Clinical Neuropsychiatry (2022) 19, 2, 121-131

CASE REPORT

NEUROPSYCHIATRIC MANIFESTATIONS OF FAHR'S DISEASE, DIAGNOSTIC AND THERAPEUTIC CHALLENGE: A CASE REPORT AND A LITERATURE REVIEW

Manuel Glauco Carbone, Filippo Della Rocca

Abstract

Objective: Calcifications in basal ganglia could be an incidental finding up to 20% of asymptomatic patients undergoing computed tomography (CT) or magnetic resonance imaging (MRI) scan. The presence of neuropsychiatric symptomatology associated with basal ganglia calcifications identifies a clinical entity defined as Fahr's Disease. This term is used in presence of calcifications secondary to a specific cause, but the variability of etiology, pathogenesis, and clinical picture underlying this condition have raised the question of the real existence of a syndrome. Several classifications based on the etiology, the location of brain calcifications and the clinical presentation have been proposed.

Method: In the present study, we describe the case of a 52 years old man with a Bipolar I disorder diagnosis and a recent onset of behavioral disinhibition and alcohol misuse. The patient came to our center, specialized for bipolar disorder, as a consequence of a progressive worsening of the clinical picture associated to behavioral disturbances (sexual disinhibition, episodes of binge-eating, alcohol misuse), initial degrees of deterioration in cognitive function, peculiar psychotic symptoms and a resistance to various psychopharmacological treatment. The patient underwent neuro-psychologic evaluation, laboratory examinations and neuroimaging.

Results and Conclusions: CT and MRI revealed basal ganglia calcification and, in presence of normal blood tests, a diagnosis of Fahr's syndrome was suggested. During the hospitalization, the patient showed a good clinical response to a psychopharmacological therapy constituted by two mood stabilizers (lithium carbonate and oxcarbazepine) and mild antipsychotics doses (quetiapine and aripiprazole). Finally, we performed a literature review on the complex and multifaceted neuropsychiatric clinical manifestations of Fahr's disease in order to provide useful elements in terms of etiology, clinical manifestation, diagnosis, and treatment.

Key words: Fahr's disease, Fahr's syndrome, neuropsychiatric symptoms, movement disorders, basal ganglia calcification

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OPEN ACCESS

Citation: Carbone, G. M., Della Rocca, F. (2022). Neuropsychiatric manifestations of Fahr's disease, diagnostic and therapeutic challenge: a case report and a literature review. *Clinical Neuropsychiatry, 19*(2), 121-131.

doi.org/10.36131/cnfioritieditore20220206

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Funding: None.

Competing interests: None.

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1. Introduction

Basal ganglia calcifications were independently described by Virchow and Bamberger in the 19th century (Bamberger, 1855; Virchow, 1855). The name Fahr's disease (FD), referring to the diffuse calcification of brain structures, was inappropriately used by some authors in the 20th century after the German physician Theodor Fahr, who had described a patient with epilepsy and diffuse brain calcifications (Fahr, 1930). An early description of the radiologic finding of symmetric brain calcifications in a patient with mental retardation was written by Fritzche in 1935 (Fritzche, 1935). In the following years, reports of isolated and familial cases of symmetrical and non-symmetrical calcified depositions in intra-axial or extra-axial sites, associated with neuropsychiatric and / or neurological manifestations, progressively accumulated (Caraceni et al., 1974; Di Rocco, 1986; Klein et al., 1997; Kuroiwa et al., 1983; Larsen et al., 1985; Lauterbach et al., 1994; Manyam et al., 2001). Classically, characteristic calcium deposits are observed in the basal ganglia, and hence one of the most broadly used eponyms for this disease is idiopathic basal ganglia calcification (IBGC) (Mufaddel & Al-Hassani, 2014). However, other brain regions, such as thalami, dentate nuclei and subcortical white matter, are also affected frequently (Saade et al., 2019). Other names generally used to indicate

this neuroradiological and neuropsychiatric clinical entity include bilateral striopallidodentate calcinosis and familial cerebrovascular ferro-calcinosis (Babbitt et al., 1969; Boller et al., 1977; Savino et al., 2016). Since the basal ganglia are not the only brain structures affected, and after the discovery of the implication of genetic factors in the onset of FD, thus no longer being idiopathic in many cases, it was proposed to change its name to primary familial brain calcification (PFBC), the term primary meaning that brain calcifications secondary to other disorders or medical conditions are not included (Legati et al., 2015; Lemos et al., 2015; Ramos et al., 1993; Ramos et al., 2019).

IBGC, also called FD or recently PFBC, is a rare and intractable disease. It is characterized by abnormal deposits of minerals including calcium and phosphate in the basal ganglia and other brain regions such as the thalamus and cerebellum. For the diagnosis of IBGC, other secondary causes of calcification should be excluded. The causative genes for familial IBGC (FIBGC) have been successively identified: *SLC20A2* (IBGC3) (Hsu et al., 2013; Jensen et al., 2016; Jensen et al., 2013; Nicolas, Pottier, Charbonnier, et al., 2013; Takeuchi et al., 2016; Wallingford et al., 2017; C. Wang et al., 2012; Yamada et al., 2014), *PDGFRB* (IBGC4) (Arts et al., 2015; Nicolas, Pottier, Maltete, et al., 2013), *PDGFB* (IBGC5) (Keller et al., 2013; K. Wang et al., 2012) and *XPR1* (IBGC6) (Erro & Schneider, 2016; Westenberger & Klein, 2014). Mutations in *SLC20A2* are the major cause of IBGC and, altogether, the first three genes account for 49% of PFBC families (Legati et al., 2015).

