JGG 2019;67:254-257

Fahr's disease: follow-up of a clinical case with severe cognitive impairment in absence of extrapyramidal disorders

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Fahr's disease (FD), also known as familial idiopathic basal ganglia calcification, is a neurodegenerative disease affecting cerebral microvessels, mainly in the basal ganglia. It mostly presents with movement disorders, dementia and behavioural abnormalities. It is considered hereditary with an autosomal dominant transmission. Fahr's disease is often underestimated and underdiagnosed. We describe a rare case of Fahr's disease: it manifested itself with cognitive and behavioural alterations in absence of extrapyramidal disorders. Diagnosis was supposed only after CT scan. Since onset of FD may only present with cognitive dysfunction without extrapyramidal signs, physicians should consider this complex syndrome when consulting patients with mental deterioration and behavioral abnormalities. Neurological and psychological examinations and CT imaging remain the basic techniques for the diagnosis of Fahr's disease.

Key words: Basal ganglia calcification, Fahr's disease, Dementia, Elderly

INTRODUCTION

The Primitive Idiopathic Calcification of the Base Ganglia, also called Fahr's Disease (FD), is a rare neurodegenerative disease of unknown aetiology characterized by the presence of idiopathic, bilateral and symmetrical calcifications, at the level of the basal ganglia, the dentate nuclei of cerebellum, the thalamus nuclei and the semi-oval centre [1]. Its prevalence increases with age and the most affected site is the globus pallidus. Symptoms and signs range from cases of asymptomatic patients to a progressive neuropsychiatric condition often associated with extrapyramidal disorders of movement. These disorders, such as stiffness, hypokinesia, tremor, choreoathetosis, ataxia and buccal dyskinesia, are followed by cognitive disorders, then pyramidal signs, psychiatric disorders and changes in sensitivity and pain [2-4]. Psychotic symptoms of Fahr's disease have the characteristics of secondary psychotic disorders and include auditory, olfactory and visual hallucinations, ideas of reference and influence, and persecutory delusional themes [5]. Other neurological features are convulsions or events similar to stroke [2]. Although dementia is a common disorder in FD, the presentation of this disease with pure dementia (without extrapyramidal disorders) has been rarely reported [2 6]. Treatment is symptomatic while the exact pathological process is not known. We report a case report of a 73-year-old woman presenting a cognitive impairment as the only manifestation of FD.

CLINICAL CASE

A 73-year-old woman with hypercholesterolemia, receiving rosuvastatin 20 mg, came to our observation for a progressive cognitive impairment started about 2 years earlier with occasional episodes of

Received: June 21, 2019 - Accepted: July 11, 2019

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visual hallucinations and ideas of reference, changes in alertness, nonconcrete reasoning, calculation, and occasional behavioural disturbances. General and neurological clinical examination was normal. Standard blood chemistry tests, including calcium, phosphorus, as well as the hormonal profile, including thyroid hormones and parathyroid hormone, were normal (PTH 46.4 pg/ml) while the 25-OH-Vitamin D dosage was reduced to 11.4 ng/ml. ECG showed a type of BAV in first-degree, the chest X-ray and ultrasound of the supra-aortic vessels were normal. The brain CT showed: normal for morphology and size the ventricular system with modest dilatation of the subarachnoid spaces of the base and of convexity on an atrophic basis, hypodensity of the periventricular white matter in relation to chronic vascular suffering, bilateral calcifications of lenticular nuclei, of the corona radiata on the left and in the ipsilateral cerebellar site (Fig. 1). Patient refused PET exam execution. Multidimensional assessment highlighted: Mini Mental State Examination corrected (MMSEc -Italian version) score was 19/30 with marked deficit of the memory and of the visuo-spatial abilities, ADL score was 5/6; Montreal Cognitive Assessment (MOCA) was also performed, showing a score of 12/30. Specifically, the following scores were found at the MOCA test: visual-spatial executive 1/5; denomination 1/3; attention 3/6; Language 2/3; Abstraction 0/2; Deferred recall 1/5; Orientation 1/5.

