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CASE REPORT

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Lethal acantholytic epidermolysis bullosa–a report on the prenatal phenotype of two cases and a review of antenatal sonographic signs of congenital denuding skin diseases

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Abstract

Background The *DSP* gene encodes the desmosomal protein desmoplakin and is located on chromosome 6. Pathogenic variants in this gene have been linked to different phenotypes that may include the skin, hair, nails, teeth, and the heart. Lethal acantholytic epidermolysis bullosa (LAEB, OMIM # 609638) is a severe and lethal form of epidermolysis bullosa, caused by biallelic pathogenic variants in the *DSP* gene.

Case presentation This report describes two fetuses from the same family, both affected by LAEB. The parents were second degree cousins. Both fetuses showed multiple sonographic abnormalities antenatally. The first fetus had a lemon shaped skull, an abnormal profile with frontal bossing, flat nasal bridge, nasal hypoplasia and micrognathia. There was increased pericardial fluid, situs ambiguous (left stomach with dextrocardia) and hypoplastic aortic arch. The kidneys were suspected as dysplastic and indeed there was also oligohydramnios. Echogenic sediment was noted in the fetal stomach. The fetus was small for gestational age (SGA) with an estimated fetal weight (EFW) under the 3rd percentile. The second fetus exhibited a novel sonographic sign - constantly open eyelids. Additional notable sonographic signs were echogenic amniotic fluid, and an abnormal profile comprising of flat nasal bridge, hypoplastic nose and micrognathia. Furthermore, hypospadias was suspected as well as abnormal scrotum. The scan revealed echogenic sediment in stomach and SGA fetus with EFW under 3rd percentile similarly to the previous pregnancy. After delivery severe extensive skin and mucosal erosion and sloughing were evident and the neonate succumbed at day 2 of life. Extensive genetic workup diagnosed LAEB in both children.

Discussion and conclusions This is the first report to describe the antenatal sonographic phenotype of LAEB. We discuss the diverse phenotypes of *DSP* gene pathogenic variants and review the specific biochemical and sonographic findings in the context of congenital skin denudation diseases.

Keywords *DSP*, Epidermolysis Bullosa, Prenatal, Ultrasound, Case report

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Background

Pathogenic variants in the *DSP* gene that encodes the desmosomal protein desmoplakin can result in several phenotypes involving the skin, hair, nails, teeth, and the heart. Three phenotypes have autosomal dominant inheritance, namely arrhythmogenic right ventricular dysplasia (ARVD) 8 (OMIM # 607450) [1], dilated cardiomyopathy with woolly hair, keratoderma, and tooth agenesis (OMIM # 615821) [2] and keratosis palmoplantaris striata II (OMIM # 612908) [3]. Another two phenotypes, Carvajal syndrome (OMIM # 605676) [4] and lethal acantholytic epidermolysis bullosa (LAEB, OMIM # 609638) [5] are inherited as autosomal recessive diseases. The latter is an extremely rare (unknown prevalence), severe and lethal form of epidermolysis bullosa causing severe skin and mucosal fragility and erosion. Only 4 case reports describing six neonates were published about LAEB to date [5–8]. All infants died during the perinatal period. This report describes the sonographic prenatal features of this disease for the first time and reviews sonographic features of other congenital denuding skin conditions.

Case presentation

An 18-year-old woman had arrived at our center at 22 weeks' gestation for a detailed anatomy scan. This was her second pregnancy, having previously experienced an early first trimester spontaneous miscarriage. She and her husband were second cousins. Previously in her current pregnancy the nuchal translucency measured 1.7 mm and pleural and pericardial effusion was noted at the time of the scan. TORCH tests and indirect Coombs test were negative. Second trimester biochemical screening for aneuploidy was notable for elevated level of alpha-feto protein of 5.53 multiples of the median. The combined first and second trimester risk for Down syndrome was 1:710. Fetal echocardiography performed at 21 weeks of gestation showed severe hydrothorax, dextro-position of the heart and poor ventricular function.

