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CASE REPORT

Normal height and novel mutations in growth hormone deficiency adults with pituitary stalk interruption syndrome

Cheng-Zhi Wang[1,2], Qian Wei[1], Ling-Ling Guo[1,3], Hong-Yan Liu[1], Qing-Hua Guo[1,4 #], Yi-Ming Mu[1 #]

1 Department of Endocrinology, The First Medical Center of PLA General Hospital, Beijing, 100853, China.
2 Department of Endocrinology, Sun Yat-Sen Memorial Hospital, Sun Yat-Sen University, Guangzhou, 510120, China.
3 Department of Endocrinology, Beijing electric teaching hospital of Capital Medical University, Beijing, 100073, China.
4 Department of Endocrinology, Hainan Branch of Chinese PLA General Hospital, Sanya, Hainan, 572000, China.

Correspondence to: Qing-Hua Guo, MD
Department of Endocrinology, The First Medical Center of PLA General Hospital, 100853, Beijing, China
tel.: +86 10 55499102; fax: +86 10 68168631; e-mail: gqh301@sina.com
Yi-Ming Mu, MD & Ph.D
Department of Endocrinology, The First Medical Center of PLA General Hospital, 100853, Beijing, China
tel.: +86 10 66936213; fax: +86 10 68168631; e-mail: muyiming@301hospital.com.cn

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Abstract

OBJECTIVE: Pituitary stalk interruption syndrome (PSIS) is a rare congenital disease which results in hypopituitarism. Patients with PSIS often exhibit short stature due to their deficiency of growth hormone (GH).

CASE PRESENTATION: Here, we present two rare cases of adults males with PSIS, in which the patients were of normal height and did not take any GH supplements. Sterility and multiple hormone deficiencies including GH were seen in both of them. Through whole exome sequencing of their DNA, we found novel mutations they shared, three in *MUC4* (c.7815G>T, c.3548C>T, c.3399C>G) and one in *NBPF10* (c.536C>A).

CONCLUSION: The present cases suggest that there are exceptions in GH deficient patients where a select few can attain normal heights without GH therapy. Genetic screening can be a predictor for prognoses of rare types of hypopituitarism.

Abbreviations:

PSIS	- pituitary stalk interruption syndrome
IHH	- isolated hypogonadotropic hypogonadism
SDS	- standard deviation scores
GH	- growth hormone
ACTH	- adrenal corticotropic hormone
F	- cortisol
TSH	- thyroid-stimulating hormone
GnRH	- gonadotropin-releasing hormone
IGF1	- insulin-like growth factor 1
n.v.	- normal value
MRI	- magnetic resonance imaging

BACKGROUND

Pituitary stalk interruption syndrome (PSIS) is a rare congenital disorder that manifests with varying degrees of anterior pituitary hormone deficiency (Fernandez-Rodriguez *et al.* 2011; Bar *et al.* 2015; Yang *et al.* 2013). A thin pituitary gland together with ectopic neurohypophysis and an interrupted stalk on MRI are typical features of PSIS (Fujisawa *et al.* 1987; Fujisawa *et al.* 1987). As diagnosis of the disease is based on MRI, many cases were initially diagnosed as growth hormone deficiency (GHD), isolated hypogonadotropic hypogonadism (IHH) or other types of hypopituitarism for the related hormones could not be transported from hypothalamus to pituitary. Among all the hormone deficiencies, GH deficiency is present most frequently in the majority of patients (Fernandez-Rodriguez *et al.* 2011; Wang *et al.* 2015; Kikuchi *et al.* 1988).

For most PSIS patients with GH deficiency, they have to receive GH therapy from childhood in order to achieve a decent height at adult age, or they may stay short stature till adulthood. In our center, there were some patients who refused GH therapy for economic reasons since currently life insurance covers little for rare diseases. After follow-up for these patients, we found something interesting that the untreated patients had achieved height gain without exogenous GH. Two males (unrelated) had reached a normal height in their adulthood.

We further sequenced their DNA and analyzed mutants found in them. Here we report several novo mutations these sporadic cases shared. One in *NBPF10* gene, three in *MUC4* gene.