SLC20A2, PDGFRB5 and PDGFB6 encode the major sodium-dependent phosphate transporters in human brain that is the type III sodium-dependent phosphate transporter 2 (PiT-2), the platelet-derived growth factor receptor (PDGFR-β) and the PDGFR-β main ligand (PDGF-B), respectively. *XPR-1* also encodes a transporter which exports inorganic phosphorus (*Pi*) out of cells.

The causative molecules might indicate that IBGC could be mainly caused by an impaired phosphate homeostasis in the brain leading to cerebrovascular-associated calcifications (Wider et al., 2009). SLC20A2-KO mice have been shown to have elevated levels of *Pi* in cerebrospinal fluid (CSF) suggesting a role of PiT-2 as an exporter of *Pi* from the CSF (Jensen et al., 2016). At the same time, SLC20A2-KO mice showed calcification in the basal ganglia and the cortex in the brain (Jensen et al., 2016). Probably, the vascular calcifications process is not only a passive tissue deposition of hydroxyapatite, but it might be also an active process regulated by blood levels of calcium and phosphorus. Specifically, hyperphosphatemia in CSF causes a phenotypic shift of the pericytes / vascular smooth muscle cells in the brain that acquire the ability to secrete bone matrix such as osteoblasts into bone tissue (Giachelli, 2003; Jensen et al., 2016). Loss of SLC20A2 led to dysregulated phosphate homeostasis and enhanced susceptibility of arteriolar smooth muscle cells to elevated phosphate-induced calcification. Together, dysregulated cerebrospinal fluid phosphate and enhanced smooth muscle cell susceptibility may predispose to glymphatic pathway-associated arteriolar calcification (Wallingford et al., 2017).

On a clinical point of view, PFBC symptoms typically occur after the age of 40, with progressive neuropsychiatric and movement disorders, although some individuals may remain asymptomatic (Amisha & Munakomi, 2021; Nicolas et al., 2015; Nicolas, Pottier, Charbonnier, et al., 2013; Takeuchi et al., 2016). However, the penetrance of PFBC is considered to be full by the age of 50 years if the presence of abnormal calcifications on CT scan is used as the major diagnostic criterion: virtually all pathogenic variant carriers reaching the age of 50 years have abnormal calcifications on CT scan (S. T. Alam et al., 2015; Donzuso et al., 2019).

Extrapyramidal symptoms (EPS) are present in most cases and can be the first manifestation of the disease, with virtually any type of involuntary movement, including rest and action tremor, parkinsonism, dystonia, choreoathetoid movements, myoclonus, and tics. Rigidity and bradykinesia are also frequent, as well as cerebellar signs. There may be a parkinsonian gait, cerebellar ataxia, and/or spasticity (Koratala & Morales Lappot, 2019; Saleem et al., 2013).

Psychiatric manifestations are also very frequent in PFBC patients, who may complain of mild depression and/or anxiety ranging to hallucinations and other psychotic symptoms (Kahn, 2019; Shakibai et al., 2005). Behavioral problems can include apathy, disinhibition, aggressiveness, obsessive-compulsive, or impulse control disorders. Cognitive impairment may range from mild memory and attention deficit to frank dementia of frontal-subcortical profile (Benke et al., 2004; Donzuso et al., 2019). Patients with intellectual disability and early-onset cognitive decline have been reported (Calabro et al., 2014). A broad variety of language problems can be present in these patients, reflecting the variable combination of affected brain areas (Santos et al., 2014). Speech may be dystonic, spastic, scanned, and slurred, and fluency may be reduced. Eye movements have probably not been examined in depth in PFBC families (Mishra et al., 2020). Migraine, often with aura, and vertigo are also frequent in this disease, and they can be the only manifestation for many years (Mufaddel & Al-Hassani, 2014; Siddiqui et al., 2021). Epilepsy is present in some cases, including different seizure types, as well as syncope, stroke, and stroke-like episodes (Demir et al., 2020; Khalid et al., 2020; Rangaswamy et al., 2016). Up to one-third of patients may be asymptomatic, even at advanced age and with extensive calcified areas visible in the neuroimage, and this implies that the incidental diagnosis in patients undergoing brain computed tomography (CT) scan for other reasons is possible (Modrego et al., 2005; Srivastava et al., 2010).

The different genetic subtypes of PFBC cannot be distinguished on clinical grounds (Nicolas, Pottier, Charbonnier, et al., 2013).

Bilateral calcifications of the basal ganglia are visualized on CT scans. Furthermore, pathologic calcium deposits in encephalic structures can be found in a variety of conditions. It seems that some brain areas, especially the globus pallidus, are prone to calcification (Shamsh Tabrez Alam et al., 2015). Thus, the main goals when evaluating a patient with brain calcifications are:

to rule out metabolic disorders and other causes of secondary calcifications. Special care should be taken to rule out potentially treatable conditions, such as hypoparathyroidism or phenylketonuria;

to find out about the possible familial nature of the disease since this can give early clues and avoid unnecessary workup for acquired causes.

A careful family history and examination should be undertaken, including brain CT whenever possible. When planning the evaluation of relatives, appropriate genetic counseling should be offered, given the potential predictive value of CT scan and implications thereof in this setting. The differential diagnosis of PFBC must

be established with several genetic and nongenetic conditions, including mitochondrial, metabolic, infectious, toxic, vascular, and neurodegenerative diseases. No cure or a standard course of treatment is available for the treatment of FD disease, and the prognosis of the disease is hard to predict.

