Ichthyosis Prematurity Syndrome: From Fetus to Adulthood

Ichthyosis prematurity syndrome (IPS) is a rare form of autosomal recessive congenital ichthyosis caused by mutations in SLC27A4 (OMIM: 604194) encoding fatty acid transport protein 4 (FATP4) that affect keratinocyte differentiation and skin barrier formation. It is characterized by prematurity, thick caseous desquamating epidermis, and perinatal respiratory asphyxia. Despite its well-described clinical features and major perinatal mortality risk, IPS is still rarely recognized, and only a few cases have been reported.

Report of a Case | The female proband was first diagnosed with IPS as a 22-week-old fetus by amniocentesis and fetal skin biopsy, which was performed because her older brother was born prematurely at 33 weeks' gestation, owing to maternal polyhydramnios, and died at age 12 hours with ichthyosis and pulmonary obstruction. The proband's amniotic fluid contained numerous abnormal corneocytes and debris (Figure 1A). Histologic analysis of her fetal skin revealed hyperkeratosis and acanthosis with follicular plugging (Figure 1B). Transmission electron microscopy demonstrated perinuclear swelling of keratinocytes (Figure 1C) and lipid profiles with curved trilaminar lamellae in the horny layer (Figure 1D). All of these findings are characteristic of IPS.

The proband was also delivered prematurely at 31 weeks' gestation, owing to maternal polyhydramnios. Immediately after birth, she was on a ventilator for 2 days and remained in neonatal intensive care for an extended period because of respiratory asphyxia resulting from aspiration of amniotic fluid debris. At birth, she was erythrodermic with a thick caseous desquamating epidermis and hyperkeratotic scale over the scalp and eyebrows that persisted beyond age 8 weeks (Figure 2A). The vernix caseosa–like scale was shed over several weeks, leaving generalized follicular ichthyosis. Hair, eyes, teeth, mucosa, and nails were all normal. During childhood, follicular ichthyosis and skin hyperpigmentation became more prominent over the flexures (Figure 2B). She also had asthma, allergic rhinitis, and mild eosinophilia (1050/μL; normal range, 100/μL-800/μL) that persisted into adulthood. Serum IgE was not recorded. During adolescence, a 12-month treatment regimen of oral retinoids (≤1 mg/kg acitretin) had no clinical benefit. At last follow-up, age 21 years, her skin displayed generalized nonerythrodermic ichthyosis with follicular hyperkeratosis particularly over the flexures with mild hyperpigmentation (Figure 2C).

Both affected younger siblings of the proband shared a similar clinical course, with generalized follicular ichthyosis and atopic manifestations. However, both unrelated parents, the proband's only child (7-month-old son), and all 3 children from her father's previous marriage were unaffected.

Genomic sequencing of SLC27A4 on the 3 affected living siblings, including the proband (Figure 2D), and the unaffected parents revealed 2 recessive heterozygous mutations: a missense mutation, c.899A>G, p.Gln300Arg (exon 7); and a nonsense mutation, c.1336C>T, p.Gln446* (exon 10) (a new variant). Both mutations were found within the highly conserved adenosine monophosphate–binding domain of FATP4 (amino acids 103–536). Immunofluorescence staining for FATP4 (clone ab72724; Abcam) showed almost complete loss of expression in the proband's lesional skin compared with the bright mid and upper epidermal labeling in control skin (Figure 1E).

Discussion | Recent cases of IPS from Asia suggest that its frequency may be underestimated worldwide.1,2 The highest incidence of IPS reported has been in Scandinavia, with p.Gln300Arg as a frequent recurrent ancestral mutation3,4—the same maternal mutation identified in the present case, although geographically that side of the family resided in Ireland for several generations. It is plausible, therefore, that this mutation (which has not been detected in other Irish cases of IPS) has occurred on a different genetic background. Indeed, a different recurrent mutation in Scandinavia, p.Val477Asp, has also been identified in 2 Irish siblings with IPS.5

The clinical characteristics and course of our patient are similar to previous reported features of IPS,1,4,6 of which the largest case series examined 17 European families.6 The present case uniquely describes pathognomonic ultrastructural features in the skin and amniotic fluid from as early as 22-weeks' gestation. When our patient was born, genetic testing was unavailable, and therefore fetal skin biopsy was essential for the diagnosis. Consequently, through genetic counseling, the mother underwent regular antenatal ultrasonography with each subsequent pregnancy, facilitating preemptive management of polyhydramnios and perinatal respiratory asphyxia with excellent postnatal outcomes for all 3 surviving children. Our case highlights the importance of early recognition and diagnosis of IPS with coordinated multidisciplinary care for optimal management.

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Figure 1. Diagnosis of Ichthyosis Prematurity Syndrome (IPS) in Proband as a 22-Week-Old Fetus and Molecular Features of Proband’s IPS at Age 21 Years

A, Amniotic fluid contains numerous abnormal corneocytes and debris (Richardson stain; scale bar = 25 μm). B, Fetal skin biopsy from the chest wall reveals hyperkeratosis and acanthosis with follicular plugging (Richardson stain; scale bar = 50 μm). C, Transmission electron microscopy (TEM) of fetal skin shows perinuclear swelling in several keratinocytes (black arrows; scale bar = 10 μm). D and E, Higher magnification TEM images reveal lipid profiles with curved trilamellar lamellae in the stratum corneum (white arrows; scale bar = 0.5 μm). F and G, in adult skin, immunofluorescence staining for FATP4 (fatty acid transport protein-4) shows barely detectable labeling in the proband (F; sampled from right axilla at age 21 years) compared with bright staining within the upper epidermis in normal control adult skin (G) (scale bars = 25 μm).
Figure 2. Clinical Photographs, Pedigree, and Mutation Analysis of the Proband With Ichthyosis Prematurity Syndrome

A. At age 8 weeks, there is thick hyperkeratotic desquamating epidermis affecting the scalp and eyebrows. B. At age 5 years, there is hyperkeratotic cobblestoned skin with mild hyperpigmentation on the back of the neck. C. At age 21 years, there is generalized nonerythrodermic ichthyosis affecting the body and limbs with flexural hyperpigmented follicular hyperkeratosis. D. Sanger sequencing of SLC27A4 reveals 2 recessive heterozygous mutations: (1) a single-nucleotide transition, c.899A>G, in exon 7 resulting in an amino acid substitution, p.Gln300Arg; and (2) a single-nucleotide transition, c.1336C>T, in exon 10 leading to a premature termination codon, p.Gln466*. E. The family pedigree in keeping with autosomal recessive inheritance (proband is indicated with an arrow; affected siblings, black symbols; black square with slash, older brother who died of ichthyosis prematurity syndrome).


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