The pituitary gonadal axis is not responsive to GnRH administration in PCSK 1 dysfunction

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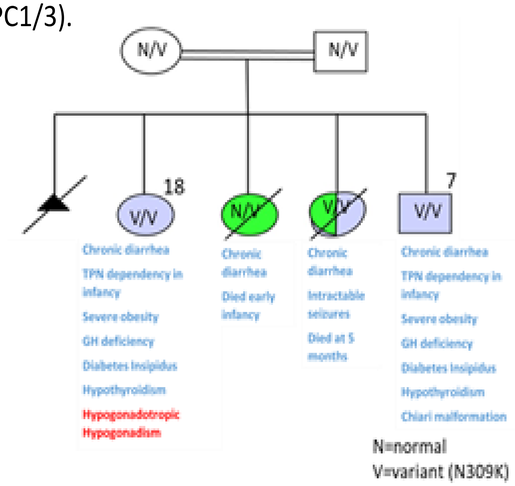
Background

*Patients homozygous for PCSK-1 gene mutation present with congenital diarrhea and hormonal defects due to aberrant prohormone processing by Prohormone Convertase 1/3 (PC1/3).

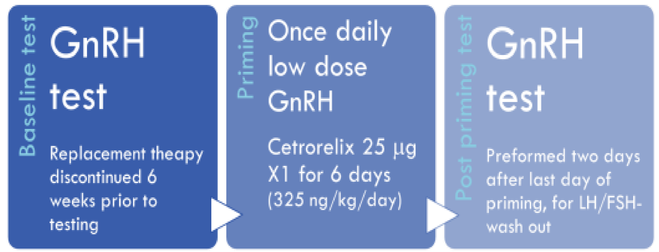
*Genetic evaluation of a consanguineous kindred presenting with congenital diarrhea and hormonal deficiencies, revealed the etiology – a malfunctioning N309K PCSK-1 gene mutation with severely decreased catalytic activity. (Wilchansky M et al. PLOS One 2014)



*Clinically, the 18y old female had congenital diarrhea followed by obesity, Diabetes Insipidus, cortisol, growth hormone and thyroid hormone insufficiency. Pubertal development, and regular menstruation were achieved only following hormone replacement therapy.

*Only 2 additional female patients were so far reported with hypogonadotropic hypogonadism due to PCSK-1 mutations. No hormone(s) in the hypothalamus-pituitary-gonadal axis (HPG) have been reported to be dependent on PC1/3 cleavage and the pathogenesis of low gonadotrophins has not yet been elucidated.

*Here we studied the effect of GnRH administration in a patient with PCSK-1 loss of function. Due to the importance of leptin signaling for the induction of puberty, we measured basal leptin and total ghrelin levels in an oral glucose tolerance test in both PCSK-1 patients.



Pre priming	LH (U/L)	FSH (U/L)
0'	0.04	1.12
20'	0.55	2.21
40'	0.75	3.27
60'	0.79	3.38

Post priming	LH (U/L)	FSH (U/L)
0'	0.09	1.08
20'	1.10	3.62
40'	1.10	3.60
60'	1.36	4.56

OGTT	0'	60'	90'	120'	180'
Ghrelin boy (pg/mL)	48	478			500
Ghrelin girl (pg/mL)	327	311	238	257	305
Leptin boy (ng/mL)	31				
Leptin girl (ng/mL)	41.6				

Methods and Results

*Hormonal replacement therapy was discontinued for 60 days. GnRH stimulation test was then performed prior and post a week of pituitary "priming" by 325ng/Kg/d of GnRH.

* Prepriming GnRH test results indicated no significant increase in gonadotropin response compared to almost undetectable basal levels.

* Interestingly post priming GnRH stimulation test did not show a significantly improved gonadotrophic cell response in basal or in peak levels of gonadotropins.

Conclusions

* The homozygous N309K mutation in the PCSK-1 gene causes hypogonadotropic hypogonadism, absence of spontaneous puberty and primary amenorrhea responsive to estrogen replacement therapy.

* Significant priming with GnRH failed to stimulate gonadotropin secretion in response to acute GnRH stimulation.

* Ghrelin is a known substrate for PC1/3 but still the two patients with a PCSK1 mutation showed normal levels of total ghrelin similar to other obese patients.

** Our findings are indicating a novel crucial role of PC1/3 in production and processing of gonadotropins within pituitary gonadotrophic cells.*