Attitude of Parents to Carrier Screening for Genetically Transmitted Diseases in India

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ABSTRACT

Carrier screening plays a pivotal role in controlling transmission of genetic abnormalities through generations. Irreparable genetic aberrations are preventable by understanding the nature of alterations and nurturing prenatal/pre-implantation diagnosis. Retrospective carrier screening of blood-linked relatives not only prevents transmission to future generations but also helps in understanding the impact on future health. However, lack of cooperation of the parents/family members poses barriers for carrier screening, and thus, abnormalities occur in recurrent pregnancies. Parental attitude toward carrier screening has been discussed in this paper based on a case having unbalanced karyotypic abnormality with a chimera extra chromosome (47,XX, +mar). This female baby was born with choanal atresia (CA), anteposed anus, and atrial septal defect to nonconsanguineous parents as second child. Owing to common problem of difficulty in breathing in father and the elder son, it could have been speculated that the father was the carrier of some genetic condition, which contributed to clinical expression; however, the parents were reluctant to undergo screening. Since there was aneuploidy with a rearranged chromosome, the possibility of normal karyotype in the parents cannot be expected, and thus, karyotyping was essential for the other child too. That was also refused. Refusal of screening by the family will necessarily put future generations of the family at risk of inheriting CA.

Keywords: Carrier screening,Choanal atresia, Chromosome aberration, Genetic testing, Prevention of genetic defects.

How to cite this article: Ganguly BB, Daruwalla D, Kadam NN. Attitude of Parents to Carrier Screening for Genetically Transmitted Diseases in India. MGM J Med Sci 2017;4(4):187-190.

Source of support: MGMIHS

Conflict of interest: None

INTRODUCTION

The balanced rearrangements resulting in alterations in sequence/structure of genes/chromosomes may not pose serious phenotypic or clinical expression. However, likelihood of four types of genetic combinations in gametes of carriers might lead to severe to fatal outcome in the offspring.1-3 When a child is born with congenital deformities or grows with delayed milestones and/or mental retardation, and is diagnosis to have chromosomal anomaly, parental genetic testing is considered essential to exclude or confirm their carrier status.2,3 A carrier is otherwise a healthy individual not affected with clinical expression; however, he/she may transmit one copy of recessive mutation or a complete balanced chromosomal translocation. When both partners are identified carriers of a similar recessive mutation, they have 1 in 4 (25%) risk in each pregnancy of having a child with disease manifestation. In case of X-linked disorders, half of the male offspring of a carrier mother will be affected clinically, whereas girls will be asymptomatic carriers. Therefore, the primary objective of carrier screening is to create alertness in the family for preventing possible health risks in offspring of present and future generations as a result of clinical expression of prevailing genetic mutation, and, thus, should be compulsory for families having an affected member.4 However, carrier screening is optional for people who do not have any prior knowledge/history about risk of recessive or suspected genetic disorders.

We report a child born with CA who was found to have unbalanced chromosomal rearrangement and whose parents were not willing for carrier screening.

CASE HISTORY

Parental attitude toward carrier screening is the focus of analysis in the present report, based on the history of a female child born to nonconsanguineous parents with a 7-year-old sibling. Antenatally, oligohydramnios was the only history of this conception. The 2.8 kg baby was born uneventfully and cried immediately after birth but developed respiratory distress and needed O2 shortly afterward. Nasogastric tube could not be passed through both the nostrils leading to a presumptive diagnosis of bilateral CA (Box 1). With help of ear, nose, and throat surgeon, the nasogastric tube could be placed through left nostril with difficulty. Distress then gradually decreased. The baby was given phototherapy for neonatal hyperbilirubinemia on 3rd day. Two other...
Genetics of CA

Choanal atresia (OMIM # 608911) is a congenital defect with 2:1 female: male ratio, exhibited by obstruction in the posterior nasal aperture with bilateral or unilateral presentation wherein bilateral CA requires medical emergency at birth. It is occasionally associated with coloboma/heart defects/mental retardation and growth impairment. Infants with bilateral CA are at an increased risk of having cerebral abnormalities, developmental delay, laryngeal tracheomalacia, and subglottic stenosis, and also with life-long nasal complications, nasal stuffiness, sleep apnea, and rhinorrhea, which may require repeat correction surgeries. Phenotypically, affected infants with either unilateral or bilateral CA can have depressed nasal bridge or mid-face retraction, craniosynostosis, and more similarities with CHARGE (coloboma, heart defects, atresia choanae, retarded growth and development, genital anomalies, ear anomalies) syndrome, which is linked to an autosomal dominant mutation in the chromodomain helicase DNA binding protein 7 (CHD7) gene at chromosome 8q12.1.1-7

A candidate gene for CA has been described in the coding region of CHD7 of 9003 bp, corresponding to a translated amino acid sequence of 3000 aa. The present case with ASD and CA may display mutations in the CDH7 gene, and the unbalanced marker chromosome could be a recombinant product of chromosome 8 (which was described with a microdeletion in CHARGE syndrome) and an acrocentric chromosome. Choanal atresia is thought to be a multifactorial disorder and about 8% of cases are hereditary, although some studies have suggested single gene models that include both autosomal dominant and recessive patterns of transmission. More commonly, CA is found to occur sporadically and to recur infrequently in siblings and in subsequent generations.

