Int J Clin Exp Med 2018;11(4):4295-4300
www.ijcem.com /ISSN:1940-5901/IJCEM0062264

Case Report

Spinal stenosis associated with PHP-Ia: a case report and literature review

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Received July 25, 2017; Accepted February 6, 2018; Epub April 15, 2018; Published April 30, 2018

Abstract: Pseudohypoparathyroidism type Ia (PHP-Ia) is an extremely rare hereditary disorder. We report the case of a 33-year-old male with PHP-Ia and typical Albright hereditary osteodystrophy phenotype, with complaints of paraparesis due to extensive cervical spinal stenosis. The spinal stenosis was caused by diffused ossification of the posterior longitudinal ligament and multilevel intervertebral disc herniation. It is a rare but important manifestation of PHP-Ia that is being increasingly reported. This report aimed to highlight the relationship between spinal stenosis and PHP-Ia through extensive literature review and recommends that all patients with evident neurological symptoms due to spondylopathy should be screened for serum calcium, phosphate and PTH level to rule out PHP. Moreover, early diagnosis and timely corrections of hypocalcemia, hyperphosphatemia and elevated PTH level as well as effective body weight control are important to prevent rare neurological complications in patients with PHP-Ia.

Keywords: Pseudohypoparathyroidism type Ia, spinal stenosis, albright hereditary osteodystrophy, GNAS gene

Introduction

Pseudohypoparathyroidism (PHP), an extremely rare hereditary disorder, is characterized by deficient target tissue response to parathyroid hormone (PTH) action, which results in hypocalcemia and hyperphosphatemia despite elevated plasma PTH levels [1]. Thus, the main neurological manifestations of PHP are tetany and pseudoseizures due to hypocalcemia [2]. Patients with PHP usually display typical characteristics, namely Albright hereditary osteodystrophy (AHO) [3], which includes short stature, round face, early onset obesity, ectopic intramembranous calcifications, brachydactyly, diffuse osteopenia and mental retardation. Dental abnormalities include enamel hypoplasia, delayed eruption and impacted teeth [4]. Spinal stenosis is rarely observed among PHP patients. According to its different pathogenesis and phenotype, PHP is classified as PHP-Ia, PHP-Ib, PHP-Ic and PHP-II [5], among which PHP-Ia is the most common type [6]. Patients with PHP-Ia usually develop resistance towards other hormones, such as thyroid-stimulating hormone (TSH), gonadotropins and growth hormone-releasing hormone (GHRH) [7], while goiter and anti-thyroid antibodies are usually absent [8].

Herein, we present the case of a Chinese man with typical AHO phenotype and delayed diagnosis of PHP-Ia, complaining of paraparesis due to extensive cervical spinal stenosis.

Case report

A 33-year-old male was referred to the spine surgery department of our hospital in October 2015. He complained of progressive stiffness, numbness of the chest, abdomen and bilateral lower limbs as well as bilateral hip pain for four months. He also suffered from progressive motor and sensation dysfunction of bilateral lower limbs for two months, which led to walking disability and confined him to a wheelchair. Additionally, he suffered from episodic spasms of bilateral lower limbs for about two months and dizziness for three days.

Physical examination on admission revealed that his height was 160 cm and his weight was 66.5 kg [body mass index (BMI): 25.9 kg/m^2]. He had brachydactyly of all extremities and restricted movement of cervical spine. The

