Ichthyosis Prematurity Syndrome: A Rare Form but Easily Recognizable Ichthyosis

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Keywords
Ichthyosis prematurity syndrome · Solute carrier family 27 member 4 · Verruciform hyperkeratotic plaques · Cobblestone appearance · Premature birth · Neonatal asphyxia

Abstract
Ichthyosis prematurity syndrome is a rare autosomal recessive genodermatosis that is associated with mutations in the \textit{SLC27A4} gene. Its onset occurs in early childhood and presents with the clinical triad of premature birth, thick caseous desquamating epidermis, and neonatal asphyxia. Here, we describe a prematurely born baby patient (33 weeks of gestation) with a homozygous variant at the initiation codon site (\textit{c.1A>G, p.Met1Val}) in the \textit{SLC27A4} gene to raise awareness of this rare syndrome despite its distinctive features as we believe it is still underdiagnosed.

Introduction
Ichthyosis prematurity syndrome (IPS, OMIM608649) is a rare autosomal recessive disorder characterized by the clinical triad of premature birth, ichthyosis, and neonatal asphyxia [1]. It is caused by a mutation in \textit{SLC27A4} (solute carrier family 27 member 4, which encodes fatty acid transport protein 4 [FATP4]) [2]. Here, we describe an IPS patient with a homozygous pathogenic variant at the initiation codon site (\textit{c.1A>G, p.Met1Val}) in the \textit{SLC27A4} gene to raise awareness of this rare syndrome despite its distinctive features as we believe it is still underdiagnosed.
A 33-week gestation baby boy was born to a healthy consanguineous parent by caesarian section due to premature rupture of the membrane and chorioamnionitis. At birth, he weighed 2.7 kg (10th centile) and 47.5 cm in length (10th centile), and his head circumference was 34 cm (10th centile). His Apgar scores were 7 and 8 at the 1st and 5th min, and he was admitted to the Neonatal Intensive Care Unit due to respiratory distress and was intubated on continuous positive pressure mechanical ventilation. At 32 weeks of gestation, antenatal course of dexamethasone was given to promote lung maturity.

On examination, the baby had no dysmorphic features. His skin examination revealed generalized thick verruciform hyperkeratotic plaques with cobblestone appearance covering all of his body including the scalp with focal areas of hair loss (Fig. 1). Mucous membranes and nails were normal. Ophthalmology examination was normal. His blood eosinophilia at birth was 1,700 cell/mm$^3$, peaked at day 7 reaching 2,300 cell/mm$^3$ and normalized at the age of 1 month. The clinical diagnosis of IPS was rendered and later proven by whole-exome sequencing revealing that he was carrying a homozygous pathogenic variant (c.1A>G, p. Met1Val) in the SLC27A4 gene with parents heterozygous for the same variant.

The proband was managed by using an incubator with 80% humidity and intravenous hydrocortisone at a dose of 1 mg/kg/dose 6 h for 7 days. Skin was managed conservatively by applying frequent, generous amount of petroleum jelly. Over the next 4 weeks, ichthyosis resolved gradually and completely (Fig. 2). The patient developed recurrent pneumonia with recurrent admission to the hospital and was treated with intravenous antibiotics.

**Discussion/Conclusion**

IPS is a rare autosomal recessive disorder, first recognized in 1993 [3]. Leaute-Labreze et al. [4] suggested the term “Self-Healing Congenital Verruciform Hyperkeratosis,” because skin findings improve spontaneously unlike other forms of congenital ichthyosis, although some patients may persist with skin xerosis or atopy [5]. Neonatal asphyxia is thought to be
due to aspiration of skin debris that shed into amniotic fluid [5]. Antenatal ultrasound may show separation of chorionic and amniotic membranes and polyhydramnios with starry sky appearance [4, 5]. Histopathology of skin is pathognomonic with acanthosis, hyperkeratosis, and characteristic aggregates of curved lamellar structures in the perinuclear cytosol of the stratum corneum and stratum granulosum [6]. Perivascular inflammation with eosinophilia was seen in some cases [6].

On electron microscopy, some authors described it as worm-like structures in corneocytes [4]. Transient blood eosinophilia like in our patient has been noticed occasionally [1]. Respiratory complications are the leading cause of death due to inhalation of debris [1]. Considering that lung pathology might be due to aspirating skin debris, we believe that systemic steroids might help mitigating the respiratory complications [7].

IPS was previously reported due to mutation within SLC27A4 that encodes FATP4 [2]. The described c.1A > G, p. Met1Val variant in our patient was previously reported in dbSNP (rs746178942) and in the gnomAD database, resulting in loss of the initiation codon leading to pathological effect on FATP4 protein [8]. The FATP families are transmembrane proteins that transport exogenous fatty acids into cells and activate them. They also function as acyl-CoA synthetases with specificity for very long-chain fatty acids (VLCFA), reducing VLCFA-CoA synthetase activity and incorporation of VLCFA into neutral and polar lipids [2].

Animal studies suggest that multiple FATPs specifically FATP4 are important for skin barrier function, particularly during embryonic and neonatal period, but are not vital postnatally as other FTAPs may compensate [9]. This may explain spontaneous skin improvement soon after birth [2].

We are presenting and emphasizing the pathognomonic and special cobblestone appearance of ichthyosis in IPS. We also think that systemic steroids may improve the prognosis.

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Fig. 2. Photograph of the patient at the age of 1 month showing resolution of ichthyosis.
Statement of Ethics

Written informed consent was obtained from the parent/legal guardian of the patient for publication of the details of this medical case and any accompanying images. The case complied with the Declaration of Helsinki. This case is a part of a study approved by the International Review Board (IRB), Ministry of National Guard – Health Affairs (Protocol # RC20/108/R).

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Sultan Al-Khenaizan and Asma AlSwailem were involved in contact with the patient, photography, obtaining written consent, and diagnosis of the patient. Mohammed Ali AlBalwi contributed to molecular genetic diagnosis and is the supervisor of the study. All authors contributed to literature review, manuscript writing, and manuscript reviewing.

Data Availability Statement

All patient data are available in this manuscript.

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