Early diagnosis of CADDS in an infant with neonatal cholestasis who developed pancreatic exocrine insufficiency and interstitial lung disease.

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Introduction

- **ABCD1** and **BCAP31** (formerly **DXS1375E**) are contiguous genes located on chr Xq28.
- Contiguous **ABCD1/DXS1375E** deletion syndrome (CADDS) is an extremely rare syndrome involving **ABCD1** and **BCAP31**, with only 9 cases reported to date.
- Neonatal cholestasis and early infantile death underpin the severity of this disorder, but the underlying pathophysiology is poorly understood.
- We report the tenth case of CADDS in a male infant diagnosed through rapid whole genome sequencing and provide an extension to the phenotypic and biochemical features of the disorder.

Case Report

- The proband is a 6-month-old male of non-consanguineous parents, born at 38 weeks small for gestational age (birthweight 2.44kg). He has triangular facies with a broad forehead and a pointed chin. He presented with persistent cholestasis, hypotonia, sensorineural hearing loss and failure to thrive.
- He developed steatorrhea in the setting of pancreatic exocrine insufficiency, managed with Creon and fat-soluble vitamin supplementation. His MRI brain at 3 weeks showed normal myelination.
- Rapid trio whole genome sequencing at 1 month of age, and orthogonal validation with microarray, identified a 67 kb de novo deletion on Xq28 involving **ABCD1** and **BCAP31**, leading to the diagnosis of CADDS.
- At 6 months, he has profound hypotonia, global developmental delay and severe failure to thrive (weight 3.55 kg \(Z=-7\)). He is nutritionally supported with a medium chain triglyceride-based formula and was transitioned to continuous nasojejunal feeds due to recurrent vomiting.
- A lung CT carried out in the setting of increased work of breathing showed unexplained diffuse interstitial opacities.
- He has ongoing cholestatic liver disease that has been managed with ursodeoxycholic acid (UDCA) from 1 month of age. Cholic acid was introduced at 6 months after liver fibroscan showed no evidence of cirrhosis.
1. Peroxisomal biogenesis disorder-like biochemical profile

**Peroxisomal studies**

<table>
<thead>
<tr>
<th>Fatty acid profile</th>
<th>2 days</th>
<th>1 month</th>
<th>3 months</th>
<th>6 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>C24/C22 ratio 1.727 (RR: 0.550-1.050)</td>
<td>34</td>
<td>196</td>
<td>199</td>
<td>178</td>
</tr>
<tr>
<td>C26/C22 ratio 0.144 (RR: 0.0-0.3)</td>
<td>212</td>
<td>291</td>
<td>626</td>
<td>418</td>
</tr>
<tr>
<td>Pristanate 0.01 (RR: 0-2.5 µmol/L)</td>
<td>1287</td>
<td>267</td>
<td>585</td>
<td>644</td>
</tr>
<tr>
<td>Phytanate 0.9 (RR: 0-20.0 µmol/L)</td>
<td>206</td>
<td>65</td>
<td>76</td>
<td>26</td>
</tr>
</tbody>
</table>

**RBC Plasmalogens**

- Plasmalogen C16:0/Hb ratio 125 (RR: 140/500 µg/g Hb)
- Plasmalogen C18:0/Hb ratio 184 (RR: 261/475 µg/g Hb)

**Bile acids**

- Plasma bile acids 252 (RR: 1-62 µmol/L)
- Urine bile acids THCA ++

2. Cholestasis, liver dysfunction and pancreatic exocrine insufficiency

<table>
<thead>
<tr>
<th>Liver function</th>
<th>2 days</th>
<th>1 month</th>
<th>3 months</th>
<th>6 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALT (RR: &lt; 50 U/L)</td>
<td>34</td>
<td>196</td>
<td>199</td>
<td>178</td>
</tr>
<tr>
<td>ALP (RR: 100-350 U/L)</td>
<td>212</td>
<td>291</td>
<td>626</td>
<td>418</td>
</tr>
<tr>
<td>GGT (RR: 0-40 U/L)</td>
<td>1287</td>
<td>267</td>
<td>585</td>
<td>644</td>
</tr>
<tr>
<td>Total bilirubin (RR: &lt; 15 µmol/L)</td>
<td>206</td>
<td>65</td>
<td>76</td>
<td>26</td>
</tr>
<tr>
<td>Conjugated bilirubin (RR: 0-15 µmol/L)</td>
<td>14%</td>
<td>66 %</td>
<td>73 %</td>
<td>62%</td>
</tr>
<tr>
<td>INR (RR: 0-1.2)</td>
<td>92</td>
<td>2.7</td>
<td>316</td>
<td>1.1</td>
</tr>
</tbody>
</table>