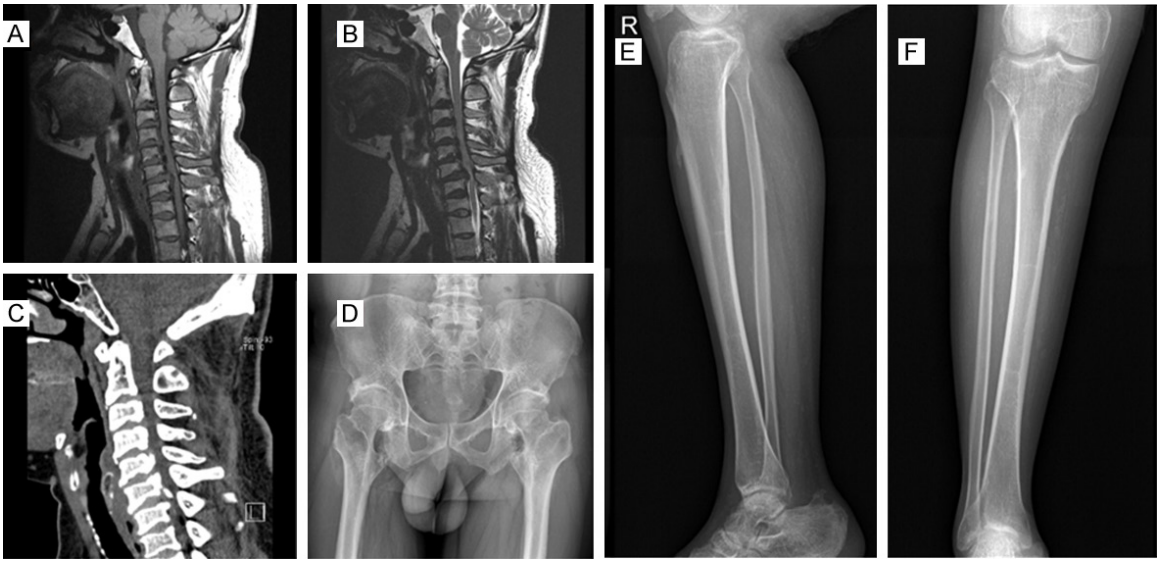

Figure 1. Cervical MRI, CT and X-ray of the pelvis and right lower limb. T1 and T2 weighted sagittal cervical MRI scan confirmed remarkable cervical stenosis with signal changes of the cervical spinal cord (A and B). Spine CT reconstructions showed evident cervical spinal stenosis due to diffused ossification of the posterior longitudinal ligament and multilevel intervertebral disc herniation (C). X ray of the pelvis and right lower limb indicated degeneration of the bilateral hip joints, diffused muscle ossification, and osteoporosis of pelvis and right limb (D-F).

muscle tone of bilateral lower limbs was remarkably increased and the muscle power of bilateral lower limbs was slightly impaired (level 4/5), without muscle atrophy. Hoffmann and Babinski signs were positive on both sides, and the deep tendon reflex of left lower limb was hyperactive with knee clonus.

Three-dimensional reconstruction of the computed tomography (CT) images revealed evident cervical spinal stenosis due to diffused ossification of the posterior longitudinal ligament and multilevel intervertebral disc herniation. A magnetic resonance imaging (MRI) of the brain and entire spine indicated marked cervical stenosis due to intervertebral disc herniation within C2/3, C3/4, C4/5, C5/6 and C6/7. Moreover, signal changes of the cervical spinal cord were noted. The X-ray of the chest, pelvis and bilateral lower limbs showed degeneration of bilateral hip joints, diffused muscle ossification, and osteoporosis of pelvis and right lower limb (**Figure 1**). Additionally, the patient had decreased bone mineral density (BMD), with the lowest BMD Z-score of -2.0.

The laboratory examination revealed considerably high iPTH of 214.4 pg/ml [reference range (RR): 12-72 pg/ml], decreased serum calcium level of 2.04 mmol/L (RR: 2.20-2.65 mmol/L), high serum phosphate level of 1.49 mmol/L (RR: 0.81-1.45 mmol/L) and low potassium level of 3.08 mmol/L (RR: 3.50-5.30 mmol/L). Thyroid function test showed a serum TSH level of 9.396 mIU/L (0.55-4.78 mIU/L) and serum free T4 level of 1.17 ng/dl (0.89-1.76 ng/dl). Based on the clinical features and laboratory tests, the diagnosis of PHP was made.

Genetic test revealed a heterozygous frameshift mutation in the causative gene of PHP-Ia, guanine nucleotide-binding protein alpha (GNAS) gene that simulates activity of the polypeptide 1, NM_080425.2, c.2277dupC, p.Val760Argfs*23. Sanger sequencing confirmed the de novo mutation (**Figure 2**). The genetic test was performed by BGI (Shenzhen, China) with next-generation sequencing coupled with DNA target-capture array on Illumina HiSeq2000 platform. The genetic test further confirmed the diagnosis of PHP-Ia.

