Early diagnosis and treatment of a newborn with a POU1F1 mutation

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Introduction

POU1F1 (Pit-1) encodes a pituitary-specific homeodomain transcription factor that is crucial for the development and differentiation of anterior pituitary cell types.

Mutations in POU1F1 result in combined pituitary hormone deficiency (CPHD). Specifically, POU1F1 mutations cause growth hormone (GH), thyrotropin (TSH) and prolactin (PRL) deficiency.

The R271W mutation exhibits a dominant-negative effect leading to mutant polypeptides that disrupt the activity of the wild-type gene when overexpressed.

Case report

Presentation & family history

Full-term infant born following spontaneous, uneventful pregnancy.

Mother’s history is notable for CPHD (GH / TSH / PRL).

Results

Laboratory results

<table>
<thead>
<tr>
<th>Laboratory</th>
<th>Unit</th>
<th>Normal range</th>
<th>Day 2</th>
<th>2 months</th>
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<td>4.7</td>
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<td>PRL</td>
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CPHD confirmed → central hypothyroidism, GHD, PRL deficiency

Genetic testing

• Blood was sent to the laboratory of Dr. Roland Pfaffl of the University of Leipzig (Germany) for genetic analysis.

• Sequencing of POU1F1 revealed the same p.R271W mutation as the mother.

• The residue maps to the C-terminal end of the POU-homeodomain (see right) http://www.uniprot.org/uniprot/P28069

Treatment challenges

• GH substitution:
  → few cases with GH substitution beginning during neonatal period:
    (starting dose = 0.021-0.033mg/kg/day)
    → favorable outcomes when GH treatment initiated before 1 year of age

• Treatment during pregnancy:
  → thyroid substitution needs to be adapted during pregnancy
  → to our knowledge, there is currently no recommendation for the growth hormone substitution during pregnancy

References


Abbreviations

BMP: bone morphogenic protein
DMRT5: dub1-like and mal-3-related transcription factor 5
FSH: follicle-stimulating hormone
FT4: free thyroxine
GH: growth hormone
IGFBP3: insulin-like growth factor binding protein 3
IGF1: insulin-like growth factor 1
LH: luteinizing hormone
PRL: prolactin
POU1F1: Pit-1
TSH: thyroid-stimulating hormone
TH: thyroid hormone
TSHR: thyrotropin receptor
SF1: Steroidogenic factor 1
SHH: sonic hedgehog

Diagnostic challenges

CPHD in neonates:
  → symptoms are non-specific
  → neonatal screening (TSH & T4) is needed to detect central hypothyroidism

Possible consequences:
  → inverse relationship between age at hypothyroidism diagnosis/treatment and intelligence quotient
  → risk of brain injury due to severe, repeated hypoglycemia

Cross-references

http://www.uniprot.org/uniprot/P28069

Imaging studies

Cranial MRI: hypoplastic adrenohypophysis

Radiographs (knee): delayed bone maturation

Residue 271