A first combination case of 21-hydroxilase deficiency and CHARGE syndrome confirmed by genetic analysis

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Introduction

21-hydroxilase deficiency (21OHD)

autosomal recessive inheritance
Disease gene : *CYP21A2*

Cause of over 90% Congenital Adrenal Hyperplasia cases

- Adrenal crisis due to salt wasting form
- Ambiguous genitalia (female)
- Penile enlargement (male)
- Hyperpigmentation
- Postnatal virilization
- Linear growth

?

CHARGE syndrome (CS)

autosomal dominant inheritance
Disease gene : *CHD7*

Verloes criteria[1)]

Major criteria
- Coloboma
- Choanal atresia/stenosis
- Hypoplasia/aplasia of semicircular canal

Minor criteria
- Rhombencephalic dysfunction
- Hypothalamo-hypophysial dysfunction
- Malformation of the internal external ear
- Malformation of mediastinal organs (heart, oesophagus)
- Intellectual disability

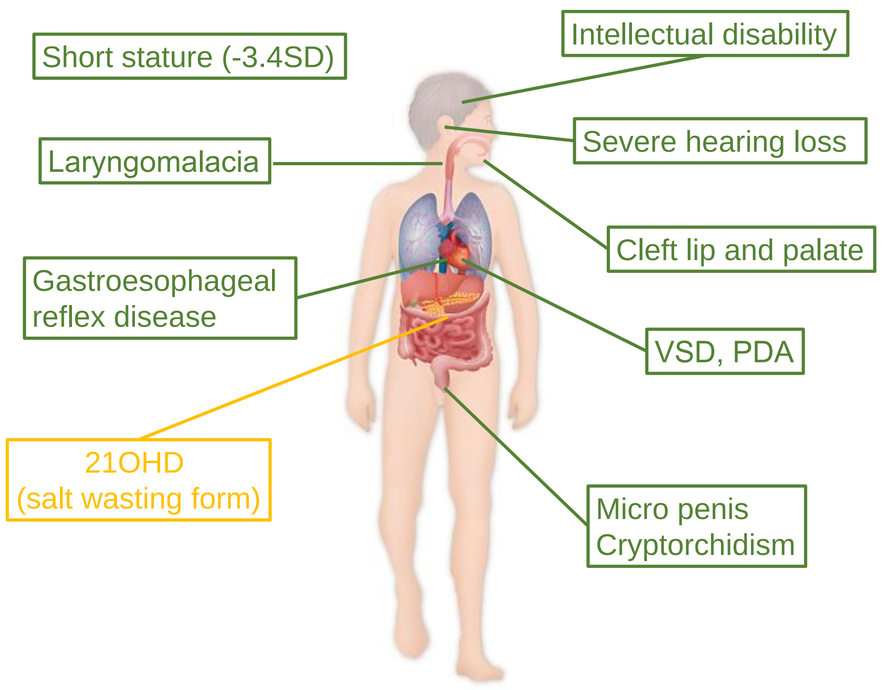
Typical:3 major or 2 major and 2 minor, Partial:2 major and 1minor
Atypical:2 major but no minor, or 1 major and 2 minor

Case Report: 7 year-old boy

【Clinical course】

- No problems in perinatal period, 37 weeks of gestational age.
- No consanguinity of parents.
- His brother suffered from 21OHD (simple virilizing form)
- At birth, having cleft lip and palate, ventricular heart septal defect, patent ductus arteriosus.
- No symptoms of 21OHD.
- No pigmentation of scrotum nor penile enlargement.
- At the age of 7 days, developing heart failure due to VSD. Diuretic drug started.
- At the age of 9 days, showing electrolyte abnormality, hypoglycemia and high values of 17-hydroxyprogesterone:18.3ng/mL(<3.5ng/mL). Clinically diagnosed with 21OHD and treated with fludrocortisone acetate and hydrocortisone.
- Genetic analysis: VS2-13A/C>G/I172N in *CYP21A2*. The same mutation of his brother.
- When he was referred to our hospital at the age of 3 months, he had various complications added to 21OHD symptoms.

【Summary of Complications】



Why does he show such various complications?
Not common features of 21OHD.

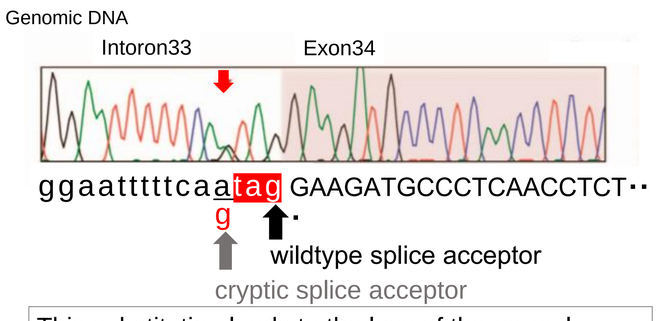
Suspected CS from his symptoms.