Fahr disease was diagnosed basing on absence of biochemical abnormalities and somatic features suggestive of a mitochondrial or metabolic disease or other systemic disorder, progressive neuropsychiatric manifestations, bilateral calcifications of brain regions.

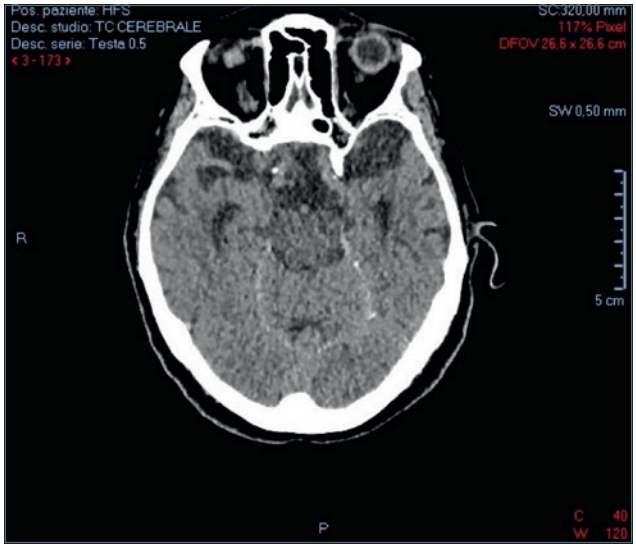

Figure 1 Brain CT: bilateral calcification of lenticular nuclei and left corona radiata, a clinical condition compatible with Fahr's disease.

The patient started therapy with vitamin D3, citicoline 500 mg x 2/day, haloperidol 0.2% 4 drops/day, with frequency reduction of visual hallucinations episodes. At one year of follow-up, the MMSE scored was 15/30 and the patient showed aggressive behaviour; moreover, execution of many activities of daily life was compromised (ADL score was 2/6). At 18 months of follow-up the MMSE totals a score of 9/30, ADL are further compromised (ADL 1/6) and extrapyramidal disorders remain absent, even in the presence of a good control of visual hallucinations with haloperidol 0.2% 3 drops × 3/day.

DISCUSSION

We present a rare case of FD involving exclusively cognitive and behavioural disabilities. FD, described for the first time by Karl Theodor Fahr in 1930, is an unusual degenerative neurological disorder whose prevalence is probably < 0.5% [7]. Diagnosis of Fahr's Syndrome requires demonstration of etiological cause linked to the characteristic calcifications. According to our knowledge there are few cases described in the literature with same clinical features of the case showed [2 6 8-10]. The first case of FD with pure and pre-senile dementia without extrapyramidal symptoms or metabolic abnormalities has been described in a patient with bilateral strio-pallido-dentate calcinosis and cortical atrophy prevalently in parietal-temporal areas with mild periventricular hyperintensity [6]. Considering instrumental diagnosis, TC study, in some cases, can be integrated with a PET study. Benke et al. [2] have shown, using PET studies in patients with Fahr's disease and rapidly progressive dementia with predominant frontal lobe syndrome, a massive reduction in glucose metabolism of basal ganglia and in frontal lobe, related with the clinical condition of disinhibition and personality changes. F-Dopa striatal PET didn't show nigro-striatal dopaminergic dysfunction. Brain metabolism studied by Benke et al. can explain cognitive and behavioural problems in FD with dementia and with or without mild parkinsonian symptoms [2]. Unfortunately, our patient refused PET execution. Basing on the age of onset, two clinical patterns are described: the first with early onset, about 30 years, with schizophrenia psychosis in absence of movement disorders; the second with late onset, about 50 years, in which progressive dementia and movement disorders prevail. The pathogenesis of cognitive disorders is linked to destruction of connections between ganglia and cortex, with subsequent fronto-temporal atrophy, formation of neurofibrillary cortical aggregates and both cortical and basal neuronal loss. The psychotic

