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ORIGINAL PAPER

Prenatal screening and counseling for genetic disorders

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Abstract

Introduction: The carriers of the same autosomal recessive disorder are usually unaware of onset of the genetic diseases in the children even if screenings are available for many of these disorders. In this paper, we report the experience of the Prenatal Diagnosis Center of AOU Federico II and we discuss the role of the screening for beta-thalassemia (BT), cystic fibrosis (CF) and for other rare genetic disorders.
Materials and Methods: We analyzed retrospectively the indication for Prenatal Diagnosis (PD) of all the couples referred to our center from January 1993 to May 2013. We divided our sample into three groups: couples at high risk for BT, for CF and for other rare genetic disorders.
Results: From January 1993 to May 2013, we performed 1269 PD for genetic disorders. There are still couples who discovered to be carriers of BT by screening after the birth of the affected child ($n = 51$ (11,3%)); the majority of the people were screened for CF carrier after the birth of an affected child ($n = 155$ (80,7%)) or through the cascade screening ($n = 28$ (14,6%)). Large-scale screenings for rare genetic conditions are not available and people were screened only if they have a positive familial history.
Conclusion: Parental screening is available for many severe and rare diseases whose genetic origin is known. The proportion of patients referred for very high-risk indications increased over time with an higher demand for rare disease. An adequate counseling is fundamental to identify women at risk for having affected child. Screening, counseling and PD of genetic diseases is a complex matter and needs for a continuous update.

Keywords

Beta-thalassemia, cystic fibrosis, genetic counseling, prenatal screening, rare genetic diseases

History

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Introduction

Public demand for prenatal screening, counseling and prenatal diagnosis (PD) of genetic diseases has increased during the past decade worldwide. PD is an area where technology is a advancing rapidly offering an increasing array of tests to women getting information about the health of the fetus. Many of this genetic disorder are life-threatening or chronically debilitating diseases. The carriers of the same autosomal recessive disorder are usually unaware of onset of the genetic diseases in the children even if screenings are available for many of these disorders. The aim of the screening is to enable carrier couples to be informed of the risk of having an affected child, making possible consideration of all reproductive options. Preconceptional consultation in primary care is fundamental to identify couple at risk for genetic disorders, to propose the available preconceptional screenings and to start pregnancy conscious of all the possible risks [1]. The most widespread carrier screenings are those for beta-thalassemia (BT) and cystic fibrosis (CF), that are the two most frequent genetic disorders in our area. However, large-scale screenings for rare genetic conditions are not available and people were screened only if they have a positive familial history. In this paper, we report the experience of the Prenatal Diagnosis Center of AOU Federico II and we discuss the role of the screening for BT and CF and for other rare genetic disorders, highlighting important ethical and socio-economical issues related to genetic counseling and parental screening.

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Materials and methods

We analyzed retrospectively the indication for PD of all the couples referred to our center from January 1993 to May 2013. We divided our sample into three groups: couples at high risk for BT, for CF and for other rare genetic disorders. The Rare Diseases Act of 2002 defines rare disease any disease generally considered to have a prevalence of fewer than 200 000 affected individuals in the United States [2]. Differences among groups were evaluated using Chi-square test for categorical variables and ANOVA test for continuous variables. The indications for parental screening were retrospectively collected. Data were analyzed by SPSS 18.0.

Results

From January 1993 to May 2013, we performed 1269 PD for genetic disorders. Among these, 190 (14.9%) were amniocentesis and 1079 (85.1%) were chorionic villus samples (CVS). 528 (41.6%) couples were referred to our centre for PD of BT, 192 (15.1%) underwent a PD for CF and 549 (43.3%) for other rare genetic disorders. Clinical and

Table 1. Clinical and anamnestic characteristics of women at risk for having a children affected by BT, FC and other rare genetic disorders.

