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원 저

가성부갑상선기능저하증 환자의 분자유전학적 및 임상적 특징: 단일기관의 경험

부산대학교 어린이병원 소아청소년과

김민지 · 윤주영 · 유석동 · 이준 · 전종근

Molecular and Phenotypic Characteristics of Patients with Pseudohypoparathyroidism: Single Center's Experience

Min-ji Kim, Ju Young Yoon, Sukdong Yoo, Jun Lee, Chong Kun Cheon

Department of Pediatrics, Pusan National University Children's Hospital, Yangsan, Republic of Korea

Purpose: Pseudohypoparathyroidism (PHP) is caused by genetic and epigenetic alteration in the GNAS locus, and characterized by the resistance to multiple hormones and the Albright's hereditary osteodystrophy (AHO) phenotype. This study investigated the phenotypic characteristics and molecular features of PHP.

Methods: Eight patients who diagnosed as PHP were enrolled at Pusan National University Children's hospital and clinical features, biochemical and genetic findings were retrospectively reviewed.

Results: Of a total of 8 patients, 5 were diagnosed with PHP1a, and 3 were diagnosed with PHP1b. Patients with PHP1a had three different mutations in the GNAS gene, and patients with PHPIb had imprinting defect in differentially methylated regions (DMRs) of the GNAS locus. Two novel GNAS variants were identified in patients with PHP1a, including c.313-2A>T and c.1094G>A. All patients with PHP1a displayed AHO features; short stature (80%), brachydactyly (80%), a round face (80%), obesity (40%), heterotopic ossification (60%), and intellectual disability (60%), whereas only one patient (33.3%) with PHP1b showed AHO feature such as a round face. When phenotypic features between PHP1a and PHP1b patients were compared, patients with PHP1b showed a tendency of higher current height standard deviation scores (SDS) compared to patients with PHP1a, (-3.2±2.1 vs.-1.1±0.8; P=0.06)

Conclusions: This study summarizes the phenotypic and genetic features of the PHP patients. Although we found considerable clinical overlap between PHP1a and PHP1b, further long-term follow-up is needed to evaluate the growth and development of children with PHP, as well as the effects of end-organ resistances to endocrine hormones.

Key words: Pseudohypoparathyroidism, GNAS, Mutation

Introductions

Pseudohypoparathyroidism (PHP) is a rare disease characterized by end-organ insensibility to the effects of parathyroid hormone (PTH) and other peptide hormones that works through the alpha subunit of the stimulatory G protein (Gsα) coupled receptors which activate adenylyl cyclase [1]. Although there are insufficient data, the prevalence of PHP was estimated to be 0.34/100,000 in Japan[2]. PHP can be categorized into four types (1a, 1b, 1c, 2) based on clinical features, hormonal resistance, genetic or epigenetic distur-

책임저자: 전종근, 경상남도 양산시 금오로20
부산대학교어린이병원 교수연구동 519호
Tel: 055) 360-3181, Fax: 055) 360-2181
E-mail: chongkun@pusan.ac.kr

bances of *GNAS* locus.

The *GNAS* gene is located at chromosome 20q13.3 and mainly encodes Gsα, which is critical role in the activation of adenylyl cyclase and the generation of cAMP, a second messenger involved in downstream signalling[3]. In addition to responses to PTH, this signaling pathway is involved in the action of several other hormones, including growth hormone releasing hormone (GHRH), luteinizing hormone (LH), follicle-stimulating hormone (FSH) and thyroid-stimulating hormone (TSH). Although *GNAS* is expressed from both maternal and paternal tissues, *GNAS* is expressed only from the maternal gene in the proximal renal tubule, thyroid, gonads, and pituitary gland. The *GNAS* locus has several independent imprinted site, which contains at least 4 distinct DMRs and give rise to several transcripts besides GSα, specifically extra-large αs (XLas), neuroendocrine secretory protein (NESP55), 1A (also known as A/B), and antisense (NESP-AS)[4]. Familial cases are caused by isolated demethylation of *GNAS* A/B: Transcription Start Site (TSS)-DMR, which is caused by 3 kb and 4.4 kb heterozygous maternal microdeletion in the syntaxin-16 (*STX16*) gene[5].

