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Fahr Syndrome Secondary To Pseudohypoparathyroidism: About a case

[1]Dr. Habibi Sanae, [2]Dr. Bourkadi Ghita, [3]Pr. Abourazzak Sanae, [4]Pr. Hida Mustapha

Pediatric Endocrinology Diabetology Department, CHU Hassan II Fez

Faculty of Medicine and Pharmacy of Fez

Epidemiology and Health Sciences Research Laboratory

Corresponding Author: Dr. Habibi Sanae, Pediatric Endocrinology Diabetology Department, CHU Hassan II Fez

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Abstract

Fahr syndrome is a rare anatomical and clinical entity. It is characterized by symmetrical, bilateral intracerebral calcifications located in the basal ganglia. These calcifications are most often associated with dysparathyroidism, in particular hyperparathyroidism, more rarely hypoparathyroidism or pseudohypoparathyroidism. Pseudohypoparathyroidism is a rare disease characterized by resistance of target tissues to parathyroid hormone.

We describe the case of an 11-year-old child with these two rare conditions.

Keywords: Basal ganglia calcification, Fahr's syndrome, Pseudohypoparathyroidism (PHP)

Introduction

Fahr syndrome (FS), named in honor of its discovery by Theodor Fahr in 1930, is characterized radiologically by the presence of non-arteriosclerotic, bilateral and symmetrical striato-pallido-dentate calcifications [1]. It is a rare condition whose pathophysiological mechanisms are debated, as evidenced by the numerous names that describe it. SF presents a wide variety of clinical manifestations and its causes are mainly linked to disturbances in phosphocalcic metabolism [1; 2].

Pseudohypoparathyroidism (PHP) is a rare pathological entity characterized by resistance to the action of PTH at renal level. This resistance is due to a genetic anomaly at the GNAS locus, which encodes the alpha-stimulating subunit of G proteins (Gs-α). Heterozygous mutations causing loss of function and epimutations responsible for loss of expression are associated with a wide spectrum of pathologies, but their mechanisms remain incompletely understood.

Observation

A young 11 year-old girl was admitted in emergency department for management of generalized tonic-clonic

seizures with loss of consciousness, in whom the clinical examination found a positive trousseau and chvosteck, with no cranial nerve abnormalities,.

The biological investigations revealed severe hypocalcemia of 48mg/l, with elevated phosphatemia 82 mg/l, elevated PTH 512 ng/ml (9-77 pg/ml); 24-hour hypocalciuria, low vitamin D (11.8ng/l) and normal magnesemia (19mg/l) consistent with pseudohypoparathyroidism. Bilateral, symmetrical calcifications of the capsule lenticulocaudate nuclei and front parietal subcortical white matter were observed on cerebral CT, suggesting Fahr's syndrome.

An ophthalmological examination was requested, but returned with no particular findings. A genetic study was requested, but not carried out due to lack of availability at the hospital.

In terms of treatment, the patient was put on oral calcium supplements with active vitamin D, with symptomatic improvement.

Discussion

On the basis of brain imaging studies in patients with neurological or psychiatric symptoms such as seizures, dyskinesia, dementia and depression, Fahr syndrome is suspected in the presence of calcification of the basal ganglia of the brain (BGC). [20,21].

Fahr's syndrome, first described by the German pathologist Karl Theodor Fahr in 1930, represents classical clinical manifestations of pseudo-hypoparathyroidism. It clinically manifests by convulsions, extra-pyramidal and neuro-psychiatric signs [5].

Despite the lack of knowledge about the prevalence of Fahr's syndrome, there have been reports of basal ganglia calcifications (BGC) ranging from 0.3% to 1.2% on routine radiological examinations.[11,13]Kazais found that there was a 1.02% incidence of symmetrical intracranial calcifications by analyzing 7040 brain CT scans. Patients with pseudo-hypoparathyroidism had more extensive calcifications.

Fahr syndrome is mainly caused by hypoparathyroidism and pseudohypoparathyroidism. [5, 7,8]. Approximately half of BGC patients present with neuropsychiatric manifestations and deficits. Headaches, dizziness, movement disorders (such as Parkinson's tremor, dystonia and cerebellar ataxia), myoclonus and seizures are the most common neurological symptoms. [3,6] Stroke-like events, speech disorders, coma, cognitive impairment and syncope may also recur. [14,15,16,17] At the onset of the disease, psychiatric symptoms are generally more prominent than neurological symptoms[9], with a wide variety of symptoms ranging from depression to psychosis[4,8,9,17,18].

Investigations should be carried out to identify hypoparathyroidism and pseudohypoparathyroidism in the presence of cerebral calcifications, especially if associated with neuropsychic signs.

Typical signs of pseudohypoparathyroidism include elevated PTH and phosphoremia, normal levels of 1, 25-dihydroxyvitamin D and magnesium, with low urinary calcium excretion.

Treatment of Fahr's syndrome focuses on the identifiable cause of the problem [19].Early treatment, particularly in hypoparathyroidism and pseudohypoparathyroidism, can prevent calcifications and the onset of neurophysiological disorders. [4, 5, 17].

In general, normalization of blood calcium levels has a positive impact on seizures and psychiatric signs, expect for dementia [2].

In symptomatic patients, seizures respond poorly to anticonvulsants and resolve when normal plasma

calcium levels are reached. [4] It should be emphasized that the prognosis is uncertain and impossible to predict, and is not related to the extent of calcification [17]. Neurological deterioration is the main cause of death [17].

Different types of PHP have been identified on the basis of their characteristics: type Ia (hereditary Albright osteodystrophy), Ib, Ic and PHP 2 [11].

PHP Ia was the most common subtype, characterized by a blunted cAMP and phosphaturia response after administration of exogenous PTH. In addition, the PHP Ia patient usually presented with hereditary Albright osteodystrophy (AHO), which brings together several specific phenotypic features: short stature, obesity, extremity abnormalities such as brachydactyly, brachymetacarpia and more or less diffuse subcutaneous calcifications; mental retardation is often present [10].

This type corresponds to a genetic defect within or upstream of the imprinted GNAS gene, which codes for the alpha stimulatory G protein (Gs-α) [22].It is also associated with resistance to thyroid-stimulating hormones.

Although type 1b does not have the same physical appearance as type 1a, it is biochemically similar. This type is linked to a disruption of STX16 responsible for a methylation defect in exon A/B of GNAS1.

Type 2 does not have the physical characteristics of type 1, but administration of exogenous PTH increases urinary cAMP levels, without producing phosphaturia, revealing a deficiency downstream of the Gαs subunit. To date, no gene has been identified. [11]

Type 1c is also mentioned in some sources. [23] The phenotype of patients is identical to that of type 1a, but with normal Gsactivity. It is unclear if it should be considered as a separate entity because it is also caudate by a GNAS mutation. [24]

Finally, pseudo-pseudohypoparathyroidism (PPHP); which includes patients with AHO with decreased Gsactivity. Progressive bone heteroplasia is a severe form of PPHP, characterized by heterotopic ossification that extends progressively, deep into connective tissue and skeletal muscle [12].

Conclusion

Fahr's syndrome is a rare neurological condition that contrasts severe, non-specific clinical manifestations with simple, effective treatment. Even at an advanced stage, clinical signs improve considerably after correction of metabolic phosphocalcic disorders.

Although rare, pseudohypoparathyroidism should be suspected in the presence of hypocalcemia with elevated PTH after ruling out hypomagnesemia and vitamin D deficiency. A genetic study remains necessary to confirm the diagnosis.

This present case highlights the difficulty of an early diagnosis of these two rare conditions.

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