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Case Report

Basal ganglia calcification: a Fahr's disease case report ☆,☆☆,★,★★

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ARTICLE INFO

Article history:

Received 26 June 2021

Accepted 18 July 2021

Keywords:

Fahr disease

Idiopathic Basal Ganglia Calcification

Computed Tomography

neuroradiology

ABSTRACT

Idiopathic basal ganglia calcification (IBGC), known as Fahr's disease, is a rare neurological disorder characterized by metabolic, biochemical, neuroradiological and neuropsychiatric alterations caused by symmetrical and bilateral intracranial calcifications. The disease has, in most cases, an autosomal dominant pattern of inheritance and genetic heterogeneity. Overlap of neuropsychiatric symptoms is common with movement disorders accounted for 55% of the manifestation. Here we present the case of a 58-year-old woman, presenting to the emergency department because of an accidental fall. Her past medical history was unremarkable and she denied any neurological symptoms apart from insomnia and anxiety. Patient was sent to the emergency department to perform a Brain Computed Tomography (CT) exam that showed bilateral symmetrical calcifications in cerebellar white matter, the corpus striatum, the posterior thalami, and the centrum semiovale of both cerebral hemispheres. Being a case of IBGC without relevant symptoms, diagnosis was mainly obtained thanks to the characteristic features of CT examination.

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☆ Acknowledgements: The authors report no involvement in the research by the sponsor that could have influenced the outcome of this work.

☆☆ Competing Interests: We confirm that this work is original and has not been published elsewhere nor is it currently under consideration for publication elsewhere. Publication is approved by all authors and by the responsible authorities where the work was carried out. Each author has participated sufficiently in any submission to take public responsibility for its content. The authors have no conflicts of interest.

* Patient consent: Informed consent was obtained from all individual participants included in the study.

** Computed Tomography assessment of Idiopathic basal ganglia calcification

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<https://doi.org/10.1016/j.radcr.2021.07.042>

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Introduction

Fahr's disease, also known as familial idiopathic basal ganglia calcification (FIBGC), was first described in 1930 by Karl Theodor, a German neurologist.

It is a neurological condition characterized by abnormal bilateral deposits of calcium. It commonly has an autosomal dominant inheritance, with a slight predominance between 40-50 age. [1] Classical symptoms include both motor and psychiatric disorders. Calcifications are typically symmetrical, most frequently located in the basal ganglia, but also in dentate nuclei, thalamus, brainstem, centrum semiovale, and subcortical white matter [2]. Calcified areas are easily identified as spontaneous hyperdense lesions on unenhanced brain Computed Tomography (CT) exam, which represents the gold standard technique for an accurate diagnosis.

We describe the case of a 58-year-old woman with few clinical signs at presentation.

Case report

A 58-year-old Caucasian female was referred to our emergency department after an accidental fall.

The patient was in good clinical condition, alert and conscious, arriving at the department autonomously.

Her medical history was negative for drug use and previous injuries. Accession to family's medical history was unattainable due to woman's adoption. She reported insomnia and anxiety since the age of 50. No other significant symptoms were documented. Clinical examination was negative. Blood test revealed the absence of significant abnormalities. Therefore, a CT exam of the brain was performed: it showed bilateral symmetric calcifications in white matter, basal ganglia, thalami, dentate and nuclei of the cerebellum. Encephalic CT scan provided very suggestive findings (Fig. 1). Clinical monitoring and radiological re-evaluation was recommended in 3 days in order to detect vascular phenomena not visible at beginning (Fig. 2 and Fig. 3).

