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CASE REPORT

Ichthyosis prematurity syndrome caused by a novel missense mutation in FATP4 gene-a case report from India

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Key Clinical Message

Ichthyosis prematurity syndrome (IPS) is reported mainly from Scandinavia where most of the cases are homozygous or compound heterozygous for the nonsense mutation c.504C>A (p.Cys168*) in exon3 indicating a common ancestor for this mutation. The occurrence of IPS in an Indian patient suggests that it is more widespread than previously reported.

Keywords

FATP4, Indian patient, novel sequence variant, SLC27A4.

Introduction

Ichthyosis prematurity syndrome (IPS; OMIM608649) is a rare autosomal recessive disorder of cornification caused by mutations in fatty acid transport protein four gene (FATP4) [1, 2]. Key features of IPS are premature delivery, thick caseous desquamating epidermis and respiratory symptoms at the time of birth, which recover into a lifelong ichthyosis with severe itching [3]. IPS is mainly described in the Scandinavian population; however a few reports in entirely distinct populations have been published [4, 5]. Here, we describe a first Indian IPS patient with a novel homozygous missense mutation c.530T>C(p.Leu177Pro) in the FATP4 gene.

The patient, a male, was born at 31 weeks of gestation by Cesarean section with a birth weight of 1815 g. The pregnancy was complicated by polyhydramnios, chorioamnionitis and premature rupture of fetal membranes. The parents were consanguineous and a sibling born 18 months earlier was a preterm female who reportedly died of respiratory distress in the early neonatal period. No other family members were affected.

Immediately after birth, the patient had respiratory depression requiring resuscitation, and subsequently ventilator support and supplemental oxygen. The X-ray showed features of aspiration pneumonia. The skin was erythrodermic with thick vernix caseosa-like scales accentuated over the scalp, back, arms, gluteal region, and thighs (Fig. 1A–C). After a few weeks, the scales subsided and were replaced by a generalized mild ichthyosis with pruritus (Fig. 1D and E). At the ages of 5 and 6 months, the patient was hospitalized for management of obstructive airways disease.

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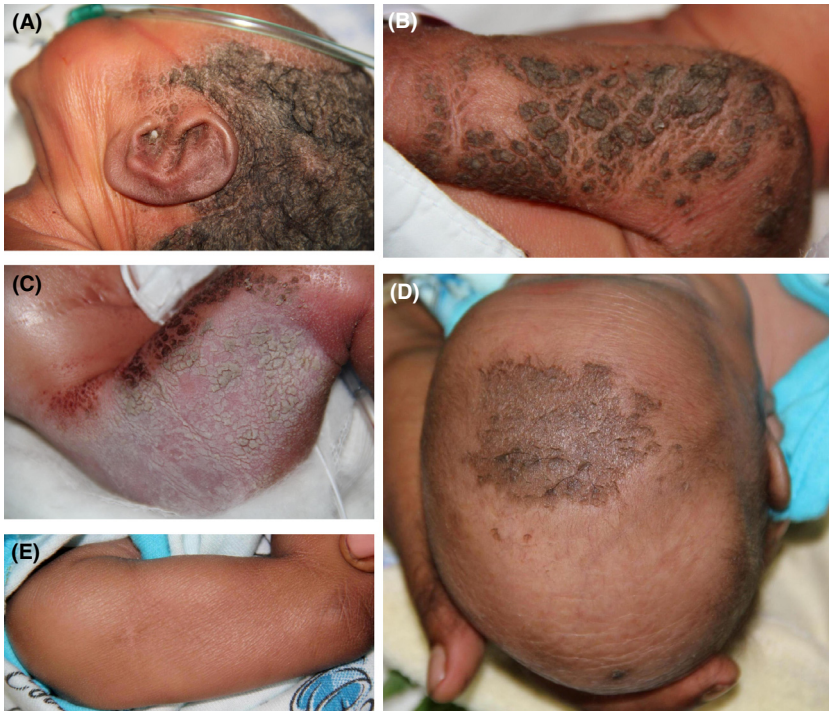

Figure 1. Benign progression of skin phenotype in IPS patient. At 48 h after birth caseosa – like scales were widely present across the body including scalp (A), arm (B) and changes in color of occluded (whitish) and nonoccluded (brownish) areas on thigh (C). Skin conditions rapidly improved with reduction in scales on the scalp at 2 months of age (D) Mild ichthyosis on the arm at 2 months of age (E).

Peripheral eosinophilia with 15% eosinophils was detected at birth in our patient with white blood cell count over 20,000 cells/mm^3 (normal 4000–12,000 cells/mm^3). At 5 months of age, the WBC count was 31,500 cells/mm^3 with 45% eosinophils and total serum IgE was 1951.6 IU/mL (normal 1–29.0).

