Rare disease

Ichthyosis prematurity syndrome with separation of fetal membranes and neonatal asphyxia

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Summary

Ichthyosis prematurity syndrome (IPS) is a rare inherited skin disorder. Children are born prematurely with thick skin and have been found to develop neonatal asphyxia due to occlusions in the bronchial tree from debris in the amniotic fluid. At 31 weeks of gestation, separation of amniotic and chorionic membranes was identified as well as polyhydramnion. The child was born 2 weeks later, with thickened skin with a granular appearance and required immediate ventilation and intensive care. At 2 years of age, the patient has developed an atopic skin condition with severe itching, recurrent skin infections, food intolerance and periods of wheezing. Prenatal observation of separation of foetal membranes or dense amniotic fluid may be signs of IPS and severe complication immediately after birth.

BACKGROUND

Ichthyosis prematurity syndrome (IPS), also known as ichthyosis congenita type IV, is a very rare autosomal recessive disease. IPS is part of the heterogeneous group of keratinisation disorders called autosomal recessive congenital ichthyoses (ARCI). The ARCI diseases are all associated with mutations in genes of importance for the intercellular lipid layer and cornified cell envelope in the epidermis.¹ All forms of ARCI share a hyperproliferation in the corneal layer of the skin with resultant general hyperkeratosis and scaling.² Other examples of ARCI are harlequin ichthyosis, lamellar ichthyosis and non-bullous congenital ichthyosiform erythroderma.³

IPS has been associated with a triad of premature birth, usually between gestation weeks 30 and 34, thick caseous desquamating epidermis at birth and neonatal asphyxia.⁴

The condition appears to be very rare except in regions of Scandinavia where there is an estimated heterozygote carrier rate of 1 in 50.^{5 6} There have been cases reported in the Middle East, southern Europe and Africa,⁶ but to date less than 30 cases have been reported. This report presents detailed clinical findings of an additional case of IPS, the first one in Iceland, which exhibited polyhydramnion and separation of the amniotic and chorionic membranes. Follow-up during the toddler period is also described, with emphasis on problematic skincare at an early age.

CASE PRESENTATION

A 41-year-old pregnant female was admitted to hospital because of rapidly increasing abdominal size. She was in her 31st week, with her third child. Previous medical examinations had been normal during the pregnancy, including routine ultrasound scans at week 12 and 20. A new ultrasound at admission showed polyhydramnion with unusually dense amniotic fluid with sediment, as well as separation

of the chorionic and amniotic sacs (figure 1). At 32 weeks and 5 days the membrane ruptured and a caesarean section was performed because of a breech position. Birth weight was 2360 grams and corresponded to gestational age.

The amniotic fluid was yellowish-brown coloured and murky and the child was coated in a thick layer of light brown vernix caseosa-like material. The whole body, including the face, had thickened skin with a granular or cobblestone quality (figure 2). Her fingers and toes were flexed because of the thickened skin on the palms and soles, but otherwise all joints had normal range of movement. The finger and toenails were noted to be unusually long. The child immediately required ventilating and was flaccid and pale. Apgar score was 1, 6 and 7 at 1, 5 and 10 min, respectively.

INVESTIGATIONS

An arterial blood sample taken 40 min after birth showed a pH of 6.93 with a pCO₂ of 12.8 kPa (96 mm Hg). A chest radiograph revealed that the right lung was deviated medially because of widespread atelectases. Laboratory tests showed elevation of white blood cells (53×10⁹/L) of which 11% were eosinophils. Genetic testing revealed that the baby was homozygous for the p.C168X non-sense mutation (c.504c > a) in exon 3 (ENS3) of the SLC27A4 gene which codes for the fatty acid transporter protein 4 (FATP4), confirming the diagnosis of IPS.

DIFFERENTIAL DIAGNOSIS

The two fetal sacs normally fuse before gestational week 14, but after that time separate sacs are rare, but have been described in relation to pregnancies with Down's syndrome and other diseases of aneuploidy as well as after amniocentesis or operations of the pregnant uterus.⁷ It has also been reported to happen spontaneously in pregnancies of children with restrictive dermopathy.⁸

Figure 1 A) Separation of the amniotic- and chorionic sacs was noted at week 31. The intermembrane space was filled with clear translucent fluid. B) The amniotic fluid surrounding the child was dense with sediment.

TREATMENT

The child was placed on a respirator with high inspiratory pressure and subsequently on a high frequency oscillating ventilator, which led to a marked improvement in the child's condition, with decreased inhaled oxygen percentage. Several hours later an increased oxygen need was again noted and a cardiac ultrasound revealed pulmonary hypertension with a strained right ventricle and a wide open ductus arteriosus with right to left flow. Nitrous oxygen treatment was added to her oscillator treatment and on her 3rd day she had shown good response and her respiratory distress had greatly improved. Respiratory assistance was discontinued on day 4 with no further need of extra oxygen or positive pressure breathing.

OUTCOME AND FOLLOW-UP

At the age of 2 the child has developed normally physically and mentally. She has very dry skin, with an extreme itching dermatitis which requires constant supervision as well as treatment with ointments and antihistamines. Recurrent skin infections have also been troublesome. The child suffers from severe food allergies against fish, eggs, milk, wheat, peanuts and sesame seeds and has been admitted to hospital due to recurrent episodes of wheezing. At the age of 1, IgE was found to be 1791 kU/l (normal <23kU/l) and a year later 2456 kU/l (normal <40 kU/l). This is the first child born in the family with ichthyosis, but an older sibling has been diagnosed with psoriasis. Maternal grandfather and an uncle had also been diagnosed with psoriasis.

