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Fahr's syndrome and clinical correlation: a case series and literature review

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Abstract

Introduction: *Fahr's disease is characterized by bilateral calcium deposition within the basal ganglia, cerebellar dentate nucleus and subcortical brain white matter. The main clinical manifestations are rigid or hyperkinetic syndrome, mood disorders and cognitive impairment. The correlation between neurological impairment and symmetrical basal ganglia calcification is not so frequent. Aim of the study was to report the results of neurological assessment of three sporadic cases of Fahr's disease highlighting a correlation between the clinical syndrome and neuroimaging.*

Case reports: *Three adults of aged 32, 55 and 70, were studied. They all showed a heterogeneous clinical spectrum. One case developed neuropsychiatric symptoms, whereas the others complained of the tremorigen syndrome. Brain computed tomography scans revealed several calcifications in basal ganglia, cerebellar white matter and dentate nuclei.*

Conclusions: *The pathogenesis of Fahr's disease is probably secondary to the dysfunction of cortico-basal connections and their interhemispheric relations. No significant correlation between calcifications and neurological symptoms is proved.*

Key words: *basal ganglia calcification, hypokinetic syndrome, hypoparathyroidism, hypocalcaemia.*

Introduction

Fahr's disease (FD) is characterized by idiopathic calcification within the basal ganglia, cerebellar dentate nuclei and bilateral white matter, so the term 'bilateral striopallidodentate calcinosis' (BSPDC) appears to be the most appropriate [43,44].

Clinical manifestation occurs at any age without overrepresented ages of onset. Idiopathic BSPDC is clinically heterogeneous. Patients with calcification may exhibit neurological and/or psychiatric symptoms with different degrees of severity and ages of onset. Others can remain asymptomatic throughout life [2]. 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 [27,72] and recently greatly increased (from 1.3% to 20.6%) in recent studies [52,71].

Between 2% and 12% of brain scanners detect the presence of calcification levels within the lymphatic vessels [14-17]. Small "physiological" calcifications, especially located in the globus pallidus, can be evidenced and their prevalence increases with age.

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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.

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 [19,70]. 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). PDGFB and PDGFRB code for the platelet-derived growth factor beta (PDGFb) and its receptor, and the platelet-derived growth factor receptor beta (PDGFR-b), respectively [28,53,69].

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 [38].

In published studies, these three genes account for approximately 50% of cases [8,10,23,26,52,54, 73,74]. However, in most of these studies, only the SLC20A2 gene was examined, and only by Sanger sequencing. Comprehensive analyses of all the three genes are scarce as stated by a recent study [67].

One of known causes associated with basal ganglia calcinosis is hypoparathyroidism. Related causes can be infections, such as Epstein-Barr and human immunodeficiency [50], lupus erythematosus [57], perinatal hypoxia [58], radiation or chemotherapy [14], carbon monoxide poisoning and prolonged use of anticonvulsants [15].

The pathophysiological mechanism of calcium and other mineral deposits in extracellular and perivascular zones is still unknown. To date several hypotheses have been formulated, such as interruption of the local blood-brain barrier, altered metabolism within neuronal-glial calcium networks, changes in the extracellular matrix [6]. Calcium and other mineral deposits were found in the walls of capillaries, arterioles, and small veins and in perivascular spaces [23]. Neuronal degeneration and gliosis surrounding these accumulations have been reported [33].

Mucopolysaccharides, traces of aluminium, arsenic, cobalt, copper, molybdenum, iron, lead, manganese, magnesium, phosphorus, silver, and zinc are also present [23,42,51,64].

At the molecular level, calcification generally develops within the vessel wall and in the perivascular space, ultimately extending to the neuron.

Due to defective iron transport and free radical production, tissue damage occurs which leads to the initiation of calcification. It occurs secondarily around a Nidus composed of mucopolysaccharides and related substances. Progressive basal ganglia mineralization tends to compress the vessel lumen, thus initiating a cycle of impaired blood flow, neural tissue injury and mineral deposition. Basal ganglia concretions are recognized as basophilic globules tracking the vessels of arteries, veins and capillaries [59].

Electron microscopy also shows the evidence of a connection between spherical and hemispherical bodies formed in the adventitia of the blood vessel and surrounding glial cells while intima is usually preserved with deposits within the pericytes [30].

