

# A case of testotoxicosis due to a constitutive mutation of the LH receptor initially presented as a central precocious puberty at 3 years old.



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Nothing to disclose

## BACKGROUND

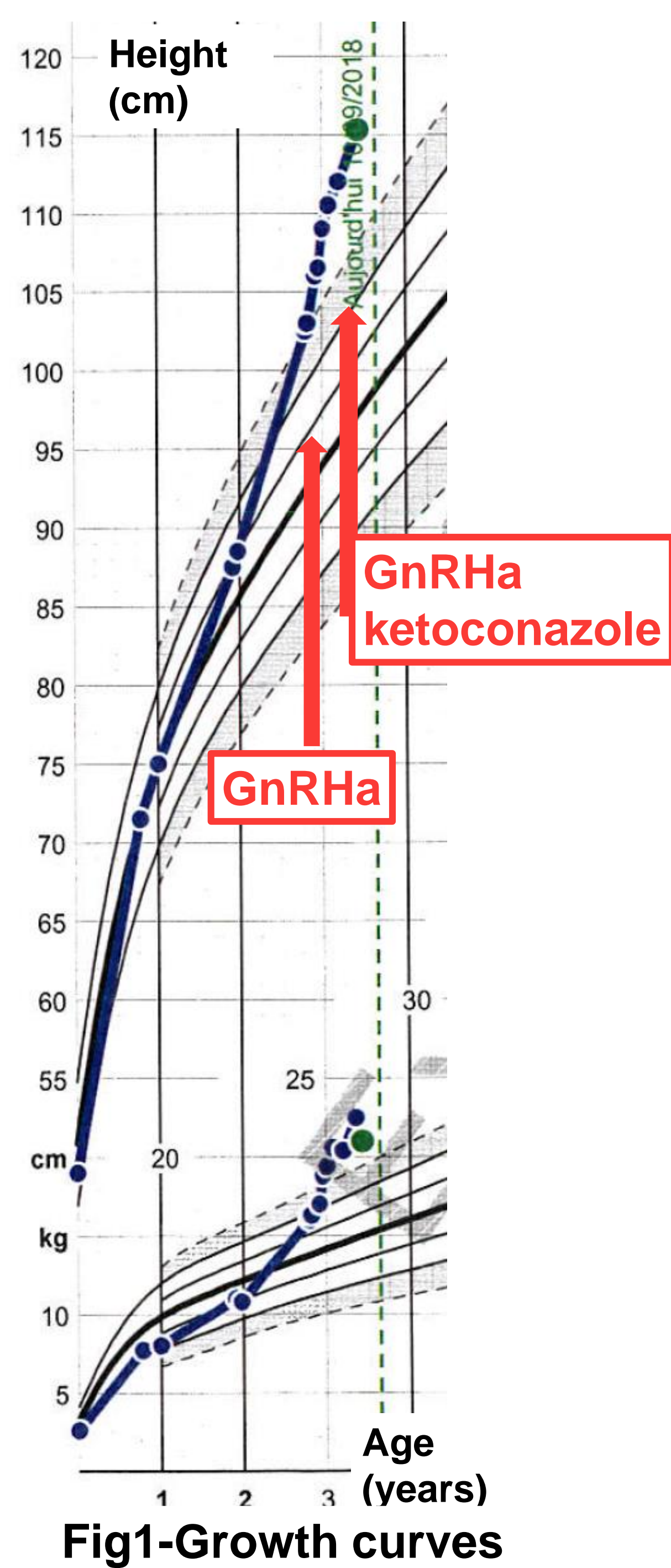
A thirty four months old boy was referred for precocious puberty. He was the first child of healthy non-consanguineous parents. His father was suspected to have enlarged testis during early childhood, without any investigation. His final height was 180 cm, uncompatible with precocious puberty. The boy had no exposure to oestrogenic endocrine-disrupting chemicals. He had presented secondary sexual characteristics for five months: pubic hair, enlarged testicular volume to 6 ml (Tanner stage P2A1G2) and enlarged penile size. He had a deepening voice and aggressive behavior. He had a significant growth acceleration with an advanced bone age (six years according to the Grulich and Pyle atlas). His height was 103 cm (3 SDS).