In the present study we describe the case of a 52-year-old man with a Bipolar I disorder and a recent onset of behavioral disinhibition, episodes of binge-eating, alcohol misuse and a noticeable pharmacological resistance.

2. Case Presentation

Mr. S is a 52-year-old man, accountant and business consultant, married for about 30 years with two children. According to DSM-5 criteria (*Diagnostic and statistical manual of mental disorders : DSM-5*, 2013), he presents a history of Bipolar I disorder (BID) and he had arrived at our department as a result of the re-exacerbation of a manic episode with food and alcohol binges, inadequate and disinhibit behaviors.

The patient suffers from mild degree arterial hypertension, type 2 diabetes mellitus, hypercholesterolemia and metabolic syndrome. His medications included Amlodipine 10 mg/day, Irbesartan 300 mg/day, Hydrochlorothiazide 12.5 mg/day, Rosuvastatin 20 mg/day, Metformin 2500 mg/day, Insulin glargine 40 U/day and Glimepiride 4 U/day.

He denied use of psychostimulants and illicit drugs lifetime.

On psychic examination, the patient was alert, lucid, well oriented in space and time, good ability to memorize and recall memories. Hyperintense gaze, mimic and gestures hyper-represented. Logorrheic and hyper-phonic speech. Euphoric mood, hyperactive with difficulty in maintaining the same position during the interview, he got up several times. He presented high hedonic-volitional drive and hypersexuality. Nuanced ideas of grandeur and hypertrophic esteem. The patient denied anomalies of sense-perceptions. No insight of illness. The food pattern tended to hyperphagia with reported episodes of food and alcohol binges, increased smoking. Reduced need for sleep. He reported unsteady gait and difficulties in swallowing.

At the entrance the patient presented a BMI> 40, blood pressure of 150/85 mmHg and 75 of heart rate. Electrocardiogram showed a sinus rhythm with PR in the limits and a QTc of 390 msec.

His longitudinal evaluation revealed family loading for psychiatric illnesses in the maternal line for affective disorders. No complications at birth, pregnancy and delivery. No developmental disorder or delays in learning were referred. Mr. S had no history of impulse-control disorders, alcohol or food binges and bizarre or inadequate behaviors.

The psychiatric anamnesis revealed cyclothymic and hyperthymic temperamental traits with a slight tendency to seasonality, sensitivity to criticism and judgment, elements of the panic-agoraphobic spectrum and hypochondriacal features.

Psychiatric history showed mild mood fluctuations, in both polarities, from the age of twenty, in temporal relationship of stressful life events, which have never led the patient to consult a psychiatrist. The patient also described sporadic increasing in anxiety levels with subcritical and critical episodes with neurovegetative expressiveness (sweating, trembling, pallor).

About four years ago, in apparent absence of stressful life events, the patient developed a symptomatology characterized by mood decline, anhedonia, abulia, lack of appetite (weight loss of 20 kg less than 3 months), emotional lability, feelings of sadness, ideas of guilt, self-depreciation, partially structured ideas of death, hypochondriacal delusions, auditory and visual misperceptions, panic attacks, inversion of the sleep-wake rhythm with daytime clinophilia. The food intake was also influenced by a difficulty in swallowing, initially for liquids and then also for solids, described by the patient as a pharyngeal globus sensation.

Initially, the patient started a psychotherapeutic approach with little benefit and the following year, he decided to undergo a psychiatric evaluation. It was set up a psychopharmacological therapy based on escitalopram up to 20 mg/day with little benefit and then on duloxetine up to 90 mg/day and alprazolam with little transient benefit on the anxiety dimension and a slight amelioration of the swallowing. About 6 months later, the patient showed a progressive worsening and contacted another psychiatrist, who prescribed aripiprazole 10 mg/day and sertraline 100 mg/day with partial and momentaneous clinical benefit.

Approximately 8 months later the patient arrived at our outpatient services, where lamotrigine 200 mg/day and nortriptyline 75 mg/day were introduced, and aripiprazole was suspended with gradual clinical benefits. In the following months, the patient, as a result of reported psychophysical well-being, decided independently to suspend psychopharmacological therapy.

At the moment of the current admission, occurred about 5 months after the first evaluation in our outpatient service, the wife reported inadequate, bizarre and uninhibited behaviors of Mr. S with surprising episodes of alcohol and alcohol binges. In agreement with the colleagues of the outpatient services, it was decided to plan his first lifetime hospitalization.

We set up a psychopharmacological therapy with oxcarbazepine 600 mg/day, lithium carbonate 600 mg/day, aripiprazole 10 mg/day and quetiapine 25 mg/day.

CT scan was performed, and it showed the presence of calcific deposits on both lenticular nuclei, radiate crowns, the posterior pole of the thalamus and the dentate nuclei, with bilateral and symmetric distribution. Thin parietal calcifications of the carotid siphons and the left vertebral artery, the latter dominant with respect to the contralateral.

These neuroimaging findings were suggestive of FD.

The first thought was obviously that these calcific depositions were secondary to an alteration of the calcium-phosphorus metabolism (parathyroid dysfunctions, renal insufficiency, vitamin D deficiency, intestinal malabsorption, etc.) or to an infectious process (HIV, CMV).

We performed various diagnostic tests such as electroencephalographic (EEG), cerebral MRI, DaT-SPECT scan, chest x-ray, hepatic ultrasound, echocardiogram, eco-color-doppler of supra-aortic trunks with specialist cardiological, nephrological, endocrinological and genetic examinations.