CASE PRESENTATION

Case 1

A 32-year-old male was admitted to department of endocrinology for growth retardation. Born in a difficult labor with breech delivery, he denied a family history and consanguineous parents. His father was 163 cm, his mother 164 cm. His growth had always been retarded. He was diagnosed with a GH deficiency at the age of 8, after which he took euthyrox for nearly two years. At the age of 10, he stopped taking euthyrox and started to take traditional Chinese medicine instead. During this period his height increased very slowly every year (less than 2 cm/y) and he was only 150 cm tall at age 25. He grew 30cm from age 25 to 28, and had never received any exogenous GH. He is currently married without children. During his hospital admission, he was also diagnosed with fatty liver and osteoporosis. During his physical examination, his height was measured at 180 cm (1.20 SDS compared to chronological age) with unclosed osteoepiphysis, with a weight of 79.7 kg (birth weight 4.0 kg). He has no beard or armpit hair, and his penis is 5 cm long with a small testicular volume of 1 cm^3 for both testes. He is of normal intelligence, and no midline abnormality was observed.

On MRI scanning, a thin pituitary gland together with ectopic neurohypophysis and an absent pituitary stalk were observed. In laboratory examinations, multiple hormone deficiencies were observed: FT4 4.7pmol/L n.v. (10.42-24.32), TSH 7.67mU/L n.v. (0.35-5.50), T<0.02nmol/L n.v. (8.4-28.7), ACTH (8am) 11pmol/L n.v. (0-10.12), F(8am) 48.9nmol/L n.v. (198.7-797.5). His GH level was less than 0.05 ng/dl n.v. (0.06-5.0) with a low IGF1 level of less than 25 ng/ml, n.v. (117-252). He failed to response to GnRH stimulation test (both basal LH and stimulated LH levels were less than 0.07 mIU/ml).

Tab. 1. Mutation list of cases

Chromosome	Position	Gene	Nucleotide variation	Amino Acid Change
1	145297661	NBPF10	c.536C>A	p.A179D
3	195510636	MUC4	c.7815G>T	p.Q2605H
3	195514903	MUC4	c.3548C>T	p.T1183M
3	195515052	MUC4	c.3399C>G	p.H1133Q

Chrom	Pos	Coverage	Mutation Call:Relative To CDS	Gene	CDS	Amino Acid Change	Mutation Call:Relative To CDS	Amino Acid Change
1	145297661	1142	c.536C>AC	NBPF10	4	p.A179DA	c.536C>A	p.A179D
3	195510636	124	c.7815G>GT	MUC4	2	p.Q2605HQ	c.7815G>T	p.Q2605H
3	195514903	201	c.3548C>CT	MUC4	2	p.T1183MT	c.3548C>T	p.T1183M
3	195515052	156	c.3399C>CG	MUC4	2	p.H1133QH	c.3399C>G	p.H1133Q