Mineral composition of the calcifications varies with the anatomical site and their proximity to vasculature calcifications. It may be due to the abnormal metabolism of calcium and phosphorus while some reports tend to contradict this finding [1,3,29].

In a review of 4219 computed tomography (CT) scans, it was deduced that most calcifications occur bilaterally and symmetrically while a few occur unilaterally and there was no abnormality in metabolism of calcium, denying the pathophysiologic significance of concurrent altered calcium metabolism [31]. Calcifications commonly occur in basal ganglia, thalamus, dentate nucleus, cerebral cortex, cerebellum subcortical white matter, and hippocampus [29,46].

It has been suggested that the hyperintense T2-weighted images in MRI sequences may reflect a slowly progressive metabolic or inflammatory process in the brain with consequent calcification, probably causing the neurologic deficits observed [2]. Single-photon emission computed tomography (SPECT) studies showed a marked blood flow decrease. The criteria for the diagnosis of bilateral striopallidodentate calcinosis (BSPDC) include [37,72] evidence for bilateral basal ganglia calcification; progressive neurological or neuropsychiatric manifestations; onset of symptomatology in the fourth or fifth decade of

life (earlier onset is also likely to occur). There are no biochemical abnormalities and clinical features suggesting the presence of mitochondrial, metabolic disease or other systemic disorders; calcifications are not due to infection, trauma, or toxic causes; moreover, autosomal dominant inheritance (chromosome 14q9) for basal ganglia calcification has been discovered [17] (Table I). Brodaty *et al*. [7] excluded such a locus in the absence of neurological, cognitive and psychiatric symptoms. Further, in hypothyroidism the locus is on 11p [24]; in pseudohypoparathyroidism it is on 20q [37]; in Down's syndrome it is on 21q [48], excluding the possibility that a single gene may be responsible for the calcium and other mineral deposits.

Table I. Pathological conditions associated with calcification of the basal ganglia

Idiopathic hypoparathyroidism
Secondary hypoparathyroidism
Pseudohypoparathyroidism
Pseudo-pseudohypoparathyroidism
Hypothyroidism
Neonatal anoxia
Carbon monoxide poisoning
Lead poisoning
Fahr's disease
Basal ganglia calcification (idiopathic family)
Hastings-James syndrome
Cockayne syndrome
Hyalinosis skin
Tuberous sclerosis
Parkinsonism
Vascular diseases
Cerebral haemorrhage
Radiation therapy
Therapy with methotrexate
Cytomegalic inclusions disease
Encephalitis
Toxoplasmosis
Cysticercosis

Bilateral striopallidodentate calcinosis is frequently suspected in normal aging [2,62]; nevertheless, in the literature there is no clear evidence for establishing when calcifications can be attributed to normal aging or to a pathological process. Considering clinical presentations of BSPDC (Table II) in the presence of family history, diagnosis can be proposed in the absence of one of the first 2 criteria. Whereas when family history is negative, meeting the first 5 criteria is sufficient for the diagnosis of BSPDC only if the calcifications are typical of BSPDC [36,46]. Calcifications are more commonly reported in the globus pallidus; additional reported sites

Table II. Clinical presentations of Fahr's disease as reported in the literature

Radiologic findings
Bilateral symmetrical calcifications of basal ganglia and dentate nucleus
Thalamus, centrum semiovale, cerebellum, and cerebral white matter
Psychiatric symptoms
Cognitive deterioration: dementia, delirium, confusion
Psychotic symptoms: hallucinations, delusions
Catatonia
Irritability
Aggression
Personality disorder and personality changes
Mood disorders: depression, manic symptoms
Anxiety, panic attacks, and obsessive behaviours
Others symptoms
Parkinsonism and movement disorders
Seizures
Headache
Dysarthria
Tremor
Orthostatic hypotension
Vertigo
Paresis
Stroke
Syncope
Ataxia

include putamen, caudate nucleus, internal capsule, dentate nucleus, thalamus, cerebellum, and cerebral white matter [44]. Several cases were diagnosed incidentally [25,61,65,68,72] during routine assessment of psychiatric or somatic symptoms, which may suggest the possibility of underestimated diagnosis of BSPDC.

