Combined glucocorticoid and mineralocorticoid deficiency related to a new NNT mutation : a case report

E.Doye [1], CL.Gay [1], S.Castets [1], F.Roucher-Boulez [2], Y.Morel [2], I.Plotton [2], M.Nicolino [1]

[1] CHU Hospices Civils de Lyon, Service d'Endocrinologie Pédiatrique, Lyon, France ; [2] Hospices Civils de Lyon, Laboratoire d'Endocrinologie Moléculaire et Maladies Rares, Lyon, France

BACKGROUND

Familial glucocorticoid deficiency is an autosomal recessive disorder characterized by specific failure of adrenocortical glucocorticoid production in response to adrenocorticotropic hormone (ACTH).
Mutations of the NNT (nicotinamide nucleotide transhydrogenase) gene have recently been implicated in familial glucocorticoid deficiency.

OBJECTIVE

To describe a new case of familial glucocorticoid deficiency with combined mineralocorticoid insufficiency and extra adrenal manifestations.

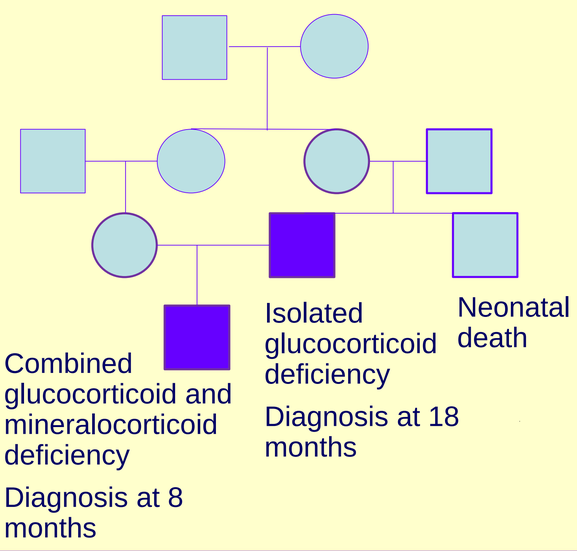
RESULTS

Suffering from a febrile viral respiratory disease, an eight-month-old boy presented with status epilepticus caused by hypoglycemia. Multiple medical complications occurred, and invasive ventilation was required for 18 days. The results of blood tests performed during hypoglycemia revealed adrenal insufficiency. Renin and aldosterone levels were high but considered consistent with the mild hyponatremia and severe hypotension. Subsequent measurements revealed persistent high renin levels with low aldosterone concentration and hyponatremia, confirming the diagnosis of partial mineralocorticoid deficiency. ACTH levels remained high after six months of suitable treatment.

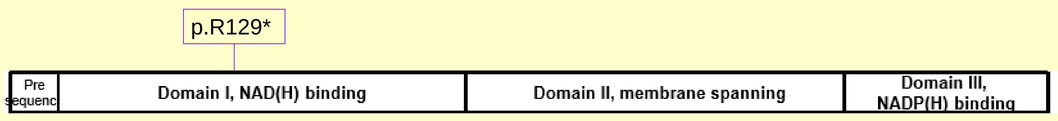
	Diagnosis : during hypoglycémia and severe hypotension	At one month	At six months
Natremia (mmol/L)	135	126	136
ACTH (ng/L)	1382	>2000	>2000
Cortisol (nmol/L)	<20	-	<20
Renin (ng/L)	2880	278	177
Aldosterone (pmol/L)	-	179	72

ADRENAL INSUFFICIENCY → Hydrocortisone and sodium supplementation

PARTIAL MINERALOCORTICOID DEFICIENCY → Fludrocortisone supplementation



His parents are consanguineous and his father has a glucocorticoid deficiency since he was 18 months old, without mineralocorticoid deficiency during childhood. Genetic analysis revealed a new homozygous NNT mutation (p.Arg129*) for the child and his father.



NNT encodes an integral protein of the inner mitochondrial membrane that acts as a proton pumping transhydrogenase. This enzyme uses energy from the mitochondrial proton gradient to produce high concentrations of NADPH needed for glutathione and thioredoxin antioxidant systems. NADPH is a cofactor of P450 enzymes, notably in steroidogenesis. NNT is a critical enzyme for reactive oxygen species detoxification in adrenocortical cells.

Why it affects adrenal hormone production preferentially remains unknown. All tissues rich in mitochondria may be affected.

Associated disorders :
- Thyroid stimulating hormone deficiency.
- Bradycardic sinus rhythm without cardiopathy.
- Neurological sequelae including severe hypotonia.

CONCLUSION

This case illustrates combined glucocorticoid and mineralocorticoid deficiency related to a new NNT mutation and underlines intra-familial phenotype heterogeneity. NNT gene should be considered when the most common etiologies of adrenal deficiency have been eliminated even if there is mineralocorticoid deficiency, in order to limit the serious consequences by a delayed diagnosis especially in offspring and to investigate any associated disorders.

References

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Adrenal
Emilie Doye
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