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 30.5cm (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**, **muscular hypotonia.** 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**

Tab. 1.: Metabolic Profile	Initial profile (~day 10 of life)	Subsequent profile (day ~28 of life)	Reference
ACTH (basal)		247 ng/l	7.2 – 63 ng/l
Cortisol (basal)	15.9 µg/dl	12.5 µg/dl	6.2 -19.4 µg/dl
Renin		>300 pg/ml	1.7-23.9 pg/ml
Urinary Cortisol Excretion		6.6µg/d	10.8-71.3 µg/d
Sodium	123 mmol/l	132 mmol/l	134 – 145 mmol/l
Potassium	7.89 mmol/l	4.7 mmol/l	3.3-4.6 mmol/l
Creatine kinase (CK)		1990 U/l	<295 U/l
Creatine kinase – MB		115 U/l	7-25 U/l
Triglycerides		1259 mg/dl	<150 mg/dl
Glyceroluria	Massive		

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**.

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-hypertriglyceridemia. 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.

This syndromic association was first described in 1980 by Guggenheim (1), followed by several case reports showing similar findings. In 1985, contiguous deletion of Xp21 could be identified as the cause (2).

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 U/l, 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 hypoglycemia).
- 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.

Acknowledgements and literature

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Literature:

(1) Guggenheim MA et al, Glycerol kinase deficiency with neuromuscular, skeletal, and adrenal abnormalities. Ann Neurol 1980 May;7(5):441-9.

(2) Wieringa B et al: Glycerol kinase deficiency syndrome explained as X-chromosomal deletion. Cytogenet Cell Genet 1985 40:777.

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