PHP1a is caused by reduced Gsα activity due to a maternally-derived inactiving mutation in exon 1-13 of *GNAS* gene[5]. PHP1a is characterized by resistance to several endocrine hormones including PTH, TSH, GHRH, LH, and FSH, and heterogeneous expression of characteristic physical features, such as Albright hereditary osteodystrophy (AHO) phenotype, including round faces, short stature, obesity, brachydactylies and intellectual disabilities[1]. PHP1b is caused by methylation defect in the DMRs located upstream of *GNAS* exons 1-13[6]. These patients show resistance to PTH and occasionally partial resistance to TSH, and lack AHO features. Most cases are caused by loss of methylation at the exon A/B DMR of *GNAS* locus, and some cases of paternal uniparental disomy (UPD) involving chromosome 20q (patUPD20q) have been reported[7]. In the present study, we investigated the phenotypic and genetic characteristics of 8 Korean patients with PHP.

Materials and Methods

1. Study design and clinical data collection

A total of 8 patients, who were clinically and genetically diagnosed as PHP were enrolled in this study. A retrospective chart review was performed including phenotypic characteristics and genetic features of patients with PHP from 2009 to 2020. Written informed consent was obtained from all participants. Height, weight, and body mass index (BMI) were expressed as standard deviation scores (SDS) according to the 2017 Korean national growth charts for children and adolescents[8]. Short stature was defined as less than -2.0 SDS of height, while obesity and weight excess was defined as more than +2.0 and +1.0 SDS of BMI respectively. Intellectual disability was defined in case of psychomotor retardation or delayed speech or need of assistant teacher and extra school help. It assessed at diagnosis using the Bayley Scales of Infant Development II, Korean Wechsler Preschool and Primary Scales of Intelligence (K-WPPSI), or Korean Wechsler Intelligence Scales for Children (K-WISC) according to the age of patients. Brachydactyly was diagnosed if clinically present with variable shortening of IV-V metacarpals with normal length of phalanges.

2. Hormonal analysis

Thyroid function tests were performed by measuring free thyroxine (fT4), and TSH serum levels using immunoradiometric assays (Immunotech s.r.o., Praha, Czech Republic). At the time of beginning treatment, PTH assays was performed using a CLIA kit (San Diego, CA, USA). We classified patients with elevated TSH levels with normal fT4 as TSH resistant. Also, we classified individuals with elevated serum intact PTH sometimes associated with hypocalcemia and hyperphosphatemia as PTH resistance.

3. Mutational analysis

Genomic DNA was extracted from peripheral leucocytes using the DNA extraction kit according to the manufacturer's instructions. Direct sequencing of *GNAS* gene was conducted in all patients first. In patients who showed negative results on Sanger sequencing and no AHO signs, genomic rearrangements were assessed by methylation-specific multiplex ligation-dependent probe amplification (MS-MLPA). Single-nucleotide polymorphism (SNP) microarray was performed additionally to exclude patUPD20q.

4. Statistical analyses

All the analyses were performed using IBM SPSS version 22.0 (SPSS Inc, Chicago, IL, USA). Data were expressed as mean±SD for normally distributed continuous variables, as median and minimum-maximum ranges for not normally distributed continuous variables, and as frequencies for categorical variables. When comparing two groups, *t*-tests were used for continuous variables with normal distributions, or Mann-Whitney tests were used to analyze continuous variables with non-normal distributions. Pearson chi-square and Fisher's exact tests were used for categorical variables. $P<0.05$ (two-tailed) was considered as statistically significant.

