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Case Report

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Rare clinical case of harlequin ichthyosis: opportunities and difficulties of prenatal diagnosis

Nodira Normuradova[1]

[1]Center for the Development of Professional Qualifications of Medical Workers Ultrasound Diagnostics Department, Tashkent, Uzbekistan

Abstract

Objective: Harlequin ichthyosis (MIM 242500) is a rare autosomal recessive skin disorder caused by a congenital disorder of epidermal keratinization and associated with a mutation in the ABCA12 gene of chromosome 2q35. We report a case of a fetus at 25 weeks of gestation with harlequin ichthyosis and a deletion of chromosome 15q11.2-q12.

Case(s): The results of an ultrasound examination at 13 weeks 2 days and 18 weeks of pregnancy showed no pathology. Two previous male children were presumably born with harlequin ichthyosis (genetic diagnosis was not performed due to unavailability at that time) and died on the first day of life. Analysis of amniotic fluid using SNP - array technology at 23 weeks revealed a deletion of 15q11.2-q12. Subsequent ultrasound examination at 25 weeks of pregnancy showed signs of harlequin ichthyosis, including an abnormal flat facial profile, a constantly open large mouth, and a large number of inclusions in the amniotic fluid. Considering the family history, a diagnosis of harlequin ichthyosis was made, leading the family to decide to terminate the pregnancy. A male child was born, weighing 800 g, with a typical harlequin ichthyosis phenotype, and died 2 hours after birth.

Conclusion: In case of a suspicion of this disease in a family, prenatal diagnosis of harlequin ichthyosis can be carried out by prenatal chromosomal microarray analysis using tissue obtained from chorionic villus sampling, amniocentesis or cordocentesis in the early terms of pregnancy. Ultrasound signs of the disease typically manifest after 24 weeks of pregnancy.

Keywords: Harlequin ichthyosis, fetus

Introduction

Harlequin ichthyosis (MIM 242500) is the most severe and often fatal form of autosomal recessive congenital ichthyosis.[1,2] Children are born with a characteristic appearance: the skin is hard and thick, with deep cracks, resembling a thick "coat of armor", with severe damage to the eyelids (ectropion), nostrils, lips (eclabion) and ears.[3,4] It is known that the disease is caused by a mutation in the ABCA12 gene on chromosome 2q35.[3] Harlequin ichthyosis frequency is about 1 in 300,000 newborns and occurs in both sexes.[4]

For newborns with harlequin ichthyosis, the risk of death in the neonatal period is very high, and affected infants rarely survive beyond the first few weeks of life.[4] Affected infants have markedly impaired skin barrier function and are more susceptible to infection.[3] However, over the past 20 years, the chances of long-term survival have increased considerably, mainly due to the administration of systemic retinoids and advances in intensive neonatal care.[5] But still, carriers of homozygous mutations have a higher mortality rate.[6] In the first months of life, the hyperkeratotic layer peels off, revealing a diffusely erythematous, scaly epidermis that persists for the rest of the patient's life.[5]

Previously, prenatal diagnosis of harlequin ichthyosis was performed using fetoscopy and ultrasound-guided fetal skin biopsy.[1] Currently, widely introduction of DNA diagnostics into medical practice improves early and reliable prenatal harlequin ichthyosis diagnostics among women with a family history.[1,3] Ultrasound exa-

Correspondence: Nodira Normuradova, Center for the Development of Professional Qualifications of Medical Workers Ultrasound Diagnostics Department, Tashkent, Uzbekistan, **e-mail:** n.normuradova@mail.ru, **Received:** February 3, 2024, **Accepted:** March 13, 2024

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ORCID ID: N Normuradova 0000-0002-0365-6510

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mination of a fetus affected by harlequin ichthyosis has characteristic facial signs, but they appear late, often in the third trimester of pregnancy. We present a case of diagnosis of harlequin ichthyosis in a fetus at 25 weeks of gestation, in which high-resolution chromosomal SNP microarrays showed a deletion of 15q11.2- q12.