Electroencephalographic (EEG) showed low amplitude path characterized by a low regular alpha rhythm, from mostly bi-anterior beta frequencies and from theta potentials at 6-7 Hz in the central temporal area of non-specific significance. Cerebral MRI confirmed the presence of hypo-intensities bilaterally in the nuclei of the base and of the dentate nuclei, compatible with the FD type MRI framework. DaT-SPECT scan did not highlight scintigraphic findings of bilateral nigro-striatal degeneration. The chest x-ray

showed a slight parenchymal thickening and fibrotic striae at the level of the middle lobe. Hepatic ultrasound revealed an enlarged liver with disomogeneous echo-structure due to steatosic infiltration. A mild carotid atherosclerosis emerged from the eco-color-doppler of supra-aortic trunks. Echocardiogram showed good cardiac function with a slight increase in wall thickness of the left ventricle.

Calcium-phosphorus metabolism alteration and/or a viral infection were excluded. Blood examinations, including blood count, sodium, potassium, calcium, magnesium, chloride, phosphates, vitamin D, PTH, electrophoresis, creatinine, glomerular filtration rate, TSH, ft3 and ft4 were within normal ranges. Vitamin B12, folate, ceruloplasmin levels and the urinary copper level were also normal. Blood culture, urine culture and VDRL (venereal diseases research laboratory) testing were negative. CMV, HIV and Mantoux (purified protein derivative) tests were negative. No substance use, abuse or withdrawal were diagnosed. Ethanol, salicylates, acetaminophen, and tetrahydrocannabinol (THC) tests were all negative.

Blood tests showed values beyond the range of serum glucose, liver function enzymes (GOT, GPT, GGT), CK, uric acid, triglycerides and cholesterol. The 24-hour urine showed a slight degree of hyper-proteinuria and hypercalciuria (344 mg/24h with a range of 100-321).

In the light of these results both the endocrinologist and the geneticist agreed on the diagnosis of FD.

Over the days at our clinic, we have witnessed a progressive clinical improvement of mood, sleep and inappropriate or bizarre behaviors were not reported.

The hospitalization, which lasted about 25 days, allowed us to regularize the eating attitudes of the patient with a loss of about 6 kg, normalization of triglycerides and cholesterol, partial return of glycemic values. It should be noted that during the whole period the patient did not show symptoms and/or signs of alcohol withdrawal and craving.

During the first check-up carried out about 30 days after the discharging, the patient was euthymic, but his wife reported disinhibited and inadequate behaviors with episodes of food binge.

The following clinical examinations (the last one about 1 year after discharge) confirmed a sufficient psycho-affective compensation but highlighted a progressive worsening of cognitive abilities with interferences on working dimension forcing him to leave work. Moreover, a marked worsening of the motor skills was revealed with extreme difficulty in swallowing, in the coordination of the movements, coarse distal tremor and unsteady gait.

3. Discussion

This case report might offer interesting diagnostic and therapeutic challenges.

About 40% of patients with a diagnosis of FD could initially present neuropsychiatric symptoms (Ghormode et al., 2011). Usually, two patterns of presentation in FD disease are known, including early onset (mean age 30.7 years) psychiatric symptoms with minimal movement disorder, and late onset (mean age 49.4 years) associated with dementia and movement disorders. Psychotic symptoms in FD include auditory and visual hallucinations, perceptual distortions, delusions and fugue state. It also may present neurologically "asymptomatic" that is, lacking movement disorders, seizures, or stroke-like events, but with pronounced rapidly progressive cognitive and behavioral abnormalities (Bourgeois, 2010; Mohapatra & Satapathy, 2016; Younas et al., 2016).

Mr. S showed a complex and varied symptomatology. As a young man he presented mild mood swings in both polarities, associated with hypochondriac ideas with excessive fear of death, fluctuations in anxiety with panic attacks, spontaneously regressed within a short time. On the other hand, at the age of 48, he reported more pronounced mood swings, partially responsive to pharmacological treatments, with the progressive onset of inappropriate, bizarre and socially disinhibited behaviors and alcohol and food binges. Furthermore, there are also noteworthy symptoms that at first, we considered unreliable as the difficulty in swallowing mainly of liquids and the consequent development of hypochondriac ideas with delusional character or the presence of complex visual hallucinations having fantastic and terrifying character. Moreover, in just one year we have witnessed a progressive deterioration of cognitive abilities with marked impairment of social and working functioning dimension. From a motor point of view, excluding dysphagia, motor changes had a later onset and a slower progression than the neuro-cognitive symptomatology.

Basal ganglia have been primarily involved in the control of motor functions and in many cognitive processes based to their connections with the frontal cortex. Basal ganglia and thalamic regions are involved in various aspects of motivation, emotional drive, planning and cognition for the development and expression of goal-directed behaviors and motor control through cortico-basal and cortico-thalamic circuits (Nelson & Kreitzer, 2014).

Psychiatric symptoms in FD could be explained by abnormalities in the basal ganglia, which are central to the pathophysiology of psychiatric conditions and by interruption of the dorsolateral prefrontal circuit involving the thalamus (Nelson & Kreitzer, 2014). Furthermore, mesocortical and mesolimbic alterations, rich in dopaminergic innervation, could explain psychotic symptoms (hallucinations and delusions) (McCutcheon et al., 2019).

Diagnosis of FD was performed through clinical and neuroimaging features as well as the exclusion of secondary causes of cerebral calcification. As said before, FD treatment is only symptomatic. However, the response to psychopharmacological treatments is variable. Patients with FD are more susceptible to neuroleptic malignant syndrome when treated with antipsychotic drugs (Ghormode et al., 2011). Atypical antipsychotics, considering their reduced risk of EPS, are the drug of choice because the disease itself causes motor symptoms (Ahmad et al., 2019). On the other hand, the use of anticonvulsants is not only suitable for managing the affective state but also for preventing the onset of seizures.

