

ORIGINAL PAPER

Fahr's syndrome: diagnosis issues in patients with unknown family history of disease

M. LAZĂR^{1,2)}, DANIELA ADRIANA ION²⁾, A. STREINU-CERCEL^{1,2)},
ANCA IOANA BĂDĂRĂU²⁾

¹⁾"Prof. Dr. Matei Bals" National Institute for Infectious Diseases, Bucharest

²⁾"Carol Davila" University of Medicine and Pharmacy, Bucharest

Abstract

Fahr's disease (FD) is a rare clinical neurodegenerative entity, occurring in fourth or fifth decade or elderly patients, consisting in symmetric polytopic calcifications, in one or more of the following areas: basal ganglia, cerebral white matter, thalami, internal capsules, cerebellum, which can lead to pyramidal, extrapyramidal, cerebellar symptoms, alteration of sensitive perception and psychiatric manifestations. The purpose of this paper is to present the FD-diagnosis with unknown family history of disease, based on calcification pattern, symptomatology and lab tests. A three years retrospective study was effectuated on 1942 patients, aged between 20 and 96-year-old, presenting neurological and psychiatric symptoms, which required differential diagnosis with FD. All the patients were evaluated by CT-scans and levels of serum calcium and alkaline phosphatase were measured in cases with cerebral calcification, in order to exclude abnormal calcium-phosphorus metabolism. Cerebral and cerebellar calcification were found in 176 cases, seven cases presenting a calcification pattern suggestive for FD and in six from the seven cases a positive diagnosis of FD was established.

Keywords: Fahr's syndrome, Fahr's disease, basal ganglia calcification.

Synonyms: Fahr disease (FD), cerebrovascular ferrocalcinosis, progressive strio-pallido-dentate calcinosis, familial idiopathic basal ganglia calcifications (FIBGC).

Introduction

According to medical reports, FD may have familial aggregation, with autosomal recessive or autosomal dominant transmission – Geschwind DH *et al.* [1] have described a locus IBGC1 on chromosome 14q involved in the idiopathic basal ganglia calcification. The expressivity within the family is variable and the age of the onset is decreasing progressively with each transmission in the family in case of the autosomal dominant inheritance. There are also cases with no family history of disease, apparently with no genetic component.

In the etiology of basal ganglia calcifications, may play a role also infectious disease (*Brucella*, EBV-infections, tuberculosis, AIDS), hyperparathyroidism, hypoparathyroidism, tuberous sclerosis, lupus, motor neuron disease.

The onset of disease is insidious, usually in middle-aged patients, consisting in various neurological and psychiatric symptoms: mild motor and mental disability, epilepsy, muscular tetany, depressive and association disorders, memory loss, attention deficit. In time, these manifestations become more frequent and their severity increase. Lauterbach EC *et al.* [2] describe also an early adult onset of FD, in 20–40-year-old persons, associated with schizophrenic symptoms, hallucinations and catatonia.

In the cases without modification of 14q chromosome,

the neurological and psychiatric symptoms are mild or absent [3].

This paper emphasize the fact that clinical findings in FD are nonspecific and may be associated with various pathological entities and a positive diagnosis must include CT-evaluation – bilateral basal ganglia calcifications being the best diagnostic element. We also want to establish which calcification pattern is suggestive for FD.

Patients and Methods

A three years retrospective study was effectuated on 1942 patients, aged between 20 and 96-year-old, presenting neurological and psychiatric symptoms, which required differential diagnosis with FD. The patients were divided into three cohorts according to age: first cohort 20–40-year-old including 215 patients, second cohort 40–60-year-old including 831 patients, and third cohort over 60-year-old including 896 patients. The men:women ratio was 1.2:1.

All the patients were evaluated by CT-scans – we used a Somatom Emotion 6 scanner, 2 mm collimation and reconstructions of 4 cm thickness with no overlap for primary evaluation and 2 mm thickness with no overlap for multiplanar and volumetric reconstructions. Levels of serum calcium and alkaline phosphatase were measured in patients with cerebral calcification in order to exclude abnormal calcium-phosphorus metabolism.

☒ Results

Most common symptoms and pathological associations

Eight hundred and sixty-nine patients manifested more than one of the below mentioned symptoms and in consequence the statistic was effectuated based on the main symptomatology of the patient.

Cohort 1

Depressive disorders (67 cases), anxiety (46 cases), attention deficit (29 cases), cephalalgia (26 cases), hallucinations (23 cases), epileptic manifestation (18 cases), and schizoid manifestations (six cases).

Pathological entities: cranio-cerebral trauma (32 cases), mastoiditis (16 cases), drug abuse (14 cases), meningitis (12 cases), encephalitis (eight cases), brain tumor (seven cases), Bourneville disease (four cases), arterial-venous malformation (three cases), subdural hematoma (two cases), and Sturge-Webber syndrome (one case).

