Spinal Stenosis with Paraparesis in a Korean Boy with Albright’s Hereditary Osteodystrophy: Identification of a Novel Nonsense Mutation in the GNAS

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Abstract. Children with Albright’s hereditary osteodystrophy (AHO) suffering from spinal cord compression are rarely reported worldwide. The association of compressive myelopathy with AHO is not still well known. AHO is a rare heterogeneous group of inherited disorders and results from the GNAS mutation. AHO manifests in two different phenotypes, pseudohypoparathyroidism type Ia (PHP-Ia) and pseudopseudo-hypoparathyroidism (PPHP), which may happen in the same family members. We present the case of a 15-year-old boy with AHO features, who was later diagnosed with PHP-Ia. He suffered from cervical myelopathy with paraparesis due to spinal stenosis. His mother with AHO phenotype was diagnosed with PPHP without spinal stenosis. Genetic analysis revealed a novel heterozygous nonsense mutation within exon 1 of GNAS (c.49A>T; p.Lys17*) in both of them. This is the first clinically, biochemically, and genetically identified child case of spinal stenosis and paraparesis associated with PHP-Ia, having a novel GNAS mutation in Korea.

Key words: Spinal stenosis, paraparesis, Albright’s hereditary osteodystrophy, Pseudohypoparathyroidism Type Ia, Pseudopseudo-hypoparathyroidism, G proteins, Children.

Introduction

Albright’s hereditary osteodystrophy (AHO) is a syndrome characterized by typical physical findings including short stature, round face, central obesity, brachymetacarpia, brachydactyly, and, in some cases, mental retardation. Pseudohypoparathyroidism (PHP) is a rare disorder manifested by end-organ resistance to parathyroid hormone (PTH). AHO phenotype with hormone resistance is known as PHP type Ia (PHP-Ia), while AHO phenotype without hormone resistance is termed pseudo-PHP (PPHP). PHP-Ia and PPHP are derived by heterozygous loss-of-function mutations affecting the GNAS gene [1]. Maternal transmission of GNAS gene mutation causes PHP-Ia, whereas paternal transmission leads to PPHP. Both rare inherited disorders may happen in the same family members [2,3].

Spinal stenosis and compressive myelopathy was rarely reported among AHO patients, mainly adults. The association of symptomatic spinal stenosis with AHO is not well-known but it can be a significant medical problem with poor prognosis.

Herein, we describe a Korean boy with AHO features and delayed diagnosis of PHP-Ia, suffering from cervical spinal stenosis and paraparesis, having a novel GNAS mutation, while his mother had PPHP with AHO phenotype of the same novel gene mutation.

Case Report

A 15-year-old boy was referred to the pediatric clinic at Inha university hospital for asthma induced dyspnea. He had suffered from allergic asthma since childhood. He had a history of developmental delay and moderate cognitive impairment (Intelligence Quotient 45), but there was no history of seizure or tetany. At the age of 13, he underwent laparoscopic assisted trans-anal Soave surgery for Hirschsprung disease, which was later diagnosed due to slowly progressive chronic constipation. Subsequently, he had been managed with oral thyroxin replacement
therapy for primary hypothyroidism. At the age of 14, he had developed progressive weakness in both lower extremities after several falls, and spine magnetic resonance imaging (MRI) revealed multi-leveled congenital cervical spinal stenosis and compressive myelopathy at C3-5 level (Figure 1). After 4 months, he eventually underwent decompressive cervical laminoplasty due to progressive spastic paraplegia. At 2 months postoperatively, he was wheelchair-bound with residual weakness and partial improvement in strength. Physical examination showed short stature (140cm, -6.7 Standard deviation score) and normal body mass index (22 kg/m², 60 percentile) with bodyweight 42 kg(-0.8 Standard deviation score). Typical somatic features of AHO including round face, poorly arranged teeth, brachydactyly of hands and feet, and short neck were observed (Figure 2). His puberty stage, Tanner III, was within the normal range. The neurologic signs of cranial nerves were intact. His both ankle clonus signs were positive and deep tendon reflexes of bilateral knees and ankles were hyperactive. Spastic hypertonia of lower extremities was observed. Laboratory evaluation revealed mild hypocalcemia (serum calcium 7.7 mg/dL; normal 8.2-10.8 mg/dL), mild hyperphosphatemia (serum phosphate 5.9 mg/dL; normal 2.5-4.7 mg/dL). He also showed marked elevated serum PTH (339.7 pg/mL; normal 13.0-54.0 pg/mL) level and reduced serum 25-OH vitamin D₃ (13 ng/mL; normal 30-75 ng/mL) level. The thyroid function test was normal (free T4 0.93 ng/dL, T3 105.4 ng/dL, TSH 2.27 mIU/L).The radiologic examinations of both hands showed short fourth and fifth metacarpus with thick cortices, subcutaneous ossifications. Radiologic features of the cervical spine were kyphosis and post-laminoplasty state of C3-7.