Genetic analysis of *CHD7* at age of 5 years

【Genetic analysis】

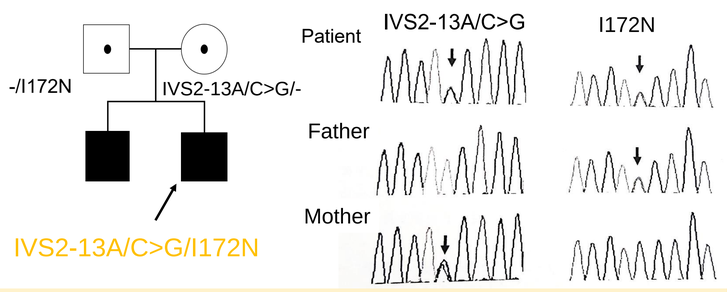
① A rare substitution that led to an alteration in the splicing acceptor and an ectopic premature termination within the 33 intron of *CHD7* [2)]

CHD7 Ex33 SP acceptor-4 A>G (GRCh37, Chr8:61769000 A>G)



This substitution leads to the loss of the normal acceptor site and gain of a cryptic splicing acceptor three bases upstream of the WT splice acceptor site. Moreover, the variant RNA contains a termination codon UAG (TAG) immediately after the cryptic splicing acceptor, leading to a loss of 610 C-terminal amino acids from the full-length

② IVS2-13A/C>G /I172N
Compound heterozygous mutations(*CYP21A*)



Discussion

✓Genotype-phenotype correlation in 21OHD

Genotype-phenotype in 21OHD has been known in previous reports.[3)4)5)] Generally, IVS2-13A/C>G mutation appears as 50% of salt wasting form and I172N mutation mainly appears as simple virilization form. Although our patient was salt wasting form, his brother was simple virilization. This difference of phenotype may depend on residual enzyme activity.
His external genitalia had weak virilization. In our case, may be strongly influenced by CS than 21OHD.

✓Why does his external genitalia have weak virilization; androgen excess in 21OHD v.s. androgen deficiency in CS?

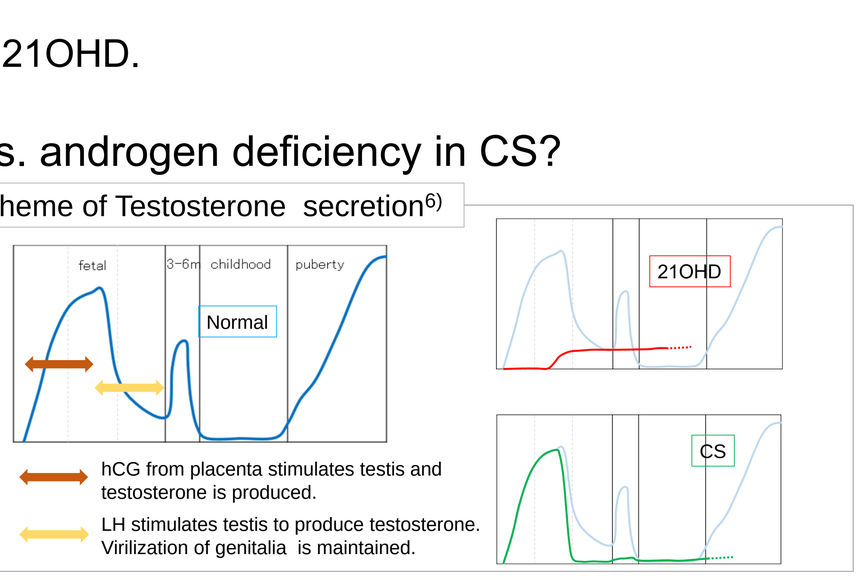
<Premise> In 21OHD, adrenal androgen excess induces acceleration of virilization.
In CS, hypogonadotropic hypogonadism induces external genital hypoplasia.

<Hypothesis>

①In 21OHD, an excess amount of secreted adrenal androgen during fetal period may be less than the required amount to maintain virilization during latter fetal period.

②The role of *CHD7* is still uncertain.*CHD7* may have some special role in the formation of external genitalia during fetal period.

Scheme of Testosterone secretion[6)]



Conclusion

We report a first combination case of 21OHD and CS confirmed by genetic analysis. We consider that this case occured accidentally. When the patients have atypical symptoms, we should consider that they have another disease additional to the primary disease.
An interesting point in our case is that his external genitalia had weak virilization. However, the cause is not clear. When a female case will be reported in the future, a clinical feature of a combination case with 21OHD and CS may be more clear.

References

1)Verloes A. Am J Med Genet A. 2005 2) Katoh-Fukui Y, et al. Hum Genome Var. 2018 3) Tajima T et al, J Clin Invest. 1993 4) de Carvalho DF et al, Eur J Endocrinol. 2016 5) New MI et al, Proc Natl Acad Sci USA. 2013
6)The Japanese Society of Pediatric Endocrinology, webtext diagnosis and treatment in DSD

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