In 125 cases, patients manifested more than one of the above-mentioned symptoms.

Cohort 2

Depressive disorder (282 cases), equilibrium disorder (132 cases), anxiety (108 cases), cognitive impairment (91 cases), cephalalgia (67 cases), personality disorder (62 cases), memory loss (53 cases), extrapyramidal syndrome (21 patients), and schizoid psychosis (15 cases).

Pathological entities: cranio-cerebral trauma (52 cases), meningitis (19 cases), stroke (23 cases), brain tumor (four cases), Parkinson disease (19 cases) and subdural hematoma (seven cases).

In 323 cases, patients manifested more than one of the above-mentioned symptoms.

Cohort 3

Depressive disorder (263 patients), memory loss (151 patients), cognitive impairment (116 patients), equilibrium disorder (89 cases), cephalalgia (79 cases), anxiety (74 cases), vascular dementia (72 patients), and extrapyramidal syndrome (52 patients).

Pathological entities: Alzheimer disease (114 cases), cranio-cerebral trauma (72 cases), stroke (58 cases), Parkinson disease (41 cases), meningitis (six cases), cerebral aneurysm (three cases), and brain tumor (12 cases).

In 421 cases patients manifested more than one of the above mentioned symptoms.

In 119 cases there was family history with neuropsychiatric disorders, however no documented FD.

Cerebral and cerebellar calcifications were found in 176 cases: 18 cases between 20 and 40-year-old, 53 cases between 40 and 60-year-old and 105 cases over 60-year-old.

There was no relevant gender predominance regarding the found calcifications.

CT-scan is the most appropriate exploration to diagnose and characterize the cerebral and cerebellar calcifications.

Plain skull radiography is not recommended because small calcifications can be overlooked, especially in the early stages, when they are not very dense. If massive calcifications are present, they may appear as a cluster of granular conglomerate calcifications located above sella turcica on the side view and with symmetric paramedian disposition on the anterior view (Figure 1).

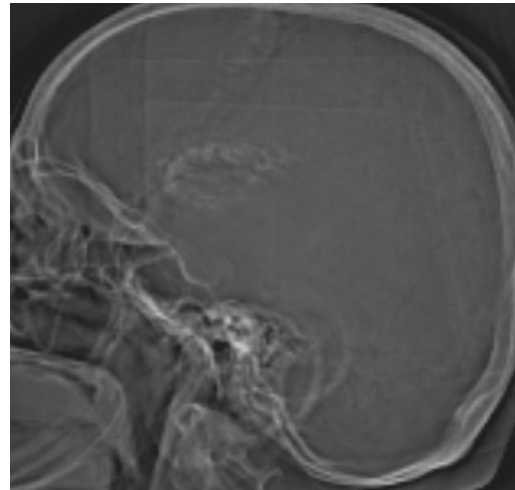


Figure 1 – CT-topogram: cluster of calcifications above sella turcica.

MRI-exam cannot diagnose brain calcifications, may show a high intensity signal area in T2-weighted images, corresponding to a nonspecific metabolic or inflammatory process (which eventually may calcify) [4] and therefore it is not specific in evaluation of FD.

Following symmetric calcifications patterns were found in CT-scans: micronodular, “cloudy” (Figure 2), thin linear (Figure 3), thick linear, nodular and massive (Figures 4 and 5) with various specificity, as shown in the Table 1.

Table 1 – Symmetric calcification pattern

Pattern	Micro-nodular (<3 mm)	Cloudy	Thin linear	Thick linear (>3 mm)	Nodular	Massive
Specificity for FD	(-)	(+++)	(+++)	(+)	(+)	(++)

(-) No specificity, (+) Low specificity, (++) Moderate specificity, (+++) High specificity.

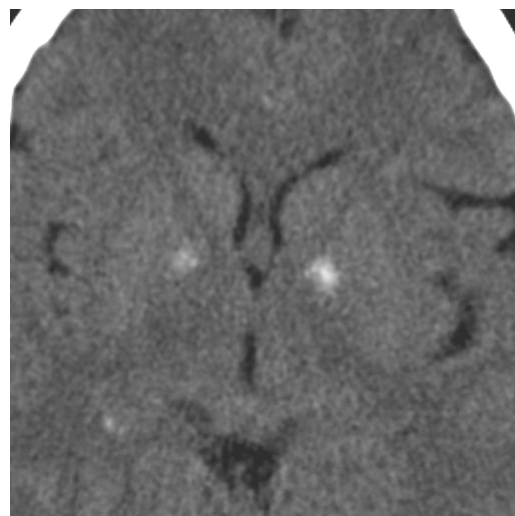


Figure 2 – Symmetric calcifications with cloudy pattern in globus pallidus.