The patient has been treated with vitamin D supplement and calcium after being diagnosed with PHP-Ia. His serum level of calcium, phosphorus, and PTH became normal within 2 months but he is still wheelchair-bound and has significant neurologic deficits with regard to lower extremities function. On follow-up computerized tomography (CT) scan 18 months after the surgery, the spinal stenosis and kyphotic curvature were worse and more prominent than the prior CT findings. The patient’s mother had typical AHO features such as round face, short neck, short stature (150cm, -2 Standard deviation score), central obesity (body weight 65kg, body mass index 29.3), brachydactyly, and mild mental retardation, but did not show any laboratory evidence of hormone resistance (Table 1). Radiographic findings of her cervical spine were within the normal ranges.

**Genetic analysis.** Blood samples were collected from the patient and patient’s mother after obtaining informed consent. Genomic DNA was extracted from peripheral blood leukocytes using a Wizard genomic DNA purification kit (Promega, Madison, WI, USA). All of the exons and adjacent intronic region of GNAS gene were amplified by PCR using primers designed by the authors upon request and a Thermal Cycler 9700 (Applied
Cycle sequencing analysis was performed using the BigDye Terminator Cycle Sequencing Ready Reaction kit (Applied Biosystems). The heterozygous nonsense mutation in exon 1 of the \textit{GNAS} gene, \textit{GNAS} NM_000516.4:c.49A>T (p.Lys17*), was identified in both the patient and his mother (Figure 3). The A>T transversion results in an amino acid substitution from Lys to stop codon at codon 17. This is a novel \textit{GNAS} mutation associated with AHO feature.

\textbf{Discussion}

We present a son and his mother with unique features of AHO and endocrine disorders of PHP-Ia and PPHP respectively. Direct sequencing of the whole coding region of the \textit{GNAS} gene in affected family members identified a heterozygous mutation in exon 1 of \textit{GNAS}. The c.49A>T (p.Lys17*) mutation is a de novo finding that produces a premature stop codon and truncated protein, which lacked most protein domain.

Although many \textit{GNAS} gene mutations in AHO patients have been reported up to recently, the genotype for symptomatic spinal stenosis has not been reported in the literature thus far. Spinal stenosis and progressive myelopathy are rare complications of AHO, or PHP and PPHP. Currently we were able to search 11 published case reports with AHO combined with spinal cord compression, including only two children [8]. The correlation between spinal stenosis induced-myelopathy and AHO or \textit{GNAS} has been little known.

It has been suggested several mechanisms of the association of symptomatic spinal stenosis with AHO. Chronic hypocalcemia and hyperphosphatemia of this disorder frequently can cause extraskeletal calcifications, which may lead to various deformities of the vertebral canal [9-11]. All these changes may make spinal cord fragile and compressible. Central obesity, which is a common manifestation of AHO, further precipitates a degenerative change of vertebral body, ligaments, and joints.

The most common site involved in spinal stenosis is cervical spine, which is followed by thoracic spine [8]. Furthermore mental retardation and extrapyramidal motor problems in AHO patients cause them to fall more easily, which may result in spinal compression [12]. In our patient, PHP-Ia had been later diagnosed after surgical decompression for relieving cervical cord compression. His cognitive impairment and near-normal laboratory finding (serum calcium and phosphate levels) can make it difficult to diagnose regardless of unique AHO phenotype. Few reports of AHO with spinal cord decompression surgery have been described.
and show various prognoses, ranging from full recovery to paraplegia [8,13]. Based on clinical suspicion, earlier diagnosis and intervention may delay and prevent the progression of this disorder with neurologic complication. Although no clear genotype-phenotype correlations have been observed in GNAS, further studies to evaluate a possible relationship between the novel nonsense mutation and the presence of symptomatic spinal stenosis are needed.

Hirschsprung disease has various genomic causes that are known to have connections with the onset of typical symptom. GNAS also is thought to be one of the most complex gene loci in the human genome. In this patient, we suspect the potential association of the GNAS and the genetic cause of Hirschsprung disease but we could not find certain relationships of genetic backgrounds between Hirschsprung disease and PHP-Ia.

In summary, we reported a case of 15-years-old boy with PHP and his mother with PHP, in whom a novel nonsense GNAS mutation was identified. He mainly suffered from cervical spinal stenosis and myelopathy, a rare complication of AHO. This is the first clinically, biochemically, and genetically identified child case of spinal stenosis and paraparesis associated with PHP-Ia, having a novel GNAS mutation in Korea.

References