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Prenatal Diagnosis of Lamellar Ichthyosis

Dr. Pritti K. Priya, DGO, MD(Path), Eur Dip(Mol. Cytogenetics), Assistant Professor, Incharge Genetic Lab, Dept. Of Obstetrics and Gynecology

Dr. Vineet V Mishra, MD, Phd, Professor and Head of Department, Obstetrics and Gynecology, IKDRC-ITS

Dr. Ashish Jagati, MD, Skin, Assistant Professor, Dept. of Dermatology, V.S. Hospital

Correspondence Author: Dr. Vineet V Mishra, MD, Professor and Head, Department of Obstetrics and Gynecology, Institute of Kidney Diseases and Research Center, Dr. HL Trivedi Institute of Transplantation Sciences (IKDRC-ITS), Civil hospital campus, Asarwa , Ahmedabad, India.

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Abstract

Lamellar ichthyosis type 1 (LI1) is a rare autosomal recessive skin disorder for which a gene has been localized on chromosome 14q11. We report the identification of a missense mutations in theTGM1 gene in a child affected with LI1 and prenatal diagnosis in subsequent pregnancy by mutation study of the fetus by chorionic villus sampling which revealed the similar mutation in homozygous state. Lamellar ichthyosis is an autosomal recessive genetic disorder, which means the defective gene is located on an autosome, and both parents must carry one copy of the defective gene in order to have a child born with the disorder. Carriers of a recessive gene usually do not show any signs or symptoms of the disorder but the risk to have affected child is there.

Keywords: Lamellar ichthyosis, Prenatal diagnosis, TGM-1.

Introduction

Lamellar ichthyosis (LI) is an autosomal recessive disorder that is apparent at birth and is present throughout life. LI has an equal incidence in male and female individuals and is estimated to occur in approximately 1 per 100,000 to 300,000 live births [1,2]. The newborn is born encased in a collodion membrane that sheds within 10-14 days. Later on it manifests as dry scales, resulting in a rough-dry skin texture. Although the disorder is not life threatening, it is quite disfiguring and causes considerable psychological stress to affected patients [3]. This form of lamellar ichthyosis is caused by a homozygous missense mutation in TGM1gene [4,5].

As LI is an autosomal recessive condition, genetic counselling is important and parents who are carriers should be informed regarding the risk of transmission in subsequent pregnancy and role of prenatal diagnosis, which is possible by doing mutation study.

Case Report

A 26 year old female who was 12 weeks pregnant was referred to us for prenatal diagnosis of skin disorder with which her first child was affected. It was a non-consanguineous marriage. He is a 7 year old male child. The child had typical large, dark, plate-like scales covering his skin on whole body ***[Figure 1]***. He was having nail dystrophy along with alopecia. Associated eye related features like ectropion, eclabium and bilateral conjunctivitis were quite evident ***[Figure 2]***. He had

history of frequent respiratory infections. On clinical findings it was suspected to be lamellar ichthyosis. The younger sister who was 5 years old was absolutely normal. For prenatal diagnosis it was important to know the mutation in the index case so firstly, mutation study was conducted for the affected child. Hence, genomic DNA was isolated from the blood sample of the affected child and direct mutation analysis was done on the Next Generation Sequencer platform (NGS). A homozygous missense mutation was found on TGM1 gene – it was further confirmed on Sanger sequencer ***[Figure 3]***.

In the meanwhile chorionic villus sampling (CVS) was carried out at 13 weeks and chorionic villi sample was tested for the mutation. Mother's blood was also tested to rule out maternal cell contamination. The results showed similar mutation in homozygous condition. The results were conveyed to parents and they opted for termination of pregnancy. For their third pregnancy, the parents requested PND for LI.

Discussion

Autosomal recessive congenital ichthyoses (ARCI) comprise a clinically and genetically heterogeneous group of disorders of keratinization characterized by skin desquamation over the whole body, often associated with erythema [6]. There are 5 different types of inherited Ichthyosis disorders that include the following:

- Ichthyosis Vulgaris
- Lamellar Ichthyosis, Type 1 to Type 5
- Epidermolytic Hyperkeratosis (or Bullous Ichthyosis)
- Congenital Ichthyosiform Erythroderma
- X-Linked Recessive Ichthyosis

Lamellar Ichthyosis (LI) is a rare, inherited skin disorder that manifests as dry scales, resulting in a rough-dry skin texture. It is of 5 different types – Type 1, Type 2, Type 3, Type 4, and Type 5. The diagnosis for LI usually involves complete medical history assessment, physical examination, and genetic testing. Infants with this condition are typically born with a tight, clear sheath covering their skin called a collodion membrane. Males and females are equally affected.

The newborn presents encased in a tough, film-like membrane that fissures when stretched. This collodion membrane is shed by 10-14 days, revealing generalized erythema and scaling. The disease is characterized by generalized scales, which range from fine and white to thick, dark, and plate-like. The scales are arranged in a mosaic pattern resembling fish skin.

