

Development of a patient with severe pseudohypoaldosteronism due to mutation in the alpha subunit of ENaC

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Case report:

We present a 6 year old arabic boy, born preterm (33+1GW). The parents are related and healthy.

At day 9 the boy was presented with failure to thrive, vomiting and fever. Hyponatremia (126 mmol/l) and hyperkalemia (8,9 mmol/l) but no metabolic acidosis was documented.

The diagnostic work-up showed elevated levels of aldosterone 3000 ng/l (normal: 70-830 ng/l) and renin 1000 ng/l (normal: 5.9-132 ng/l) while 17-Hydroxyprogesterone, ACTH and cortisol were normal.

Recurrent problems of the lower respiratory tract made the hypothesis "systemic form of PHA1" very likely. A sweat test showed elevated chloride excretion.

The molecular sequencing of the genes for the epithelial sodium channel (ENaC) revealed a new mutation in the gene for the alpha subunit of the ENaC (SCNNA). This mutation leads to an exchange of only one amino acid (c.1678 G>A / p.Gly560Ser).

This mutation is near the second transmembrane domain, in a region which is presumed to be important for the ion sensitivity.

Maybe this is the reason for the severity of the illness in our patient, even though the mutation is just an exchange of one amino-acid. The patients published in literature with an equal phenotype do have stop- or frameshift-mutations.

The heterozygous parents do not have any clinical symptoms.

The now 7 year old boy develops well - both somatic (actual height -0,14 SDS, BMI -0,4 SDS) and mental, nevertheless we observed some life-threatening events in the first month of life. For example led the infection with a rota virus to a severe electrolyte imbalance with hyperkalemia of 10 mmol/l.

In the first years of life he suffered from very frequent infections with the need for hospitalisation due to respiratory insufficiency also together with hyperkaliaemia and hyponatremia. He needed fluid therapy, oxygen, inhalation treatment, intravenous antibiotic and anti-inflammatory therapy.

Now he still needs sodium supplementation, but the amount could be reduced from ~40 to ~15 mmol/kg/d. Also he needs resonium and sodium bicarbonate, all is given by percutaneous gastrostomy.

The clinical course of our case seems to be similar to other patients reported, because of the less frequent infections and the lower amount of sodium needed to correct the electrolyte imbalance

Pseudohypoaldosteronism type 1:

Salt wasting (hyponatremia, hyperkalemia and metabolic acidosis) is mostly caused by hypoaldosteronism.

Pseudohypoaldosteronism type 1 (PHA1) is a rare disease which is characterised by hyponatremia, hyperkalemia and metabolic acidosis despite of high levels of aldosterone and renin. This means there is a resistance for aldosterone.

This aldosterone resistance is caused either by a mutation of the mineralocorticoid receptor gene (NR3C2) or one of the genes coding for the epithelial sodium channel (ENaC).

Mutations in the mineralocorticoid receptor gene causes autosomal dominant PHA1, also called renal form, because the only symptom is salt loosing in infancy.

The second one is responsible for the systemic form of PHA1 and is inherited in an autosomal recessive pattern. It is a severe illness which includes severe salt loosing and characteristically recurrent problems with the lower respiratory tract.

ENaC consists of three different subunits: α , β , γ . The genes are SCNN1 α (Chromosom 12), SCNN1 β and SCNN1 γ (Chromosom 16)

It is a highly selective channel for small positiv ions like sodium and lithium. The channel is located in the apical membrane of polarized epithelial cells particularly in the kidney, the lung and the colon and is regulated by aldosterone.

In the last years the number of case reports on ENaC mutations and PHA increased, allowing better understanding of the disorder. There is no clear genotype/phenotype correlation and the clinical course differs significantly.

The disease severity has been defined as requiring frequent hospitalizations, persistent critical salt wasting and potentially life-threatening hyperkalemia, significant respiratory dysfunction and growth failure.

Conclusion:

1. PHA 1 has to be included - as a rare cause - in the differential diagnosis of severe salt wasting syndromes in newborns
2. a secure access way for the supplementation of the therapy is most important
3. To avoid trivial infections, consequent immunisation should be performed
4. The development with adequate therapy can be normal also in the severe phenotype