Results

1. Patients' clinical characteristics

All patients were born from non-consanguineous parents. Among the patients with PHP, 62.5 % (5 patients) were diagnosed with PHP1a, 37.5% (3 patients) with PHP1b. The clinical and auxological characteristics of 8 patients are shown in Table 1. The average age at diagnosis was 12.5± 35.6 years (range: 3.1-18.5) for patients with PHP1a and 9.5±10.5 years (range: 7.3-13.3) for patients with PHP1b (Table 2). For the presenting symptoms or signs, three of five patients with PHP1a (case 1, 3, 4) presented with hypocalcemic seizure or carpal spasm, one (case 5) with short stature and development delay. The other (case 2) was diagnosed with genetic testing in family members (case 1) with no symptoms at the time, but additional clinical features such as hypothyroidism and brachymetacarpia occurred during regular hospital follow-up. Although same mutation, case 2 were presented with different phenotype like hypothyroidism, normal stature and obesity differently from case 1. Three patients with PHP1b were initially presented with hypocalcemic seizure at diagnosis.

All patients with PHP1a displayed AHO features; short stature (80%), brachydactyly (80%), a round face (80%), obesity (40%), heterotopic ossification (60%), and intellectual disability (60 %), whereas only one patient (33.3%) with PHP1b showed AHO feature such as a round face. Four

patients (80%) with PHP1a and three patients (100%) with PHP1b showed basal ganglia calcification on brain computed tomography. Only one patient with PHP1a (case 3) presented with subcutaneous calcification.

Laboratory findings at presentation and molecular analysis are summarized in Table 3. All patients with PHP1a showed resistance to PTH (209.3±108.5 pg/mL, normal range: 10–65 pg/mL), and four (80%) of them showed resistance toward TSH (7.8±2.7 pg/mL, normal range: 0.5–6.0 μIU/mL), necessitating thyroxine medication. All patients with PHP1b displayed resistance to PTH (206.4±184.6 pg/mL), but none of them showed TSH resistance. When compared phenotypic features between PHP1a and PHP1b patients, current height SDS showed the tendency of patients with PHP1b to have higher height SDS than patients with PHP1a (−3.2 vs −1.1; P=0.068) (Table 2).

2. Molecular analysis of the patients with PHP1a and PHP1b

Among five patients with PHP1a, 3 distinct mutations in the *GNAS* gene were identified by direct sequencing. Two were novel likely pathogenic mutations according to the ACMG guidelines;

Table1. Phenotypic Characterization of Patients with Pseudohypoparathyroidism

Cases	Subtype	Age at Dx (year)	Clinical presentation	Brain CT	Development delay	AHO	HSDS	WSDS	BMI SDS
Case 1	1a	18.5	Carpal spasm, numbness on both extremities	Calcification at bilateral basal ganglia and subcortical white matter, thalamus	Normal development	BR, RF, HO, SS	−2.3	−1.1	−0.0
Case 2	1a	16.5	Family test	Calcification in both cerebrum, cerebellum, both basal ganglia and thalamus	Normal development	BR, OB	−1.4	1.9	3.3
Case 3	1a	15.3	Hypocalcemic seizure, numbness on both extremities, carpal spasm	Multiple calcifications at bilateral basal ganglia	Developmental delay	RF, SS, OB, SC, BR	−5.2	−0.2	2.7
Case 4	1a	3.1	Hypocalcemic seizure	Multiple calcifications in frontal lobe, bilateral basal ganglia	Developmental dealy	RF, SS, HO	−3.1	−1.2	0.2
Case 5	1a	12.9	Developmental delay, short stature	NA	Developmental delay	BR, RF, HO, SS	−3.9	−0.4	1.7
Case 6	1b	13.3	Hypocalcemic seizure	Calcification at bilateral basal ganglia and subcortical white matter, thalamus	Normal development	SS, RF	−2.1	−1.4	−0.4
Case 7	1b	7.3	Hypocalcemic seizure	Multiple calcification	Normal development	−	−0.7	0.0	0.5
Case 8	1b	8	Hypocalcemic seizure	Multiple calcification	Normal development	−	−0.4	1.0	1.4