Clinically, the collodion babies may encounter dehydration, electrolyte imbalance, temperature malfunction and increasing sepsis risk because of relatively severe skin damage. Therefore, morbidity and mortality rates are fairly high in these cases. Type 1 of Lamellar Ichthyosis cannot be clinically distinguished from type 2 of Lamellar Ichthyosis, because they have similar signs and symptoms. So mutation study is required to distinguish the two as TGM1 gene is involved in LI1 and ABCA12 in LI2.

In our case genetic testing confirmed that it was type 1 Lamellar Ichthyosis as mutation was present in TGM1 gene. Once the mutation is confirmed in the index case prenatal diagnosis becomes feasible. On prenatal diagnosis the fetus was found to have similar mutation in homozygous state. Parents decided for termination of pregnancy. On examination, the fetus looked almost normal except for the colour of the skin which was red. Prenatal diagnosis by ultrasound has been reported in cases of Harlequin Ichthyosis but not for lamellar ichthyosis [7].

The first gene associated to the disease has been the *TGM1* at chromosome 14q11.2 [8,9]. The TGM1 gene encodes transglutaminase 1 (TG1). TG1 is an enzyme important in the formation of the cornified cell envelope, responsible for barrier function in stratified squamous

epithelia, by the cross-linking of a variety of structural proteins.

Until 2005, the causative gene had not been identified, PNDs had previously been performed by using electron microscopic examination of fetal skin biopsy specimens. However, PND for harlequin ichthyosis (HI) and LI by fetal skin biopsy has suffered from several difficulties. First, PND needs to be performed during the later stages of pregnancy. Second, fetal skin biopsy is technically difficult. Finally it requires excellent skin biopsy site selection, is time-consuming and, is not without risks to the fetus. Preimplantation genetic diagnosis (PGD) may be available for families in which the disease-causing mutations have been identified. Both disease-causing alleles of an affected family member must be identified before prenatal testing can be performed. Since ARCI is genetically heterogeneous, a prenatal test not showing mutations in *TGM1* does not guarantee a neonate will be unaffected by ARCI.

Conclusion

Lamellar ichthyosis is an autosomal recessive genetic disorder, and both parents must carry one copy of the defective gene for the child to have the disorder. Carriers of a recessive gene do not show any signs or symptoms LI, but the risk to have affected child is present. Thus, prenatal diagnosis or PGD may be performed for families in whom the disease-causing mutations have been identified for better management of the subsequent pregnancy and appropriate counselling.

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List of Figure

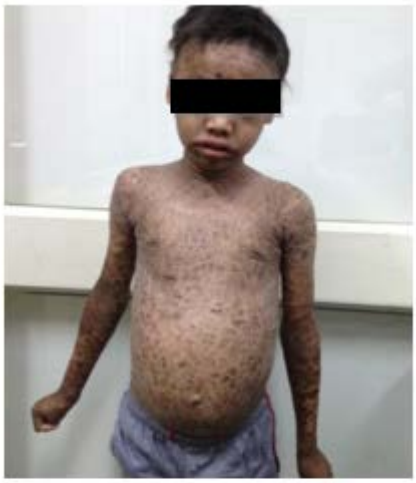

Figure 1: Clinical features of proband: Severe hyperkeratosis with fissures covering the face and chest

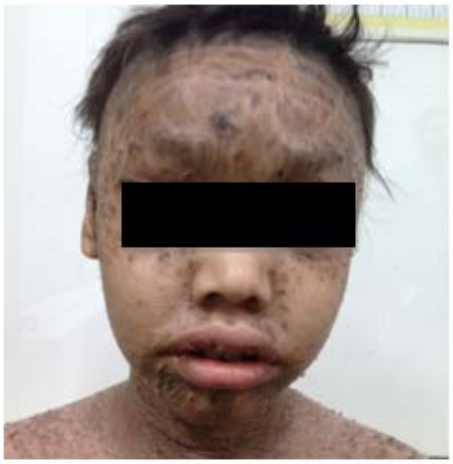

Figure 2: Clinical features of proband: Severe hyperkeratosis with fissures covering face with evident ectropion, eclabium

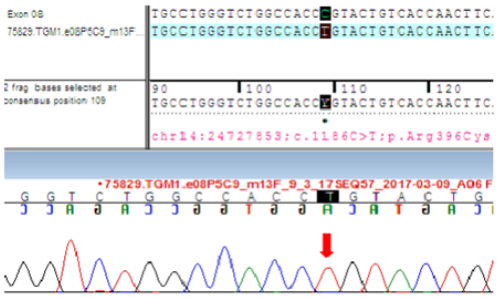

Figure 3: Sequence chromatogram and alignment to the reference sequence showing the variation (chr14:24727853G>A; c.1186C>T; p.Arg396Cys) detected in homozygous condition in fetus.