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The clinical characteristics of 10 cases and adult height of six cases of rare familial male-limited precocious puberty

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Abstract

Objectives: Familial Male-Limited Precocious Puberty (FMPP) is a rare autosomal-dominant genetic condition with sexual dimorphism. We aim to summarize the clinical characteristics of FMPP patients and emphasize the use of a therapeutic regimen involving letrozole, spironolactone, and GnRHa, to augment clinician's understanding of the disease, thus enhancing patient care.

Methods: We retrospectively analyzed the clinical data of 10 FMPP patients and conducted follow-up assessments of adult height in six patients.

Results: Out of the 10 FMPP cases, five had the *LHCGR M398T* mutation, three exhibited the *LHCGR A564G* mutation, and two had the *LHCGR T577I* mutation. All patients initially presented with symptoms like penile enlargement, frequent erections, and rapid growth. Their median age at diagnosis was 4.67 years with bone age being 9 years. Four patients were untreated with a median adult height of 162 cm. Six patients underwent treatment between ages 3.58 and 5.5 years noting decreased frequency of erections, slower growth rate, and delayed bone age progression. Secondary Central Precocious Puberty (CPP) developed between ages 5 and 6.5 years in all cases, necessitating additional GnRHa treatment. Two treated cases reached an adult height of 176 cm and 173 cm, respectively, without any significant adverse effects.

Conclusions: The most prevalent genotype among FMPP patients in this study was the *LHCGR M398T* mutation. Early intervention using a regimen including letrozole and spironolactone, and later GnRHa, appears beneficial in limiting physical signs and improving adult height without major side effects. However, the longer-term effects on fertility require further investigation.

Keywords: familial male-limited precocious puberty; peripheral precocious puberty; adult height; letrozole; psychological problem

Introduction

Familial male-limited precocious puberty (FMPP), also known as familial testotoxicosis, represents one of the rare causes of male peripheral precocious puberty, constituting nearly 18.5 % of non-CAH gonadotropin-independent precocious puberty in males [1]. FMPP often exhibits familial clustering and is categorized as a sex-limited autosomal-dominant disorder with a penetrance exceeding 90 % [2]. The disease is a result of activating mutations in the luteinizing hormone/chorionic gonadotropin receptor (*LHCGR*) gene. This genetic alteration leads to autonomous activation of LHCGR on Leydig cells in the testes, even without the stimulation of luteinizing hormone (LH). The activation occurs via the mediation of Gs proteins, continuously stimulating the adenylate cyclase, leading to elevated and accumulated levels of cAMP, thereby causing gonadal hyperactivity. This autonomous synthesis and secretion of testosterone by Leydig cells cause enlargement of the penis, premature pubic hair growth, and maturation of the seminiferous tubules, which manifests as testicle enlargement and even ejaculation, all indicative of male precocious puberty [3].

In girls, prepubertal follicle development necessitates the dual action of both luteinizing hormone (LH) and follicle-stimulating hormone (FSH) according to the two-cell-two-gonadotropin theory of estrogen biosynthesis [4]; hence, *LHCGR* gene mutations in girls do not result in precocious puberty. Signs of puberty in FMPP commonly appear between 1 and 4 years of age, such as enlargement of the penis, enlargement of testes, early appearance of pubic hair, growth

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spurts, accelerated bone aging, and elevated levels of testosterone [5]. Rapid progression of bone age can lead to premature closure of the growth plate, which may result in short stature in adulthood.

Due to the rarity of FMPP, only scattered cases or familial cases are reported in China, and it is challenging to carry out long-term follow-ups, leading to limited data on adult height. This article seeks to enhance clinicians' understanding of the disease by summarizing the clinical characteristics of 10 FMPP children, monitoring growth rate and bone age progression during treatment, observing changes in hormone levels, and comparing adult heights with or without treatment. It also offers experience in treating FMPP with letrozole, spironolactone, and GnRHa. Moreover, the paper addresses concern for the psychological issues associated with precocious puberty.

Subjects and methods

Subjects

This study is a retrospective case series analysis. We amassed data from a cohort of 10 children and their family diagnosed with FMPP who presented to the Department of Pediatric Endocrinology of the First Affiliated Hospital of Sun Yat-sen University within the timeframe of August 2011 to May 2022. We undertook analysis of the patients' distinctive clinical features and relevant genetic testing outcomes. These included their growth velocity during therapeutic intervention, the progression of bone age (BA), fluctuations in hormone levels, and the attained adult height, either in the presence or absence of treatment.