Case(s)

Pregnant woman I., 34 years old, fourth pregnancy. The spouses are in a consanguineous marriage, the spouses are maternal cousins, of Uzbek nationality. The first child is alive and well, male, 14 years old. The next two male children were presumably born with harlequin ichthyosis (based on phenotype) and died on the first day of life. Genetic testing was not performed due to unavailability of the test at that time.

Ultrasound examination at 13 weeks 2 days of pregnancy: CRL 72 mm, NT 2.1 mm; at 18 weeks of pregnancy assessment of fetal anatomy without features, fetal movements not limited, regular. The fetal facial profile was regular, at the time of the study the fetus was making swallowing movements, the area of the upper lip and mouth was visualized without any features. The amniotic fluid had isolated inclusions. Given the medical history, the woman was offered amniocentesis followed by molecular karyotyping, which she refused. At 23 weeks of pregnancy, an ultrasound examination diagnosed a flat facial profile (Figure 1), as well as an increase of inclusions in the amniotic fluid. Given the medical history and the appearance of ultrasound markers, invasive diagnosis was strongly recommended. The woman agreed to the procedure and amniocentesis was performed at 23 weeks of pregnancy. Study of amniotic fluid using high-resolution chromosomal SNP microarrays showed a deletion of 15q11.2-q12, with the need to rule out Prader-Willi syndrome and Angelman syndrome. During an ultrasound examination at 25 weeks of pregnancy, characteristic ultrasound signs of harlequin ichthyosis appeared: the facial profile has become even more flattened, a large open mouth, with anechoic linear structures in the chin area (cracks in the skin), hyperechoic linear structures in the eyelid area (Figure 2), the appearance of a large number of inclusions in the amniotic fluid (Figure 3). Taking into account the family history, a conclusion was made about harlequin ichthyosis. The couple were informed about modern disease treatment options with retinoids, but the family decided to terminate the pregnancy. A male child was born, weighing 800 g, with a typical harlequin ichthyosis phenotype (Figure 4), and died 2 hours after birth. The parents refused to undergo genetic diagnosis due to insufficient funds.

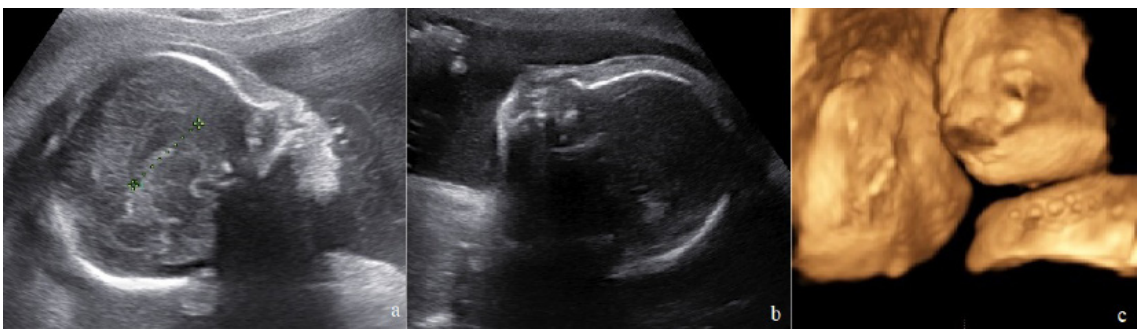

Fig 1. Ultrasound image of the fetal facial profile with harlequin ichthyosis: a) at 23 weeks of pregnancy, b) at 25 weeks of pregnancy, c) 3D image of a face at 25 weeks of pregnancy

