PSEUDOPSEUDOHYPOPARATHYROIDISM AS A CAUSE OF FAHR SYNDROME: HYPOPARATHYROIDISM NOT THE ONLY ONE

H. Ozisik^{1,*}, B.S. Yürekli¹, R. Tuncel², N. Ozdemir⁴, M. Baklaci³, O. Ekmekci², F. Saygili¹

¹Ege University, Faculty of Medicine, Dept. of Endocrinology, ²Dept. of Neurology, Dept. of Physical Medicine and Rehabilitation, Izmir, ⁴Celal Bayar University, Faculty of Medicine, Dept. of Endocrinology, Manisa, Turkey

Abstract

Introduction. Fahr's syndrome is an infrequent disorder characterized by bilateral symmetrical calcification of basal ganglia and the cerebral cortex. It can be seen genetic, idiopathic, or secondary to endocrine diseases. This disease is related to different metabolic disorders particularly with diseases of the parathyroid gland.

Case 1. A 63-year-old female patient applied to our clinic due to having hypoparathyroidism with bilateral basal ganglia calcification in head computed tomography(CT). She had subtotal thyroidectomy 25 years ago. In the neurological examination, mild symmetrical parkinsonism was determined. In laboratory examination Ca:8 mg/dL (8.6-10.2), P:5.1 mg/dL (2.3-4.5), PTH:9.53 pg/mL (15-65) were detected. Calcitriol 0.25 µ/day was added to her treatment. Her parkinsonism disappeared after the treatment.

Case 2. A 49-year-old male patient was consulted when he was admitted to the department of neurology in our hospital. The physical examination demonstrated the characteristics of Albright's hereditary osteodystrophy. The neurological examination shows bilateral symmetrical bradykinesia, dysphagia, and moderate dysarthria. In the laboratory examination PTH: 46.5 ng/L(15-65), Ca:8.6 mg/dL (8.6-10.2), P:2.7 mg/dL (2.3-4.5) were detected and were all within the normal ranges. Consequently, pseudopseudohypoparathyroidism was decided as a diagnosis. G protein alpha subunit mutation (Gsa) was not detected due to technical limitations.

Conclusion. When a patient is diagnosed as Fahr's syndrome, we should keep in mind parathyroid disorders. Fahr's syndrome must be evaluated in patients showing intracranial calcification accompanied by parathyroid diseases.

Key words: Fahr, hypoparathyroidism, pseudopseudohypoparathyroidism.

INTRODUCTION

Fahr's syndrome is an infrequent disorder characterized by bilateral symmetrical calcification

of basal ganglia and the cerebral cortex. It could be genetic, idiopathic, or secondary to endocrine diseases (1). This disease is related to different metabolic disorders especially in the parathyroid gland (2). Hypoparathyroidism is a well-known reason for this extensive cerebral calcification (3). Pseudohypoparathyroidism (PHP) is a heterogeneous group of rare endocrine disorders characterized by normal renal function and resistance to parathyroid hormone (PTH) action, manifesting with hypocalcemia, hyperphosphatemia. Pseudopseudohypoparathyroidism is a variant of pseudohypoparathyroidism 1A (PHP 1A), in which laboratory levels of calcium, phosphorus, parathyroid hormone (PTH) are normal. The pathognomonic feature of the two disorders is Albright hereditary osteodystrophy (AHO). Albright's hereditary osteodystrophy patients present various physical manifestations involving round face, short stature, strabismus, ectopic calcifications, brachydactyly with short metacarpals and mental retardation (4). We present two cases of Fahr syndrome with hypoparathyroidism and pseudopseudohypoparathyroidism due to its rarity.

CASE 1

A 63-year-old female patient applied to our clinic due to hypoparathyroidism with bilateral basal ganglia calcification in the cranial computed tomography (CT) (Fig. 1). Her medical history revealed total thyroidectomy operation 25 years ago. The neurological examination demonstrated mild symmetrical parkinsonism. Laboratory examination revealed hypocalcemia, hyperphosphatemia and hypoparathyroidism. Laboratory levels were: Ca:8 mg/dL (8.6-10.2), P:5.1 mg/dL (2.3-4.5), PTH:9.53 pg/mL (15-65). She was taking calcium carbonate 2 times a day during the laboratory examination. Calcitriol 0.25 mcg was added to her treatment, in surveillance her

*Correspondence to: Hatice Ozisik MD, Ege University, Faculty of Medicine, Department of Endocrinology, Izmir, 35040, Turkey, E-mail: drhaticege@hotmail.com

calcium levels were detected between 8-9 mg/dL. Her parkinsonism symptoms regressed after this medical treatment.

CASE 2

A 49-year-old male patient was admitted to the neurology department in our hospital. His

Figure 1. Bilateral basal ganglia calcification.