This study describes three heterogeneous sporadic cases of BSPDC in the absence of demonstrated familiarity. The quantity of calcifications is correlated with the symptomatic status, even though different clinical features are not solely justified by location and severity of calcifications. Thus, the correlation between neurological impairment and symmetrical basal ganglia calcification is not always the same. Brain CT aspects were similar, whereas the clinical neurological manifestations were different. Nowadays, a literature review shows evidence that there is no definite pathogenesis of basal ganglia calcifications.

Genetic tests described in clinical cases were obtained in specialized centres for genetic research on rare diseases.

Clinical cases

Case 1

A 55-year-old man presented with a five-year progressive cognitive decline including dysexecutive syndrome, apathy, along with severe disturbance of reasoning, calculation and sequential tasks.

Moreover, memory loss and depressive mood were expressed without any other psychiatric disorders, such as delusions or hallucinations. Finally, he was unable to perform daily life activities, with decreased verbal fluency, apathy and inability to make decisions. His family history was positive for mood and cognitive impairment; however, brain CT scan did not prove calcifications. Neurological examination disclosed extrapyramidal features with postural tremor and orofacial dyskinesia at lips and tongue.

Mini Mental State Examination (MMSE) score was 23/30 (Italian version); neuropsychological tests showed immediate and recent memory deficits, particularly in remote memory. Despite hospitalisation in psychiatry ward, he continued to wander, interaction was absent, he demonstrated poor self-care and disorganised behaviour (e.g. handling the faeces). Nevertheless, the patient was spatiotemporally oriented and was able to recognise people. He was consistent in his verbal responses with rapid and unclear speech (dysarthric speech) and sometimes words could not be understood. Routine blood tests disclosed normal ionic calcium levels (1.12 mmol/l) including calcium, phosphorus, thyroid hormones and parathormone. Serologic tests for syphilis and HIV were negative. He was treated with carbolithium (600 mg/day) and selective serotonin reuptake inhibitor (SSRI). Brain CT showed extensive bilateral calcifications in the dentate nuclei of the cerebellum, basal ganglia and centrum semiovale (Fig. 1). Brain magnetic resonance imaging confirmed multiple small patchy hypersignals in the same areas (Fig. 2). Molecular diagnosis was made by sequencing of the entire coding region of SLC20A2, PDGFRB, and PDGFB and copy number analysis of SLC20A2 giving normal findings. Bilateral striopallidodentate calcinosis was therefore possible based on clinical features and neuroimaging (bilateral basal ganglia calcification, dysarthria and neuropsychiatric symptoms). The patient showed partial improvement in behavioural symptoms with Carbolithium discontinuation; hence quetiapine (25 mg/day) was added. Symptomatology ameliorated within the 60 following days, specifically with the reduction of orofacial dyskinesia at lips and tongue. Despite partial initial benefits, he showed progression of the disease with a severe depressive syndrome.

Case 2

A 70-year-old woman with a previous history of bronchial asthma and hypertension with neurological symptoms occurring for 20 years, showed mild tremor in the upper limbs. Hypothyroidism was disclosed; T3 and T4 results were always normal. During the following 10-15 years tremor increased progressively up to involving the chin and the voice.

Two years later, memory loss and depressive mood were demonstrated. Mini Mental State Examination (MMSE) score was 23/30 (Italian version); other neuropsychological tests showed deficit in attentional capacity, in spatiotemporal orientation and praxis functions. Complete haematochemical examinations, including thyroid and parathyroid hormones, phosphorus/calcium, liver function tests, complete blood count, along with sedimentation, were normal even when frequently repeated over years. Electroencephalogram (EEG) was unremarkable. Brain CT scan highlighted the symmetrical

