Letter to the Editor

Prenatal sonographic evidence of hypohidrotic ectodermal dysplasia and postnatal genetic testing of a family line of child

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Introduction

The rapid evolution of high technology has not only brought about significant transformations in human lifestyles and living environments but has also been linked to an elevated susceptibility to genetic diseases. Among the various subtypes of ectodermal dysplasia (ED), hypohidrotic ectodermal dysplasia (HED) emerges as the most prevalent. Predominantly inherited in an X-linked recessive pattern (XLHED), this condition exhibits a considerably higher prevalence in males compared to females. Characterized by the presence of two or more ED or morphological defects affecting sweat glands, hair, teeth, and fingernails, XLHED is often a result of mutations in the gene responsible for encoding ectodysplasin A (EDA) (1). Alternately, autosomal recessive and autosomal dominant inheritance patterns can be attributed to mutations in genes such as Wnt family member 10A (WNT10A), EDA receptor (EDAR), and EDAR-associated death domain (EDARADD), among others. Common clinical manifestations of HED encompass reduced sweating, tooth hypoplasia, and either sparse or complete baldness of the hair (2). Ectodermal development initiates during the embryonic period, leading to the manifestation of symptoms in infancy for individuals with XLHED. However, evidence of XLHED is seldom detected through prenatal ultrasound examinations during the fetal period.

Case presentation

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient's parents for publication of this article and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

During a routine ultrasound examination at 23 weeks gestation, the alveolar bone of the fetus in a 22-year-old pregnant woman was identified as thinner than the typical fetal alveolar bone, and there was an absence of visible tooth germ echoes (see *Figure 1A-1D*). The presence of evidence suggesting fetal XLHED was taken into consideration.

The parents rejected the diagnosis of the mentioned disorder following genetic counseling. The 22-year-old mother of the fetus and the 27-year-old father were both in good health. Prenatal puncture was suggested to the couple, but the mother declined, expressing concerns about the