Detailed fetal anatomy scan at our center at 22 weeks' gestation revealed a lemon-shaped skull, an abnormal profile with frontal bossing, flat nasal bridge, nasal hypoplasia and micrognathia. There was increased pericardial fluid, situs ambiguous (left stomach with dextrocardia) and hypoplastic aortic arch. The kidneys were suspected as dysplastic and indeed there was also oligohydramnios. Echogenic sediment was noted in the fetal stomach. Some of the sonographic abnormalities are depicted in Fig. 1. Furthermore, the scan illustrated small for gestational age (SGA) fetus with estimated fetal weight (EFW) under the 3rd percentile. Following genetic counseling, the couple chose to undergo a genetic analysis. Fetal DNA was obtained through cordocentesis due to anhydramnios. Chromosomal microarray (CMA) was normal, however, the couple opted to terminate the pregnancy at 23 weeks and 6 days of gestation considering the grave prognosis suggested by the sonographic findings. The parents decided they did not want any further genetic work-up.

The woman returned to the clinic three years later at 28 weeks and 5 days of gestation after an abnormal detailed anatomy ultrasound scan in the community. The scan demonstrated constantly open eyelids, echogenic amniotic fluid, and an abnormal profile comprising of flat nasal bridge, hypoplastic nose and micrognathia. In addition, hypospadias was suspected as well as abnormal scrotum. The scan revealed echogenic sediment in stomach and SGA fetus with EFW under 3rd percentile similarly to the previous pregnancy. Major sonographic abnormalities are depicted in Fig. 2 and Supplementary Video clip 1. The couple opted to continue the pregnancy without any genetic evaluation.

The patient gave birth to a male neonate at 35 weeks and 2 days of gestation following preterm premature rupture of membranes (PPROM). The baby weighted 1,340 g and Apgar scores were 9 and 10 in one and five minutes, respectively. On physical examination, the neonate was completely devoid of skin covering on his body, and had brown skin peelings on wide areas, as shown in Fig. 3. The fingers were sticky, short and underdeveloped. Nevertheless, he had fingernails. The neonate had abnormal facies including hypoplastic nasal ala, lack of eyelids, micrognathia and small, low, deformed ears. Milia was noted on the nose and chin. The newborn exhibited hypospadias and left undescended testis. With parental consent blood was drawn for genetic analysis.

The neonate was given supportive care including vaseline dressings, fluids and was placed in a heated and moisturized incubator. He seemed to be in great pain, and therefore morphine drip was administered. The neonate succumbed 31 h post-delivery.

Exome-trio analysis revealed a novel homozygous nonsense variant in exon 3 of the *DSP* gene: chr6:7558373 C > T [hg19]; NM_004415.4: c.298 C > T, p.(Gln100Ter). This variant is extremely rare. It is not carried by any of the ~ 800,000 individuals whose exome or genome sequences were deposited in the gnomAD database v4 1.0 (https://gnomad.broadinstitute.org/). This premature stop codon is expected to cause nonsense-mediated mRNA decay, i.e. no Desmoplakin protein will be produced. Both parents were heterozygous for this variant. No other variants of potential clinical significance in recessive genes, shared between the parents, were identified. Nor any de-novo or x-linked variants were found.

Exome sequencing of the first fetus revealed the same homozygous variant. Based on the American College of Medical Genetics (ACMG) classification criteria [9], this variant is classified pathogenic, using the following