Methods

We extracted the clinical data of the patients from electronic medical records, paper-based documentation, and collective case repositories. Relevant patient details encompassed demographics such as sex and age, individual and familial history, symptoms at onset, findings from physical examinations, outcomes of laboratory tests, results from genetic sequencing, prescribed treatments, and growth rate. Additionally, telephonic follow-ups were conducted the adult height and to document any psychological distress correlated with FMPP.

Literature search

Using "familial male-limited precocious puberty," "familial precocious puberty," and "peripheral precocious puberty" as keyword to search in PubMed, Wanfang Database, and China National Knowledge Infrastructure (CNKI), we collected and summarized the clinical features of the FMPP patients reported in the literature.

Results

Cases presentation/features

We herein present the results of the 10 FMPP patients diagnosed via genetic testing from the First Affiliated Hospital of Sun Yat-sen University. Five cases possessed the *M398T* mutation in the *LHCGR* gene (including one father-son pair with *c.1703C>T*, two maternally related brothers with *c.1193T>C*, and one maternally related single patient with *c.1193T>C*), three displayed the *A564G* mutation in LHCGR (including one father-son pair and one maternally related patient with *c.1691A>G*), and two displayed the *T577I* mutation in *LHCGR* (including one father-son pair with *c.1730C>T*). All the 10 cases developed enlarged penises, frequent erections, and accelerated growth. Among them, seven children were identified and diagnosed at a median age of 4.67 years (range: 4.33–5.25 years), with median bone age at diagnosis of nine years (range: 6.75–13.5 years). Three cases were diagnosed in adulthood along with their son. Among the patients, six children exhibited a median difference of 4.21 years (range: 2.5–8 years) between bone age and chronological age, a median testicular volume of 5.5 mL (range: 4–9 mL), and seven children exhibited a median testosterone level of 3.27 ng/mL (range: 1.53–7.64 ng/mL). Only one out of the seven immediately developed central precocious puberty when diagnosis, while the basal LH value, basal FSH value, and GnRHa stimulation test of the remaining six could be diagnosed as peripheral precocious puberty. Four of the cases were not treated, while six received treatment individually (usually letrozole and spironolactone at the same time and GnRHa afterward when CPP occurred).

Among the four untreated cases, the median adult height was 162 cm (range: 160–172 cm). One patient presented with a CA of 4.67 years, height for bone age was −1.62 SD, and the predicted adult height (PAH) using the BP (average) method was 167.6 cm. Ultimately, the measured adult height was 172 cm compared to the target height of 165.5 cm. The other's adult heights were 161 cm, 160 cm, and 163 cm, with respective target heights (THt) of 162 cm (father's height 156cm), 164 cm (father's height 160 cm), and 165 cm (father's height 167 cm). All these fathers had below-average stature, suggesting the possibility of FMPP, but without genetic confirmation.

Among the six patients that received treatment, five pretreatment heights for age were +1.07 SD, +4.21 SD, +4.24 SD, +1.38 SD, and +3.24 SD, while their heights for bone age were −3.36 SD, −1.30 SD, −3.34 SD, −2.20 SD, and −2.59 SD, respectively. After treatment with the aromatase inhibitor (letrozole, the initial dose was 1.67–1.92 mg/m^2 and the dose was controlled in the range of 1.5–2.0 mg/m^2 during treatment) and the androgen antagonist (spironolactone, 1 mg/kg BID), a decrease in the frequency of penile erections and slowing of the growth velocity (GV) was observed. During the treatment, GV varied between 6.0–10.8 cm/year (CA 5–8 years, BA 9–11 years), 4.2–11.3 cm/year (CA 3.7–8.8 years, BA 7–12.3 years), and 3.8–4.7 cm/year (CA 5.6–7.2 years, BA maintained at 13 years) in three patients. Two patients are still undergoing treatment, at 9-month and 3-month durations, with their GV reduced to 8 cm/year.

Among the two patients still receiving treatment, one showed no sign of CPP. The remaining five patients developed secondary CPP, diagnosed at ages 6.1 years, 6.5 years, 5.75 years, 5 years, 5.75 years (i.e., 1 year, 3 years, 3 months, 9 months, and 3 months after starting letrozole), with bone ages of 9.9 years, 10 years, 13 years, 11.5 years, and 13.5 years, respectively. These patients were additionally treated with GnRHa, with treatment durations of 3.25 years, 4.83 years, 1.00 years, and 0.83 years. Their height-for-bone-age improved compared to pretreatment levels. One case of the three was lost to follow-up, and the adult heights of the other two patients were 176 cm and 173 cm (with less than 1 cm of growth in the last year), compared to pretreatment predicted adult heights (PAH) of 154 cm (HtSDSBA −3.36 SD) and 169 cm (HtSDSBA −1.3 SD). Their genetic heights were, respectively, 165 cm and 171.5 cm. The details of clinical chareateristics of the patients are showed in Table 1 and Table 2. The adult heights of various FMPP treatment regimens reported in literature are showed in Table 3.

