Contiguous gene syndrome involving NR0B1 (DAX1) deletion with congenital adrenal insufficiency

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Take Home: The association of massive glyceroluria in a newborn with muscular hypotonia and symptoms of adrenal insufficiency may be caused by contiguous gene deletion in Xp21.3, involving NR0B1 (DAX1), DMD (Dystrophin), GK (Glycerokinase) and IL1RAPL1.

Introduction

In contrast to monogenic diseases, contiguous gene syndrome (CGS) describes a clinical phenotype caused by a deletion or duplication of several neighbouring genes. Angelman or Williams-Beuren syndrome are examples demonstrating that deletion of several adjacent genes causes a complex clinical syndrome. However, identification of CGS requires knowledge of (often very rare) combinations of clinical and laboratory findings pointing towards a specific chromosomal region. We present a 1 year old boy with hyponatremia, massively elevated creatine kinase and glyceroluria indicating a complex contiguous deletion of several neighbouring genes.

Case report

- Preterm twin born at 30 weeks of gestation, birth weight 1710 g (78. Perc.), length 42 cm (71. Perc.), HC 30.5 cm (93. Perc.). Non-consanguineous German parents. Initially delayed cardiopulmonary adaptation requiring CPAP support for 12 days.
- Profound and recurrent hyponatremia beginning at one week of age. No apparent neonatal hypoglycaemia was documented. However, because of reduced oral intake, parenteral nutrition was necessary for 17 days, subsequently nasogastric tube feeding until day 46, potentially masking predisposition for hypoglycaemia.
- No other specific syndromic aspects

Further results and discussion

- Initial laboratory evaluation showed normal basal cortisol (see Table 1).
- Massive glyceroluria and elevated triglycerides pointed towards Glycerokinase (GK)-deficiency with pseudo-hypertriglyceridaemia. CK levels and muscular hypotonia suggested congenital muscular dystrophy.
- Coding genes for these diseases lie in close proximity on chromosome Xp21.3, together with NR0B1 (DAX1), which may cause congenital adrenal hypoplasia. Thus, contiguous gene deletion in this region was hypothesized, and further detailed endocrinological evaluation was initiated. Now low urinary cortisol excretion, elevated ACTH/renin, persisting hyponatremia and an absent adrenal gland in ultrasound indicated adrenal insufficiency. Replacement therapy was started.

Array-CGH showed deletion of NR0B1 (DAX1), GK and DMD on Xp21.3. Additionally, IL1RAPL1 was partially deleted, potentially causing a variable spectrum of mental retardation, and further genes without known clinical association. Fortunately, the neighbouring gene for ornithine carbamoyltransferase (OTC), causing an urea cycle disorder, was not affected.

Clinical course until the age of now 14 months:
- Hydrocortisone and fludrocortisone replacement therapy was continued.
- Muscular hypotonia is persisting and CK levels remain increased to 6000-26000 UI, underlining the clinical relevance of DMD deletion.
- So far, there are no signs indicating clinical relevance of glycerokinase deficiency (which might cause mild predisposition to ketotic hypoglycaemia).
- Furthermore, DAX1 mutations may be associated with hypogonadotropic hypogonadism. In this patient, gonadotropin and testosterone levels showed a regular infantile “mini puberty” (max testosterone 6.12 ng/ml). However, this may not finally exclude the development of hypogonadotropic hypogonadism in future.

Conclusions

Contiguous deletion of x-chromosomal genes leads to a complex disease pattern involving multiple systems. The association of adrenal insufficiency, elevated creatine kinase and glyceroluria in variable combinations strongly indicates a contiguous gene syndrome with deletion of Xp21.3.

Knowledge of this disease may facilitate timely diagnosis and treatment, and thereby significantly improve the prognosis of severely affected neonates, who may present with life-threatening metabolic derangements in early infancy.

Genetic results

Array-CGH showed deletion in region of Xp21.3
- NR0B1 (DAX1, complete deletion)
- GK (Glycerokinase, complete deletion)
- DMD (Dystrophin, complete deletion)
- IL1RAPL1 (partial deletion)

The neighbouring gene for ornithine carbamoyltransferase (OTC), causing an urea cycle disorder, was not affected.

Tab. 1.: Metabolic Profile

<table>
<thead>
<tr>
<th>Metabolic Profile</th>
<th>Initial profile (day 10 of life)</th>
<th>Subsequent profile (day ~28 of life)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACTH (basal)</td>
<td>247 ng/l</td>
<td>7.2 – 63 ng/l</td>
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<tr>
<td>Cortisol (basal)</td>
<td>15.9 µg/dl</td>
<td>12.5 µg/dl</td>
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<tr>
<td>Renin</td>
<td>&gt; 500 pg/ml</td>
<td>1.7-23.9 pg/ml</td>
<td></td>
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<tr>
<td>Urinary Cortisol Excretion</td>
<td>6.6 µg/dl</td>
<td>10.8-71.3 µg/dl</td>
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<tr>
<td>Sodium</td>
<td>123 mmol/l</td>
<td>132 mmol/l</td>
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<tr>
<td>Potassium</td>
<td>7.89 mmol/l</td>
<td>4.7 mmol/l</td>
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<tr>
<td>Creatine kinase (CK)</td>
<td>1990 UI</td>
<td>&lt;295 UI</td>
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<tr>
<td>Creatine kinase – MB</td>
<td>115 UI</td>
<td>7-25 UI</td>
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<tr>
<td>Triglycerides</td>
<td>1259 mg/dl</td>
<td>&lt;150 mg/dl</td>
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<tr>
<td>Glyceroluria</td>
<td>Massive</td>
<td></td>
<td></td>
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</tbody>
</table>

Acknowledgements and literature

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Literature:

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