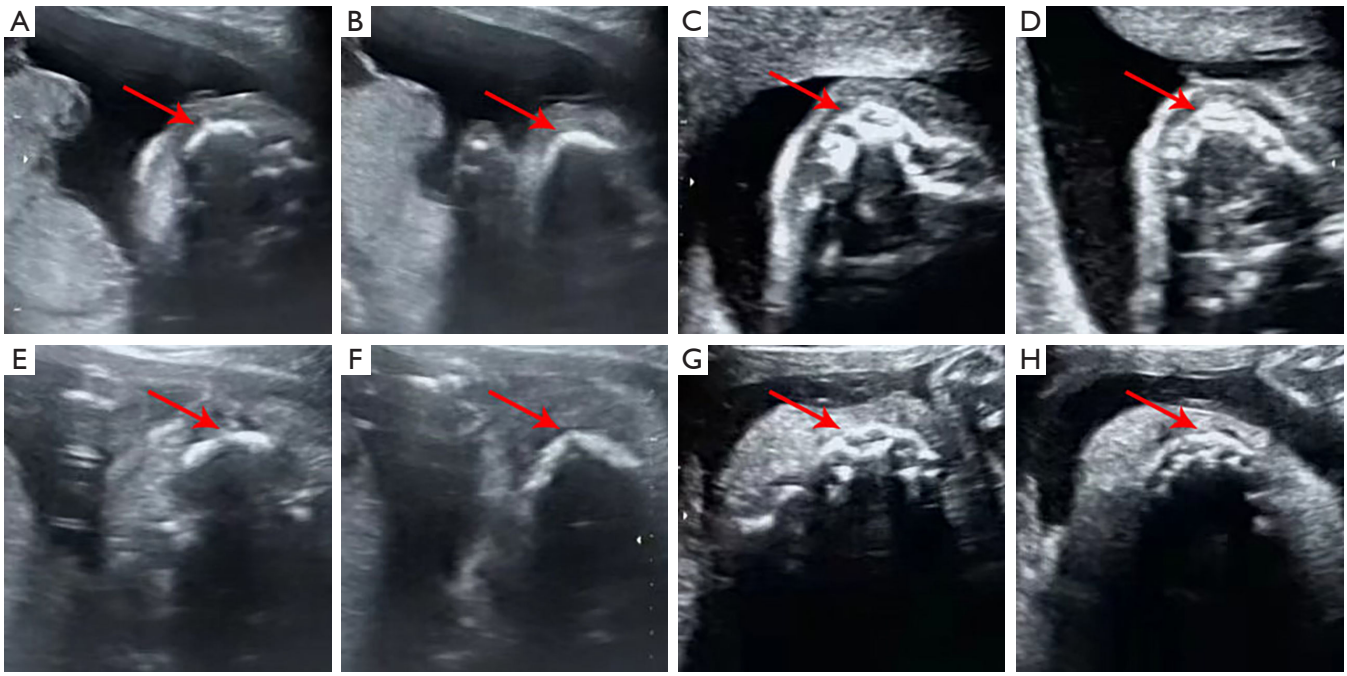


Figure 1 Comparison of intrauterine ultrasound images between the patient and normally observed fetus. At 30 weeks of pregnancy, the alveolar arch thickness was 3.5 mm in the patient and 7.6 mm in the normally observed fetus. (A,B) Ultrasonography of the alveolar bone of the affected fetus at 23 weeks of gestation, the red arrow in (A) is the upper the alveolar bone, the red arrow in (B) is the inferior alveolar arch. (C,D) Ultrasonography of the alveolar bone of the normally observed echogram of the alveolar bone of fetus at 23 weeks' pregnancies, the red arrow in (C) is the upper the alveolar bone, the red arrow in (D) is the inferior alveolar arch. (E,F) Ultrasonography of the alveolar bone of the affected fetus at 30 weeks of gestation, the red arrow in (E) is the upper the alveolar bone, the red arrow in (F) is the inferior alveolar arch. (G,H) Ultrasonography of the alveolar bone of the normally observed echogram of the alveolar bone of fetus at 30 weeks' pregnancies, the red arrow in (G) is the upper the alveolar bone, the red arrow in (H) is the inferior alveolar arch.

risks associated with cord blood puncture.

At 30 weeks, the alveolar bone of the fetus remained thinner than typically observed (see *Figure 1E-1H*), the alveolar arch thickness of this fetus was 3.5 mm, compared to 7.6 mm of the normally observed fetus, and there was still an absence of significant dental embryonic echogenicity.

The parents opted to proceed with the pregnancy, and a male newborn was delivered spontaneously at 40 weeks of gestation. Two months after birth, the family underwent genetic testing, utilizing a combination of high-throughput sequencing and Sanger sequencing. An EDA gene mutation was identified in the propositus (see *Figure 2* and *Table 1*). The patient exhibited a hemizygous mutation on the antisense strand, involving the substitution of the G base for the A base at position 467 of the coding region, specifically at the 69176947 base [1–3] on the X chromosome. Genetic testing of the parents did not reveal any mutations in the EDA gene (see *Figure 2*), confirming the *de novo* origin of the variant.

The patient, currently at one year and six months old, has not experienced the eruption of any teeth from both the upper and lower alveoli (see *Figure 3A,3B*). Additionally, there is thinning of the alveolar bone beyond the normal thickness. The patient exhibits sparse hair and eyebrows, along with localized peeling on the palms of the hands (see *Figure 3C*). Furthermore, the skin continues to display dryness and eczematous features (see *Figure 3D*).

Discussion

Our report shows prenatal ultrasound evidence of alveolar bone alteration, raising the diagnostic suspicion of congenital ED. Such fetal findings were confirmed after birth by genetic testing. Fetal tooth germs can be visualized via ultrasound as early as 13 weeks of gestation (3), and it is customary for a healthy fetus to exhibit at least 6 dental

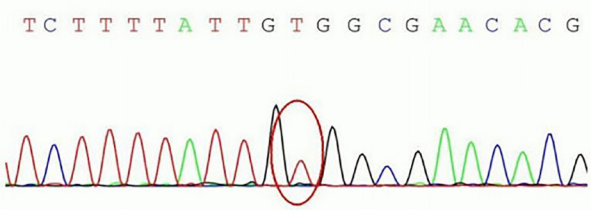
Testing results

1. Target area capture high-throughput sequencing parameters

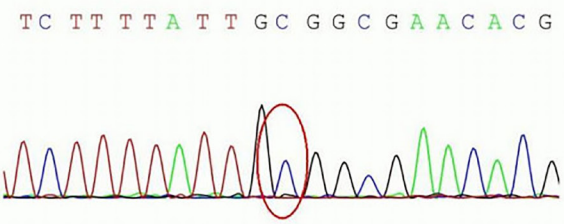
No.	Sample No.	Name	Coverage of target area	Average depth of target area	20X coverage of target area
1	QX2200686101	**	99.90%	174.100	99.80%