4. Commentary

As mentioned above, neuropsychiatric features are the onset symptoms in around 40% of patients with FD (Ghormode et al., 2011). A brief description of the clinically different syndromic variants of the neuropsychiatric features of the disease appears indicated in **table 1**.

Among neuropsychiatric features, symptoms of mood spectrum disorder, psychotic spectrum disorder and neurocognitive disorder are the most common ones.

Table 1. *Clinical presentations of Fahr's Disease*

Neuropsychiatric features

- Mood disorders: depressive, mixed, hypomanic, and manic episode, even associated to psychotic symptoms.
- Psychotic symptoms: hallucinations (visual, auditory, gustatory, somatosensory, olfactory, autoscopic, hypnopompic, hypnagogic, simple, complex, bizarre, misinterpretation, illusions and pareidolias) and delusions (simple, structured, complex, bizarre, specific).
- Irritability, nervousness, emotional dysregulation, emotional lability, aggressiveness, lack of impulse control, regressive behaviors and behavioral disinhibition.
- Anxiety and panic-agoraphobic spectrum symptoms.
- Obsessive-compulsive spectrum symptoms.
- Personality disorders.
- Cognitive and psychomotor impairment: memory and attention deficit, delirium, confusion, delirious mania, akinetic catatonia, agitated catatonia, etc.

Neurological and somatic symptoms

- Parkinsonism, movement disorders, rigidity, bradykinesia, impaired coordination, ataxia, dysarthria, tremor, vertigo.
- Seizures, stroke, hemiparesis, paresis, headache, syncope, orthostatic hypotension.

Neuroradiological findings

- Bilateral symmetrical calcifications of basal ganglia and dentate nucleus
- Other sites of calcifications: thalamus, centrum semi-ovale, cerebellum, cerebral white matter,
- Asymmetric calcification in multiple brain areas (intra-axial and extra-axial).

Differential diagnosis of brain calcifications

- Intra-axial calcifications (basal ganglia, cerebellum): neoplastic formations (oligodendrogliomas, astrocytoma, medulloblastoma, metastatic tumors), vascular disorders (angiomatous and arteriovenous malformations, dystrophic calcification in chronic infarction, chronic vasculitis, aneurysms), infections (TORCH, tuberculosis, neurocysticercosis, cerebral hydatid cyst disease, HIV), congenital causes (Sturge-Weber syndrome, tuberous sclerosis, lipomas, neurofibromatosis), endocrine/metabolic disorders (diabetes mellitus, hypoparathyroidism, pseudohypoparathyroidism, hyperparathyroidism).
- Extra-axial calcifications: meningiomas, Dural osteomas, calcifying tumours, abnormal physiological calcifications.

4.1 Mood Spectrum Disorder in Fahr's disease

Mood dysregulation symptoms are widely reported among the FD clinical presentations (Chang et al., 2015; Lester et al., 2006; Lo Buono et al., 2015). Casamassima *et al.* (Casamassima et al., 2009) reported a case of a patient with FD affected by BID with psychotic symptoms. Both neurological and psychiatric symptoms were represented in the clinical picture, and it had been proven that the patient was partially or completely resistant to several pharmacological trials. On the contrary, a marked improvement of the symptomatology was obtained after a 10 sessions-cycle of electroconvulsive therapy (ECT), followed by a complete and sustained resolution of mood, cognitive, motor, and behavioral symptoms during the next 4 years.

On the same line, Cormack *et al.* (Cormack et al., 2016) reported an original case describing treatment refractory unipolar depression in a patient with FD receiving benefit from ECT. In this case, a 53-year-old married man with childhood-onset FD and autosomal dominant dystonia presented a severe unipolar, treatment-resistant, major depressive disorder. He was admitted without injury to psychiatry after defenestrating from a bridge approximately 55 feet high. Psychiatric history included depressive episodes involving neuropsychiatry involvement from 1998 to 2008 and 3 previous hospital admissions for suicide attempts. ECT was given 2 to 3 times per week for a total of 14 treatments. Objective and subjective improvements in mood symptomatology were noted by the seventh treatment. Improvements in motor and speech ability were subjectively noted by the tenth treatment. On discharge, his HAM-D-29 was 13, CGI-severity score was 3 (moderately), and CGI-improvement score was 1 (very much improved). His speech markedly improved, because initially he was unable to communicate independently and required technological assistance. He also displayed decreased resting tremor and gait disturbance. Given his clinical improvement, the patient and clinician elected to discontinue ECT. Before discharge, follow-up with a community mental health team was established.

A different therapeutic approach was adopted by Roiter *et al.* (Roiter et al., 2016) that discussed the case of a 58 years-old patient presenting his first delusional-manic episode. Neuroimaging showed mild frontal and occipital cortical atrophy, white matter posterior ischemic lesions, and small basal ganglia calcifications. Seven years later, he presented a second manic episode with new emergent hyperkinetic choreiform symptoms. Taking into account movement disturbances, the presence of basal ganglia calcification, and worsening of cortical atrophy, led to perform a differential diagnosis between PFBC, secondary Fahr's syndrome, calcifications due to ageing, super-sensitivity psychosis, and dementia. Valproate, quetiapine, and tetrabenazine were sequentially administered and yielded a good therapeutic response as regards manic and movement symptoms.