Variable	FC $N = 192$ (15.1%)	BT $N = 528$ (41.6%)	Rare genetic disorders $N = 549$ (43.3%)
Age*			
Years (mean ± SD)	31.4 ± 0.4	29.2 ± 0.2	30.8 ± 0.2
Amniocentesis*			
N (%)	17 (8.9%)	45 (8.5%)	148 (26.1%)
Gestational age			
Weeks (mean ± SD)	18.6 ± 3.9	17.7 ± 2.2	17.3 ± 2.1
CVS*			
N (%)	175 (91.1%)	483 (91.5%)	421 (73.9%)
Gestational age			
Weeks (mean ± SD)	11.5 ± 1.2	11.5 ± 1.4	11.8 ± 1.3
>1 PD in our center*			
N (%)	72 (37.5%)	292 (58.3%)	232 (40.8%)
Twin pregnancies			
N (%)	2 (1.0%)	8 (1.5%)	3 (0.5%)
Number of pregnancies*			
Median	3	2	2

*$p < 0.001$ (ANOVA Test).

Table 2. Number of PD for rare genetic disorders stratified by prevalence (number of cases).

>1:50 000 $N = 372$ (67.8%)	1:50 000–1:100 000 $N = 99$ (18.0%)	<1:100 000 $N = 78$ (14.2%)
Acondroplasia (11)	Argininosuccinic Aciduria (5)	APECED Syndrome (1)
Alpha-thalassemia (6)	Carbonic Anhydrase II deficiency (2)	Bruton's disease (2)
Angelman Syndrome (6)	Choroideremia (2)	Canavan Disease (5)
Autosomal dominant deafness 3A (5)	Friedreich's Ataxia (1)	Carbamoyl phosphate synthetase deficiency (3)
Centronuclear myopathy (3)	Galactosemia (3)	Pyruvate CarboxilaseDeficiency (1)
Congenital 21-OH deficiency (12)	Glycogen Storage Disease Type Ib, II and III (13)	Ethylmalonic encephalopathy (2)
Congenital Disorders of Glycosilation 1a (1)	Holt-Oram Syndrome (2)	Fanconi Anemia (6)
Facioscapulohumeral muscolar dystrophy 1° (1)	Krabbe Leukodystrophy (8)	Glycogen Storage Disease Type IV (2)
Familial Adenomatous Polyposis I (1)	Lynphoisticytosis (1)	Gangliosidosis Type 1 and 2 (7)
Fragile X Syndrome (40)	MEN 1 e 2 (3)	HHH Syndrome (1)
Glycine encephalopathy (3)	Methylmalonic Aciduria (14)	Lesch-Nyhan syndrome (4)
Haemophilia A and B (63)	Mucopolysaccharidosis Type I, IIIA and IIIB (17)	Lysinuric Protein Intolerance (1)
Huntington's Disease (11)	Papillon-Leage-Psaume Syndrome (1)	Maple syrup urine disease type II (1)
Myotonic Dystrophy Type 1 (16)	Propionic Acidemia (2)	Metatropic Dysplasia (1)
Muscular Dystrophy (99)	SCID (5)	Molybdenum cofactor deficiency (1)
Neuromuscular ceroid lipofuscinosis (1)	Shwachman Diamond Syndrome (1)	Mucopolysacharidosis Type II (19)
Ornithine Transcarbamylase Deficiency (4)	Smith-Lemli-Opitz (11)	Niemann-Pick Disease (11)
Propionic Acidemia (2)	Spinocerebellar Ataxia 1 and 2 (5)	Nonketonic hyperglycinemia (6)
Phenylketonuria (10)	Zellweger Syndrome (3)	Progeria (1)
Pyruvate Kinase Deficiency (1)		Schimke immuno-osseous dysplasia (1)
Rett Syndrome (3)		Wiskott Aldrich Syndrome (2)
Spinal Muscolar Atrophy (57)		
Spinocerebellar Ataxia 3 (4)		
Tuberous Sclerosis (9)		
Von Hippel-Lindau Disease (1)		
X-Linked hydrocephalus (2)		

anamnestic characteristics of each group were reported in Table 1. The group of rare genetic disorders includes more than 70 different diseases; the frequencies of genetic disorders stratified by prevalence are reported in Table 2. 69 (12.6%) out of 549 PD were performed for autosomal dominant diseases, 237 (43.2%) for autosomal recessive diseases and 243 (43.2%) for recessive X-linked disease. Indications for parental screening were reported in Table 3. For 77 (14.6%) out of 528 couples carriers of BT, data were missed, while we did not have missing data among FC carriers couples and for the group of rare genetic disorders.