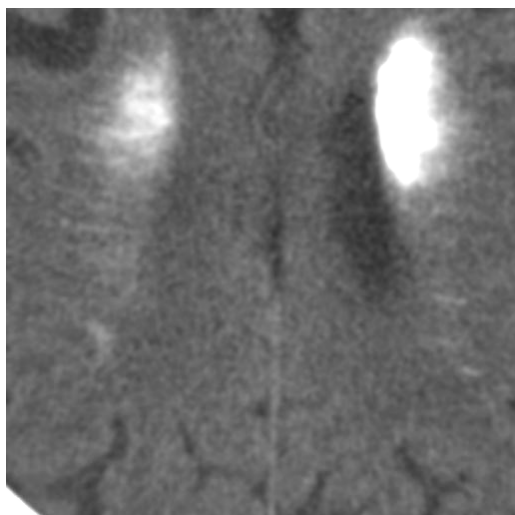


Figure 3 – Symmetric paraventricular calcifications with cloudy and thin linear pattern.



Figure 4 – Massive symmetric calcifications in the lentiform nucleus, thalamus, capsula interna and caput nuclei caudati with extension in the frontal white matter, associated with important cortical and subcortical frontal atrophy.

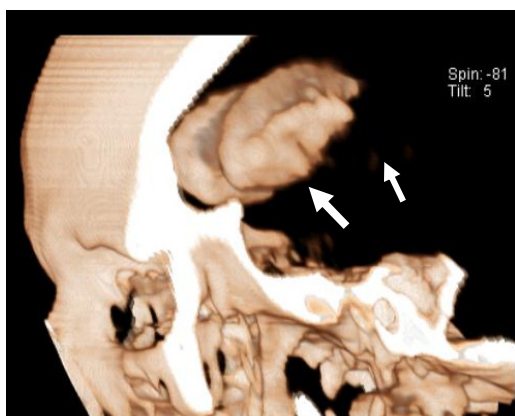


Figure 5 – CT-volumetric reconstructions with densitometric color encoding (the same case as Figure 4).

The asymmetric unilateral calcifications have no specificity for FD.

Calcifications were found in the basal ganglia (149 cases), caput nuclei caudati (three cases), cerebral white matter (43 cases), thalamus (two cases), and cerebellum (one case). In 22 cases, we found multicentric calcifications. Only in seven cases, CT-aspect was suggestive for FD.

Fifty-four cases with low level of serum calcium were found and three cases with high-level of serum calcium and alkaline phosphatase.

In one of the seven cases considered after CT-evaluation to be Fahr's disease, we found a low value of serum calcium (patient underwent thyroid surgery with manifest post surgical hypoparathyroidism).

The diagnosed six FD cases were found in cohort 1 (one case), cohort 2 (two cases) and in cohort 3 (three cases). No infectious, toxic or traumatic causes were found in the six FD cases.

In the six cases we encountered calcifications in the basal ganglia bilateral (all six cases), thalamus (two cases), caput nuclei caudati (one case), cerebellum (two cases), capsula interna (two cases), white matter (two cases). Others CT-findings were cortical and subcortical fronto-temporal atrophy (three cases), cerebellar cortical atrophy (two cases), moderate ventricular enlargement (three cases), chronic ischemic lesions (two cases) and retrocerebellar arachnoid cyst (one case).

Clinical manifestations present in the six cases of FD from the study-cohorts are: depressive disorder (four patients), chronic headache (three patients), cognitive impairment (three patients), extrapyramidal syndrome (two patients), equilibrium disorder (two patients) and schizoid psychosis (one patient).

Most frequent CT-findings were represented by cerebral and cerebellar atrophy in 1203 from the 1942 patients. Depressive disorder was the most frequent clinical finding in the study cohorts and in the six cases of FD.

Discussion

The criteria used in diagnosis of FIBGC are [5, 6]:

- Bilateral calcification of the basal ganglia on neuroimaging or other brain regions, although in isolated cases patients from families with FIBGC may not present such findings;
- Progressive neurological dysfunction and/or neuropsychiatric manifestations;
- Age of onset is typically the fourth or fifth decade, may be present also earlier in life;
- Absence of biochemical abnormalities and somatic features suggestive of a mitochondrial or metabolic disease or other systemic disorder;
- Absence of an infectious, toxic, or traumatic cause;
- Family history consistent with autosomal dominant inheritance.

If the patient fulfills the last criterion, the diagnosis can be established in the absence of one of the first two criteria. The diagnosis problem occurs when the last criterion is negative or cannot be documented. In this situation, meeting the first five criteria could be sufficient for a positive diagnosis of FD only if the calcifications are suggestive.