Discussion

Primary familial brain calcification (PFBC) also known as Fahr's disease, is a genetic disorder characterized by abnormal vascular calcium deposition in the basal ganglia. Patients are usually in good health in their youth and tend to develop this progressive neurodegenerative disease later in adulthood. The prevalence of this disease is more or less unknown due to insufficient investigations of first-degree relatives of the patients. It commonly has an autosomal dominant inheritance, with a slight predominance between 40-50 age. Clinical manifestations are variable and may vary from asymptomatic patients to more severe courses, even in different patients within the same family. Serious forms may result in a progressive worsening with psychosis, cognitive impairment, dementia,

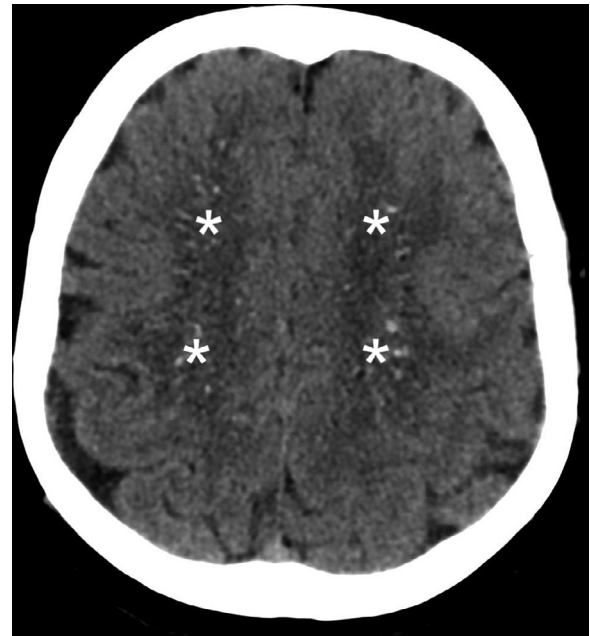


Fig. 1 – Axial CT scan showing bilateral calcifications in the corona radiata (*)



Fig. 2 – Axial CT scan showing bilateral calcifications in the head of caudate nucleus (yellow arrows) (Color version of figure is available online)

gait disturbance, basal ganglia movement disorders (parkinsonism, dystonia, dyskinesia), and cerebellar signs (ataxia and dysarthria) [5]. The term “disease” refers to the primary form, which is based on genetic alterations. On the other hand, the term “syndrome” has been suggested when a secondary, and potentially treatable, cause is found, and it has been associ-

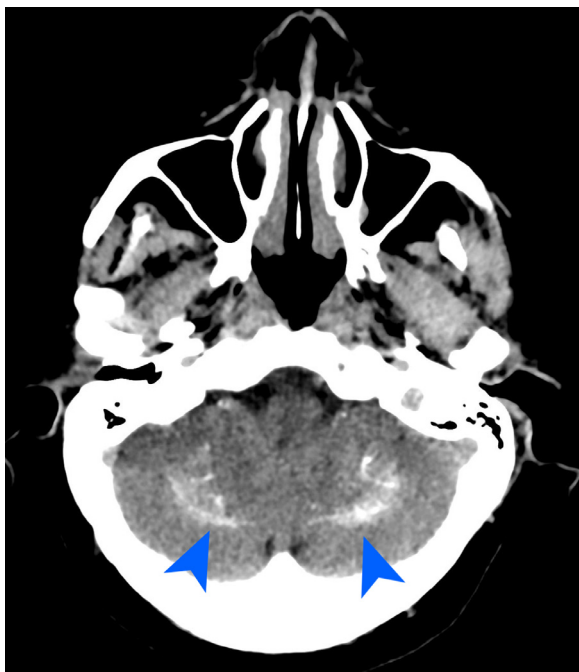


Fig. 3 – Axial CT scan showing bilateral calcifications in both hemispheres of cerebellum, especially cerebellar dentate nuclei (blue arrowheads) (Color version of figure is available online)

ated with different conditions, especially endocrine disease [8] (Table 1). Current literature reports several studies on the genetic etiology of the disease; two main genes have been identified so far: SLC20A2 and PDGFB. Nevertheless, these two genes do not account for all cases of Fahr's Disease confirming the genetic heterogeneity of the disease, as suggested by

linkage studies [9]. Table 2 lists all possible known mutations (Table 2).