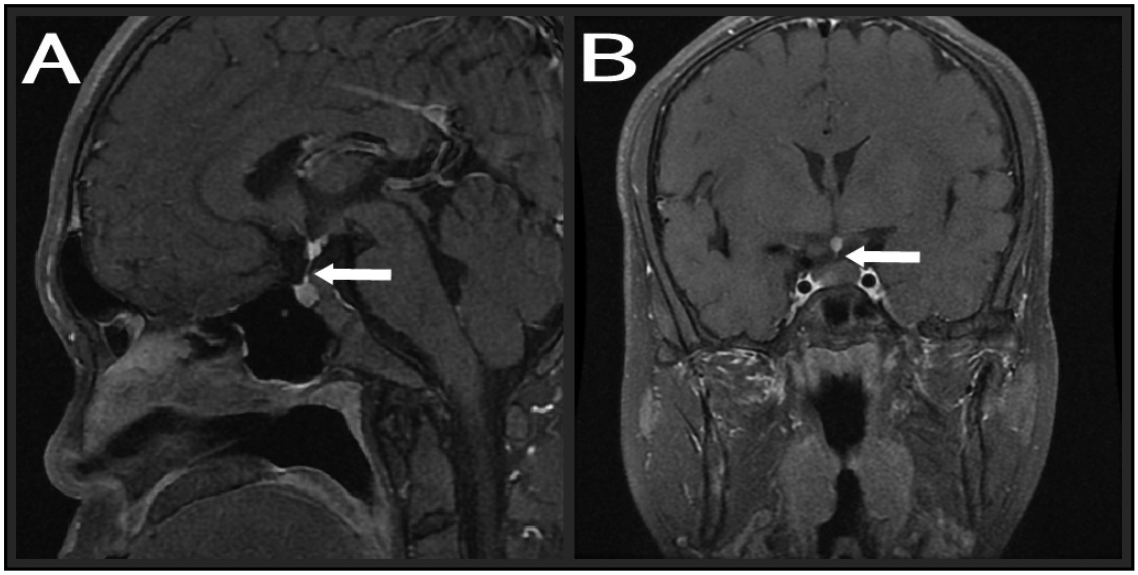

Fig. 1. Pituitary MRI of case 2
A. sagittal view, arrow: very thin pituitary stalk
B. coronal view, arrow: thin pituitary stalk with ectopic posterior pituitary in infundibular recess

After this admission, he was given prednisolone acetate 7.5 mg per day (5 mg in the morning, 2.5 mg at afternoon), euthyrox of 50 ug per day, calcium carbonate 600 mg per day, along with injection of testosterone undecanoate at 2000U for every 3 weeks.

Case 2

An 18-year-old man was admitted to our department for absence of puberty. He sought for treatment for the same ailment when he was 15 years old, and was given traditional Chinese medicine. No GH was used during his life. He denied family history of this disease.

This man has hyposmia and a normal intelligence. He is now 171 cm tall (-0.28SDS compared to chronological age). His weight is 71.8 kg and his bone age is nearly 12 years old. His has a penile length of 3 cm and a testicular volume of approximately 1.5 cm^3 for both testes. He has very little beard and pubic hair. No midline abnormality is observed either.

On MRI scanning, a very thin pituitary stalk along with an ectopic posterior lobe was observed (Figure 1). His hormonal status is listed as below: FT4 18.36pmol/L n.v. (10.42-24.32), TSH 4.25mU/L n.v. (0.35-5.50), T 0.82nmol/L n.v. (8.4-28.7), ACTH (8am) 12.2pmol/L n.v. (0-10.12), F(8am) 335.7nmol/L n.v. (198.7-797.5). His GH was 0.15 ng/dl (normal range 0.06-5.0) with an IGF1 level of 301 ng/ml (normal range 117-252). For GnRH stimulation test, though his basal LH is less than 0.07 mIU/ml, his stimulated LH after 30min is 5.48 mIU/ml.

After this admission, he was given injection of human chorionic gonadotropin at 2000U for every 2 weeks.

Sequencing analysis

Whole exome sequencing was applied to these two cases. The paired reads of every case were aligned to Grch37.3 Human Genome and SNPs, Indels were called by NextGENe 4.1.2 (SoftGenetics, LLC. State College, PA. http://www.softgenetics.com). Variants that were only found in these two cases were discovered. Only the coding and nonsynonymous variations that were present on one percent or lesser frequency in the East Asian and Han Chinese of 1000 Genomes and in East Asian of ExAC are selected for study. And the variations which were predicted as benign by Polyphen2 or set as benign and Likely benign of clinical significance on ClinVar submissions were filtered. Analyses were performed by NextGENe 4.1.2.

Four mutations in two genes were found, three in *MUC4* (c.7815G>T, c.3548C>T, c.3399C>G) and one in *NBPF10* (c.536C>A), details of the mutations are listed in Table 1. Variant in *NBPF10* is displayed in Figure 2.

DISCUSSION

Here we present two unrelated PSIS cases with normal height and had never used GH. Both of these cases have deficiency for GH and gonadal hormone. Their bone age is delayed and they have little male indicators. After reviewing their growth history, we found it interesting that they seemed to have lagging catch-up growth similar to a constitutional delay of growth (One have height gain of 30 cm after age 25, the other had grown up to 171cm at age 18).