The first condition in order to be suggestive for FD is the symmetry – asymmetric or unilateral calcifications can exclude a FD diagnosis. A symmetric disposition should be analyzed further in order to observe a specific pattern: cloudy and/or thin linear pattern located in the basal ganglia (first lesions occur in globus pallidus) can be found in the early type of disease. The thin linear pattern can be explained by the wall-calcifications in the capillary vessels and calcium deposits in the adjacent area of the capillary. An increased degree of calcification of the surrounding capillary area can be linked to the “cloudy” pattern mentioned above. In later stages of disease, the degree of calcification becomes higher and lead to a massive calcification aspect. Usually this last pattern is associated with the “cloudy” and/or thin linear pattern that can be found in the peripheral area of the massive calcifications.

If both first and sixth criteria are negative, even if the patient satisfies the other four remaining conditions, a diagnosis of FD is unlikely – young symptomatic patients may represent exceptions, because the clinical manifestations sometimes may precede imaging visible calcification.

The third criterion is nonspecific and cannot exclude alone a positive diagnosis of FD.

Due to the polymorphic clinical manifestations of the disease and to the high number of cases with cerebral and cerebellar atrophy, which are associated with progressive neuropsychiatric manifestations, is impossible to establish a positive FD diagnosis only on clinical findings. Therefore the symptoms must be correlated with imagistic and laboratory investigations in order to narrow down the differential diagnosis possibilities.

Connections can be made between the brain calcifications and patients symptoms due to the cell-loss in that specific area: lesion of globus pallidus can lead to depression, motivation and cognitive disorder, putamen is implicated in reinforcement learning, caudate nucleus in learning and memory, particularly regarding feedback processing [7]. Thalamic lesion occurred in our patients in the thalamus pulvinar and lateral posterior nucleus, but in final stages of disease

the calcification could affect the whole thalamus with awareness and sensory deficits, arousal disorder. Cerebellar calcifications, especially of the dentate nucleus lead to initiations and control of volitional movements disorders.

☞ Conclusions

The present paper emphasize that a positive FD-diagnosis can be meet also in patients with unknown family history of disease based on a suggestive calcification pattern correlated with neuropsychiatric manifestations, in absence of biochemical abnormalities, infectious, toxic or traumatic causes. The calcium deposits with thin linear or cloudy pattern have a high-specificity, while the symmetric micronodular and asymmetric unilateral calcifications are non-suggestive for FD.

References

- [1] GESCHWIND D. H., LOGINOV M., STERN J. M., *Identification of a locus on chromosome 14q for idiopathic basal ganglia calcification (Fahr disease)*, Am J Hum Genet, 1999, 65(3):764–772.
- [2] LAUTERBACH E. C., CUMMINGS J. L., DUFFY L., COFFEY C. E., KAUFER D., LOVELL M., MALLOY P., REEVE A., ROYALL D. R., RUMMANS T. A., SALLOWAY S. P., *Neuropsychiatric correlates and treatment of lenticulostriatal diseases: a review of the literature and overview of research opportunities in Huntington's, Wilson's, and Fahr's diseases. A report of the ANPA Committee on Research, American Neuropsychiatric Association*, J Neuropsychiatry Clin Neurosci, 1998, 10(3):249–266.
- [3] BRODATY H., MITCHELL P., LUSCOMBE G., KWOK J. J., BADENHOP R. F., MCKENZIE R., SCHOFIELD P. R., *Familial idiopathic basal ganglia calcification (Fahr's disease) without neurological, cognitive and psychiatric symptoms is not linked to the IBGC1 locus on chromosome 14q*, Hum Genet, 2002, 110(1):8–14.
- [4] AVRAHAMI E., COHN D. F., FEIBEL M., TADMOR R., *MRI demonstration and CT correlation of the brain in patients with idiopathic intracerebral calcification*, J Neurol, 1994, 241(6):381–384.
- [5] MANYAM B. V., *What is and what is not 'Fahr's disease'*, Parkinsonism Relat Disord, 2005, 11(2):73–80.
- [6] ELLIE E., JULIEN J., FERRER X., *Familial idiopathic striopallidodentate calcifications*, Neurology, 1989, 39(3):381–385.
- [7] PACKARD M. G., KNOWLTON B. J., *Learning and memory functions of Basal Ganglia*, Annu Rev Neurosci, 2002, 25:563–593.

Corresponding author

Mihai Lazăr, Associated Assistant, MD, Department of Radiology and Medical Imaging, “Prof. Dr. Matei Balș” National Institute for Infectious Disease, 1 Dr. Calistrat Grozovici Street, Pav. 4, Sector 2, 021105 Bucharest, Romania; Phone +40722–462 136, e-mail: mihai.i.lazar@gmail.com

Received: May 10th, 2009

Accepted: August 10th, 2009