Diagnostic criteria of Fahr's disease have been modified, and derived from Moskowitz et al. 1971, Ellie et al. 1989, Manyam 2005 [3,4] and it can be stated as follows:

- 1 Bilateral calcification of the basal ganglia visualized on neuroimaging. Other brain regions may also be observed.
- 2 Progressive neurologic dysfunction, which generally includes a movement disorder and/or neuropsychiatric manifestations.
- 3 Age of onset is typically in the fourth or fifth decade, although this dysfunction may also present in childhood.
- 4 Absence of biochemical abnormalities and somatic features suggestive of a mitochondrial or metabolic disease or other systemic disorder.
- 5 Absence of an infectious, toxic, or traumatic cause.
- 6 Family history consistent with autosomal dominant inheritance

Generally, in symptomatic patients the measurement of the total volume of calcification seems to be associated to an amount of calcium, whereas asymptomatic patients have less CT manifestations. Nevertheless, location and neurological symptomatology are not directly correlated. [6,7]

Curiously, our affected patient, despite the lack of observed symptoms and the old age, revealed a significant amount of calcifications on neuroimaging assessment. The absence of biochemical abnormalities and somatic features suggestive of a mitochondrial or metabolic disease or other systemic disorder, the negative history of previous trauma, infectious, intoxication, was conclusive for Fahr's Disease. Our patient was adopted when she was very young and she never met her biological family, hence the genetic criterion of Manyam cannot be proven in this specific case.

Table 1 – Highlights difference between Fahr's syndrome and Fahr's disease

	Fahr's Syndrome	Fahr's Disease
Age of Onset	30 to 40 years old	40 to 60 years old
Genetic Traits	None	Autosomal dominant or recessive
Radiological Findings	Symmetrical and bilateral intracranial calcifications.	Coarse, progressive, bilateral and symmetrical striato-pallido-dentate calcifications.
Associated Conditions	Endocrinopathies: Idiopathic hypoparathyroidism secondary hypoparathyroidism, pseudo-hypothyroidism, hyperparathyroidism, or presence of any of the following conditions: Brucellosis infection (intrauterine or perinatal), neuroferritinopathy, tuberous sclerosis, mitochondrial myopathy, lipoid proteinosis	None
Treatment	Treatment directed to specific aetiology and adjunctive symptomatic treatment.	No specific remediation, only symptomatic treatment.

Table 2 – Known mutations as a cause of Fahr's Disease.

SLC20A2 (8p1.21)	Encodes the inorganic phosphate transporter PiT-2, a transmembrane protein associated with phosphate homeostasis in various tissues, including the brain, and its mutations result in a reduction of phosphate transport. [10] Mutations in SLC20A2 gene are responsible for most cases identified so far and over 40 pathogenic variants have been reported in patients with Fahr's Disease [10]. Pattern of calcification: more severe calcification overall in the lenticular, caudate, vermis, and subcortical white matter.
DGFRB (5q32) and PDGFB (22q13.1)	Are involved in pericytes recruitment, blood-brain barrier regulation, and angiogenesis [11,[12,13]. Pattern of calcification: no calcification in vermis and cortical
XPR1 (1q25.3)	is a gene encoding a retroviral receptor with phosphate export function and involved in phosphate homeostasis [14]
MYORG 9p13.3	Identified as a novel genetic cause for autosomal-recessive PFBC in Chinese patients [15], but its role in the pathogenesis of PFBC is yet unknown

Conclusions

Fahr's disease is essentially a diagnosis of exclusion after ruling out most frequent metabolic disorders. Blood test revealed the absence of significant abnormalities: haemogram, renal function test, as well as PTH, TSH and VIT.D were also normal. These findings were essential to exclude a secondary form. In our case report, five of the diagnostic criteria were met even though the patient showed a few clinical manifestations. The missing criterion, on which it was not possible to investigate, was the family history, as the patient had been adopted.

Declaration

All the authors confirm that written, informed consent for publication of our case was obtained from the patient(s).

Availability of data and material

material and data are all available

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Data obtained in this study did not interfere with course of treatment for patients included.

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