More than one genetic affliction within the same family: Two case reports

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Genetic disorders, though rare, are still responsible for 2-3% of babies having congenital or genetically-determined abnormalities at birth. Rarer still is the possibility of more than one genetic disorder afflicting the same family. In spite of that, such families do exist and it is important that clinicians focus not only on the prevention of known genetic disorders in a family but also on screening for other common genetic disorders and prevention of these disorders in all families.

Case 1

A twenty-six year old female patient was referred by a gynecologist for pre-conceptional genetic counseling because her previous child had Down syndrome. Karyotype of the proband, which had been done previously, had shown Robertsonian translocation 46,XX,t(13;21). The couple was advised to get their blood karyotypes done. Along with that, as advised to all women who visit our medical genetics out patient department for preconception counseling or in the early antenatal period, we advised beta thalassemia carrier screening for the couple. The wife was found to be carrier of a balanced translocation, her karyotype being 45,XX,t(13;21) and the husband's karyotype was normal (46, XY). In addition, the couple found to be carriers for mutations in the *HBB* (beta globin) gene, the wife being carrier of the IVS 1-5(G→C) mutation for beta thalassemia and the husband being carrier of the HbE mutation. They were thus counseled about the risk of recurrence of Down syndrome and the risk of occurrence of beta thalassemia in their offspring and the possibility of prenatal diagnosis was also explained to them. The couple was also counseled regarding the importance of getting their extended family members screened for both the balanced translocation and thalassemia mutations running in their respective families. In line with the fair degree of understanding that the couple had acquired, three years later, the consultand's sister came to us with the concern of knowing the possibility of Down syndrome or thalassemia in her unborn child. She was not found to be a carrier of thalassemia mutation but was found to be carrying the balanced translocation (Fig 1). Amniocentesis and fetal karyotype was done for her at 16 weeks of pregnancy after due counseling. Karyotype of the fetus was 45,t (13;21) i.e. the fetus was carrying a similar balanced translocation as the mother. The family opted to continue the pregnancy.

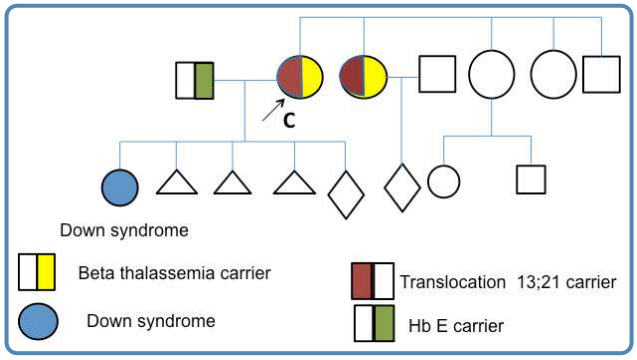

Figure 1 Pedigree of family 1.

Later, the parents of the proband came back to us at 10 weeks of pregnancy, for prenatal diagnostic testing. Chorionic villus sampling was done followed by karyotype of fetus and mutational analysis for beta thalassemia. The fetal karyotype showed 44 autosomes and 2 sex chromosomes. DNA mutational analysis for beta thalassemia revealed that the fetus was a carrier of the maternal beta thalassemia mutation. As the fetus was not affected

with either Down syndrome or beta thalassemia, the family opted to continue the pregnancy. Despite the rare situation of two genetic disorders being present within these two related families, both the couples were able to have healthy children after appropriate counseling and testing.

Case 2

A 28 year old woman presented to us at 6 weeks of gestation with history of a previous child being affected with transfusion-dependent thalassemia. She had been referred for prenatal diagnosis for the same in context of the present pregnancy. While talking to her 33-year old husband who had accompanied her to the OPD, it became apparent that he had subnormal intelligence. On further evaluation it was found that he had developmental delay and behavioral problems noticed since 3 years of age. He had never been to school, could not read, write or do simple calculations though he could take care of himself and helped in all the household work. The family history revealed presence of intellectual disability in the brother and maternal uncle and mild intellectual disability with behavioral problems in the mother and maternal aunt (Fig 2). In light of this family history suggestive of X linked inheritance, Fragile X syndrome was suspected. Southern Blot Analysis for Fragile X revealed increased triplet repeats in the FMR1 gene confirming our provisional diagnosis. Meanwhile, DNA mutation analysis of the *HBB* (beta globin) gene in the couple suggested that the husband was carrier for mutation of HbE and the wife was carrier for the IVS1-5(G-C) mutation of beta thalassemia. Both the mutations were confirmed in their previous affected child. So, there were 2 genetic disorders in this family, both of whose molecular bases were confirmed and hence prenatal diagnosis could be provided. Regarding intellectual disability, the family was counseled that the risk of fragile X in male offspring of the couple is negligible and all female offspring will be carriers of the mutation for fragile X. Carriers have variable severity of cognitive dysfunction that cannot be differentiated/ predicted by any DNA test. In this family there were two carrier females with some degree of manifestations. Targeted mutation analysis in chorionic villus sample collected at 11 completed weeks of pregnancy showed that the fetus was carrying both the thalassemia and HbE mutations like their previous child. The family opted for termination of the pregnancy.

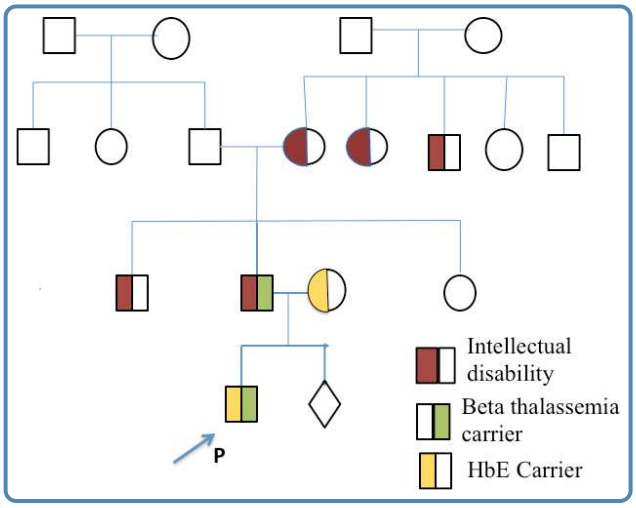

Figure 2 Pedigree of family 2.

Discussion

The first case emphasizes that the presence of a single disease should not divert attention from routine screening for other common genetic disorders. Beta thalassemia screening is advisable for each and every couple that is planning for childbirth because of the high carrier frequency of the disease in India.[1] High performance liquid chromatography of hemoglobin is an easy screening method for thalassemia which is widely available and the results of which are easily interpretable. Also noticeable and to be highlighted in this case is the importance of extended family screening for the already known genetic traits or diseases in the family. The second case again beautifully illustrates the fact that although genetic disorders are rare in occurrence, presence of more than one genetic disorder in the same family though less probable, is possible. With detailed and careful history, proper clinical evaluation and appropriate testing such families can be recognized and provided with the right course of medical action. It reiterates the fact that a family could have more than one genetic affliction and therefore we, as clinicians, should be vigilant enough to offer genetic counseling and appropriate investigations to the families at risk of a child with a serious genetic disorder or a disorder with handicap. These cases also stress the importance of pre-pregnancy genetic counseling, pedigree drawing and use of molecular and cytogenetic

investigations for genetic counseling and prenatal diagnosis.[2,3] This will only be possible with awareness about genetic investigations and counseling amongst primary care physicians, pediatricians and obstetricians.

References

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2. Phadke S R, et al. *Natl Med J India* 2002; 15: 363.
3. Ranganath P and Phadke SR. *Perinatology* 2013; 14: 1-6.