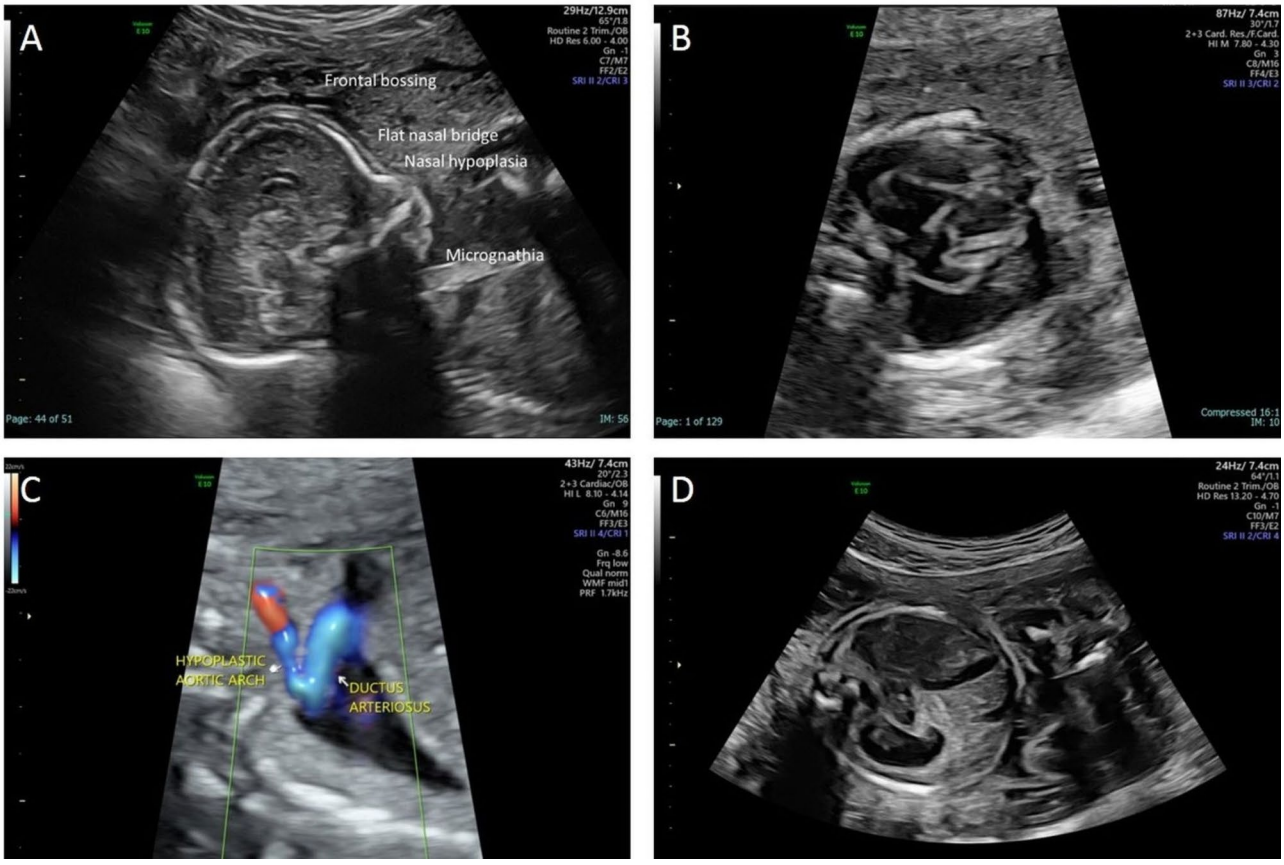

Fig. 1 Sonographic features of the first fetus at 22 weeks of gestation:
A. Abnormal profile consists of frontal bossing, flat nasal bridge, hypoplastic nose and micrognathia
B. Large amount of pericardial effusion
C. Hypoplastic aortic arch
D. Oligohydramnios and echogenic sediments in the fetal stomach

