



Case Report

## Sporadic Fahr's disease in Valle Camonica: Two case reports

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### Abstract

*Fahr's syndrome, or idiopathic basal ganglia calcification (IBGC), is a rare neurological disorder characterized by abnormal deposition of calcium in brain. The main clinical manifestations are rigid or hyperkinetic syndrome, mood disorders and cognitive impairment. It is usually inherited (known as familial idiopathic basal ganglia calcification) most commonly as an autosomal dominant trait, but it may also occur sporadically. We report two cases of sporadic Fahr's disease in patients suffering from autoimmune, hematologic and metabolic disorders.*

**Keywords:** Basal Ganglia, Calcifications, Autoimmune Diseases, Neurological Disorder

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### Introduction

Basal ganglia calcifications are associated with a variety of neurological and metabolic disorders, and calcifications could be also frequent incidental findings on neuroimaging of asymptomatic individuals. Pathological basal ganglia calcification is due to various causes, such as metabolic disorders, infectious and genetic diseases, and others. Hypoparathyroidism and pseudohypoparathyroidism are the most common causes of pathological basal ganglia calcification. Indeed, a certain degree of calcification of basal ganglia can be considered “physiological” with aging, and it could be an incidental finding in 15–20% of asymptomatic patients undergoing computed tomography (CT) older than 50. [1]. Fahr's disease, bilateral striopallidodentate calcinosis (BSPDC), and idiopathic basal ganglia calcification are three of the more than 30 names used to identify a rare neurodegenerative condition characterized by the presence of bilateral calcification of the basal ganglia and other parts of the brain [2]. This condition has a wide range of possible clinical manifestations, usually marked by neuropsychiatric symptoms (i.e. dementia, schizophrenia-like psychosis, mood disorders), and extrapyramidal movement disorders [2]. Some patients can remain asymptomatic throughout life. The prevalence of BSPDC is unknown, but an incidence of basal ganglia calcification ranging from 0.3% to 1.2% has been reported in routine radiological examinations in older reports and recently greatly increased (from 1.3% to 20.6%) in recent studies [3]. Between 2% and 12% of brain scanners detect the presence of calcification levels within the lymphatic vessels. Small “physiological” calcifications, especially located in the globus pallidus, can be evidenced and their prevalence increases with age. When these findings are present in subjects younger than 40 years old, involving simultaneously the globus pallidus, putamen, cerebellar dentate nucleus and white matter (Pale-toothed grooved-calcinosis), they are considered to be pathological [3]. Normal serum levels of calcium and parathyroid hormone help to differentiate primary familial brain calcification from other disorders, such as hyperthyroidism or hypoparathyroidism. The disease displays heterogeneity of symptoms, and some individuals with

brain calcification can be asymptomatic [3]. Primary familial brain calcification is usually inherited in an autosomal dominant manner, and, thus far, mutations in three genes have been found to cause the disease: SLC20A2, PDGFB, and PDGFRB. SLC20A2 encodes for the sodium-dependent phosphate transporter 2 (PiT2) [3]. PDGFB and PDGFRB code for the platelet-derived growth factor-beta (PDGF-b) and its receptor, and the platelet-derived growth factor receptor beta (PDGFR-b), respectively. The latest study identified in multiple families with PFBC mutations in XPR1, a gene encoding a retroviral receptor with phosphate export function. These mutations are implicating with phosphate homeostasis in PFBC [3].

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

- Bilateral calcification of the basal ganglia visualized on neuroimaging even if these can be found also in their brain regions.
- Progressive neurologic dysfunction, which generally includes a movement disorder and/or neuropsychiatric manifestations.
- Age of onset is typically in the fourth or fifth decade, although this dysfunction may also present in childhood.\*
- 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 (ex acute lymphocytic leukemia, radiation therapy, lead intoxication)
- Family history consistent with autosomal dominant inheritance [4].

Symmetrical calcification of the basal ganglia occurs in a variety of familial and non-familial conditions; hence it doesn't necessarily direct us towards a definitive diagnosis of Fahr's syndrome.

