Exaggerated Cortisol Response in Heterozygous Carriers with a Mutation in the Melanocortin-2 Receptor (MC2R) Gene

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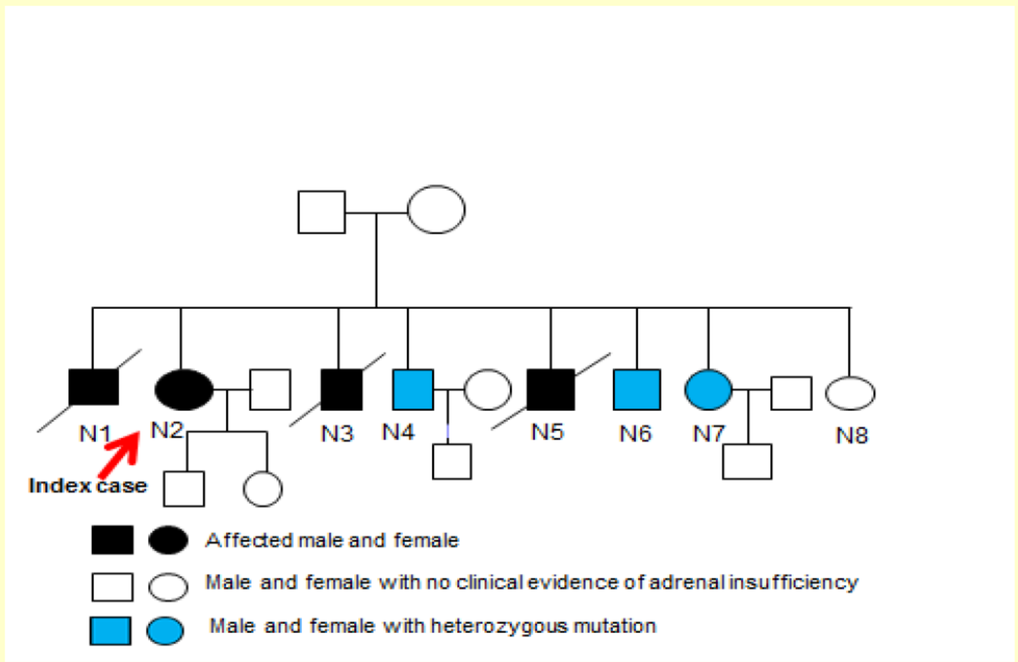
INTRODUCTION

Familial glucocorticoid deficiency (FGD) is a rare autosomal recessive disease characterised by ACTH resistance and isolated glucocorticoid deficiency.
Mutations of ACTH receptor, known as MC2R, and melanocortin-2 receptor accessory protein (MRAP) account for approximately 25% and 15% to 20% of cases respectively.
To date there is no strong evidence that heterozygous carriers have abnormal cortisol secretion.

CASE: PEDIGREE

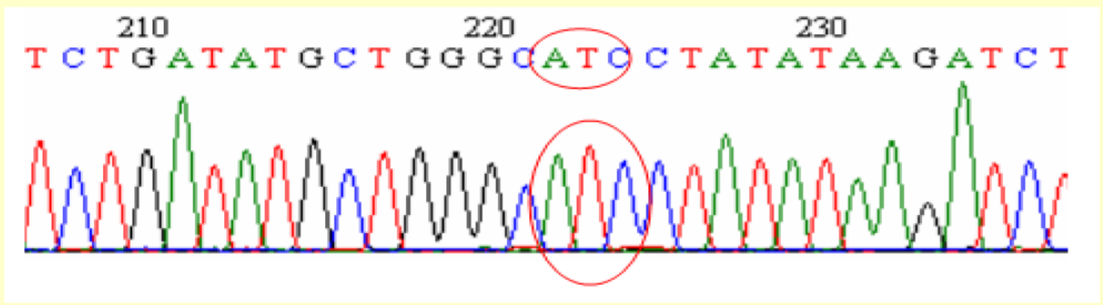
We studied a pedigree with a MC2R mutation where the index case (N2) presented with severe hypoglycaemia at three years of age in 1970s and was subsequently diagnosed with adrenal insufficiency (Figure 1).
Of eight siblings, two brothers died as neonates (N1 & N3), with hindsight due to adrenal insufficiency and a third brother (N5) was diagnosed with adrenal insufficiency when he presented comatose at two months and remained profoundly handicapped and later died (Figure 1).

Figure 1: The pedigree of the index case and family members



The index case was found to have a homozygous missense mutation c.221G>T, leading to p.S74I (substitution of serine with isoleucine at position 74) in the MC2R gene.

Figure 2: Nucleotide substitution of Guanine with Thymine at position 221 in MC2R gene in index case



STUDY OF HETEROZYGOUS CARRIERS

We studied three of her siblings with heterozygous S74I mutation in the MC2R gene (N4, N6 and N7).
The mean age of heterozygous carriers was 31.3±2.5 years.
They had generalised slightly tanned skin, but no significant hyperpigmentation. They were normotensive and had no symptoms suggestive of glucocorticoid deficiency.
Short synacthen testing with 250 mcg tetracosactide in the heterozygous carriers showed baseline mean ACTH levels of 53.7±31.9 ng/L (normal range <46 ng/L), 0 minute mean cortisol levels of 506±168 nmol/L, 30 minute mean cortisol levels of 952±85 nmol/L, and 60 minute mean cortisol levels of 953±36 nmol/L.

Table 1: Clinical Features of Heterozygous S74I mutation carriers and results of short synacthen testing

	N4	N6	N7
Age (years)	33	31	29
Gender	Male	Male	Female
SBP/DBP (mmHg) [lying] [standing]	135/75 130/70	100/70 110/70	80/50 80/50
ACTH at 0 min (<46 ng/l)	41	30	90
Cortisol at 0 min (nmol/l)	359	469	690
Cortisol at 30 min (nmol/l)	855	1007	996
Cortisol at 60 min (nmol/l)	990	952	919
Plasma Renin Activity (0.5 – 6.8 ng/ml/hr)	2	-	4.2
Aldosterone (140 – 1400 pmpl/L)	501	277	960
MC2R mutation	Heterozygous carrier S74I	Heterozygous carrier S74I	Heterozygous carrier S74I

CONCLUSION

The study of heterozygous MC2R mutation carriers demonstrated slightly elevated baseline ACTH levels with a relatively high baseline cortisol level and an exaggerated cortisol response to synacthen test.
These findings suggest there is no evidence of glucocorticoid deficiency despite elevated ACTH levels in heterozygous carriers with MC2R mutations.

References

Familial Glucocorticoid Deficiency: Advances in the Molecular Understanding of ACTH Action, Chan et al, Hormone Research, Vol. 69, No. 2, 2008
Hereditary isolated glucocorticoid deficiency is associated with abnormalities of the adrenocorticotropin receptor gene. Tsigos C et al, J Clin Invest 1993;92:2458-2461

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