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PRENATAL EXCLUSION OF AUTOSOMAL RECESSIVE LAMELLAR ICHTHYOSIS BY MUTATION ANALYSIS OF TRANSGLUTAMINASE 1 GENE

Gynecology

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ABSTRACT

Background: Congenital lamellar ichthyosis (LI) is a rare autosomal recessive genetic skin disorder characterized by generalized hyperkeratosis and scaling. Two other forms of autosomal recessive congenital ichthyosis are harlequin ichthyosis (most severe and often fatal form) and nonbullous ichthyosiform erythroderma. Transglutaminase1 (TGM1) mutation has been found to be associated with LI in affected individuals. Prenatal diagnosis of LI is possible due to availability of molecular genetic testing with an advantage of having earlier diagnosis before 20 weeks.

Case Report: A 27-year-old G3P2L1D1 with third degree consanguinity was referred at 12.6 weeks' gestation for prenatal diagnosis and genetic counselling. She had first female child manifesting clinical features of congenital lamellar ichthyosis. Couple seeked preconceptional counselling and they were referred to geneticist along with affected child. Affected child was evaluated by molecular genetic testing and detected to have homozygous mutation for Transglutaminase 1 gene. Couple was also tested for the same genetic mutation and they were found to be heterozygous carriers for TGM1 gene related LI. Therefore, preconceptional genetic counselling and evaluation of affected child and couple provided us molecular diagnosis. In present pregnancy, chorionic villous sampling was done for prenatal diagnosis in fetus and sample was sent for TGM1 mutation analysis. Sanger sequencing was done and fetus was found to be heterozygous for TGM1 mutation. Pregnancy was continued till term and healthy female child was born by caesarean section with no skin lesions. Postnatal course was uneventful and baby was discharged on day 5 of birth.

Conclusion: This case report concludes that prenatal molecular genetic diagnosis is possible quite earlier in gestation, if index case has been evaluated completely.

KEYWORDS

Congenital ichthyosis, autosomal recessive lamellar ichthyosis, prenatal diagnosis, genodermatoses, transglutaminase 1 gene mutation, harlequin ichthyosis

INTRODUCTION

Autosomal recessive congenital ichthyosis (ARCI) is defined as rare nonsyndromic skin disorders caused by genetic defects in keratinization. ARCI comprise three major subtypes, lamellar ichthyosis (LI), congenital ichthyosiform erythroderma (CIE), and harlequin ichthyosis (most severe form)[1]. LI and CIE have combined prevalence of approximately 1 in 2,00,000 to 3,00,000 population.

LI is characterized clinically by presence of large, thick, dark plate-like scales covering whole body surface area without serious background erythroderma. Massive hyperkeratosis is noted on histopathological examination.

TGM1 gene mutations are the most common cause of ARCI[2]. Till date, six genes have been identified in association with ARCI, namely, *TGM1, ALOXE3, ALOX12B, NIPAL4, CYP4F22, and ABCA12*. ARCI is genetically highly heterogenous.

Prenatal diagnosis of lamellar ichthyosis can be made by mutation analysis of pathogenic gene variants[3]. Only few cases of prenatal diagnosis by mutation analysis of LI have been reported in literature so far.

This case report highlights the genetic evaluation of proband and approach to prenatal exclusion of lamellar ichthyosis in fetus by mutation analysis.

CASE REPORT

We report here a case of a 27 years old married for 7yrs G3P2L1D1 with third degree consanguinity who was referred to us at 12.6 weeks' gestation for prenatal diagnosis in view of previous first female child affected with lamellar ichthyosis (LI) (figure 1). There was no significant family history or history of similar affection in other family members on pedigree analysis.

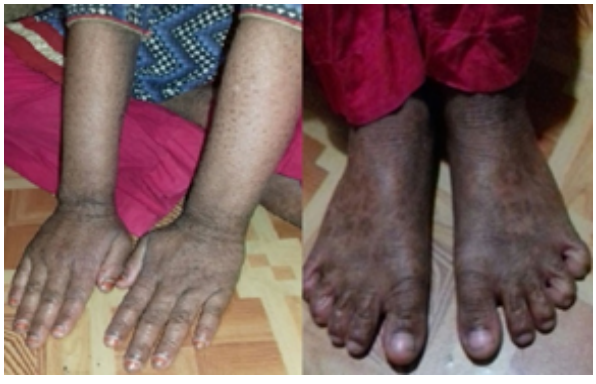

Figure 1-Affected female child with characteristic skin lesions

During her first pregnancy, she underwent elective cesarean section at term gestation in view of breech presentation and delivered a female child with scaly dried skin at birth. Clinical diagnosis of congenital LI was made. Molecular diagnostic testing for mutation analysis was not done. Couple was referred to us for pre-conceptional counseling prior to her second pregnancy. Geneticist's opinion was taken for the couple. Affected child was evaluated and found to have homozygous missense mutation in intron 6 of the Transglutaminase 1 gene (chr14:24728908 A>C; c.984+2T>G) by Sanger sequencing. Couple was tested for the same mutation and both were confirmed to be carriers for the same. Prenatal testing was done in her second pregnancy by chorionic villous sampling (CVS) at 11 weeks' gestation for TGM1 mutation and sample was negative for the known mutation. She delivered a healthy male child at term by repeat caesarean. Unfortunately, this baby died on day 42 of birth due to aspiration.