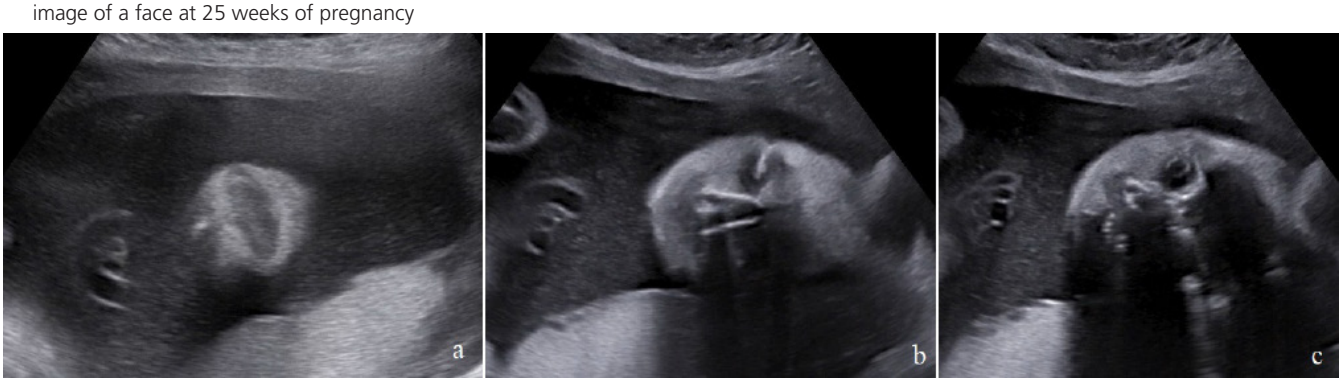

Fig 2. Ultrasound image of the fetal face with harlequin ichthyosis: a) mouth and lips of the fetus, b) hyperechoic strands in the eyelid area, c) section at the level of the lenses

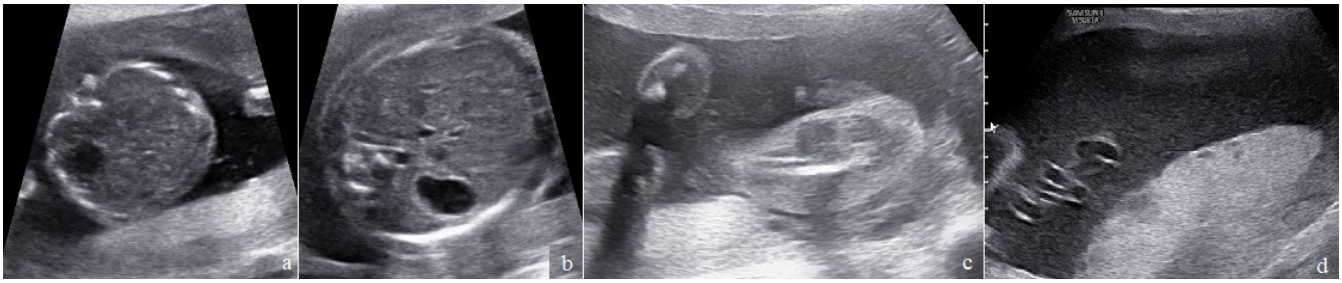

Fig 3. Section of the fetal abdomen and ultrasound image of the amniotic fluid: a) a section of the fetal abdomen at the level of the stomach at 18 weeks of pregnancy, b) the same section at 25 weeks of pregnancy, a double contour is noted, c) the sex of the fetus is male, d) multiple inclusions in the amniotic fluid.