PSIS is a congenital defect, with the development of imaging technologies, it is gradually discovered and found to cause a small number of hypopituitarism cases. Currently, treatment for the disease is hormone

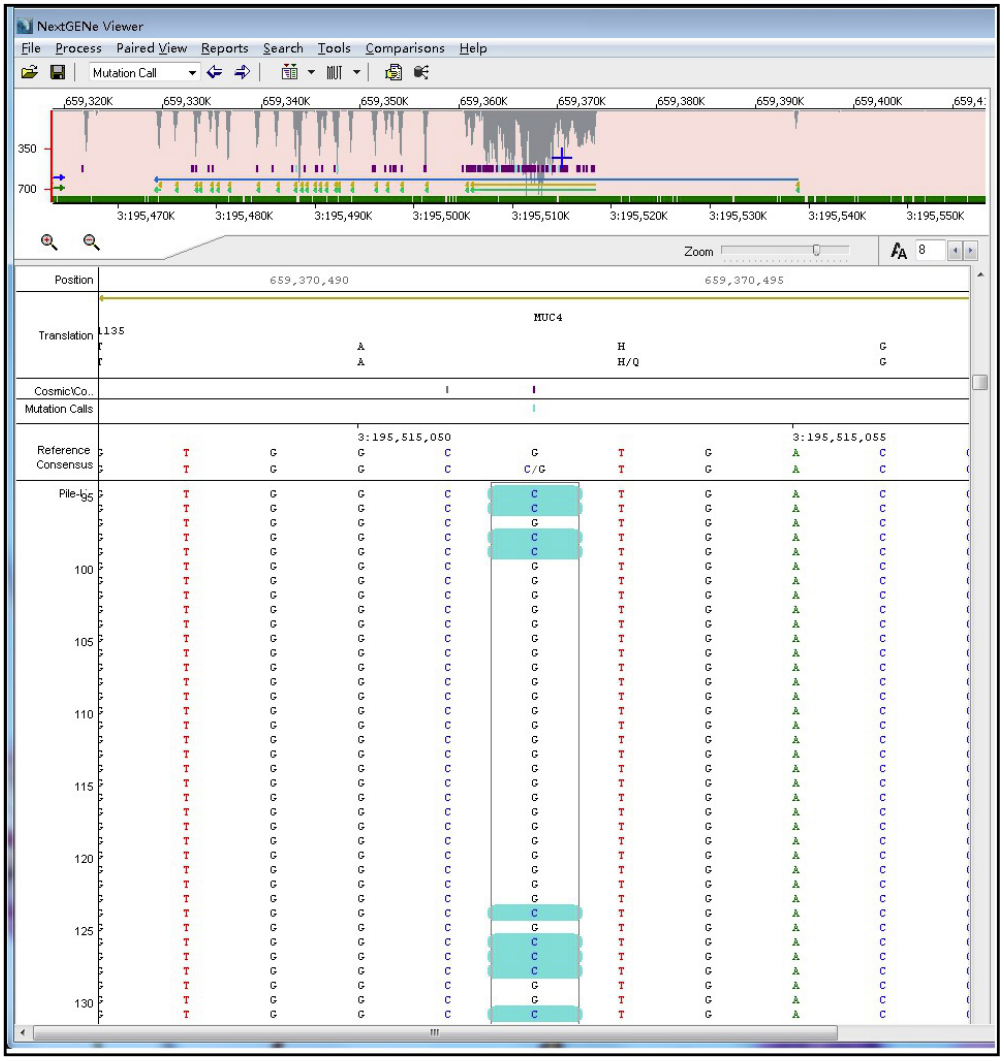

Fig. 2. Mutation in *NBPF10*

Heterozygous mutation in *NBPF10*, part of the nucleotides have been changed from C to A.

