Chronic adrenal insufficiency due to a mutation of Nicotinamide Nucleotide Transhydrogenase 1 (NNT1) : case report

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INTRODUCTION

Congenital adrenal insufficiency represents a life–threatening condition. Among its multiple causes, mutation of NNT1 (Nicotinamide Nucleotide Tranhydrogenase) is the most recently discovered, causing an autosomal recessive disease. We had the opportunity to observe one case. NNT1 is a gene coding for a membrane protein which protects cells from oxidative stress and is expressed in many tissues (heart, thyroid, kidneys , adipose tissue) and is particularly important in adrenal glands which possess a high oxidative potential.
As few cases have been published until now (1) we describe one of them

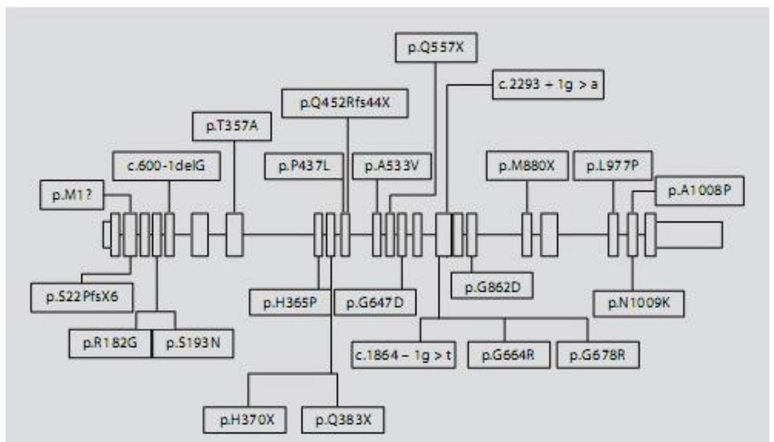

Figure 1 : mutations in NNT

CASE REPORT

In a consanguineous (parents first cousins) Algerian family, a first born female child deceased at the age of four years, in the context of an urinary infection. A second female child presented in Algeria melanodermia detected at the age of eight months. At this time, plasma ACTH at 500 pg/ml and undetectable aldosterone levels indicated global adrenal insufficiency. She was then treated with 20mg/m^2/d hydrocortisone, without mineralocorticoid replacement therapy. Melanodermia disappeared under treatment. However, ACTH levels remained incompletely corrected at one year of age When she was eight years old, during holidays in France, she suffered from asthenia, muscular weakness, bone pain and anorexia, without melanodermia. External genitalia were normal
Biologically, cortisol was undetectable, all intermediate plasma adrenal steroid compounds undetectable too, 17 hydroxyprogesterone included. ACTH was 356 pg/ml. Renin plasma activity was moderately increased (56pg/ml vs *normal values between 30-44pg/ml*), witnessing a residual moderate mineralocorticoid deficiency. SRY sequencing was negative. All known causes of *adrenal hyperplasia* were eliminated by hormonal exams. Other causes of adrenal hypoplasia were eliminated by Sanger sequencing method (STAR, CYP11A1,MC2R and MRAP) . Exon sequencing of NNT 1 gene revealed a p.Met337Val or c.1009A>G homozygous mutation in exon 9. This mutation corresponded to the NADH binding domain of the protein (Pr Y Morel, Lyon, France).
Extension investigations (growth, liver functions, cardiac ultrasound, skeletal X rays) were normal. Then hydrocortisone and fludrocortisone doses were adjusted.

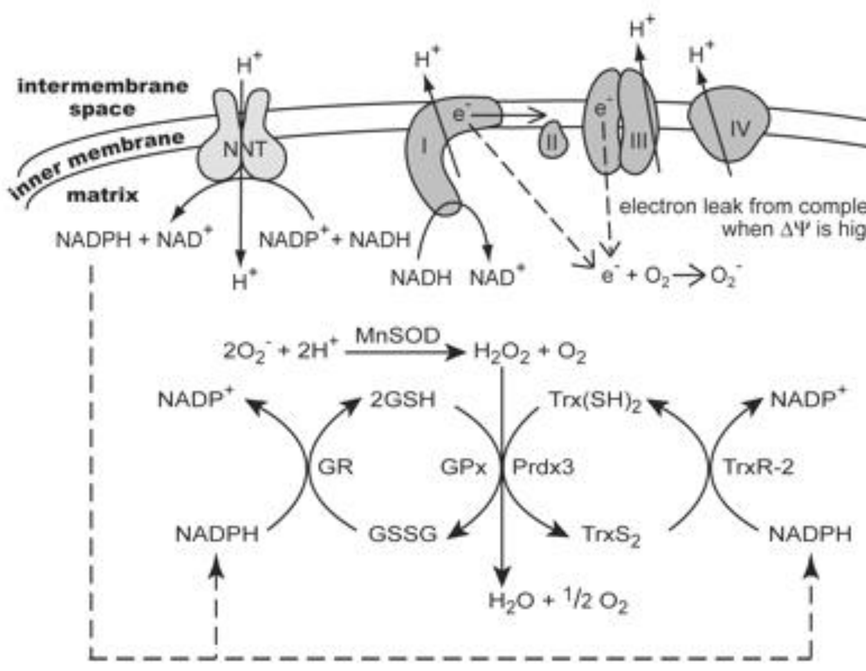

Figure 2: role of NNT

CONCLUSIONS

According to the literature intrafamilial severity of NNT1 mutation may be variable. Follow up extension investigations, especially cardiac, are mandatory, given the organs where the gene is expressed.

REFERENCES

1- F. Roucher-Boulez, et al. *NNT* mutations: a cause of primary adrenal insufficiency, oxidative stress and extraadrenal defects *European Journal of Endocrinology* (2016) 175, 73–84

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