Abbreviations: Dx, diagnosis; CT, Computed Tomography; AHO, Albright hereditary osteodystrophy; HSDS, height standard deviation score; WSDS, weight standard deviation score; BMI, body mass index; BMISDS, BMI standard deviation score; BR, brachydactyly; RF, round face; HO, heterotopic ossification; SS, short stature; OB, obesity; SC, subcutaneous calcification; NA, not available; +, positive; −, negative.

c.313−2A>T (PM2, PM6, PP3, PP4), c.1094G>A (p.Cys365Tyr) (PM1, PM2, PP2, PP3, PP4). Case 1 and 2 were siblings and had the same mutation, c.312+5G>A. Among three patients with PHP1b, one patient (case 7) displayed altered methylation in *GNAS* DMRs, with a loss of methylation in the NESP and NESP−AS domains in the maternal allele. All patients with PHP1b did not have deletion of *STX16*, or *GNAS* DMRs. Two patients with PHP1b (case 6, 8) were revealed as patUPD20q (Table 3).

Tables 2. Clinical Comparison between PHP 1a and PHP1b Patient

	PHP1a (N=5)	PHP1b (N=3)	*P*−value
Age at diagnosed (years, mean±SD)	12.5±35.6	9.5±10.5	0.881
Sex (male:female)	5:0	1:2	0.113
Current Height (mean±SD)	−3.2±2.1	−1.1±0.9	0.068
Current Weight (mean±SD)	−0.2±1.7	−0.1±1.5	0.921
Current BMI (mean±SD)	1.6±2.1	0.5±0.9	0.293
Obesity (n, %)	2.0 (40)	0.0 (0)	0.464
Weigh excess (n, %)	1.0 (20)	1.0 (33.3)	>0.990
Brain calcification (n, %)	4.0 (80)	3.0 (100)	>0.990
DD/ID (n, %)	3.0 (60)	0.0 (0)	0.191
Tetany (n, %)	3.0 (60)	2.0 (66.6)	1.001
AHO features (n, %)	5.0 (100)	1.0 (33.3)	0.107
Serum Ca (mmol/L, mean±SD)	7.7±1.3	6.6±2.6	0.319
Serum PTH (pg/mL, mean±SD)	209.3±108.5	206.4±184.6	0.977
Serum TSH (uIU/mL, mean±SD)	7.8±2.7	4.3±1.3	0.088
PTH resistance (n, %)	5.0 (100)	3.0 (100)	>0.990
TSH resistance (n, %)	4.0 (80)	0.0 (0)	0.142

Abbreviations: SD, standard deviation; BMI, Body Mass Index; DD, developmental delay; ID, intellectual disability; AHO, Albright's hereditary osteodystrophy; PTH, parathyroid hormone; TSH, thyroid stimulating hormone; PHP1a, pseudohypoparathyroidism 1a; PHP1b, pseudohypoparathyroidism 1b.

Table 3 Biochemical, Hormonal Results and Molecular Analysis of Patients with Pseudohypoparathyroidism

Cases	Subtype	Ca (mg/dL) (ref: 8.8-10.6)	P (mg/dL) (ref: 2.6-4.6)	PTH (pg/mL) (ref: 10-65)	TSH (uIU/mL) (ref: 0.5−6.0)	GNAS mutation	GNAS methylation defect	Hormone resistance
Case 1	1a	5.7	7.5	336.1	4.1	c.312+5G>A		PTH
Case 2	1a	8.3	7.4	165.2	11.3	c.312+5G>A		TSH, PTH
Case 3	1a	8.5	4.2	309	7.9	c.313−2A>T*		TSH, PTH
Case 4	1a	7.3	9.5	82.19	9.3	c.1094G>A* (p.Cys365Tyr)		TSH, PTH
Case 5	1a	9.0	4.6	154.1	6.6	ND	ND	TSH, PTH
Case 6	1b	5.2	10.6	418	5.7	ND	NESP, NESPAS, XL, exon1A: UPD	PTH
Case 7	1b	6.3	8.6	77.8	3.1	ND	NESP, NESPAS: maternal methylation defect	PTH
Case 8	1b	8.4	5.1	123.4	4.3	ND	NESP, NESPAS, XL, exon1A: UPD	PTH