- Congenital or early-onset finding along with intellectual disability or presence of systemic involvement.
- Mitochondrial (such as Mitochondrial epilepsy, lactic acidosis, and stroke-like syndrome), parathyroid diseases, and other brain calcification disorders should be evaluated in patients with latent tetany and myopathic changes related to changes in somatosensory, visual, and brain stem auditory responses.
- Basal ganglia calcification, discovered in infancy along with ophthalmologic abnormality should prompt the consideration of infectious disease.
- It is differentiated from calcified angiomas, infections, enchapalitudes, and Addison's disease by its severity and characteristic distribution.
- Absence of suggestive symptoms and signs of infectious disease (acquired immunodeficiency syndrome, Epstein Barr, mumps encephalitis, or meningoencephalitis).
- Absence of symptoms and signs suggesting for autoimmune disorders such as systemic erlupus erythematosus)

Valle Camonica is a large valley located in the province of Brescia (Lombardy, in northern Italy) with a population of 100. 161 inhabitants (Istituto Nazionale di Statistica data at January 1<sup>st</sup> 2018). We report two cases of sporadic Fahr's disease observed in Hospital of Esine, located in Valle Camonica. The first patient presented with left diabetic hemichorea, the other was affected with essential thrombocythemia and Sjogren's syndrome.

## **Materials and Results**

Case report 1: We report the case of an 80 years old man with involuntary left arms movements due to uncontrolled

diabetes mellitus treated with insulin glulisine and glargine. His medical history was positive also for previous ischemic cardiopathy, dyslipidemia. He performed brain computer tomography (CT) and Magnetic resonance (MRI) [figures 1-4] which showed abnormal calcifications in basal ganglia, cerebellum, and occipital lobe. Neurological examination showed left arms choreic movements associated with lower arms areflexia, lower limbs distal weakness (3/5 MRC in dorsal feet flexion) with bilateral stepping gait. Familial history was referred as negative for neurological disorders. His son was clinically asymptomatic. He performed lumbar puncture which resulted normal and brain magnetic resonance which confirmed CT results (figures 1-5). Blood exams, especially serum and urinary calcium and phosphorus, thyroid hormones, magnesium, alkaline phosphatase, calcitonin and parathyroid hormones, creatinine, vitamin D3 resulted all normal. Serum glucose was 359 mg/dl (normal value 74/106) and hemoglobin A1C was 8.5%.

Case report 2: We report the case of a 79 years-old caucasian woman who underwent our observation due to bradykinesia, loss of memory. Her clinical history was positive for essential thrombocythemia (ET) treated with hydroxyurea, previous diagnosis of Sjogren's syndrome (diagnosed with autoantibody SSA, Schirmer's ocular test and lip biopsy), and previous quadrantectomy for neoplasia. No familiarity for neurological diseases was reported. Neurological examination showed hypomimia, hyposmia, ophthalmoparesis at both upward and downward gaze, four limbs increased muscle tone and osteotendinous reflexes, bradykinesia, presence of frontal release signs (glabellar, sucking reflex, bilateral palmomental), positive right Hoffman sign. Neuropsychological evaluation showed mild cognitive impairment (MCI): Mini-Mental State Examination (Folstein, 1975) = 25/30, basic activities of daily living - BADL (Ford et al 1963): 5/6 lost, instrumental activities of daily living-IADL (Lawton et al 1969): 7/8 lost, Clock Drawing Test 1/10, neuropsychiatric inventory (NPI) 31/144 (due to marked anxiety and depression), Tinetti Scale: 9/16+6/12=15/28, unified Parkinson's disease rating scale- UPDRS III: 27/108. Brain Computed Tomography and Magnetic Resonance Imaging [figures 5-7] showed altered signal areas localized to both base nuclei, white matter of the semioval centers (with loss of volume), cerebellar lobes (toothed nuclei) due to accumulation of paramagnetic substances, suggestive for Fahr's disease. Spine MRI showed instead multiple conus and cauda perimedullary arteriovenous fistulas, confirmed by angiography, for which vascular surgeons suggested regular follow-up.