Given the diagnosis of PHP-Ia, the patient was started on oral calcium supplement and thyroxine replacement. In order to alleviate his neurological symptoms, the patient underwent a posterior decompression and laminoplasty. After the surgery, his symptoms including motor and sensation disturbance of bilateral lower limbs were significantly relieved. One-month post-operation, the patient walked to our clinic with the help of a walker. He was referred to the oral

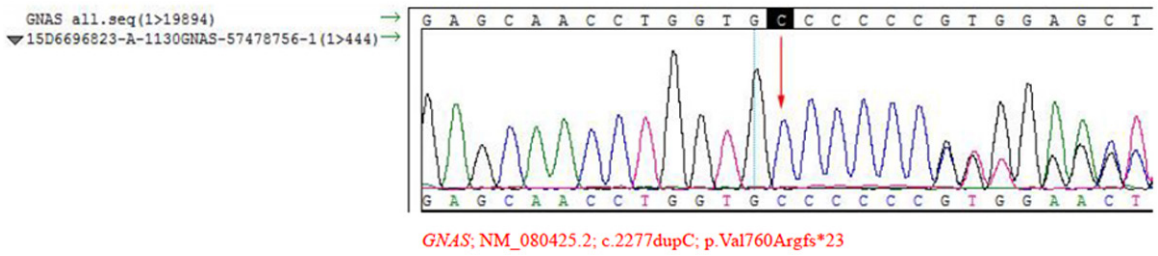

Figure 2. Sanger sequencing confirmed the de novo mutation, NM_080425.2, c.2277dupC, p.Val760Argfs*23.

and maxillofacial surgery department of our hospital in 2017 to extract multiple impacted teeth.

Discussion

PHP-Ia is an autosomal dominant disease caused by heterozygous mutations within the GNAS gene [2], which can be diagnosed by genetic test. Mapped to the chromosome 20-q13, the GNAS gene consists of 13 exons [9] s>/. GNAS gene mutation with c.348_349insC mutation was the first identified mutation [10]. So far more than 100 mutations of PHP-Ia have been identified in all exons except exon 3, while exon 5 and exon 7 are two hot-spots [5]. Among these mutations, small insertions, deletions and amino-acid substitutions predominate [11], causing deficiency of functional Gαs protein, an intermediary coupling protein that stimulates adenylyl cyclase. Maternal mutations involving GNAS exons that encode Gαs lead to PHP-Ia, while the same or similar mutations on the paternal allele lead to pseudopseudohypoparathyroidism (PPHP) [12]. The mutation observed in our patient, c.2277dupC, p.Val760Argfs*23, caused a frameshift after the 760 amino acid residues, which was a pathogenic mutation.

Another important way to diagnose PHP-Ia is to detect the Gαs activity in erythrocyte membranes [13]. Gαs activity was reported to be approximately 50% reduced in patients with PHP-Ia [13, 14].

The common musculoskeletal abnormalities of PHP are short stature, round face, obesity, subcutaneous calcification, brachydactyly, diffused osteoporosis and dental abnormalities. Our patient had all the reported abnormalities. However, spinal stenosis, which was not mentioned as a clinical manifestation in the original report of PHP [15], is becoming an increasingly recognized complication of PHP [7]. To our knowledge, there are 14 reported cases of spinal stenosis associated with PHP-Ia (**Table 1**). As seen in **Table 1**, eight of the 14 reported patients were male and almost all the patients had cervical and/or thoracic spinal stenosis. Several mechanisms of spinal stenosis associated with PHP-Ia have been described. Chronic hypocalcemia and hyperphosphatemia due to untreated hypoparathyroidism may cause extraskeletal ossifications, excessive bone formation in the vertebral canal and multiple herniated intervertebral disc (HIVD) [6], leading to paravertebral ligament ossification and hypertrophic laminae, which are the most common causes of spinal stenosis in patients with PHP-Ia [7]. Congenital short pedicles secondary to premature closure of the physes is also an important factor leading to spinal stenosis [16]. Besides, central obesity of PHP-Ia patients may result in reactive bone formation and ossifications of paravertebral ligament by increasing inflammation and by direct biochemical effects on the spine [17], which play an important role in spinal stenosis. Our patient had severe cervical spinal stenosis due to both ossification of the posterior longitudinal ligament (OPLL) and multilevel intervertebral disc herniation. Treatment of spinal stenosis includes surgical decompression and laminectomy. About half of the patients are reported to have residual deficits or progression of disease post-operation [7].