Present pregnancy was her third pregnancy and she registered at 12.6 weeks'. Her all antenatal investigations including first trimester nuchal translucency scan was normal. CVS was performed at 13 weeks'

gestation and sample sent for *TGM1* mutation analysis and karyotyping. Sanger sequencing was done and fetus was found to be heterozygous for the mutation (figure 2) suggesting that the fetus is a carrier for the disorder and is unlikely to be affected. Fetal karyotype and subsequent malformation scan was normal.

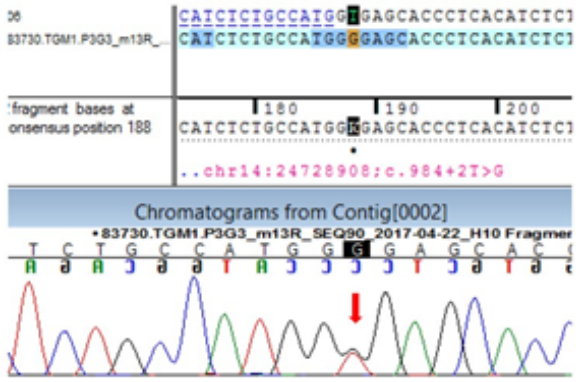

Figure 2-Sequence chromatogram and alignment to the reference sequence showing the variation [chr14:24728908A>C;c.984+2T>G (5' splice site)] detected in heterozygous condition in fetus

Therefore, pregnancy was continued till term. Antenatal course was uneventful. Elective LSCS was done at 38 weeks' in view of previous 2 LSCS and she delivered a female child weighing 2.7kg with APGAR score 9/10. Baby had no clinical features of LI at birth. Postnatal course was uneventful. Baby was discharged on day 5 of birth.

DISCUSSION

Lamellar ichthyosis is an autosomal recessive skin disorder caused by abnormal keratinization. Mutations in the transglutaminase 1 gene (*TGM1*) have been identified in several families affected with LI whereas pathogenic variants in *ABCA12* gene have been found in almost all cases of harlequin ichthyosis. *TGM1* gene is located on chromosome 14q11.2 and it encodes TGase (transglutaminase) 1 enzyme which is found in epidermis. This enzyme is involved in the process of formation of the cornified envelope. Mutation in *TGM1* gene causes reduced or absent TGase1 activity resulting into absence of cornified envelope[4,5]. A total of 56 *ABCA12* mutations have been reported (Akiyama, 2010) in 66 ARCI families including 48 HI, 10 LI, and 8 CIE families of African, European, Pakistani/Indian, and Japanese origin[6].

Genetic evaluation of index case/ affected families and mutation identification allows rapid and accurate prenatal diagnosis. Until the identification of pathogenic gene variants involved in congenital ichthyosis, prenatal diagnosis was based on examination of fetal skin biopsy samples. Histologic findings are mostly nonspecific in cases of ARCI. Therefore, fetal skin biopsy has limited role in prenatal diagnosis. It may be considered in cases where index case has not been evaluated and molecular diagnosis of proband is not available. However, this procedure is usually performed late in second trimester up to 23 weeks with inherent technical difficulties and 1-3% procedure related fetal loss rate. Therefore, final prenatal diagnosis is often late and results are available beyond the legal gestational age for medical termination in certain countries like India.

With the advances in molecular diagnostic testing and identification of mutant genes, it is now possible to perform DNA based prenatal diagnosis for ARCI by chorionic villous sampling or amniocentesis and to obtain final diagnosis earlier in gestation.

Yanagi et al reported a case of DNA based prenatal exclusion of harlequin ichthyosis where they performed amniocentesis at 16 weeks' gestation and fetal genomic DNA was extracted and analysed for *ABCA12* mutations[7].

Pigg et al described antenatal exclusion of LI in two Norwegian families by chromosome 14q11 haplotype association and direct mutation analysis. They concluded that haplotyping can be a useful tool for prenatal diagnosis in diseases with genetic heterogeneity[8].

Antenatal ultrasound may detect severe phenotypes like harlequin ichthyosis at late gestation with poor sensitivity. Few cases of harlequin ichthyosis diagnosed antenatally with two- and three-dimensional ultrasound in third trimester, with typical facial features of ectropion and eclabium, have been reported in literature[9]. But, ultrasound does not have any role in diagnosis of less severe skin conditions like lamellar ichthyosis.

Recently, in a case series by Suresh et al, short fetal foot length has been described as an important and probably first marker seen in second trimester ultrasound for diagnosis of harlequin ichthyosis[10]. However, these clinical features of HI usually manifest in late second or third trimester, limiting the role of ultrasound in making early and accurate prenatal diagnosis.

There are only few case reports from our country which suggest the presence of LI in the community and they are mainly diagnosed and reported in paediatric population. To our knowledge, only one such case of prenatal diagnosis has been reported by Sheth et al where they found two novel mutations in TGM1 gene resulting in LI in parents and affected child which was absent in fetus[11].

In the present case report, index case has been evaluated for this rare genetic condition correctly to offer prenatal diagnosis to the couple.

CONCLUSION

This case report emphasizes the need for proper evaluation of index case in such rare genetic skin disorders to provide prenatal diagnosis in future pregnancies for couples with previous affected child. By giving option of termination of an affected pregnancy, one can reduce perinatal morbidity, mortality and economic burden on the family due to severe forms of genodermatosis. Ultrasound is not helpful in detection of skin disorders prenatally unless it is a severe form like in case of Harlequin Ichthyosis. There is no noninvasive or imaging modality which can rule out genetic skin disorders. Molecular genetics has led to revolution in the prenatal diagnosis of genodermatosis. Prenatal diagnosis at an earlier gestation is possible if index case is worked up properly and molecular genetic diagnosis is available.

DECLARATIONS

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