Blood exams showed normal serum and urinary calcium, phosphorus, vitamin D, parathyroid hormone and thyroid function, alkaline phosphatase, calcitonin were all normal. She was an only child and unmarried.

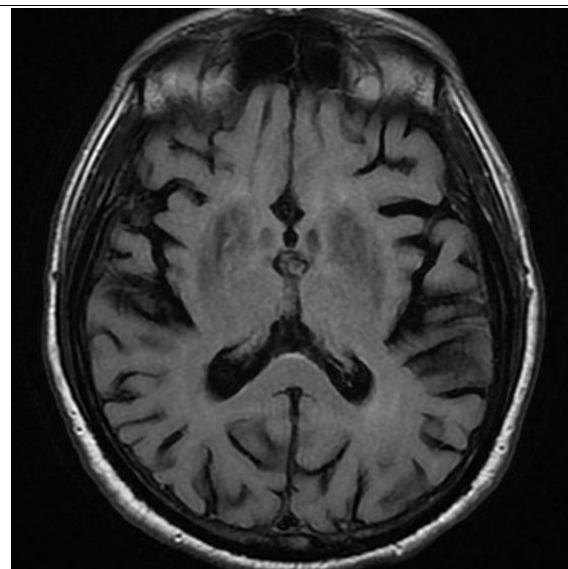


Figure 1: Patient 1 Brain MRI AX T2 flair sequence

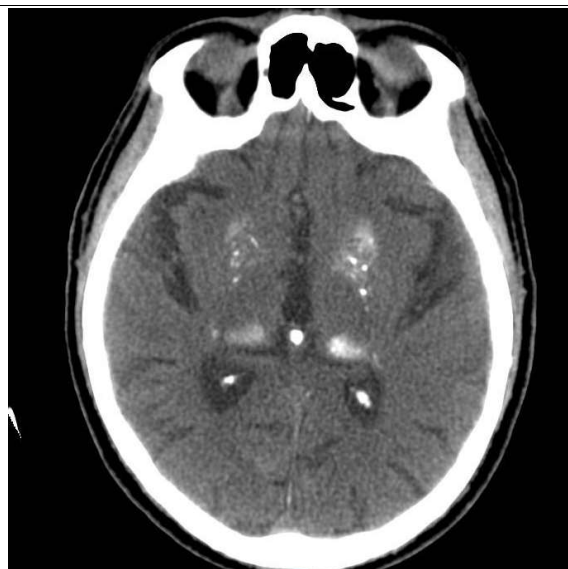


Figure 2: Patient 1 Brain CT



Figure 3: Patient 1 Brain CT

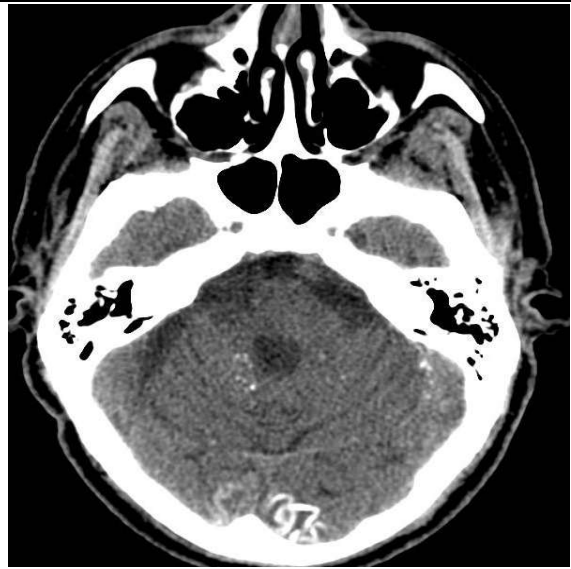


Figure 4: Patient 1 Brain CT

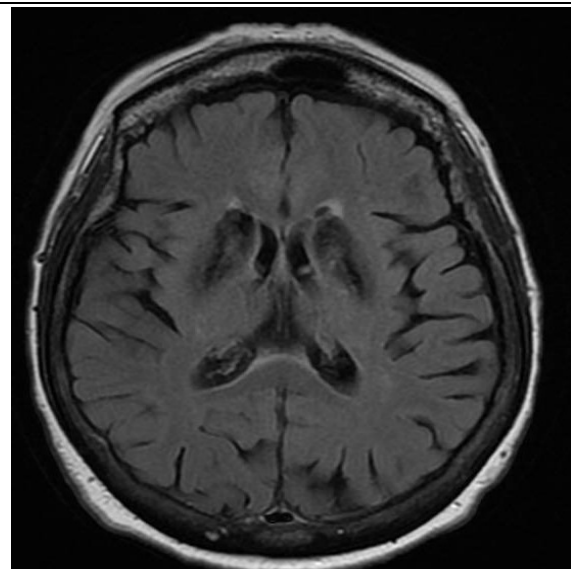


Figure 5: Brain MRI AX T2 flair



Figure 6: Patient 2 Brain CT



**Figure 7: Patient 2 Brain CT**

### **Discussion**

We presented two cases of Fahr's disease. The first patient was accidentally diagnosed after Brain CT, because he clinically presented only signs of peripheral nervous system involvement (electroneurography confirmed axonal – demyelinating sensory-motor neuropathy due to diabetes mellitus). His hemichorea promptly improved after better control of his diabetes with strict glycemic control. So, the possible co-existence of a chorea hyperglycemia basal ganglia syndrome (CHBG), a rare condition that manifests within the setting of uncontrolled nonketotic diabetes mellitus characterized by T1-T2 hyperintense abnormalities on MRI, couldn't be totally excluded (even if, in our patients, lesions are bilateral, already present at brain-computer tomography and non-only at brain MRI T1 sequences, and present typical Fahr's disease pattern).

The second case describes a possible association between Fahr's disease and Sjogren's syndrome, which has been already reported in a recent case report [6]. We didn't find in literature possible associations between Fahr's disease and essential thrombocythemia (ET); we found only a case report of Fahr's disease in a patient with thrombocytopenia [7].