Discussion

In this paper, we describe our experience on the role of parental screening for different genetic disorders in a population of pregnant women booked for PD. For a better understanding of the role of the prenatal screening in each situation we decide to divide our sample into three groups: couples at high risk for BT, for CF and for rare genetic disorders. BT and CF are the most common genetic disorders in our area and a parental screening is well accepted; the low incidence of the rare genetic disorder does not give space to a large scale screening. The increased demand for genetic counseling and prenatal diagnosis genetic and rare diseases observed in these last years was registered also in our Center [3].

As shown in Table 3, there are still couples who discovered to be carriers of BT by screening after the birth of the affected child; the percentage of these couples is really low because our region is an endemic area where the cost-effectiveness of prenatal screening is widely approved. The screening tests

Table 3. Indications for Parental screening.

Indications	CF $N = 182$	BT $N = 451$	Rare genetic disorders $N = 549$
Affected child(ren) N (%)	155 (80.7%)	51 (11.3%)	190 (34.6%)
Cascade screening N (%)	28 (14.6%)	41 (9.1%)	251 (45.7%)
Prenatal screening N (%)	–	153 (33.4%)	–
Preconceptional screening N (%)	5 (2.6%)	206 (45.7%)	–
Fetal bowel ultrasound abnormalities N (%)	4 (2.2%)	–	–
One parent affected N (%)	–	–	108 (19.8%)

are based on accurate measurements of hematological parameters, iron deficiency evaluation and separation of Hb fraction [4]. Even if screening should be offered to all women of childbearing age, the percentage of screening occurred during pregnancy is still high.

Contrary to BT, the majority of the people were screened for CF carrier after the birth of an affected child or through the cascade screening, while the percentage of couples who performed a preconceptional screening is really low. Fetal bowel ultrasound abnormalities are reported among the indications for the screening because bowel hyper echogenicity and loop dilation are associated with a risk of CF of about 3% [5]. Cascade screening is a mechanism for identifying people at risk for a genetic condition by a process of systematic family tracing. For this reason, in our series couples at risk for CF required a PD later than ones at risk for BT (Table 1). Even if a consensus conference at NIH recommended, since 1997, that CF carrier screening should be offered to all pregnant couples and those contemplating pregnancy [6], there are many difficult correlated to the introduction of a large-scale screening. First of all, there is an inability to identify carriers by clinical or biochemical means and the only possibility is the genetic test, with high costs for the couple. Moreover, the big heterogeneity of CTFR mutations interferes with the implementation of screening. Since the discovery of the first CFTR mutation (F805del) in 1989, more than 1900 different changes have been found in this gene, while the American College of Medical Genetic proposed a 25 mutation panel for the screening [7]. This panel is very sensitive for Ashkenazi Jewish descendents (97%) and less sensitive for Southern Europe (70%). Therefore, in addition to the screening for frequent mutations, according to the European recommendations, a complementary panel may be required to test population-specific mutations with a frequency above 1%; for this reason, up to 2001, we include five mutations peculiar to Southern Italy [8]. However, because screening is offered only for the more frequent mutations, a negative screening does not exclude the chance of being a CF carrier. Many studies demonstrated that often people misunderstand CF carrier screening results and they underestimate the residual risk [9]. Moreover, many CFTR mutations are of unknown clinical significance making really difficult the genetic counseling. The different survival rate of people affected by CF through the years must be discussed with the couple. Only thirty years ago, a CF patient was not expected to reach adulthood, while, nowadays, many people even live into their fifties and sixties.

In the group of rare genetic disease, the genetic study of the high risk couples was always performed after the birth of an affected child or for a positive familiar history; it is impossible to offer a parental screening for all known possible genetic disorders to the pregnant population. More than 70 different genetic diseases are included (Table 2) in PD of our Center and 78 (14.2%) procedures were performed for diseases with an prevalence less than 1 in 100 000. The demand for screening for extremely rare diseases is increasing, giving points for reflection on other important ethical issues; variable expressivity, genotype-phenotype variability, adult or early onset disease are issues that often makes really difficult the genetic counseling and the performance of the PD. For these reasons, it is really important to offer the screening and the PD after a complete counseling, to explain all the performance of PD and all the possible options of the procedure. Couples should be aware that often the results of PD are not able to predict the age of onset, the clinical course or the degree of disability. Moreover, relevant in the counseling is the explanation of the type of disease, of clinical signs, onset of disease, outcome and possible therapy. The consultant and the obstetric must outline to the high risk couples the options of the single specific genetic disorders. For example, there are no more indications for PD of the autosomic recessive disease Phenylketonuria because we know that diet influence phenotypic expression. Dietary protein restriction and supplementation with phenylalanine-free medical foods are good solutions for a normal neurological development. There is a mandatory neonatal screening that give us the possibility to perform a diagnosis within 48–72 h from the birth.