Figure 2. Albright's hereditary osteodystrophy.

chief complaints were severe dysphagia, and moderate dysarthria. The physical examination revealed the characteristics of Albright's hereditary osteodystrophy (Fig. 2). He had a round face, short stature, brachydactyly (shortened fourth and fifth metacarpals). The neurological examination demonstrated bilateral symmetrical bradykinesia, parkinsonian gait, hyperactive deep tendon reflexes, bilateral positive Hoffman's sign, mild dysmetria, severe dysphagia, and moderate dysarthria. In the laboratory examination PTH: 46.5 ng/L(15-65), Ca:8.6 mg/dL (8.6-10.2), P:2.7 mg/dL (2.3-4.5) were detected, within normal ranges. Cranial CT revealed bilateral basal ganglia, centrum semiovale, occipital cortex, dentate nucleus of cerebellum, cerebellar white matter and cortex, pontin, posterior bulbar calcification (Fig. 3). In the nerve conduction studies (NCS) and needle electromiography (EMG) all parameters were normal, but swallowing EMG displayed the supranuclear involvement. Neuropsychological tests revealed impairment of the executive functions. Consequently, pseudopseudohypoparathyroidism was diagnosed due to laboratory parameters and Albright's hereditary osteodystrophy phenotype of the patient. G protein alpha subunit mutation ($G\alpha$) could not be detected because only exon 8 can be studied in our department of genetics.

DISCUSSION

Fahr syndrome includes basal ganglia calcification secondary to other diseases and Fahr's disease (4). Fahr disease has an autosomal dominant inheritance (5). Clinical features of Fahr's syndrome can be seen in different conditions such as psychiatric diseases, heterogeneous neurological situations, epileptic disorders (6). Though many systemic diseases cause Fahr syndrome, the reason of the focal accumulation of calcium in basal ganglia can be due to disturbance of calcium metabolism and local factors (7).

Parathyroid diseases can cause Fahr syndrome. One of the possible causes is pseudohypoparathyroidism (PHP). In pseudohypoparathyroidism (PHP), resistance to the action of parathyroid hormone (PTH) results in hypocalcaemia and a high level of PTH (8).

AHO is a syndrome with a wide range of manifestations including obesity, short stature, round face, characteristic shortening and widening of long bones of hands and feet (brachydactyly) mostly affecting the 4th and 5th metacarpals and metatarsals subcutaneous ossification. AHO can be seen in

pseudohypoparathyroidism-1a (PHP-1a) and in pseudopseudohypoparathyroidism (8).

Patients with pseudopseudohypoparathyroidism have the phenotypic appearance of pseudohypoparathyroidism type 1a, but their laboratory levels are (PTH, calcium, phosphorus) normal (9).

In pseudopseudohypoparathyroidism, renal resistance to PTH is absent. $Gs\alpha$ is originated from the maternal allele alone in the renal proximal tubules, and the paternal allele is imprinted. GNAS (guanine nucleotide-binding proteins, alpha stimulating)

mutation causes PHP 1A if it is maternally inherited (10). GNAS1 gene codifies the subunit α of protein G_s , mapped in chromosome 20q13.2-20q13.3. The GNAS1 gene is codified by 13 exons. Exons 2-13 are common in all transcripts (11). Unfortunately, $Gs\alpha$ mutation could not be detected in our case because only exon 8 can be studied in our genetic department. In contrast to patients with maternally transmitted mutations that result in loss of GNAS1 function, those with paternally transmitted mutations have the phenotype of AHO but with normal serum calcium concentrations and without

Figure 3. Axial CT showing bilateral basal ganglia, centrum semiovale, occipital cortex, dentate nucleus of cerebellum, cerebellar white matter and cortex calcification.

renal tubular resistance to PTH (12).

The mechanism of calcium deposits in the brain is unknown in Fahr's Syndrome. It can be caused by neuronal calcium metabolism disorder or the damage in the blood-brain barrier (13). Complex cellular mechanisms involved in precipitation of calcium are considered to explain this pathology. Pericytes are found in the microvascular vessel wall and provide preservation of the blood-brain barrier. Genetic defects associated with pericyte dysfunction cause Fahr's disease (14, 15). Fahr's syndrome can be diagnosed in different parathyroid pathologies so it may be related to the genetic defect in pericyte function in which pericytes can differentiate into osteoprogenitor cells (16, 17). Further studies are needed to prove this hypothesis.

Iatrogenic hypoparathyroidism might be seen in the patients after thyroidectomy operations. After thyroid surgery hypocalcemia can be caused by various situations (18). In the follow-up period, neurological symptoms may develop due to this complication in these patients, like our first patient. We should be aware of Fahr syndrome in these conditions. In case of hypoparathyroidism, the normalization of calcium levels may ameliorate the neurological symptoms (19). However, normal calcium and phosphorous levels do not rule out Fahr's syndrome. In addition, Albright's hereditary osteodystrophy can be a clue for the etiology of Fahr's syndrome. It can be emphasized that, not only hypoparathyroidism, which is seen more commonly, but also pseudopseudohypoparathyroidism can cause Fahr syndrome.

In conclusion, when a patient is diagnosed with Fahr's syndrome, parathyroid pathologies should be taken into account to manage treatment correctly. Moreover, although pseudopseudohypoparathyroidism is not a true parathyroid pathology, Fahr's syndrome can be detected in this disorder.

Conflict of interest

The authors declare that they have no conflict of interest.

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