Familial testotoxicosis: outcome and possible relation to testicular malignancies

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Background

Testotoxicosis or familial male-limited precocious puberty (FMPP) is a rare disease caused by an autosomal dominant activating mutation of the luteinizing hormone receptor gene, leading to early gonadotrophin-independent precocious puberty. Phenotypic expression is limited to males. Treatment evolved over the last decades and nowadays consists of a combination of a potent anti-androgen agent and a third-generation aromatase inhibitor [1]. Since the identification of etiologic gene mutations in 1993, pre-symptomatic genetic testing provides the opportunity of early diagnosis and treatment without diagnostic delay.

Objective

Evaluation of clinical course and outcomes in families with familial testotoxicosis

Methods

Nine affected males; two generations in four families were evaluated. Information was gathered on clinical course, therapy and mutation analysis

	Age (y)	Age at diagnosis (y)	Mutation LHCGR gene	Treatment	Final height	Testicular malignancy
I -1 Patient	5	4,5	c1624A>C p.Ile542Leu	Age 4,5 y – CA Letrozole + Bicalutamide	NR	
I -2 Father	34	5	c1624A>C p.Ile542Leu	Age 5-12 y Ketoconazole	183 cm (TH 176)	non-seminoma + relapse
II -1 Patient	8	4	c1624A>C p.Ile542Leu	Age 4 y – CA Letrozole + Bicalutamide	NR	
II-2 Father	34	6	c1624A>C p.Ile542Leu	Age 6-7 y Ketoconazole Age 7-10 y Cyproterone + Spironolactone + Testolactone	187 cm (TH ?)	
III -1 Patient	10	4	c1624A>C p.Ile542Leu	Age 4 y – CA Letrozole + Bicalutamide	NR	
III -2 Father	42	2	c1624A>C p.Ile542Leu	Age 2,5 - ? Cyproterone	189 cm (TH 185)	embryonal carcinoma
IV -1Patient	19	1	c1624A>C p.Ile542Leu	Age 2-7 y Bicalutamide + Anastrozole Age 7-8 y Bicalutamide + Anastrozole + Exemestane Age 8-9 y Bicalutamide + Anastrozole + Exemestane + Ketoconazole Age 9-11 y Letrozole	171 cm (TH 177)	
IV-2 Patient	19	1	c1624A>C p.Ile542Leu	Same treatment as IV-1 patient	169 cm (TH 177)	
IV-3 Father		6	c1624A>C p.Ile542Leu	No treatment	165 cm (TH ?)	

NR: not reached yet. TH: target height . CA: current age

Results

For detailed patient information: see table.

I. Final height

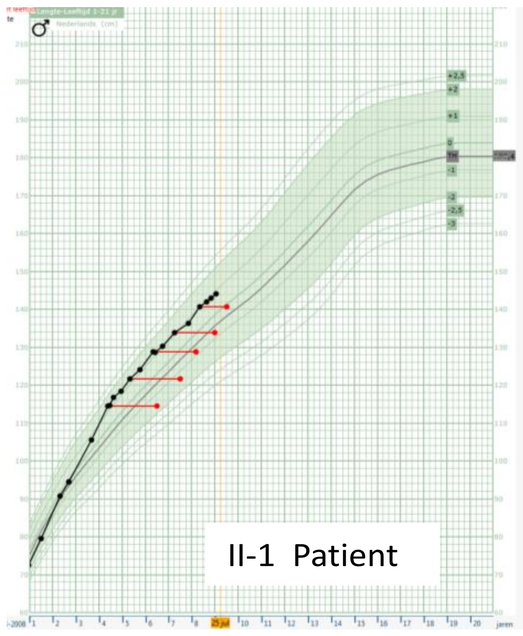
All four affected fathers were diagnosed based on clinical symptoms. Three were treated and attained normal final heights (183, 187 and 189 cm).

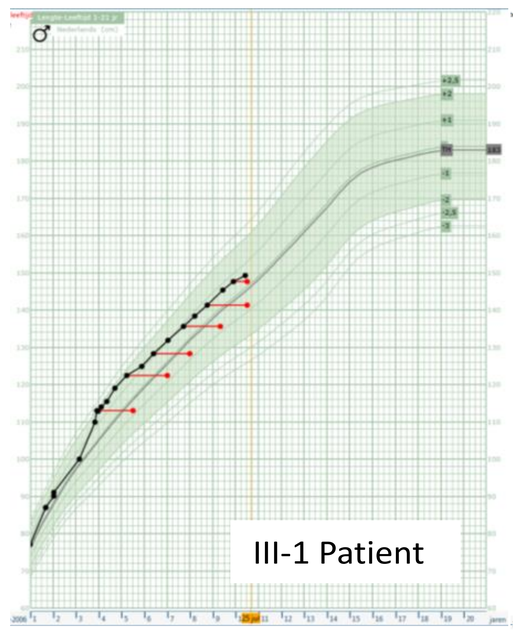
One father remained untreated and reached a final height of 165 cm. This father opted for pre-symptomatic genetic testing for his twin sons, revealing FMPP in both. Early onset of treatment (age 1,5 years) resulted in a final height in the lower part of their target height range (see growth chart IV-1 patient).

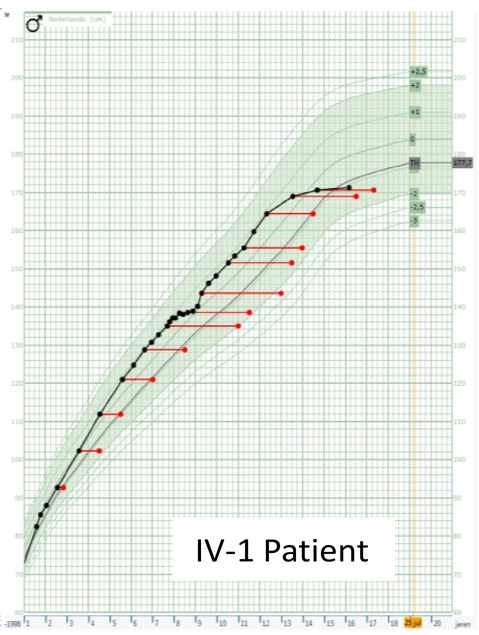
In three other families, diagnosis of FMPP in offspring was made after onset of clinical symptoms at the age of 3-5 years, followed by treatment. Treatment has resulted in a decrease of both growth rate and skeletal maturation rate, however effect on final height can not yet be evaluated.

II. Malignancy

50 % of adult FMPP patients developed testicular cancer (at age 25 and 28 years). Literature review revealed one case of a testicular malignancy (seminoma) in genetically confirmed FMPP patient at the age of 35 [2]. This man had shortly been treated with medroxyprogesterone in childhood.







Conclusions

In our case series of Dutch FMPP families, we observed that early treatment following pre-symptomatic genetic analysis has not resulted in increased final height (1 family). Furthermore, concern is raised by the fact that 50% of adults developed a testicular malignancy. We therefore suggest testicular ultrasound surveillance of adult FMPP patients.

[1] Lenz AM et al. Pediatrics 2010; 126(3): e728–e733
[2] Martin MM et al. Eur J Endocrinol 1998;139(1):101-6

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