Other criticism arise from some autosomal dominant disease. The Familial Adenomatous Polyposis (FAP), an autosomal dominant disease is characterised by predisposition to late onset colon polyposis and colorectal cancer, caused by germline mutations in the APC gene. The FAP prophylaxis is possible and consists of resection of the entire large bowel, to prevent malignant transformation, but these surgical procedures shorten the life expectancy and reduce the quality of life. We may think if is ethically correct to perform this diagnosis in a family with history of disease in one of the parents.

In many cases of autosomal dominant disease, when the mother is affected, PD has a central role for a correct management of pregnancy. For example, for women with a diagnosis of MEN 2A, it has recently been shown that PD and a correct management could improve survival and outcome drastically reducing maternal and fetal mortality. RET mutations are associated with three risk levels of developing medullary thyroid carcinoma and pheochromocytoma. Therefore, genetic counseling and PD are mandatory to assuring parents on the life-long risk of tumors, avoiding psychological distress that can further complicate pregnancy in affected women [10].

Another important issue in genetic counseling is the possible residual risk after molecular testing. For example, in couple at risk for Spinal Muscolar Atrophy, reported in our series in 57 cases (10.4%), the sensitivity of the molecular test is 93–95%; therefore, carrier test does not always identify the disease because parents may be carriers of rare subtle mutations and, moreover, the occurrence of extremely rare de novo mutations is possible [11]. Therefore, the physician must highlight the possible residual risk.

Important ethical issues are related to adult onset of the diseases, like Huntington's Disease (HD). It is a dominantly inherited human neurodegenerative disorder characterized by motor deficits, cognitive impairment, and psychiatric symptoms leading to inexorable decline and death, starts generally in every age [12]. It has an incidence of 1 in 25 000 people. In all the couples undergoing the PD, there was one parent affected, screened because of a positive familiar history. This test is available since 1993, when the gene involved in HD was discovered. It gives the possibility to confirm the diagnosis in case of people with symptoms that suggest HD or to inform a person that could develop the disease during his life. This test cannot give information about the severity of the syndrome or the age of development of the disease. The obstetricians and the geneticists must outline during the counseling the variability of phenotype and the interaction between age of onset, symptomatology and penetrance. In Huntington's disease, as in other adult onset disorders, the physician must take into account when counseling the possibility that the parents will declare a wish to continue with the pregnancy despite a positive prenatal test result; this presents other ethical questions [13]. In fact, on one hand it could prevail the parents' right to know the genetic status of their future yet unborn child for a late onset genetic disorder, on another hand it could prevail the right of the future child not to know a genetic diagnosis, or to decide for oneself when to have a diagnosis. This is very important, particularly in case where there is no cure for a condition.

In conclusion, parental screening is available for many severe and rare diseases whose genetic origin is known; the our PD Unit in collaboration with CEINGE is part of an International Network for the diagnosis of all the diseases whose genetic diagnosis is possible. The proportion of patients referred for very high-risk indications increased over time with an higher demand for rare disease. We observed an increment of the numbers of the prenatal invasive procedures and an increment of variation of the type of disease for which the PD is possible. It is impossible to screen women at childbearing age for all the possible genetic disorders; for this reason an adequate anamnesis and counseling is fundamental to identify women at risk for having affected child. A multidisciplinar team of prenatal diagnosis with a gynecologist, a genetic medical, a molecular biology medical and psychologist is necessary for the relevance of the disease. The members of the team must pay more attention in the counseling to the moral character of choices about prenatal diagnosis. Genetic counseling must promote appropriate and medical interventions when available and facilitate personal decision making when interventions are supportive. In any case screening, counseling and PD of genetic diseases is a complex matter and needs of a continuous updates.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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