2. Sanger sequencing images of the examined loci

**(NGQX2200467901-1) chrX: 69176947 presence of hemizygous variants with c.467G >A (anti-sense chain)



The father of **(SHQX2200634202-1) chrX: 69176947 No variants found (anti-sense chain)



The mother of **(SHQX2200634303-1) chrX: 69176947 No variants found (anti-sense chain)

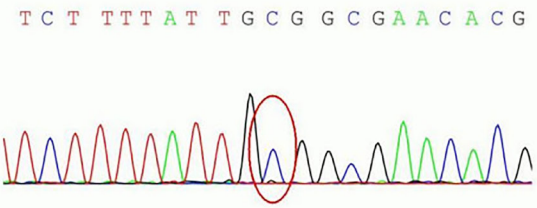


Figure 2 Pictures of genetic testing results of the patient and his parents' family line (the patient's ultrasound evidence was consistent with genetic testing).

germs in one alveolar bone (4). Recent research even suggests that ultrasonographic examination can reveal up to 10 dental germs in a healthy fetus (3).

In contrast, our patient exhibited thinning of the alveolar bone, an absence of clear echoes from the tooth germ, and hypoplastic alveolar bone. Therefore, when seeking evidence of XLHED through fetal ultrasound, it is crucial to pay attention to dental germ conditions and measure the thickness of the alveolar arch. Given XLHED's reduced sweating, the parents were advised to be vigilant about the child's living environment temperature, thereby minimizing the risk of hyperthermia and convulsions. Prolonged dry

Table 1 Report card of the patient's genetic testing (the patient's ultrasound evidence was consistent with genetic testing)

Genetics	Locus of variation (GRCh37/hg19)	Zygosity	Normal population carrier rate	Transcribed version gene subregion	Family lineage verification	ACMG variant rating	Disease information
EDA	c.467G>A; chrX-69176947 [1–3]; p.R156H	Hemicycle; 0/74; 1.00	–	NM_001399.5 exon2	Newborn	Pathogenic	(I) X-chain oligo hypohidrotic ectodermal dysplasia type 1 (XR); (II) X-linked selective dental hypoplasia type 1 (XD)

ACMG, American College of Medical Genetics and Genomics; EDA, ectodysplasin A.