An unusual case of FD with manic symptoms at the onset was described by Subedi *et al*. (Subedi et al., 2018). An 18-year-old male presented to the emergency room with symptoms of mania with chief complaints of irritability and abusiveness. The debut of the disease was referred to two months prior after he failed in the XII standard final examination. Symptoms begun acutely with insomnia and irritability, then gradually moved to overfamiliar, overtalkative, and stubborn behaviors. The predominant mood was euphoric with tendency to make big plans but would become irritable when others object on his plans and behaviors. There was no history of head injury nor any chronic physical illness. Family history was insignificant. There was no history of substance use and patient was well-adjusted premorbid. CT scan of the patient demonstrated extensive symmetrical calcification over the basal

ganglia and dentate nuclei. No underlying cause for the bilateral calcification was found. Patient was treated with sodium valproate and olanzapine, showing soon significant clinical improvement. However, patient came to follow-up after 6 months with exacerbation of signs and symptoms after stoppage of treatment. Patient was restarted with same treatment and was keeping on outpatient department (OPD) follow up.

4.2 Psychotic Spectrum Disorders in Fahr's disease

As mentioned above, primary psychotic symptoms aren't infrequent in FD clinical pictures. In some cases, clinical pictures may be misdiagnosed as schizophrenic disorder at first evaluation (Boyer et al., 2013; Naqvi et al., 2017; Samuels et al., 2018). Thus, it is important to correlate psychotic symptoms to the patient's history, both personal and familiar, and to better analyze the nature of psychosis, especially in those cases where visual hallucinations or aspects of mental confusion are detected. Shirahama *et al.* (Shirahama et al., 2010) described an interesting case of a 23-year-old woman who was arrested for two arsons with visual hallucinations and delusions of persecution, irritability, lability of mood, mental retardation and visual disorders. CT imaging demonstrated bilateral calcifications of the basal ganglia (Globus pallidus) in the patient, her mother and her grandmother. Compared to her mother, the patient displayed anticipation of disease onset (psychiatric symptoms) and the severity of her symptoms was advanced (Shirahama et al., 2010).

A case of a 55-year-old male was described by Mohapatra et al. (Mohapatra & Satapathy, 2016). The patient was premorbidly well-adjusted and without past and family history of neurological and psychiatric illness. He presented with complaints of fearfulness, suspiciousness, irritability, hearing of voices and decreased sleep for last 2 years. The onset of illness was insidious, and course was progressive. His psychotic symptoms increased in intensity over 1 year and he further developed muttering to self and smiling to self. Lastly, he developed bilateral tremors of hand. He had not received any treatment for the above-mentioned symptoms and, on mental status examination, delusion of persecution with auditory hallucination of commenting type were detected. On physical examination, he was having bilateral tremors of hand (both resting and intentional). Considering the atypical age of onset of psychosis, with presence of movement disorder, basal ganglia calcification on computed tomography scan, normal parathyroid functioning, lack of family history of basal ganglia calcification, a diagnosis of FD was considered. He was started on tablet olanzapine 5 mg/day and tablet procyclidine 5 mg/day. The patient's psychotic symptoms gradually improved over a period of 8 weeks.

Nevertheless, antipsychotic drugs had a clinically satisfactory outcome on psychotic symptoms in the case described by Nicolas *et al* in 2013 too (Nicolas, Guillin, et al., 2013). A 39-year-old woman presenting with auditory hallucinations and delusions who had no significant past medical history and had a normal social life and worked as a teacher. She had no previous psychotic symptoms or mood disorders and no familial neurological or psychiatric history. Computerized tomography scans revealed basal ganglia calcifications in the proband and in her two asymptomatic parents. Extensive etiological clinic-biological assessment excludes known causes of brain calcifications and diagnose familial idiopathic basal ganglia calcification (IBGC). Patient was treated with antipsychotic drugs (Risperidone 2 mg/day), and psychotic symptoms showed good clinical outcome (Nicolas, Guillin, et al., 2013).

In another case report (Faye et al., 2014), a 25-year-old married woman presented with a few motor symptoms, with the complaints of withdrawn behavior, headache, abnormal posturing, and reduced sleep since around 15 days and sudden onset altered behavior a night before during sleep, when patient woke up, started screaming, went to wash-room and started inducing the vomiting. She was fearful and not recognizing the family members and couldn't sleep. The episode lasted for the whole night and the next day she was brought to the hospital. Radiological findings were suggestive of bilateral basal ganglia calcification. Parathyroid hormone levels were low with no significant findings in other investigations and negative family history. Patient showed significant improvement in behavioral disturbances with risperidone, low dose of lorazepam, oxcarbazepine, and memantine.

Shouyama *et al.* (Shouyama et al., 2005) conducted an interesting study on FD concerning the evaluation of regional blood flow in patients with psychotic symptoms. They described the case of a 32 years-old patient with FD presenting with schizophrenia-like psychosis for whom a technetium Tc99 methyl cysteinate dimmer brain study was used to evaluate regional blood flow. A brain single photoemission CT (SPECT) study showed increased cerebral blood flow to the bilateral temporal lobes. It has been postulated that such perfusion abnormalities reflected psychotic symptoms, including auditory hallucinations and delusions, which suggests a disruption of the cortico-subcortical neural circuits in psychosis. The patient had received haloperidol for about 4 weeks (8 mg/day), followed by 4 weeks of risperidone (4 mg/day). About 4 weeks later, the auditory hallucinations and delusions disappeared. After discharge, the patient was treated on an outpatient basis with low-dose risperidone. On a dynamic imaging basis, Smith *et al.* (Smith et al., 1988) reported a patient with FD who showed a perfusion deficit in the basal ganglia, whereas Uygur *et al.* (Uygur et al., 1995) described a patient with FD who had decreased blood flow in the basal ganglia and frontoparietal cortex. The latter patient was 43 years of age and showed dementia, as well as cerebellar and basal ganglia dysfunction. Further, Hempel *et al.* (Hempel et al., 2001) reported a 25-year-old patient with FD who presented with frontal lobe syndrome and dementia. In that case, reduced glucose uptake in positron-emission tomographic (PET) images was not restricted to the basal ganglia, but also involved the frontal, temporal, and parietal cortices. Other authors have reported cases with hypoperfusion in both thalami (Ogi et al., 2002) and low metabolic changes of the corpus striatum and posterior cingulate (Le Ber et al., 2003). Perfusion deficits in the basal ganglia matching the distribution of calcifications in the cortex might reflect secondary deficits due to calcifications of the basal ganglia.

