CAH Diagnostic Dilemmas: Two Case Reports

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Newborn Screening Program
Overview

- Present two case reports of infants with abnormal 17-OHP dried blood spot screens
- Illustrate the challenges of confirming a diagnosis of non salt-wasting CAH

[Chemical structure of 21-hydroxylase]
Elevated 17-hydroxyprogesterone (17-OHP) on dried blood spot
Referral to pediatric endocrinologist
Newborn physical exam & electrolytes
Serum 17-OHP & steroid panel
ACTH Stimulation test
DNA mutational analysis of CYP21A2 gene (in some cases)
Birth History

Case 1

- 1470g Caucasian male delivered at 28 wks gestation to a diabetic mother
- Hypoglycemic & hypotensive - first 24 hrs
- Baby remained in NICU for 2 months - primarily feeding & growth issues
Newborn Screens/Dx Labs

- 1\textsuperscript{st} NBS @2 hrs = 16.83 ng/mL (normal)
- 2\textsuperscript{nd} NBS @14 d = 155.18 ng/mL (presumptive)
  - Serum electrolytes normal
- 3\textsuperscript{rd} NBS @34 d = 90.83 ng/mL (borderline)
  - Serum 17-OHP @40 d = 58 ng/mL (ELEVATED)
Further Diagnostic Work-up

- Urine electrolytes; androstenedione, testosterone & renin levels @43 d NORMAL
- Diagnosis: CAH, 21-hydroxylase deficiency, non-classic form
- Rx @48 d: ¼ of 5 mg hydrocortisone q 8hrs
At 15 Months of Age

- Healthy toddler at 3rd %ile for height & weight; 40th %ile head circumference
- Labs indicated mild adrenal over-suppression
- DNA analysis negative for common & rare CYP21 (21-hydroxylase) mutations
Final Disposition

- ACTH stimulation test performed: results indicated *normal adrenal response*
- Revised diagnosis - child does **NOT** have CAH
- Hydrocortisone discontinued
Challenges in this Case

- “Premie” with persistent elevations in 17-OHP
- Too sick to perform earlier ACTH stimulation test
- Delay in DNA mutation analysis
Case 2

- Full term 3470g Black/Asian female
- Ambiguous genitalia (fusion of labioscrotal fold, single vaginal urethral opening, clitoromegaly)
- Karyotype: 46, XX
Diagnostic adrenal work-up initiated
Serum 17-OHP @ 2 d = 4.23 ng/mL (normal)
Electrolytes & androstenedione normal
CAH ruled out; possible adrenal tumor?
Newborn Screens & 2nd Opinion

- 1st NBS @51 hrs = 31.82 ng/ml (normal)
- 2nd NBS @12 d = 116.17 ng/ml (presumptive)
- Possibility of CAH re-opened
- Consult with different pediatric endocrinologist
ACTH stimulation test indicated **abnormal adrenal response, but no salt-wasting**

CYP21 DNA: I172N/I172N (or complete deletion)

Diagnosis: **CAH, 21-hydroxylase deficiency, simple-virilizing form**

Rx @85 d: ¼ of 5 mg hydrocortisone q 8hrs

Referral to Disorders of Sex Development Clinic
Challenges in this Case

- Slow to rise 17-OHP level & other steroids
- Incomplete initial evaluation: no ACTH stimulation test or DNA analysis
- Differing professional judgment
21-Hydroxylase Deficiency

Adrenal Gland Hormone Production in CAH
### Different Forms of CAH

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<tr>
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<th>Salt-Wasting</th>
<th>Simple-Virilizing</th>
<th>Non-Classic</th>
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<tbody>
<tr>
<td>17-OHP</td>
<td>↑↑↑</td>
<td>↑↑</td>
<td>↑</td>
</tr>
<tr>
<td>Cortisol</td>
<td>↓↓</td>
<td>near normal</td>
<td>normal</td>
</tr>
<tr>
<td>Aldosterone</td>
<td>↓↓</td>
<td>↑*</td>
<td>normal</td>
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<tr>
<td>Androgens</td>
<td>↑↑↑</td>
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* to compensate for salt-losing tendency
In Summary ...

- CAH is a complex group of disorders that can make a correct diagnosis difficult, especially a non salt-wasting form
- Long-term follow-up by NBS programs, & strong relationships with specialists, are helpful for accurate data collection & program evaluation
Questions?