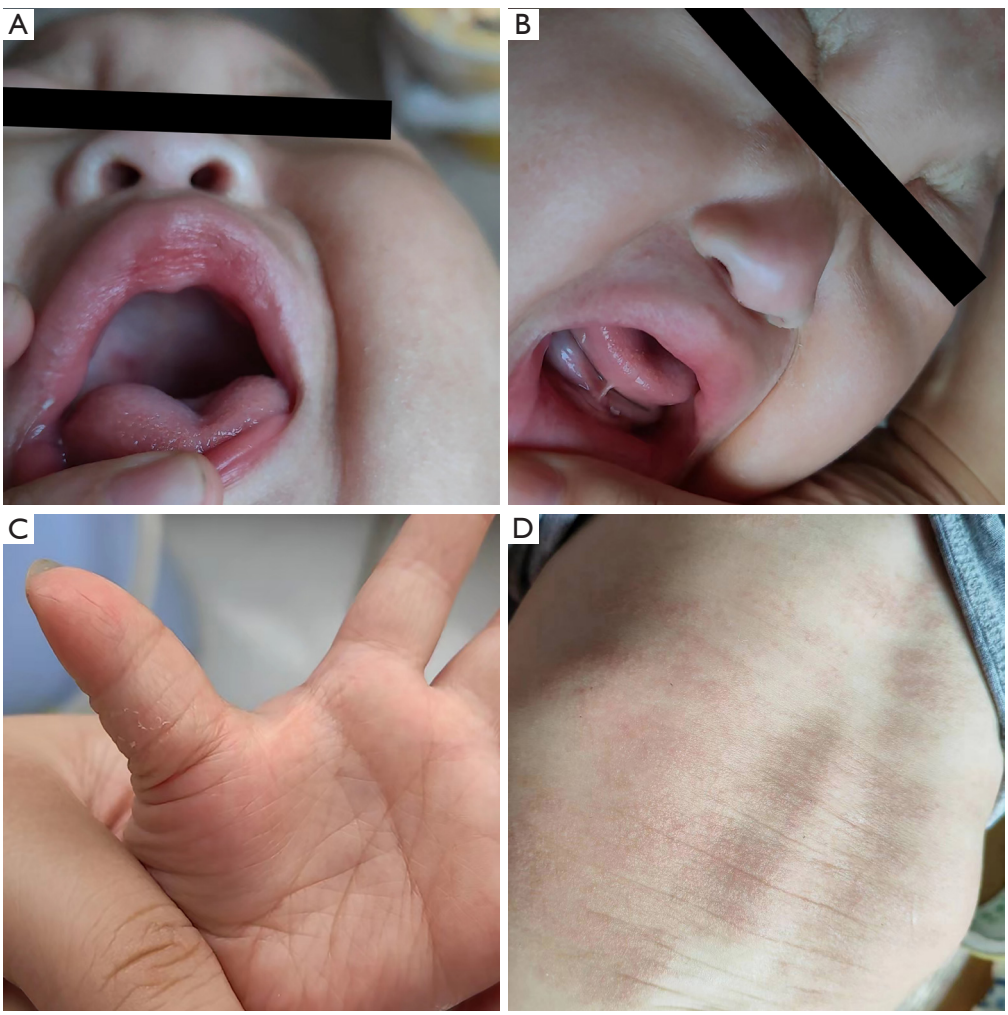


Figure 3 The patient's clinical symptoms at one year and 6 months old (these images are published with the patient's parents' consent). (A) Non-erupted upper teeth; (B) non-erupted lower teeth; (C) dry localized peeling skin on palms of hands; (D) dry eczema on the back of the skin.

skin observed in our patient was presumed to be linked to mucosal barrier damage, leading to the recommendation of long-term moisturizer use.

Dental anomalies can result in chewing difficulties and reduced nutritional intake. Considering the potential for insufficient nutrient intake, particularly with fluid diets, denture restoration should be contemplated to prevent growth retardation and enhance facial features. Symptomatic treatment has been the approach for XLHED, with ongoing research exploring potential treatments. The EDA replacement protein (FC-EDA) is currently in clinical trials and offers potential hope for X-LHED patients (4). Recent case studies propose that intrauterine injection of recombinant EDA in late pregnancy may prevent clinical manifestations of XLHED (5). In three cases treated with prenatal intrauterine injection of FC-EDA, improvements in sweat gland development and perspiration were observed. However, postnatal administration in 10 neonates showed no improvement in sweating function and teeth development (6). Therefore, considering the potential efficacy of prompt treatments, prenatal diagnosis of XLHED holds significant importance, providing a basis for prenatal treatment and protection against early infantile hyperthermia episodes.

Fetal ultrasound should be considered in cases of abnormal alveolar bone thickness, poor ossification, and reduced tooth germ. Diagnostic suspicion of XLHED raised through prenatal ultrasound must be confirmed postnatally through genetic investigations, utilizing a combination of high-throughput sequencing and Sanger sequencing. This method aids in distinguishing XLHED from other congenital ED with overlapping phenotypes (7), as well as from other skin-related congenital defects associated or not with other anomalies like cleft lip/palate or limb abnormalities [i.e., EED syndrome, cardiofaciocutaneous syndrome (8), TP63-related disorders (9)]. Another early diagnostic approach involves measuring EDA levels in amniotic fluid or cord blood (10), which can be supplemented by ultrasound-guided puncture to minimize the associated risks of cord blood or amniotic fluid puncture.

Ultrasound evidence of XLHED during the fetal period provides parents with the opportunity to gain a preemptive understanding of the disease's risks and prognosis. This early awareness enhances their knowledge of precautionary measures for postnatal care, allowing clinicians advanced insights into the patient's family genetics. It establishes a theoretical foundation for reproductive counseling, minimizing the risk of blind and excessive treatments. The necessity for long-term and individualized follow-up extends not only to the patients but also to their families, aiming to mitigate adverse outcomes (11).

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://qims.amegroups.com/article/view/10.21037/qims-23-1429/coif). J.Z. is an employee of Shanghai Lianying Medical Technology Co., Ltd., and reports that he had no financial or other conflicts with respect to this study. The other authors have no conflicts of interest to declare to this study.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient's parents for publication of this article and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

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