Hence, early diagnosis and timely corrections of hypocalcemia, hyperphosphatemia and elevated PTH level as well as effective body weight control may play an important role in preventing the rare neurological complications secondary to progressive spinal stenosis in patients with PHP-Ia.

Dental abnormalities associated with PHP have been previously reported [3, 4, 18-21], indicat-

Table 1. Previously reported cases of PHP-Ia with symptomatic spinal stenosis

No.	Author	Sex	Age	Level of spinal stenosis	Cause of spinal stenosis	Management	Outcome
1	Cullen et al., 1964 [26]	F	31	Thoracic	Hypertrophic laminae	Lower dorsal laminectomy	Walking unaided
2	Cavallo et al., 1980 [27]	M	4	Cervical, lumbar	Short pedicles	Laminectomy C2-C6	Partial recovery of motor function
3	Halloran et al., 1983 [28]	F	8	Lumbar	Short pedicles	Not available	Not available
4	Firooznia et al., 1985 [29]	F	59	Cervical, thoracic	OPLL	Not available	Not available
5	Alam et al., 1990 [30]	M	23	Thoracic, lumbar	Hypertrophic laminae	Laminectomy T1/T2, T10/T11, L4/L5	Initial improvement of function of bowel, bladder and legs and deteriorated to paraplegia
6	Okada et al., 1994 [16]	M	41	Cervical, lumbar	HIVD, short pedicles	Laminoplasty C3-C6	Gradual improvement
7	Yamamoto et al., 1997 [31]	M	37	Thoracic	OPLL	Decompression T9/T10	Gradual improvement
8	Chen et al., 2005 [6]	F	38	Cervical, thoracic	OPLL, HIVD	Not available	Not available
9	van Lindert et al., 2008 [32]	F	12	Cervical, thoracic	Short pedicles	Laminoplasty C7-T4	Complete improvement
10	Jiang et al., 2010 [33]	M	24	Cervical, thoracic	OPLL, OLF	Decompression T9-T10, laminectomy C2-C7, T1-T4	Assisted walking , residual sensory deficit and weakness of bilateral lower limbs
11	Li et al., 2011 [34]	M	24	Cervical, thoracic	OLF, hypertrophic laminae	Decompressive T9-T10 laminectomy	Improved function of lower limbs and sphincters, residual sensory deficit and weakness of bilateral lower limbs
12	Roberts et al., 2013 [15]	M	12	Cervical, thoracic	Short pedicles	Decompression and instrumented fusion of T2-T11	Walking unaided
13	Tam et al., 2014 [11]	F	44	Cervical	OPLL	Cervical laminoplasty	Residual weakness of bilateral lower limbs
14	Lee et al., 2015 [35]	M	15	Cervical	HIVD, short pedicles	Decompressive cervical laminoplasty	Wheelchair-bound with residual weakness and partial improvement in strength of bilateral lower limbs

OPLL: Ossification of the posterior longitudinal ligament; OLF, ossification of ligamentum flavum; HIVD: Herniated intervertebral disc; M: Male; F: Female.

ing that they are rare but important manifestations of PHP and should be considered for proper diagnosis. In this case, the patient presented with multiple impacted teeth. In addition, decreased BMD seen in our patient was also described in other case reports [22-24]. In contrast, increased BMD in patients with PHP-Ia was also reported [25]. Hence, the correlation between PHP-Ia and BMD remains unclear, and large-sample size and long-term observation will help to resolve this issue.

Conclusion

Herein, we reported the case of a 33-year-old male with PHP-Ia and typical AHO phenotype, with spinal stenosis as the important manifestation of PHP-Ia. Our study suggests that patients with evident neurological symptoms due to spondylopathy should be screened for serum calcium, phosphate and PTH levels to rule out PHP.

Acknowledgements

This research is supported by President Fund of Nanfang Hospital (No. 2014C012).

Disclosure of conflict of interest

None.

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