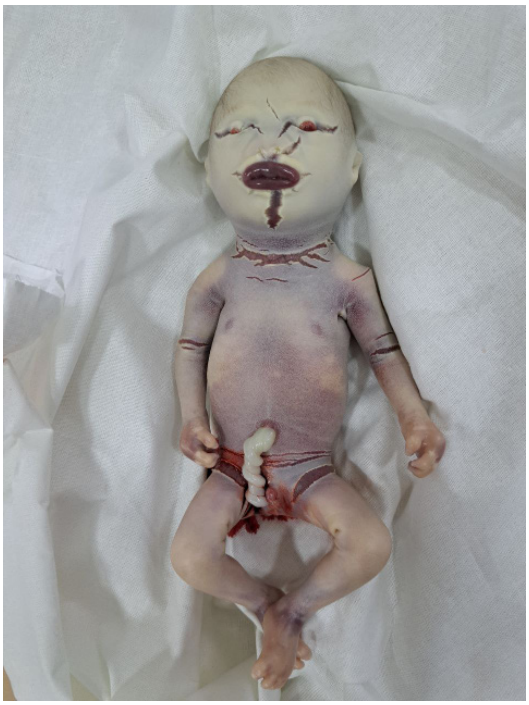

Fig 3. Phenotype of the child after birth

Discussion

The case we presented deserves attention due to the rarity of the disease and the fact that using SNP - array technology revealed the absence of heterozygosity between chromosome 15q11.2 and q12 regions with a size of 3216309 bp. Many researchers have previously reported the effectiveness of early prenatal detection of harlequin ichthyosis based on DNA diagnostics of ABCA12 gene expression associated with 2q35 deletion.[1,3] In studies by D. Castiglia et al.[1] in a fetus with growth restriction and oligohydramnios, the diagnosis was confirmed by molecular analysis of ABCA12, which revealed a new homozygous mutation p.R287X, microsatellite analysis in this case showed complete paternal isodisomy. H. Stewart et al.[7] described a male fetus with a harlequin ichthyosis, in which a deletion of the long arm of chromosome 18 with a karyotype of 46,XY,del(18)(q21.3) was found. In case of a family history, genetic studies of material obtained through an invasive procedure make it possible to establish a diagnosis earlier in pregnancy. S. Rathore et al.[2] indicate the need for prenatal genetic diagnosis for women who have previously given birth to sick children. According to the authors, DNA analysis for the ABCA12 gene mutation will enable to confirm the diagnosis at earlier stages of pregnancy. In our case, the pregnant woman initially refused invasive procedures, claiming that the ultrasound examination did not reveal any abnormalities. The woman agreed to invasive procedures at 23 weeks of pregnancy, when the first suspicious signs appeared on the harlequin ichthyosis in the fetus: abnormal flat facial profile, increased inclusions in the amniotic fluid.

Late manifestation of signs of the disease during ultrasound examination is due to the fact that hyperkeratosis of the hair canal occurs in the second trimester of pregnancy.[4] According to M. L. Arnold and I. Anton-Lamprecht[8] prenatal diagnosis of congenital ichthyosis cannot be based on impaired keratinization due to the late onset of normal keratinization. The authors, having studied skin biopsies of fetuses with suspected genodermatosis, came to the conclusion that signs of hyperkeratosis will be expressed no earlier than the 24th week of pregnancy and therefore it is impossible to reliably exclude skin diseases by biopsy before 22 weeks of pregnancy. According to S. Rathore et al.[2] in cases of unavailability of DNA analysis, the diagnosis can be established by characteristic ultrasound signs of the disease at later stages of gestation.

In the case we presented, ultrasound signs at 25 weeks of gestation were characterized by a flat facial profile and a large open mouth. Such features of harlequin ichthyosis are similar to diseases such as trisomy 21, Beckwith - Wiedemann syndrome, epidermolysis bullosa which are manifested by hypoplastic soft tissue.[9] An important method of differentiation in such cases is genetic testing.[9]

In our case, harlequin ichthyosis was caused by deletion of 15q11.2- q13. In the absence of a family history of

harlequin ichthyosis, there is a need to differentiate from Prader-Willi syndrome and Angelman syndrome, which are also caused by mutations in genes in the region of chromosome 15q11-q13.[10] Prader-Willi syndrome is characterized by obesity, muscle hypotonia, mental retardation, short stature, hypogonadotropic hypogonadism, small hands and feet in children.[10] In the prenatal period, there is a decrease in fetal activity, asymmetric fetal growth restriction and polyhydramnios.[10] Ultrasound signs of Angelman syndrome had not been described; they were often found during prenatal chromosomal microarray analysis.[10]

Conclusion

Prenatal diagnosis of congenital ichthyosis using two-dimensional ultrasound is possible only after 24 weeks of pregnancy. Diagnosis is based on the detection of an abnormally flat face profile, a large mouth that is constantly in an open position, and a large number of inclusions in the amniotic fluid.

In case of knowledge of the risk of this disease in the family, prenatal diagnosis is possible earlier in pregnancy using invasive diagnostics and genetic tests. Congenital ichthyosis in the case we presented was caused by a deletion of 15q11.2-q12.

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