replacement therapy. As GH deficiency is commonly seen in PSIS cases, GH therapy was given to those who had growth retardation. Very few studies of PSIS treatments have been done, and evaluation of GH therapy is limited to early treatment in children (Wang *et al.* 2016; Tauber *et al.* 1997; Chehadeh *et al.* 2010; Coutant *et al.* 2001). In our center, as we accumulated PSIS cases for years, and for cases of Han Chinese are often diagnosed at elder age than foreign studies, we are able to get physical information of adult patients. We gradually found that although the PSIS patients in our center have similar features on MRI, their response to GH therapy is so different: Some people are still short after GH treatment, and some can achieve decent final height in adulthood. Because of the uncertain curative effect, many patients in China refused to accept GH therapy besides of the high expense of the treatment. Therefore we have the chance to follow up the untreated PSIS patients, particularly we found 2 male patients without GH medication who were short stature in childhood but have normal height now. We then made whole exome sequencing and association analyses to these 2 cases. After data filtering, we got 4 mutations in 2 genes, one is *MUC4*, and the other one is *NBPF10*.

NBPF (neuroblastoma breakpoint family member) family consists of dozens of recently duplicated genes primarily located in segmental duplications on human chromosome 1. It has been implicated a number of developmental and neurogenetic diseases are associated to the gene family, such as microcephaly, macrocephaly, autism, schizophrenia, mental retardation, congenital heart disease, neuroblastoma, and congenital kidney and urinary tract anomalies (Vandepoele *et al.* 2005). *MUC4* is generally related with cancer and plays a role in cell migration. The mutations found in these two cases may be associated with their manifestations. As concerns have been focused on a series of genetic mutations of PSIS these years (Kim *et al.* 2003; Cruz *et al.* 2010; Reynaud *et al.* 2011; Reynaud *et al.* 2012; Reynaud *et al.* 2005), researchers; plunged into related studies. This has raised a new question: whether the growth of these "unique" patients could be predicted

by genetic mutations and when and how to give them sexual hormone supplements to make them masculine. If some of the patients could grow by themselves to get a decent height, much cost would be saved.

And there may be other compromising factors that contributed to PSIS patients' height when GH deficiency was determined. To start with, both of these 2 patients had received traditional Chinese medicine, of which the composition is very complicated. Unlike Western medicine, the system of traditional Chinese medicine is individualized and therapy cannot be replicated, thus it lacks criteria for its efficacy. Secondly, it is commonly known that sex hormones like estrogen and androgen can stimulate growth and promote epiphyseal fusion (Simm *et al.* 2008; Shim 2015; Weise *et al.* 2001). When bone epiphysis was not completely closed, partly because of lack of sex hormones, the extremely low levels of GH and other hormones like insulin, thyroid hormone could have still contributed to growth.

Case 1 have been diagnosed fatty liver and osteoporosis, these symptoms may be attributed to the hypothyroidism caused by PSIS and the side effects of prednisone. As PSIS is a syndrome that may cause multiple hormone deficiencies, we should check the whole hormonal status of the patients in time and avoid side effects as much as possible. So comprehensive recognition of rare hypopituitarism should be enhanced in the future, especially in developing countries.

CONCLUSIONS

The present cases suggest there were exceptions for GH deficiency patients who could gain a normal height without GH therapy. Multiple reasons have contributed to the unique phenomenon, genetic screening can be a predictor for prognoses of rare types of hypopituitarism.

DECLARATIONS

Ethics and consent to participate statement

This study was approved by the Ethics Committee of Chinese PLA General Hospital, China. Written informed consent was obtained from the patient for publication of this Case report. A copy of the written consent is available for review by the Editor of this journal.

Consent to publish statements

Consent for publication of the data was obtained from the patient.

Availability of data and materials statement

All the data supporting the findings in this study are presented in this article.

Competing interest

The authors declare that they have no competing interests.

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AUTHORS' CONTRIBUTIONS

CZW collected the data and wrote the manuscript. QHG and YMM designed the study. QW made the figures. LLG, HYL and XS collected the data. All authors have read and approved the final manuscript. QHG and YMM are corresponding authors.

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