**Fat-soluble vitamins**

- Vitamin A (RR: 0.6-1.8 µmol/L) 1.3<sup>†</sup> &lt;0.2<sup>‡</sup> 0.2
- Vitamin D (RR: 50-160 nmol/L) 15<sup>§</sup> 40

**Emphysema/Endocrine function**

- Faecal elastase (RR: &gt;200 µg/g) Repeated x3 at 2-4 weeks of life 0, &lt;15, &lt;15<sup>†</sup>
- AM Cortisol (RR: 100-440 nmol/L) 191 268 552
- ACTH (RR: <20 pmol/L) 15 16.2

To the best of our knowledge, we report the tenth case of CADDS. He is the first to have been diagnosed via rapid whole genome sequencing, preventing the need for a liver biopsy.

**Discussion**

Deletions are depicted with black (previous studies) and red (current study) bars. UCSC Genome Browser, GRCh38. The exact break point in Kamp et al.’s P6 is unknown, as depicted by an orange bar.4

Unenhanced CT chest at 6 months, lung windows. Axial images in the upper (A), mid (B) and lower zones (C) and coronal image (D) show diffuse smooth interlobar septal thickening (long blue arrows) and smooth interlobar fissural thickening (short blue arrows) bilaterally. In addition, patchy ground glass opacity is seen bilaterally, especially in the upper zones (blue arrowheads).

Figure 1. Location and size of chr Xq28 deletions in CADDS patients reported to date. 1-5

Deletions are depicted with black (previous studies) and red (current study) bars. UCSC Genome Browser, GRCh38.
The clinical and biochemical phenotype of CADDS cannot be solely explained by independent deficiencies of ABCD1 or BAP31. Intragenic loss-of-function (LoF) variants in ABCD1 cause X-linked adrenoleukodystrophy (X-ALD; ★) Intragenic LoF variants in BCAP31 cause the deafness, dystonia and cerebral hypomyelination (DDCH; ☆) syndrome. The severe neonatal cholestasis and early infantile death observed in CADDS are not features of X-ALD or DDCH. The proband had clinical and biochemical features akin to those seen in peroxisomal biogenesis disorders (PBD; ★). Pancreatic exocrine insufficiency and pulmonary interstitial infiltrates have previously been reported in one other case of CADDS.

The underlying pathophysiology of CADDS is poorly understood Possible synergistic deleterious effect of BAP31 and ABCD1 deficiencies on peroxisomal bile acid synthesis. Cholestasis, pancreatic insufficiency and respiratory pathology observed in CADDS is reminiscent of cystic fibrosis, warranting further investigation.

There is currently no definitive treatment for CADDS. Management is supportive. Creon supplementation led to a slow resolution of this patient’s pancreatic insufficiency. The clinical and biochemical impact of cholic acid in this patient remains to be characterized. Cholic acid has been found to have some benefit in disorders of primary bile acid synthesis and Zellweger Spectrum disorders.

Figure 2. Frequency of clinical and biochemical features reported in patients with CADDS
Early diagnosis of CADDS in an infant with neonatal cholestasis who developed pancreatic exocrine insufficiency and interstitial lung disease.

CONCLUSIONS

• Pancreatic exocrine insufficiency and pulmonary interstitial disease represent possible extensions to the CADDS phenotype.

• Other clinical and biochemical features described here are similar to those seen in peroxisomal biogenesis disorders.

• The underlying pathophysiology of CADDS is not clear. A deleterious synergistic effect between BAP31 and ABCD1 deficiencies may be impacting on peroxisomal bile acid synthesis and also contribute to the observed early infantile death.

• Rapid whole genome sequencing in the acute setting is a valuable tool for early diagnosis and can:
  • Prevent the need for invasive procedures
  • Allow early implementation of targeted therapies

• The potential benefit of cholic acid in CADDS remains to be elucidated.

Acknowledgements

We thank Dr Laura Raiti and Ms Ella Wilkins for their involvement in counselling the patient’s family within the Acute Care Genomics flagship.

Conflicts of Interest

None

References