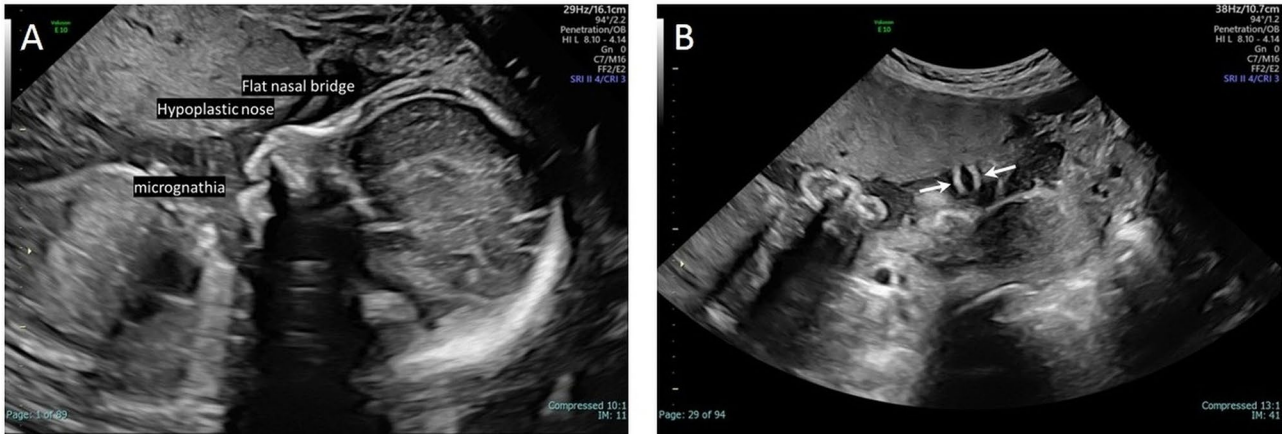

Fig. 2 Sonographic features of the second fetus at 28 + 5 weeks of gestation showing:
A. Abnormal profile with flat nasal bridge, hypoplastic nose and micrognathia
B. Constantly open eyelids (arrows)

Fig. 3 The neonate immediately after birth, completely devoid of skin covering on his body, brown skin peelings on wide areas. There are short and undeveloped fingers. The neonate exhibits abnormal facies- hypoplastic nasal ala, lack of eyelids, micrognathia and small, low, deformed ears. There is milia on the nose and chin

lines of evidence: PM2, PVS1, PP1. The genetic finding along with the clinical presentation are consistent with the diagnosis of lethal acantholytic epidermolysis bullosa (LAEB).

Oral and written informed consent was obtained for this publication during a genetic counselling from the couple.

Discussion and conclusions

DSP gene encodes the desmosomal protein desmoplakin and is located on chromosome 6p24. This is a cytoplasmic plaque protein in desmosomes- intercellular junctions that binds intermediate filaments (IF) in cells to plasma membrane. Pathogenic variants in this gene have been linked to different phenotypes that may include the skin, hair, nails, teeth, and the heart [8, 10]. In cardiomyocytes, desmoplakin defects critically impair the tethering of the desmin-IF network. This affects its attachment to the intercalated disc junctions, leading to sarcomeric disorganization and loss of tissue integrity. These changes may lead to the development of right or left-sided dilated arrythmogenic cardiomyopathies and may cause sudden death [11].

LAEB was identified in cases of complete failure of desmoplakin production or with homozygous truncating variants of the C-terminal tail enveloping the IF-binding domain. In damaged skin, the link of the keratin to desmosomes is variably reduced [10]. A consistent correlation between genotype and phenotype linking *DSP* various variants to disease has not been discovered [7]. Mode of inheritance regarding *DSP* is also variable as some clinical phenotypes are related to autosomal recessive inheritance (i.e. Carvajal, OMIM #605676) [4] and some to autosomal dominant (i.e. ARVD 8, OMIM# 607450) [1].

Epidermolysis bullosa (EB) encloses a group of genetic skin fragility disorders presenting with blistering of the skin and mucous membranes [12]. Some forms of EB involve other organs and manifest as a combination of skin disorder and other phenotypes, such as nephrotic syndrome and deafness (OMIM #609057), nephrotic syndrome and lung disease (OMIM #614748) and muscular dystrophy (OMIM #226670). One of the phenotypes

that is amenable to prenatal diagnosis is EB with pyloric atresia (OMIM #619817; #226730; #612138). This is an autosomal recessive condition due to biallelic pathogenic variants in the *ITGA6*, *ITGB4*, or *PLEC* genes, respectively [13]. Genetic prenatal diagnosis of EB is possible by amniocentesis or chorionic villous sampling. Fetal skin biopsy is hardly ever done today and is quite unnecessary in the next generation sequencing era, when searching for a genetic diagnosis. While Epidermolysis bullosa with pyloric atresia may be challenging to diagnose before birth, some sonographic markers can be suggestive of this condition. Gastric dilatation and polyhydramnios are secondary to pyloric atresia. Echogenic particles in amniotic fluid, referred to as "snowflake sign", are secondary to fetal denudation [14]. In addition, there could be other sonographic signs, such as restricted limb motion, restriction bands, angled and shortened long bones, hypotrophic muscles, abnormalities of the urinary tract and kidneys, and deformed ears and nose [14–17]. A case report by Chen et al.. also noted localized skin denudation [18]. In addition, high levels of maternal serum and amniotic fluid alpha-fetoprotein and acetylcholinesterase in amniotic fluid are generally present in pregnancies affected by fetal epidermolysis bullosa [19–21].