Interestingly, it was described the case of a 20-year-old man with FD who presented complex neurological and neuropsychiatric symptoms. The young man in few months progressively showed choreoathetotic movements, kyphoscoliosis, cognitive impairment (insight, judgement, memory, attention, abstraction, organization of thought) and developed psychotic symptoms (thought broadcasting, delusions of being controlled, ideas of reference, visual and auditory hallucinations) associated with irritability,

depressive ideas and ritualistic compulsions (hoarding and collecting). The patient was initially treated with haloperidol, perphenazine and amitriptyline without any clinical benefits and presenting marked EPS. He responded efficaciously to treatment with lithium carbonate (900 mg/day) and for the next twelve months he remained free of any psychotics symptoms and showed moderate improvement in the neurocognitive dimension (Munir, 1986).

4.3 Neurocognitive Disorders and other neurological miscellaneous symptoms in Fahr's disease

Cognitive impairment in FD may ranges from mild memory and attention deficit to frank dementia of frontal-subcortical profile (Benke et al., 2004). Patients with intellectual disability and early-onset cognitive decline have been reported. Cognitive symptoms in patients with FD include mostly dementia, delirium, and mental retardation. Some cases present with features of clear frontal lobe syndrome (Lam et al., 2007; Mushtaq et al., 2013). Cases of dementia with FD have been reported with neuropathological changes not due to Alzheimer's disease (AD) or Pick's disease (PD) (Shibayama et al., 1992). In some other cases, symptoms due to FD are hardly differentiating from the ones related to AD or PD. On this topic, Narita *et al.* (Narita et al., 2002) reported a 79-year-old Japanese female with atypical senile dementia and Fahr-type brain calcification. No remarkable history of illness was found on patient's history until age 75 years, when she started to show memory disturbance. Soon after, misidentification of relatives, stereotypy, confabulation, dyscalculia, oral tendency, collectionism, apraxia for dressing, personality changes such as irritability, aggression and disinhibition were found. She also showed visual hallucination and delusions of persecution. Brain CT demonstrated bilateral and symmetric calcification of the basal ganglia and thalamus, and MRI revealed diffuse cortical atrophy pronounced in the fronto-temporal areas. Based on the overlapping clinical symptoms of AD and PD, together with etiological clinic-biological assessment, the brain CT and MRI findings, they clinically diagnosed the patient as having 'diffuse neurofibrillary tangles with calcification' (DNTC) (Narita et al., 2002). In line with that, Weisman *et al.* (Weisman et al., 2007) illustrated "an atypical case of FD" in which they observed a progressive mental decline, pathologically confirmed, with clinical phenomena of frontotemporal dementia and motor neuron disease. A man of 66 years-old presented a wide clinical spectrum consisting of parkinsonism, cognitive impairment, psychiatric features, and pyramidal signs. He had exhibited an insidious and slowly progressive memory problem of 5 years' duration. Initially, he forgot where he placed objects; within 2 years, he had further difficulty with writing, word finding, and maintaining his golf game, and his personality changed too, becoming hyperactive with angry outbursts (Weisman et al., 2007).

Movement disorders may be absent in some cases. Modrego *et al.* (Modrego et al., 2005) reported the singular case of FD in a 50-year-old woman with progressive dementia but neither extrapyramidal symptoms nor a metabolic disorder. The first symptoms were those of a dysexecutive syndrome with alterations in abstract reasoning, calculation, sequential tasks and apathy. Three months later, memory loss and depressive mood began. Finally, she was unable to perform daily living activities, with decreased verbal fluency, apathy and inability to make decisions (Modrego et al., 2005).