## LABORATORY INVESTIGATIONS

The testosterone level was high: 190 ng/dl. The gonadotrophin hormone-releasing hormone stimulation test revealed a baseline LH and FSH of 0.1 UI/l and peaks levels of LH at 2.6 UI/l and of FSH at 1.2 UI/l. The AMH level was 26.6 ng/ml. Inhibine was 189 ng/ml. The IGF-1 level was high, correlated to the testosterone level: 306 ng/ml (3 DS). The adrenal function was normal. Tumor markers, alfa-fetoptotein and beta-human chorionic gonadotrophin, were normal. Ultrasound of the testis and the adrenal revealed no tumor. The brain MRI excluded a tumor of the hypothalamus or the pituitary gland.

## EVOLUTION AND MANAGEMENT

The diagnosis of central precocious puberty was made and a treatment with monthly intramuscular injections of gonadotrophin releasing hormone analog (GnRHa) was started. Three months later, no clinical improvement was noticed: testicular volume progressed to 8ml, and height was 109 cm (4 DS) (Fig1). LH and FSH Baseline levels were 0.7 UI/l, and 0.1 UI/l respectively. The testosterone level increased to 311 ng/dl with a lowering AMH level at 12.3 ng/ml. GnRHa treatment was switched to long action every three months associated first to cyproterone acetate and then to ketoconazole. Ketoconazole has been introduced on month 5 and was quickly efficient to control testosterone levels (Fig 2).



	Base line	Month 1	Month 2	Month 5	Month 6	Month 7
Height (cm)	103	106	110,5		115,3	
(SDS)	(3,2)	(3,8)	(4,6)		(4,9)	
Testis volume (ml)	6	8	10		10	
testosterone (ng/ dl)	190	331			<13	30
LH (UI/ l)	0,1	1,1	0,5		<0,3	0,1
FSH (UI/ l)	0,1	0,1	0,1		<0,3	0,1
AMH (ng/ml)	26,6	12,3	8,5		13,9	
IGF-1 (ng/ml)	306		359			
(SDS)	(3)		(4,1)			
Treatment initiation and evolution	0	GnRHa/ monthly	GnRHa long action + cyproterone acetate 25 mg/d	GnRHa long action + ketoconazole 15mg/kg/d	GnRHa long action + ketoconazole 15mg/kg/d	GnRHa long action + ketoconazole 15mg/kg/d

Fig2- Evolution under treatment

## GENETIC ANALYSIS

We found a mutation of the LH-receptor gene (c.1193T>C; p.Met398Thr) already reported to constitutively activate the LH receptor [1]. The diagnosis of peripheral precocious puberty was made. The mutation was inherited from his father who didn't develop precocious puberty.

## CONCLUSION

This case of testotoxicosis is unusual as it initially presented as a central precocious activation of the gonadotropic axis at a very young age, with enlarged testis. Due to resistance to GnRH agonist treatment, the diagnosis of constitutive activation of the LH receptor was then suspected and confirmed by molecular genetics. The penetrance of the M398Tmutation is incomplete in that family, other factors may influence the clinical expression. Activating mutations of the LH receptor are heterogenous. The response to ketoconazole on inhibiting adrenal and androgen biosynthesis, is mutation-dependant. That boy presenting the M398Tmutation is sensitive to ketoconazole, with good hepatic tolerance, as previously described in a French cohort [ 2]. The case questions also about the cellular mechanism of the central activation of the gonadotropic axis.

## BIBLIOGRAPHY

- 1- A new point mutation in the luteinising hormone receptor gene in familial and sporadic male limited precocious puberty: genotype does not always correlate with phenotype. Evans BA, Bowen DJ, Smith PJ, Clayton PE, Gregory JW. *J Med Genet.* 1996 Feb;33(2):143-7.
- 2- Adult height after ketoconazole treatment in patients with familial male-limited precocious puberty. Soriano-Guillen L, Mitchell V, Carel JC, Barbet P, Roger M, Lahlou N. *J Clin Endocrinol Metab.* 2006 Aug;91(8):3041-7.