LAEB is an autosomal recessive disorder that stems from biallelic pathogenic variants in the *DSP* gene. The disorder is considered as a form of a suprabasal type of EB, where blisters are superficial to basal keratinocytes. The neonatal presentation includes severe fragility of skin and mucous membranes with prompt transcutaneous fluid loss. Other features include total alopecia, neonatal teeth, and absence of fingernails. In a case report by McGrath, post-natal skin biopsy samples demonstrated anomalies in desmosomes with suprabasal clefting accompanied by spongiosis and acantholysis under light microscopy. The abnormalities above were also revealed in hair follicles and eccrine ducts [22]. Electron microscopy may identify normal or diminished amount and diameter of desmosomes, lack of inner dense plaques, and disconnected intermediate filaments. Immunofluorescence staining using antibodies against the C-terminus of desmoplakin protein tails to demonstrate the presence of the protein [8] can be also used. Furthermore, utilization of anti-keratin antibodies revealed a concentrated perinuclear staining [22].

In our cases, there was an elevated level of *alpha*-fetoprotein as described in previous data [23]. In addition, both fetuses showed several of the signs of congenital EB. The first fetus' scans revealed flat nasal bridge, hypoplastic nose, dysplastic kidneys, and SGA. The cardiac findings (dextrocardia, hypoplastic aortic arch and pericardial effusion) were never described in association with EB. The second fetus' sonographic phenotype showed some similarity to its sibling with hypoplastic nose, micrognathia, echogenic amniotic fluid and SGA. In addition, the second fetus demonstrated constantly open eyelids- a novel sonographic sign.

There are other skin conditions that can be a part of the differential diagnosis. Ichthyoses are a group of skin conditions in which there is disorganized keratinization. The abnormal keratinization manifests as scaly skin, and leads to prompt transepidermal water loss postnatally [24]. Ichthyosis prematurity syndrome (OMIM# 608649) is a rare autosomal recessive condition described by three clinical manifestations - premature birth, ichthyosis, and neonatal asphyxia [25]. It is caused by bialleilic pathogenic variants in *SLC27A4*. Aspiration of skin debris is considered to be the cause of neonatal asphyxia [26]. Maternal symptoms may include abdominal pain, contractions and PPROM, probably due to polyhydramnios. PPROM may also derive from separation of the fetal membranes [27, 28]. Prenatal ultrasound may present separation of chorionic and amniotic membranes and polyhydramnios with echogenic sediment [26, 29] in the amniotic fluid due to skin debris from the hyperkeratotic disorder, and seems to be a common finding in fetal ichthyoses [14, 28, 30–32].

Harlequin ichthyosis is a serious form of congenital ichthyoses. This is an autosomal recessive disease due to biallelic pathogenic variants in the *ABCA12* gene on chromosome 2 [33, 34].

The main manifestations encompass dry fish-like skin, made of hyperkeratosis with deep erythematous fissures between thick yellowish armor-like plaques covering the whole body. The fetus may present with inadequate growth and movement because of the dry shield-like restrictive skin. Lack of growth can impair lung development. Sonographic findings include microcephaly, flat nose and hypoplastic ears [33, 35]. In addition, stretching of the periorbital and perioral areas causes long lasting opening of *the* eyes and mouth, and outward turning of the eyelids (ectropion) and lips (eclabium) [33, 36]. Furthermore, the extremities become tense and locked in flexed position, with clasped hands and clubfeet. Short umbilical cord, polyhydramnios, echogenic amniotic fluid, and subcutaneous edema may also be visualized by ultrasound [35–37]. It is possible to diagnose the molecular background of Harlequin ichthyosis with amniocentesis or chorionic villi sampling. However, ultrasonography can also help with the diagnosis [33, 38].

