Non-invasive prenatal diagnosis of a fetus with hypohidrotic ectodermal dysplasia (HED)

Narayan V, Bhat M, Radhakrishnan P
Centre for Human Genetics, Bengaluru, Karnataka, India, Bengaluru, India

Objective
Noninvasive ultrasound marker for cost effective, rapid prenatal diagnosis of a suspected hypohidrotic ectodermal dysplasia in an advanced pregnancy with resource limited setting.

Methods
A 31 year old pregnant lady married non-consanguineously, consulted for the first time at the genetic clinic at 21 weeks’ gestation in view of her anomaly scan at 20 weeks showing fetal retrognathia. On detailed history, she had lost a two-year-old brother from a recurrent fever related illness. She has a 28-year-old younger brother who has been clinically diagnosed with HED. He has sparse scalp and body hair from the start and decreased number of teeth especially in his front jaw with a jutting out chin. He has had some social issues dealing with his appearance. The proband herself had dental repair of her incisor teeth in the past. In the family, two male cousins of her mother are also said to be similarly affected. Molecular testing has not been done in any affected family members. A 50% chance of fetus inheriting the HED was discussed. The couple declined molecular testing and invasive prenatal diagnosis in view of cost concerns and the turnaround time for results but were keen on understanding the possibility of fetus having HED. As per Hammersen (2019), a diagnosis of X-Linked HED was considered if less than six tooth germs are detected in mandible or maxilla between gestational weeks 18 and 28. A focused ultrasound was performed to look at the tooth buds in this fetus. The fetus was found to have four tooth germ cells. The family was counselled that the future baby would have the same condition as the maternal uncle although it is difficult to predict the extent to which the baby may be affected. She delivered at term and postnatal examination of the baby showed typical features of HED. Precautionary care of avoiding excessive warm environment and adequate hydration was advised. Molecular testing by next generation sequencing in the baby was done.

Results
Antenatal scan at 21 weeks showed borderline micrognathia with jaw index of 23.5 (normal cutoff-24), inferior facial angle of 66 (normal 49-81) and fronto-naso-mental angle of 130 (normal 140-152) and four tooth germ cells. Postnatal evaluation of the fetus clinically and on molecular testing confirmed the diagnosis of HED-I due to likely pathogenic hemizygous variant in EDA gene, c.1045G>A (p. Ala349Thr) and mother was found to be carrier of this EDA variant. A multidisciplinary team of dermatologist, ophthalmologist, maxillofacial surgeon, pediatric dentist was engaged in planning the timely management of the child.

Conclusion
In a resource limited country like India, the noninvasive prenatal diagnosis of HED-1 by tooth germ cell assessment after 20 weeks’ gestation is a cost-effective rapid diagnostic tool in fetus with retrognathia and those with family history of ectodermal dysplasia. With evolving studies for intraamniotic prenatal recombinant EDA protein therapy, this adds to prospects of non-invasive diagnosis followed by invasive therapy.
Images 5 & 6: Postnatal follow-up on day 2
Showing sparse curly hair, absent eyebrows and eyelashes, severe retrognathia & dry skin

<table>
<thead>
<tr>
<th>Gene (Transcript)</th>
<th>Location</th>
<th>Variant</th>
<th>Zygosity</th>
<th>Disease (OMIM)</th>
<th>Inheritance</th>
<th>ACMG Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>EDA (+) (ENST00000374552.9)</td>
<td>Exon 8</td>
<td>c.1045G&gt;A (p.Ala349Thr)</td>
<td>Hemizygous</td>
<td>Hypohidrotic ectodermal dysplasia-1</td>
<td>X-linked recessive</td>
<td>Likely Pathogenic</td>
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</tbody>
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ACMG - American College of Medical Genetics