Figure 2 A) The child's skin was red, thickened, oedematous or spongy with a granular appearance. The face was moon-shaped. B) Cobblestone appearance of the skin on the forearm. C) The fingers and toes were flexed because of thickened, hyperkeratotic skin of the palms and soles. The nails were unusually long. D) Hyperkeratosis of the skin was clearly seen on the pads of the toes and fingers and was shed during the newborn period.

No other member of the family has food allergy or atopic skin disease. The parents are unrelated.

DISCUSSION

IPS is one of the ARCI. Other examples of ARCI are harlequin ichthyosis (HI), lamellar ichthyosis (LI) and non-bullous congenital ichthyosiform erythroderma (NCIE).³ All ARCI are present at birth, distinguishing them from the more common types of ichthyosis such as ichthyosis vulgaris and X linked recessive ichthyosis with steroid sulfatase deficiency, which have delayed onset.² Children with HI are born covered with characteristic thick, plate-like, cornified skin that restrict movements and breathing. Complications in the immediate postnatal period are common and mortality is high. Most children with LI or NCIE are born with collodion skin, a tight, shiny, translucent or opaque membrane that encases the entire body and sheds over a period of days to weeks. After shedding, children with LI develop brown, plate-like scales with no erythroderma, while children with NCIE have finer whiter scales and underlying generalised erythroderma. They also have palmoplantar keratoderma, often with painful fissures and digital contractures.⁹ The diagnosis of HI, LI and NCIE is established by skin findings at birth and in infancy and confirmed by genetic testing. Among known genes for these conditions mutations in the TGM1 gene account for 50%–60% of cases and 90% or more of severe LI. Mutations in the ALOXE3 and ALOX12B genes are estimated to be present in about 10% of individuals with NCIE or intermediate LI/NCIE phenotypes. The vast majority of individuals with harlequin ichthyosis and a few individuals with LI have mutations or partial-gene deletions in the ABCA12 gene.⁹

IPS was recently found to be caused by changes in the fatty acid transporter protein 4.¹ The FATP4 gene (gene symbol SLC27A4) expresses a trans-membrane protein

that transports exogenous fatty acids into cells as well as functioning as an acyl-CoA synthetase, activating long- and very long-chain fatty acids for subsequent intracellular metabolism.¹

FATP4 is widely expressed in human tissue but seems to be most important in the epidermis, where studies have shown lethal restrictive dermopathy in FATP4^{−/−} mice but no other discernable organ damage.¹⁰ It is postulated that FATP4's lipid transport and regulatory functions are of key importance to the formation of the intercellular lipid matrix, which surrounds the keratinocytes in the stratum corneum of the epidermis. This lipid matrix has been likened to the mortar between bricks, and together these structures create the barrier that seals the skin from the outside world.¹¹ Defective formation of the lipid matrix is thought to result in loss of the epidermal barrier function and to abnormal hyperkeratosis which in turn leads to early sloughing.

The largest epidemiologic study of IPS patients to date, by Khnykin *et al*,⁶ identified 23 children and adults with IPS, showed that these patients have life-long mild follicular hyperkeratosis with dryness, scaling and itching, that can be treated to some effect with moisturising creams. Skin biopsies reveal acanthosis, hyperkeratosis and characteristic aggregates of curved lamellar structures in the perinuclear cytosol of granular cells and within cornified cells and varied eosinophilic perivascular inflammation. In this study, peripheral eosinophilia was present in all tested patients, and a majority also had elevated serum IgE. A clear propensity for development of allergies and asthma has been noted. Atopy and hypereosinophilia in these patients is postulated to be based on abnormalities in keratinocytes and the skin barrier function.⁶

Besides the triad of premature birth, thick caseous desquamating epidermis and neonatal asphyxia, children

with IPS also share several prenatal features.¹² Prenatal ultrasound shows echogenic debris in the amniotic cavity. Careful examination with ultrasound can reveal the fetus having a stomach filled with epidermal debris, hindering the passage of amniotic fluid through the child's gastroenteric system, thus causing polyhydramnion, a very common or possibly universal feature of IPS.

Directly after birth, children with IPS have been described to suffer from asphyxia. This is thought to be caused by epidermal debris which layers the airway, clogging it to a variable degree as the child takes its first breath. The physical blockage of the small airways can lead to a respiratory distress syndrome, usually requiring intubation and intensive respiratory support.⁴

The child has a distinctive appearance, with thick, desquamating, red, spongy skin, with a cobblestone appearance, and is covered in a layer of sloughed epidermis, resembling vernix caseosa, most marked in the flexures and face.

Nearly all children who survive the initial critical period recover relatively quickly after the first few days of respiratory illness. After a few weeks the skin becomes thinner, paler and dryer, retaining a slight cobblestone appearance and a tendency to dermatoglyphism.

Our case shows typical presentation of IPS with severe life-threatening complications immediately after birth, but also important prenatal signs that should alert obstetricians and paediatricians.

Learning points

- ▶ IPS is a very rare inherited skin disorder associated with a triad of premature birth, neonatal respiratory distress and skin disorder.
- ▶ Prenatal ultrasound findings include echogenic debris in the amniotic cavity as well as a stomach filled with epidermal debris, hindering the passage of amniotic fluid and causing polyhydramnion. Physical blockage of the small airways with epidermal debris has been associated with development of a respiratory distress syndrome in the newborn period.
- ▶ Separation of chorionic and amniotic membranes is a rare finding in pregnancy, but can be associated with life-threatening complications immediately after birth when associated with IPS.
- ▶ Infants with IPS are born with thick skin with cobblestone and granular appearance at birth, but after a few weeks the skin become thinner, paler and drier.
- ▶ Children with IPS later develop atopic condition with dry skin, severe itching and often suffer from recurrent skin infections.

Competing interests None.

Patient consent Obtained.

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