Immunodysregulation, Polyendocrinopathy, Enteropathy, X-linked (IPEX) syndrome is a.

rare, X linked recessive disorder caused by pathogenic variants in *FOXP3* gene. This is an autoimmune condition that is attributed to absence of development of T regulatory cells, that are a key component to the evolution of self-tolerance [39]. Manifestations consist of diarrhea, enteropathy, eczema, and insulin-dependent

diabetes mellitus [40]. Most cases of IPEX are identified during early life because of severe enteropathy presenting as serious diarrhea. Many of the infants with the disorder have dermatitis. Prenatal presentation of IPEX can be associated with prematurity, hydrops, intrauterine growth restriction and akinesia. Definitive diagnosis is made by identification of a pathogenic variant in *FOXP3* in a male (fetus) [41, 42].

As far as we know, this is the first description of prenatal sonographic findings of LAEB. As was discussed, congenital skin denudation disorders may have various intrauterine presentations that can by identified by prenatal ultrasound. Knowledge of the different sonographic signs and common manifestations, may assist clinicians to suspect a skin condition in the fetus and raise the need to go forward with genetic diagnosis. Such prenatal diagnosis may assist both dermatologists and neonatologists prepare for the care the patient requires, and schedule prenatal counseling for the family. If there is a clinical suspicion in a family without a history of skin disorders, prenatal diagnosis can be made by using fetal whole exome sequencing following proper pretest genetic counseling.

If a pathogenic variant is discovered in the *DSP* gene, the post-test genetic counselling should stress that a comprehensive understanding of the genotype-phenotype correlation is still lacking for this gene. As such, currently, it is impossible to predict the expected clinical presentation by the specific pathogenic variant, especially for novel variants. For this reason, diagnosis of a pathogenic variant in the *DSP* gene of a fetus may also project on the index patient as well as on other family members carrying the same pathogenic variant on the likelihood of developing ARVD later in life. Therefore, cardiac monitoring is recommended for carriers of the pathogenic variant. No other clinical findings such as woolly hair or keratoderma were noticed in the parents but both were referred to cardiologic surveillance. We do not have details regarding their follow-up.

In conclusion, there are sonographic characteristics indicative of severe fetal skin diseases. An acquaintance of the sonographer with this spectrum of findings may heighten the index of suspicion and prompt a referral for genetic investigation.

Abbreviations

ARVD	Arrhythmogenic right ventricular dysplasia
LAEB	Lethal acantholytic epidermolysis bullosa
SGA	Small for gestational age
EFW	Estimated fetal weight
TORCH	Toxoplasmosis, others(Syphilis, Hepatitis B), Rubella, Cytomegalovirus, and Herpes simplex
PPROM	Preterm premature rupture of membranes
ACMG	American College of Medical Genetics
IF	Intermediate filaments
EB	Epidermolysis bullosa
OMIM	Online Mendelian inheritance in men
IPEX	Immunodysregulation, Polyendocrinopathy, Enteropathy, X–linked

Supplementary Information

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Supplementary Material 1

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Author contributions
ML– drafted the workHD– substantial contribution to conception, acquisition, analysis, interpretation of dataNH - substantial contribution to acquisition, analysis, interpretation of dataMG - substantial contribution to acquisition, analysis, interpretation of dataJP - substantial contribution to acquisition, analysis, interpretation of dataSS - substantial contribution to acquisition, analysis, interpretation of dataNOS - substantial contribution to acquisition of dataSP– substantial contribution to conception, and substantively revised itAll authors read and approved the final manuscript.

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Data availability
Sequence data that support the findings of this study have been deposited in the ClinVar database with the primary ID code SUB13160998. The submission has pass the pre-validation phase and now is in the validation phase.

Declarations

Ethics approval and consent to participate
the need for approval was waived.

Competing interests
The authors declare no competing interests.

Consent for publication
Both parents provided consent for the publication, both verbally (via a phone call with one of our Arabic-speaking genetic consultants) and in writing.

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