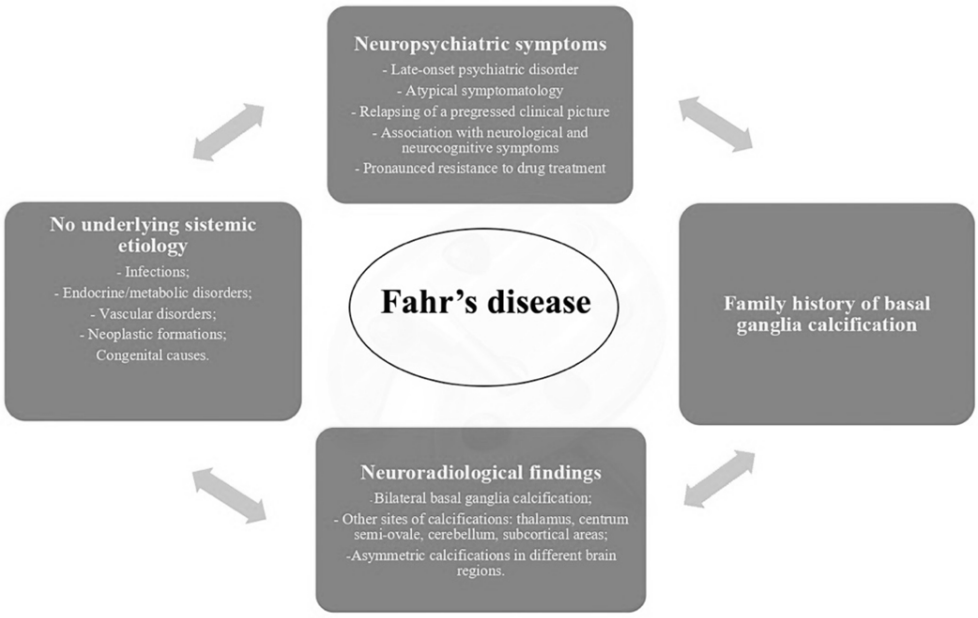
A broad variety of language problems can be present in these patients, reflecting the variable combination of affected brain areas. Santos *et al.* (Santos et al., 2014) described the case of a patient with FD that, based on the results of specific assessments, presented many difficulties in coordinating and sustaining muscle during speech with oropharyngeal dysphagia. Regarding food intake, anterior mastication was observed for solid foods; difficulty in controlling saliva, with drooling through the labial commissures; multiple swallowing for liquid and soft foods; in addition to the anterior dribbling of liquids. By cervical auscultation, the presence of cervical noises, compatible with stasis of food, was observed, being manifested by the patient as a pharyngeal globus sensation. In the opinion of the authors, speech disorders found in FD manifested themselves in complex and covered various aspects of phonological knowledge and the diseases that affect the basal ganglia have similar frames of speech-language disorders of the stomatognathic system, being able to present a picture of dysarthria (Santos et al., 2014). Speech in FD may be dystonic, spastic, scanned, and slurred, and fluency may be reduced. Eye movements have probably not been examined in depth in PFBC families. Migraine, often with aura, and vertigo are also frequent in this disease, and they can be the only manifestation for many years. Epilepsy is present in some cases, including diverse seizure types, as well as syncope, stroke, and stroke-like episodes. Otu *et al*. (Otu et al., 2015) presented a FD patient with a rare neurological presentation in a tropical setting. Patients presented with seizures, movement disorders and cognitive impairment. Some other differential diagnoses that were entertained later included rare conditions such Creutzfeldt-Jakob disease that causes progressive dementia and focal neurologic signs, but tests for this was not available. Neuro-acanthocytosis was also ruled out after laboratory testing (Otu et al., 2015). Regardless of the manifestation of epilepsy, anticonvulsant medications seem to find wide clinical use, especially in presence of movement disorders. Montilla-Uzcátegui *et al*. (Montilla-Uzcategui et al., 2016) presented the case of a 57-year-old female patient with episodes of paroxysmal choreoathetoid dyskinesias in the oromandibular region and distal region of upper and lower extremities, with fluctuating dystonic postures in the same distribution; duration was variable ranging from 30 minutes to 3 hours. Treatment was initiated with carbamazepine at the minimum effective dose of 200 mg/d, which resulted in excellent response.

5. Conclusion

FD has been poorly studied and investigated, and case series and cohort studies are necessary to deeply describe the neurological and psychiatric signs and symptoms associated with this heterogeneous disease. The ongoing progress in determining the genetic bases of this syndrome implies that clinicians need to improve their description of clinical, psychological, and quantitative cortical MRI and CT markers. Cortical brain atrophy could be implicated in the onset of psychiatric and cognitive symptoms.

Furthermore, our case suggests that psychiatrists should evaluate the cases of psychosis thoroughly when the age of presentation is atypical, and they should consider the diagnosis of FD when psychosis

Figure 1. *Diagnostic algorithm of Fahr's Disease*



presents with motor abnormalities. We also advocate the appropriate use of neuroimaging in the diagnosis of different psychiatric disorders (**figure 1**).

From a treatment viewpoint, primary goal of medical approach is to control the neuropsychiatric symptoms. According to the literature, mood stabilizers, particularly anticonvulsant medications, seem to be correlated to a good outcome in those cases who either present with psychiatric symptoms (lack of impulse control, behavioral abnormalities, maniac-depressive features) or neurological ones (neuromotor and neurocognitive). Moreover, lithium would seem to provide potential therapeutic value in the prevention and/or treatment of this neurodegenerative disease. Multiple different biological mechanisms have been shown to contribute to these protective effects including the up-regulation of neuroprotective proteins including Bcl-2 and its actions on regulation of apoptosis and cellular resilience, such as GSK-3.

In case of psychotic symptoms, antipsychotic medications seem to find clinical use although they do not always give the expected results. Positive psychotic symptoms would show a refractoriness to antipsychotics in monotherapy but a greater response to the combination with mood stabilizers. Furthermore, patients treated with antipsychotics tend to be more vulnerable to EPS, refractory to symptomatic therapy with anticholinergics and benzodiazepines.

Contradicting results emerge regarding antidepressants, in particular it would seem that SSRI and SSRI have a reduced efficacy compared to TCI. In unresponsive clinical picture, ECT has been applied with clinical improvement, especially in patients with mood disorder spectrum symptoms.

It might speculate that the use of mood stabilizers in combination with other potential or existing therapeutic compounds (low doses of antipsychotics, TCI, antihistaminergic agents or benzodiazepines depending on the clinical presentation) may be a promising prophylactic and symptomatologic approach to reduce neurological and neuropsychiatric symptoms as well as the disease progression in FD.

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