*novel variants.
Abbreviations; Ca, calcium; P, phosphorus; PTH, parathyroid hormone; TSH, thyroid stimulating hormone; ND, not detected; NESP, neuroendocrine secretory protein 55; NESPAS, neuroendocrine secretory protein antisense; XL, extra−large αs; UPD, uniparental disomy.

Discussion

In the present study, we investigated phenotypic and molecular characteristics of eight patients with PHP. All patients with PHP1a and PHP1b showed resistance toward PTH and most of whom had TSH resistance. PHP causes end-organ resistance to several endocrine hormones, primarily affecting the actions of PTH presenting with tetany or hypocalcemic seizure in most patients. In this study, 75% of PHP patients presented with convulsion or carpal spam. In comparison between PHP1a and PHP1b, no characteristic clinical differences were observed, suggesting the overlapping phenotype between the two subtypes. Short stature of patients with PHP is caused by Gsα haploinsufficiency in skeletal tissue[9]. In this study, 80% of PHP1a and 33% of PHP1b patients were of short stature, similar to the previous study in which 70% of PHP1a and 21.3% of PHP1b respectively[10]. One of the reasons for the high frequency of short stature in patients with PHP1a is that growth hormone (GH) deficiency is accompanied in 50-100% of these patients due to GHRH resistance. Mantovani G, et al.[11] reported that recombinant GH treatment increased growth velocity in eight pre-pubertal children with PHP1a. Therefore, early diagnosis of PHP, close monitoring of height and proper GH therapy should be management of patients with PHP[11].

Generally, PHP are caused by inactivating genetic variants or epigenetic alterations within or upstream of the *GNAS* locus. *GNAS* gives rise to multiple non-coding and coding transcripts, including those encoding Gsα[12]. Their promoters existed within DMRs and are methylated on the silenced allele[11]. Thus, exon 1 encodes Gsα exclusively and highest mutation frequency was located in exon 1 according to previous report[13]. Of note, in the present study, 3 different mutations in the *GNAS* gene were identified in the 5 patients with PHP1a, which were not in exon 1. Of the three mutation found, two were novel *GNAS* variants; c.313-2A>T and c.1094G>A (p.Cys365 Tyr). A novel splicing variant, c.313-2A>T, might disrupt the highly conserved splice site sequence of intron 4 and cause exon 4 skipping. However, mRNA analysis was not performed owing to the unavailability of mRNA expressed tissues. The second mutation, c.1094G>A, on exon 13, which was located in the functional domain, residues at the carboxyl-terminal of the protein that selectively affect receptor coupling[14]. The last *GNAS* mutation was c.312+5G>A, which was previous reported, caused aberrant splicing with removal of exon 4. According to the reported case of this mutation, the patients manifested as PTH resistance, TSH resistance, and mild hypogonadism plus severe AHO with short stature, mild mental retardation, and skeletal defects including congenital phocomelia[15]. In this study, c.312+5G>A identified in siblings (Case 1 and 2). Of interest, clinical phenotypes shown in the siblings with the same mutation were different, which suggests allelic heterogeneity.

Indeed, the identification of inheritance forms for patients with PHP1b is crucial for genetic counseling. Most common cause of autosomal dominant (AD) familial PHP1b is a maternally inherited 3 kb microdeletion on the maternal allele of cis-acting control elements within *STX16*, contains isolated loss of methylation at the exon 1A DMRs of *GNAS* without imprinting defects in other DMRs[16]. In the present study, there were no evidence that patients with PHP1b carried deletions at *STX16* or NESP55 DMRs. Sporadic PHP1b accounts for 80% of patients and 20% are AD PHP1b[5]. About 10% of the sporadic cases are

caused by patUPD20q[1]. In this study, among 3 patients with PHP1b, patUPD20q was found in two patients (case 6, 8).