One patient experienced gastrointestinal symptoms during treatment with letrozole and flutamide, which improved after self-discontinuation of the drugs [6]. Upon resuming the same treatment plan, the patient reported no discomfort. No adverse reactions were noted during treatment among the remaining patients.

The FMPP children may feel discomfort or even fear toward using public restrooms due to an unusually large penis. They may also show an excessive interest in the opposite sex at an early age. Additionally, due to advanced bone age, these children may experience an early spurt in height, eventually transitioning from being unusually tall to being short. Such physical differential can cause psychological stress.

Discussion

Common mutations of FMPP patients globally are *D578G* and *A578G* [11, 17], while the common mutation of Chinese FMPP patients is *M398T* [16]. In this study, the most common genotype was also the *LHCGR M398T* mutation (accounting for 50 %). This difference is presumably related to ethnicity, yet

Table 1: Clinical characteristics of 10 cases and adult heights of six cases with FMPP.

Case#	Age of onset, years	Age of diagnosis, years	*LHCGR* mutation type	Mutation source	Treatment	Treatment duration, years	AH, cm/SDS	THT, cm
1	4	5.25	*M398T*	Paternal	Letrozole + spironolactone + GnRHa	3.25	176/+0.54	165
2	2	4.33	*M398T*	Maternal	Letrozole + spironolactone + GnRHa	4.83	173/+0.05	171.5
3	3	5	*M398T*	Maternal	Letrozole + spironolactone + GnRHa	1.00		171.5
4	2–3	4.92	*A564G*	Maternal	Letrozole + flutamide + GnRHa	0.83		163
5	Shortly after birth	4.5	*M398T*	Maternal	Letrozole + spironolactone	Under treatment		173
6	4.33	4.67	*T577I*	Paternal	Letrozole + spironolactone + GnRHa	Under treatment		167
7	2–3	4.67	*A564G*	Paternal	Untreated		172/−0.11	165.5
8			*M398T*		Untreated		161/−1.92	162
9			*A564G*		Untreated		160/−2.08	164
10			*T577I*		Untreated		163/−1.59	168.5

Table 2: Initial assessment and hormone levels of seven children with FMPP.

Case#	CA/BA of onset, years	HtSDSBA	T, ng/mL	Basal LH, IU/L	Basal FSH, IU/L	Peak LH, IU/L	Peak FSH, IU/L	Testicular volume, mL
1	5/9	−3.36	2.0			1.81	1.99	4.5/4
2	3.67/7	−1.30	3.27	0.09	0.18	2.22	2.65	5/5
3	5.5/13	−3.34	4.3	0.03	0.09	0.43	0.91	8/8
4	3.58/–		7.64	<0.07	0.1	2.15	1.91	
5	4.25/6.75	−2.20	2.81	0.05	0.43	1.11	3.26	5/5
6	5.5/13.5	−2.59	5.22	<0.1	<0.1			6/6
7	4.58/9	−1.62	1.53	0.09	0.26	6.87	1.89	9/9

Table 3: The adult heights of various FMPP treatment regimens reported in literature.

Treatment regimen	Document source	Number	Outcome
Steroidal antiandrogen drugs	Lane et al. [5]	1	AH 181 cm(with GnRHa)
	Almeida et al. [7]	2	AH −2.2 SD, +0.3 SD
	Bertelloni et al. [8]	2	AH −2.0 SD, −1.6 SD
	Ito et al. [9]	1	AH 160 cm
Nonsteroidal antiandrogen drugs	–	–	–
P450 enzyme inhibitor	Almeida et al. [7]	3	Below the target height range for genetics: −2.6 SD, −2.6 SD In the target height range for genetics: −1.6 SD
	Bertelloni et al. [8]	2	Below the target height range for genetics: −2.2 SD
	Soriano-Guillén et al. [10]	5	Below the target height range for genetics: 165 cm, 165 cm In the target height range for genetics: 175 cm, 178.4 cm, 182 cm
Aromatase inhibitors	Leschek et al. [11]	28	The average AH of 28 cases: −0.4 SD
	Lane et al. [5]	3	In the target height range for genetics: 183 cm, 179 cm, 183 cm
	Yoshizawa-Ogasawara et al. [12]	1	Above the target height range for genetics: 166.9 cm
Untreated	Leschek et al. [11]	16	The average AH of 16 cases: −1 SD
	George et al. [13]	2	In the target height range for genetics: 187.9 cm, 180.3 cm
	Partsch et al. [14]	1	Below the target height range for genetics: 174 cm
	Lane et al. [5]	1	Above the target height range for genetics: 181 cm
	Bertelloni et al. [8]	1	AH is 0.2 cm higher than THt (THt is −1.8 SD)
Untreated	Li et al. [15]	1	AH for one case: 160 cm
Untreated	Su et al. [16]	6	AH for six cases: 155–164.5 cm