Sjogren's syndrome (SS) is a systemic autoimmune disorder most commonly presenting with "sicca" symptoms, which refer to dryness most often involving the eyes and mouth due to inflammation and resultant pathology of the lacrimal and salivary glands. Almost one-half of SS patients also develop extraglandular involvement implying the occurrence of signs and symptoms in organs distinct from the salivary and lacrimal glands including the joints, skin, lungs, GI tract, kidneys, and nervous system. Sjogren's syndrome frequently occurs in conjunction with other autoimmune disorders including rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE) [8]. Comparing with the case report of Colleagues our patient didn't receive the diagnosis of SLE. The role of autoimmunity in Fahr's disease is described very little in the literature. It is not clear whether central nervous calcification in Fahr's disease is a metastatic deposition, secondary to local disruption of the blood-brain barrier, or is due to a neuronal calcium metabolism disorder. The gliovascular changes caused by cerebral inflammation may be secondary to autoimmune invasion and thus facilitate calcifications within the striopallidodentate system.

Genetic testing on all patients should be performed. Due to historical reasons and owing to its geographical position, in fact, Valle Camonica experienced isolation until the end of the Second World War; only two roads and one railroad

allowed connections to the valley, and no immigration flows are known during the past centuries, suggesting that Valle Camonica inhabitants might have the qualities of an isolated population. Due to their difficulty in transport and due to their bad health they both refused to perform genetic evaluation.

**Conclusion:**

We reported two cases of sporadic Fahr's disease. We think that possible association with metabolic/autoimmune disorders should be considered (collecting also similar cases), even if a definite relationship with these conditions hasn't still been found and it can be simply coincidental, in order to better evaluate patients, promptly start symptomatic treatment and perform correct diagnosis.

**DECLARATIONS**

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