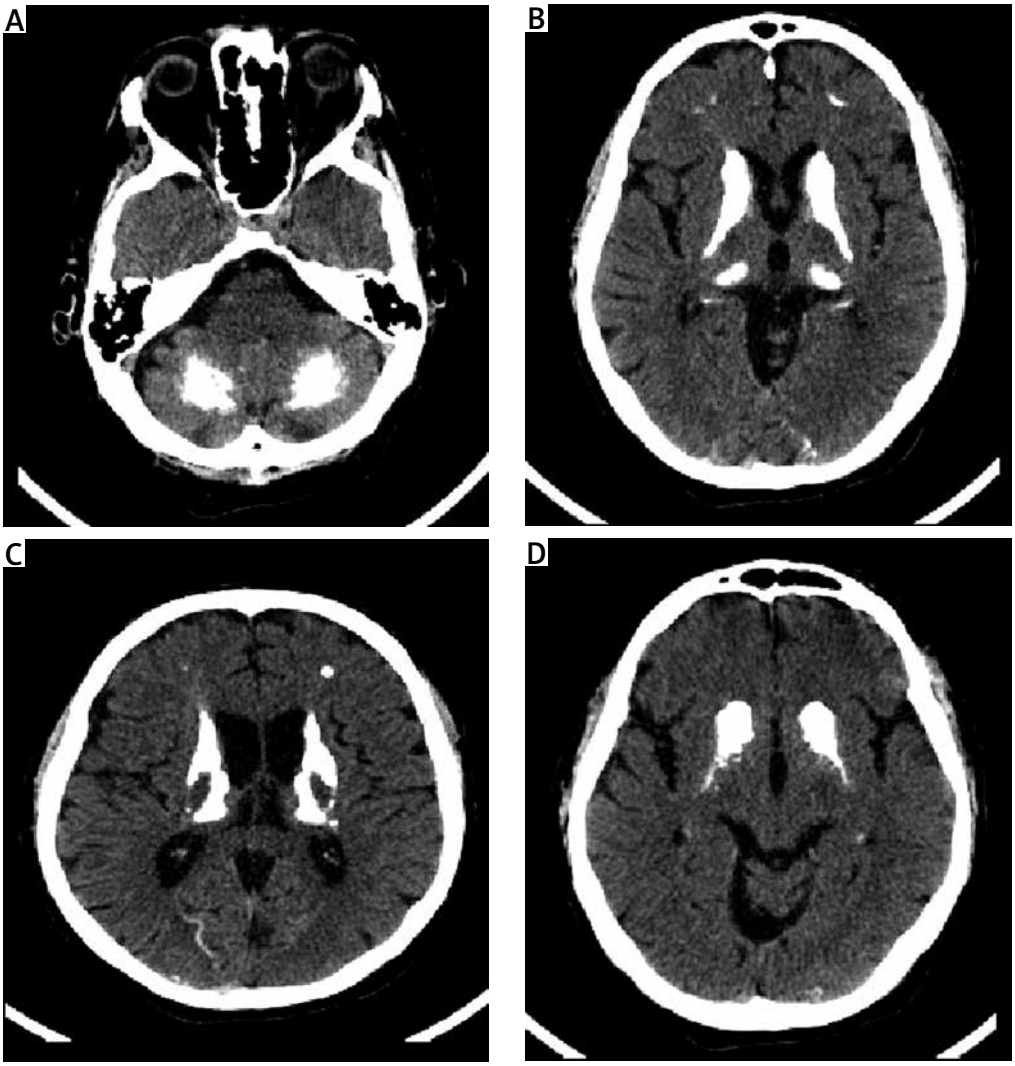

Fig. 1. Computed tomography (CT) findings in patient 1: brain CT shows brain calcification in dentate nuclei of the cerebellum (**A**), basal ganglia, thalamus and cortical (**B-D**).

distribution of mineral deposits in the lenticular nuclei, medial thalamic paraventricular nuclei and in the white matter (Fig. 3). The patient's overall clinical features alongside instrumental examinations allowed to make a diagnosis of BSPDC. After obtaining informed consent, diagnostic genetic testing was performed by sequencing of SLC20A2, PDGFRB, and PDGFB with normal findings. Levodopa was administered but the patient did not tolerate it; beta-blockers could not be used because of bronchial asthma. Within 60 days of alprazolam introduction (3 mg/day), the patient showed partial improvement in behavioural symptoms and essential tremor went into remission.

Regular follow-up during the next three years disclosed tremor recurrence with exclusive involvement of the chin.

Case 3

A 32-year-old man complained of progressive mild tremor at hands in the previous year.

