates, as revealed by a study from Israel where populations carry a wide heterogenous range of CFTR mutations beyond the ones included in the CFTR2 database (Behar DM, 2017). Canadian carrier genetic screening recommendations updated to 2016 (Wilson RD, 2016) comprise not only the costs of these programs for the national healthcare system, but also the social, financial, psychological, emotional costs for the families.

In general, NS for CF can improve the experience of diagnosis for parents.

Unresolved questions

PRENATAL SCREENING

Setting up a national prenatal screening program for CF is timely and should be implemented.

NEWBORN SCREENING

Many questions remain to be solved:

- to update the cut-off of screening test (IRT) for different laboratories in different geographic regions in order to take account also of seasonal fluctuation of IRT;
- to define the most suitable diagnostic molecular analysis kit for achieving the highest detection rate in a NS program in each geographical region (Bauca JM, 2015), considering the relevance of multiethnic populations shared with Caucasian populations;
- to highlight factors that could account for a missed diagnosis of CF (Baker MW, 2011);
- to careful assess methodological quality of trials in clinically defined groups;
- to provide proper methods for quality improvement of communication and psychosocial outcomes after NS in families of infants with carrier status, as previously described (Farrell MH, 2011) or in families of infants with inconclusive diagnosis (Ooi CY, 2015);
- to update NS guidelines in terms of sensitivity, specificity, costs and outcomes.

CARRIER SCREENING

There is a need to develop and evaluate the effects of interventions to support the disclosure of carrier status to parents and relatives following newborn screening, focusing on genetic counseling and epidemiology, as well as on decreasing in the incidence of CF (Castellani C, 2009). There is some more difficulty for disclosure of carrier status for mild mutations (Castellani C, 2016). No studies are available concerning the benefits on medical, social and ethical perspectives. Setting computer programs that can successfully educate individuals considering genetic testing for CF have to be implemented (Castellani C, 2011).

Further studies are needed to define the best carrier screening method, to evaluate the net cost of screening, the effect on quality of life in terms of anxiety associated with testing, the potential benefits related to information of risk for any subsequent pregnancy, and for alerted relatives (Castellani C, 2016).

NBS for CF should be considered as a relevant tool in order to increase survival in CF. The integration of NBS within well-established CF care structures, supporting interaction of obstetricians, primary caregivers, pediatricians, CF centers, and health authorities is mandatory in the future (Naehrlich L, 2021)

Keywords

Carrier Status; Genetic Predisposition to Disease; Heterozygote; Screening;