A novel CHD7 mutation in an adolescent presenting with pubertal and growth delay


Background

Mutations in the gene encoding the Chromodomain Helicase DNA-binding protein 7 (CHD7) are found in >80% of patients with CHARGE syndrome (Coloboma, Heart Defects, Choanal Atresia, Retarded growth and development, Genital hypoplasia, Ear abnormalities and/or hearing problems) and in 6% of patients with Kallmann syndrome.

Clinical diagnostic criteria (Verloes 2005):
- Major criteria (3 Cs):
  - Coloboma
  - Choanal atresia
  - Hypoplastic semi-circular canals
- Minor criteria:
  - Rhombencephalic dysfunction
  - Hypothalmo-hypophyseal dysfunction
  - Abnormal middle or external ear
  - Malformation of mediastinal organs
  - Mental retardation

Diagnostic CHARGE criteria interpretation:
- Typical: 3 major or 2 major & 2 minor criteria
- Partial/incomplete: 2 major & 1 minor criteria
- Atypical: 2 major or 1 major & 3 minor criteria

Objective

To describe the diagnostic challenges of CHARGE syndrome using the example of a patient harboring a novel CHD7 mutation.

Case Presentation

A 14-year-old male presented for evaluation of delayed growth and puberty.

Family history:
- Delayed puberty in both parents

Past medical history:
- Born full term; eutrophic after an uneventful pregnancy
- Surgical repair of bilateral choanal atresia (5th day of life)
- Normal development, began walking at 18-months, history of imbalance during childhood - not formally investigated

Clinical examination:
- Anthropometry: Height -2.04 SDS; Weight -1.74 SDS
- Tanner: A1P2G1; Microenosis (4x1cm)
- Ogival palate, left helix anteversion, low set ears

Investigations:
- Cardiac US and ECG: normal
- Ophthalmologic exam: normal
- ORL: conductive hypoacusia, abnormal lateral and posterior semicircular canal function
- Olfactory testing (“Sniffi-Sticks”): anosmia
- MRI (see right)
  - semi-circular canal hypoplasia
  - olfactory bulb hypoplasia
  - decreased anterior pituitary volume (160mm3)
  - vestibular malformation, cochlear & R 7th cranial nerve malformation

Laboratory testing:
- Partial gonadotropin deficiency, otherwise normal pituitary function

Table: LHRR Stimulation Test

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<thead>
<tr>
<th>Testosterone (nmol/l)</th>
<th>LH (mU/l)</th>
<th>FSH (mU/l)</th>
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<td>0.3</td>
<td>0.1-1.76</td>
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Discussion & conclusions

We describe a novel CHD7 mutation (c.4323T>G, p.Tyr1412Asp) located in the Helicase C domain in a patient with CHARGE syndrome who remained undiagnosed until adolescence, despite the presence of suggestive features. Genetic testing promotes the broadening of phenotypic and genotypic spectrum of CHARGE syndrome and may give insight to the mild end of phenotypic spectrum, ensuring follow up and appropriate genetic counselling.

References

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