In practice, it is still difficult to diagnose PHP1b in the absence of typical symptoms or one or several biochemical features, e.g. hypocalcemia or hyperphosphatemia. In the present study, the age at the time of diagnosis of patients with PHP1b was 9.5 years old, which was similar to the results reported in Japan[14]. According to the previous report, phenotype related to PHP1b due to patUPD20q was relatively high birth weight, obesity, macrocephaly, development delay, and tall stature, which was noticed during infancy and persisted until later in life[17]. Unlike previous studies, patients with patUPD20q displayed normal development, and were below average in height in this study. Some previous studies suggested genotype–phenotype consistency in patUPD20q varies depending on the length of the area where UPD occurs[18]. However, there is no sufficient data on the level of genotype–phenotype correlation for the UPD site, so a larger study is needed for this.

The limitation of this study is that the genetic test results in case 5 are negative. However, based on the clinical features of the characteristic AHO, it was reasonable for PHP1a. However, further tests such as whole genome sequencing (WGS) will be necessary to determine the genetic cause of the mechanism underlying PHP1a.

Conclusion

Understanding the molecular cause of PHP explains distinctive clinical features and enables confirmation of the diagnosis. In the present study, the phenotypic and molecular features of *GNAS* inactivation disorders were investigated in which *GNAS* inactivation give rise to different clinical features, according to the type of mutations and their inheritance patterns. Therefore, specialized expertise is needed to manage each of the many clinical aspects and potential complications of PHP and related disorders.

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Conflicts of Interest

The authors have nothing to declare.

요 약

목적: 가성부갑상선기능항진증은 *GNAS* 부위의 돌연변이에 의해 발생하며, 여러 호르몬에 대한 저항성과 올브라이트 유전성 골이영양증을 특징으로 한다. 이 연구는 가성부갑상선기능항진증의 표현형 특성과 분자유전학적 특징을 조사하고자 하였다.

방법: 부산대학교 어린이병원에 등록된 가성부갑상선기능항진증으로 진단된 환자 8명의 임상적 특징과, 생화학적, 유전학적 검사 결과들을 포함한 의무기록을 후향적으로 조사하였다.

결과: 총 8명의 환자 중 5명은 PHP1a로 진단되었고 3명은 PHP–1b로 진단되었다. PHP1a 환자는 *GNAS* 유전자의 3가지 서로 다른 돌연변이를 가졌고, PHP–Ib 환자는 DMR (differential methylated region) 각인 *GNAS*의 소실을 보였다. 두 개의 새로운 *GNAS* 변이(c.313–2A>T, c.1094G>A)가 PHP1a 환자에서 발견이 되었다. 모든 PHP1a 환자는 저신장(80%), 단지증(80%), 둥근 얼굴(80%), 비만(40%), 이소성 골화(60%), 지적 장애(60%) 등의 올브라이트 유전성 골이영양증의 특징을 보였으며, PHP1b 환자의 경우는 한 명(33.3%)만이 둥근 얼굴과 같은 올브라이트 유전성 골이영양증의 특징을 보였다. PHP1a 환자와 PHP1b

환자의 표현형 특징을 비교하였을 때, 현재 키 SDS만이 PHP1b 환자에서 PHP1a 환자보다 각각 더 높은 경향성을 보였다(P=0.06).

결론: 본 연구는 한국인 PHP 환자들의 임상적 표현형 및 유전학적 특징을 요약하였다. PHP1a와 PHP1 환자들 간에 상당한 임상적 중복이 있었지만, 다른 장기 말단 저항의 영향뿐만 아니라 PHP로 진단받은 소아의 성장과 발달을 평가하기 위해서는 더 장기적인 추적 연구가 필요하겠다.

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