Abnormalities were noted, viz., anteposed anal opening and a systolic murmur. Subsequently, two-dimensional echocardiography detected arterial septal defect (ASD). The baby did well after opening up of left-sided atresia, though noisy breathing persisted.

In view of the three physical deformities, karyotyping was considered as the first line of genetic diagnosis for exclusion of chromosomal association with the clinical condition. Routine conventional cytogenetic analysis was carried out on day 6 after birth, following standard phytohemagglutinin-stimulated culture of the peripheral blood in serum-supplemented Roswell Park Memorial Institute 1640 medium (GIBCO, USA) for 72 hours at 37°C.2 G-banding karyotyping using IKAROS imaging software (MetaSystems, Germany) detected an abnormal karyotype with 47,XX,+mar in all 25 metaphases examined (Figs 1A and B). The marker was confirmed as an acrocentric chromosome from its participation in acrocentric association with “D/G” group chromosomes (Fig. 1A); however, it was not a complete “D/G” group member but a recombinant one. It was a rearranged chimeric chromosome wherein an acrocentric chromosome was a partner, which can be called as an unbalanced translocation. This rearrangement indicates partial trisomy of two different chromosomes and appeared as the marker in the present case.

DISCUSSION

Genetic screening and testing are poised to play a great role in reducing incidence of genetic defects. Unfortunately, as the present case shows, there is severe lack of awareness in the general public. They do not cooperate fully for carrier screening even if offered free. Grinzaïd et al17 reported that despite efforts by medical and Jewish communities, many people of those communities in the reproductive age group remain unaware of the benefits of genetic screening, thus carrying the risk of bearing children with genetically transmitted diseases. Morgan et al18 and Qureshi et al19 also reported lack of awareness in the public about genetic screening during their surveys of screening programs for genetic diseases. In cases of known genetic diseases, prenatal or pre-implantation genetic diagnosis will cause definite reduction of the prevalence of these diseases, as demonstrated by studies of Cousens et al20 and Dondrop et al21 who reported 90% reduction in the incidence of birth of children with Tay–Sachs disease in the Askenazi

Box 1: Genetics of CA

- Father had nasal deformity since birth for which he had undergone surgical correction. The 7-year-old sibling also used to suffer from chronic cold and cough due to nasal blockade. Therefore, one common clinical symptom was identified in both children with a possibility of paternal transmission. The father was explained about the nature of the abnormality present in the newborn baby, in view of which necessity of carrying out his and his wife’s stepwise karyotyping was explained to him. He was also told that if one of the parents was detected to have the chromosomal aberration, his elder child will also require karyotyping. He was not willing. His greater concern was about the mental development of their newborn child because the elder sibling is “very intelligent." The family declined for further counseling and testing of themselves and their second child stating that “we have already so much of tension and we do not want to increase it further.”

It was apparent that meiotic nondisjunction in one of the parents must have occurred resulting in aneuploidy with an extra chromosome in the proband. Chance of parents carrying normal karyotype was least possible in the present case. In case it turned out to be normal, it would have been due to a de novo mutation during gametogenesis in one parent. So normal karyotype would have been found in both parents and also the elder sibling. Neither maternal nor complete family history of either side of both the parents could be collected due to lack of cooperation. Their refusal was not due to financial constraints because financial grant was provided by the institution.

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Jewish community as well as in the incidence of hemoglobinopathies.

In addition to financial implications and lack of awareness, which dissuade prospective parents in India to undergo carrier screening for genetic diseases, another important factor is fear of stigmatization and psychological trauma, if they test positive for genetic mutations. These perceived fears have to be alleviated by good prescreening and postscreening counseling. In India, 90% of medical colleges do not have medical genetics and genetic counseling in their curricula.22

American College of Obstetrics and Gynecology23 and American College of Medical Genetics24 have described in detail as to how genetic counseling must be carried out. The individuals undergoing genetic testing must be explained about the purpose, importance, and appropriateness of the tests. They must be told about what information is expected from the tests, their sensitivities and specificities, possible consequences of mutations, and possible risk of psychosocial trauma and stigmatization. A proper “informed consent” should be taken after thoroughly educating the subjects about purposes and
limitations of the tests and the potential consequences of positive tests which will help them to make informed decisions.  

To conclude, the present case illustrates that to reduce the incidence of genetically transmissible diseases, we must spread awareness in common public about importance of carrier screening, so that their attitude toward screening becomes positive. Also medical genetics and genetic counseling must be made a part of curriculum in all medical colleges. Authorities at national level must frame policies to achieve these goals.

ACKNOWLEDGMENT

Authors wish to acknowledge the support provided by Mahatma Gandhi Mission Trust for this article.

REFERENCES