AH, adult height; GnRHa, gonadotropin-releasing hormone analog; THt, target height.

no correlation between genotype and phenotype has been found. Most patients exhibited symptoms at ages 2–3, with diagnoses made at ages 4–5. At this point of diagnosis, bone age was significantly advanced (the median BA-CA was 4.42 years, with a range of 2.5–8 years). Concurrently, there was testicular enlargement to early-pubertal size. However, the testosterone levels reached mid-to-late puberty levels, which did not match the testicular developmental state. In this study, all patients were diagnosed with peripheral precocious puberty at their initial visit except for one case, which was identified as secondary central precocious puberty.

The treatment regimen of letrozole and spironolactone can improve the clinical manifestations of patients in the short term. After medication, the frequency of penile erections significantly decreases, even to the point of nonerection, and growth velocity (GV) slows down. During the treatment, central precocious puberty (CPP) may commonly occur. Regular monitoring is recommended and, if necessary, combined treatment with GnRHa can be beneficial for inhibiting the activity of the hypothalamic–pituitary–gonadal (HPG) axis. The incidence rate of secondary CPP in this study was higher than in previous literature, which may be related to the long interval between symptom onset and consultation and the long-term stimulation of the central nervous system by testosterone.

In this study, the AH of treated FMPP patients significantly improved as compared to the PAH prior to treatment. Furthermore, the adult height of treated FMPP patients was superior to that of untreated FMPP patients. Case 1 and case 8 are father and son, carrying the same mutation. The father, not having received treatment, has an AH of 161 cm, while the son, post-treatment, achieves an AH of 176 cm. On the

contrast, case 7 and case 9 are also father and son, carrying the identical mutation, with neither having been treated. The father's AH is 160 cm, while the son's is 172 cm. Regarding the difference in adult height between case 7 and case 9, one consideration is that patient 7, compared to other FMPP patients, had already developed CPP at initial evaluation, but his HtSDS did not significantly fall behind, indicating that growth rate was satisfactory and growth potential was not noticeably impaired, despite advanced bone age. As is well-known in cases of central precocious puberty, if growth and bone age increase at a balanced rate, it will not affect adult height. There are many factors influencing adult height. It is a pity that patient 7, who neither receive treatment nor had regular follow-ups, could not provide a growth curve. Details about his exercise, diet, and sleep conditions are unknown. Also, it's unclear how FMPP patients grow when untreated; thus, it's premature to definitively determine the reason for the father-son adult height difference. On the other hand, the discrepancies in clinical presentations between father and son might be related to the variable expressivity of LHCGR mutation in FMPP. Literature suggests that carriers of FMPP gene mutations can exhibit precocious puberty-like symptoms, or have such symptoms without impacts on adult height. For case 1 and case 8, though it cannot be ruled out that the son's increased height compared to his father's was related to expressivity, but considering the family history of case 1, where six out of four generations have similar disease history with adult heights ranging from 155 cm to 164.5 cm, and son's significantly decreased HtSDS for BA before treatment, the likelihood that the medications of letrozole, spironolactone, and GnRHa contributed to the improvement of his AH was considered higher.

In the present study, the treatment regimen consisting of letrozole and spironolactone displayed no significant adverse reactions. There was only one case wherein gastrointestinal reactions were observed when taking letrozole and flutamide orally; however, upon discontinuation of the treatment for 6 months and resuming the original regimen, the gastrointestinal reaction did not recur. This is in line with both domestic and international literature, indicating that this treatment regimen maintains good safety profiles. Still, it's necessary to monitor its effects on long-term fertility and to conduct larger sample size studies [15].

Patients with FMPP often deal with psychological issues due to an enlarged penis, premature maturation, high aggression levels induced by elevated hormone levels, and adult short stature. It is advised that these conditions be detected and addressed early, contributing to the imperative reasons for treating FMPP in children.

Conclusions

In conclusion, in this study, the *LHCGR M398T* mutation (accounting for 50 %) proved to be the most common genotype in FMPP in Chinese. Given that FMPP patients frequently suffer from impaired adult height and related psychological issues, early treatment is recommended. The letrozole and spironolactone regimen can improve patients' clinical presentation in the short term. However, during the treatment process, CPP is prone to occur in combination, suggesting a combined therapy with GnRHa. The treatment plan of letrozole and spironolactone (with GnRHa for accompanied CPP) can improve the adult height in FMPP patients without significant side effects, but the effects on long-term fertility need to be observed.

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