Ultrastructural studies of the skin biopsy showed pathognomonic aggregations of curved membranous structures in the cytosol of granular and cornified cells (Fig. 2A and B). The sequencing analysis of FATP4 gene in our patient reveal novel, previously undescribed homozygous missense mutation c.530T>C that is predicted to lead to a p.Leu177 Prosubstitution in the ATP/AMP-binding domain of FATP4 (Fig. 2C). The clinically normal parents were heterozygous for the same allele. The p.Leu177is conserved among species and was not found in 100 normal population-matched Indian alleles.

The clinical features and course of our patient was similar to previously described characteristics of IPS [1–4]. Ultrastructural examination and mutational analysis of FATP4 gene confirmed IPS diagnosis. All previously reported IPS patients from Scandinavia are either homozygotes or compound heterozygotes for the nonsense mutation c.504C>A(p.Cys168X) in ATP/AMP-binding domain [2], while our patient is the first one reported to be homozygous for missense mutation in this domain. Apparently, both nonsense and missense mutations in the ATP/AMP motif affect fatty acid activation and transport, leading to abnormalities in lipid metabolism and IPS pathology.

It is apparent that the frequency of IPS worldwide is underestimated. Providing sufficient knowledge of the disorder to obstetricians and neonatologists worldwide may improve awareness about IPS features and reduce significant obstetric and neonatal morbidity due to preterm delivery and associated severe life threatening neonatal asphyxia.

Acknowledgments

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Conflict of Interest

None declared.

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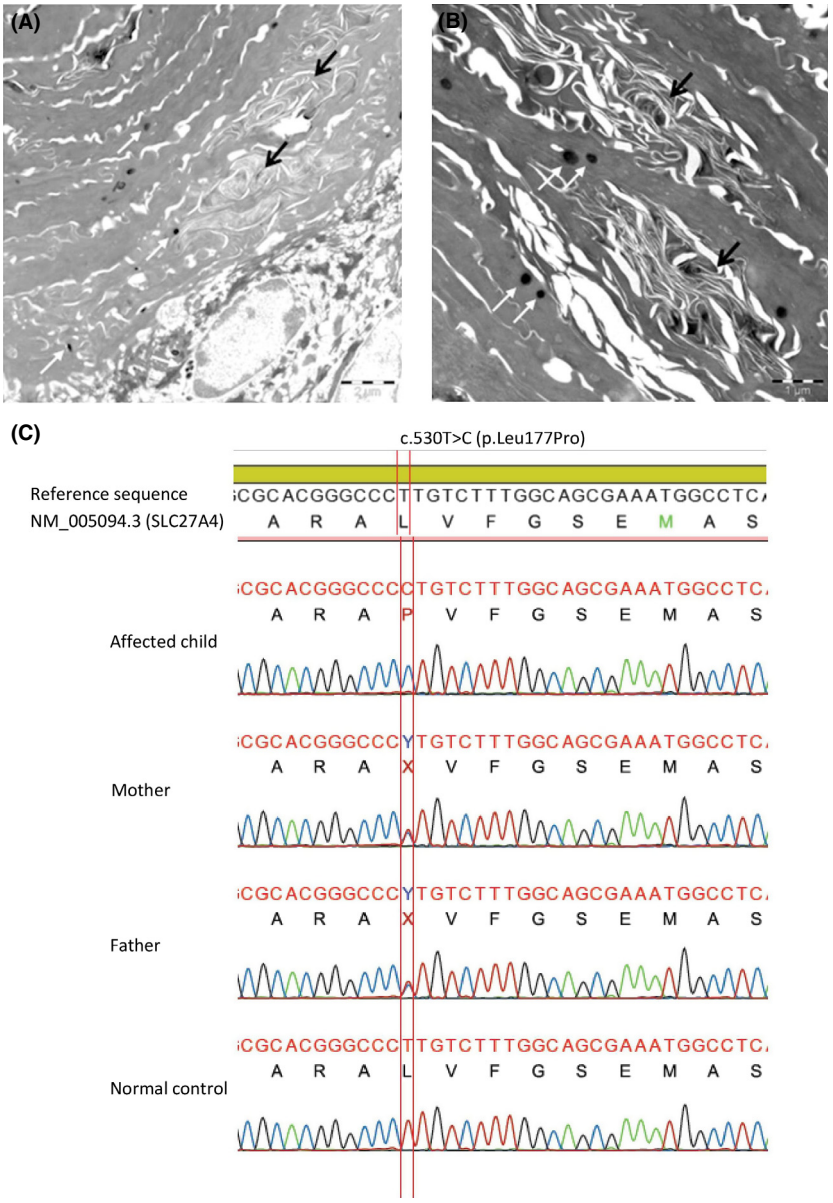

Figure 2. (A, B) Ultrastructurally the IPS skin showed aggregations of curved membranous structures in the cytosol of granular and cornified cells (black arrowheads) with lipid droplets (white arrowheads) interspersed with curved and linear arrays of lamellar material within corneocytes. (C) Sanger sequencing reveal novel FATP4 mutation c.530T>C (p.Leu177Pro) in the proband and parents.

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