symptoms of Fahr's disease have characteristics of secondary psychotic disorders and include auditory, olfactory and visual hallucinations, ideas of reference and influence, and persecutory delusional themes [11]. The most common symptoms of Fahr's syndrome in adults include parkinsonism, dystonia, ataxia, chorea and extrapyramidal syndromes. Some patients may present convulsions and pyramidal disorders [12]. Currently, CT is the most valuable method that exceeds magnetic resonance imaging (MRI). CT results are important for a correct differential diagnosis respect to fronto-temporal dementia (FTD) [13-17]. If basal ganglia calcifications are secondary to a known cause, the disease is called Fahr's syndrome [18 19]. This syndrome is associated with many alterations of calcium-phosphorus metabolism disease (hyper-hypoparathyroidism, pseudohypoparathyroidism) [20-22], CNS infections (AIDS, Citalomegalovirus), SLE but also to neoplasms such as angiomas and cerebral gliomas. In our case patient manifested PTH in the normal range. A possible association between Fahr's syndrome and head injuries [23] and schizophrenia has also been reported [24]. Calcifications occur more often in elderly patients and may be symptoms of many diseases such as toxoplasmosis, cytomegalovirus, syphilis, tuberculosis, torulopsis, cysticercosis, tuberous sclerosis and others [22 26 27]. It is worth mentioning that calcifications are quite commonly found in clinical practice and may be encountered as physiological calcifications in the pineal gland or choroid plexuses as well as on the walls of blood vessels. The deposits consist of calcium, zinc, iron, aluminium, magnesium, silicon, copper and phosphorus [3 25]. There are significant differences in the distribution of calcifications between individual patients. This may indicate the different mechanisms of their formation. The location within the brain structures as well as contact with blood vessel are the most important factors determining the chemical composition of the deposits. On this basis, two types of mineralization were described, non-vascular and perivascular. FD pathophysiology is not yet known. Some reports describe the inheritance of Fahr's syndrome, mainly in an autosomal dominant way [26 27]. Estimating prevalence is challenging due to the vast diversity of presenting symptoms and incomplete penetrance of the disease. However, with the most conservative estimations, the minimal prevalence of variants of known genes is 4.5 p. 10,000 (95% CI [3.4-5.5] p. 10,000). Population genomic analysis reveals that this is not a very rare disease, and it has been underestimated and underdiagnosed so far [28]. Four genes have been proved to be related to primary familial brain calcification; namely, SLC20A2, PDGFRB, PDGFB and XPR1. However, in the majority of patients, the syndrome does not have a genetic background. There are some suggestions that intracerebral calcium deposition is secondary to local disturbance of the blood-brain barrier or neuronal calcium metabolism disorder [29]. An important argument in favour of vascular theory was given by studies using cerebral flow scintigraphy that provided evidence of altered blood flow to the calcification sites [30]. Furthermore, inflammatory conditions, such as meningitis or encephalitis, are considered in pathogenesis of Fahr's syndrome [31]. There is no cure for FD, nor there is a standard course of treatment, which is limited to symptomatic therapy, remembering that a peculiar characteristic of these patients is the poor response to treatment with neuroleptics with greater frequency of side effects and poor response to Levodopa [4], most probably due to the insensitivity of postsynaptic striatal structures rather than to the presynaptic damage observed in primary parkinsonism [32].

CONCLUSIONS

Fahr's disease is a neurodegenerative disorder presenting with a wide array of neuropsychiatric symptoms and is underestimated and underdiagnosed. Since individuals with FD may present at onset only with cognitive dysfunction without extrapyramidal signs, physicians should consider this complex syndrome, counselling patients with mental deterioration and behavioural abnormalities. Neurological and psychological examinations and CT imaging remain the basic techniques for the diagnosis of Fahr's disease.

Conflict of interest

The Authors declare to have no conflict of interest.

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How to cite this article: Castagna A, Coppolino G, Leonardi G, et al. *Fahr's disease: follow-up of a clinical case with severe cognitive impairment in absence of extrapyramidal disorders.* Journal of Gerontology and Geriatrics 2019;67:254-7.