His personal history was positive for Hashimoto thyroiditis. Neurological examination showed only mild rest and action tremor without further signs of extrapyramidal features. Neither dismetry nor any other cerebellar signs were present. General examinations were normal. The patient's relatives were examined and no abnormalities were detected. The thyroid

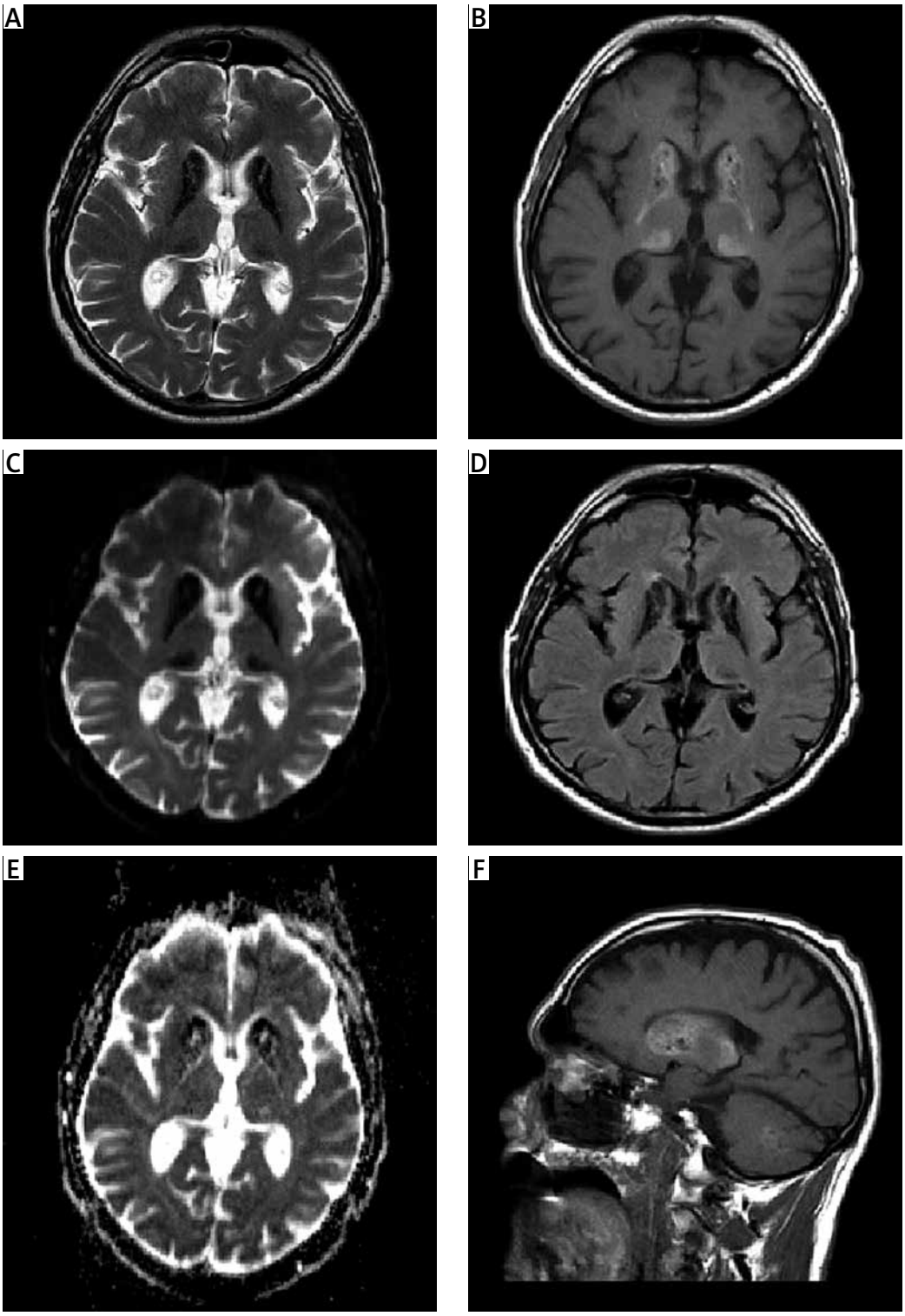

Fig. 2. Magnetic resonance imaging (MRI) findings in patient 1: (**A, D**) T1 and (**B**) T2-weighted image, (**C**) diffusion weighted imaging (DWI) and (**E**) apparent diffusion coefficient (ADC) map, (**F**) fluid-attenuated inversion-recovery (FLAIR) image. Calcified areas show high- or low-intensity signals on MRI T1-weighted images. On T2-weighted image calcification is depicted as low-intensity signals. Multiple small patchy hypersignals on FLAIR sequence. Dark spots are noted on both the DWI and the corresponding ADC map.

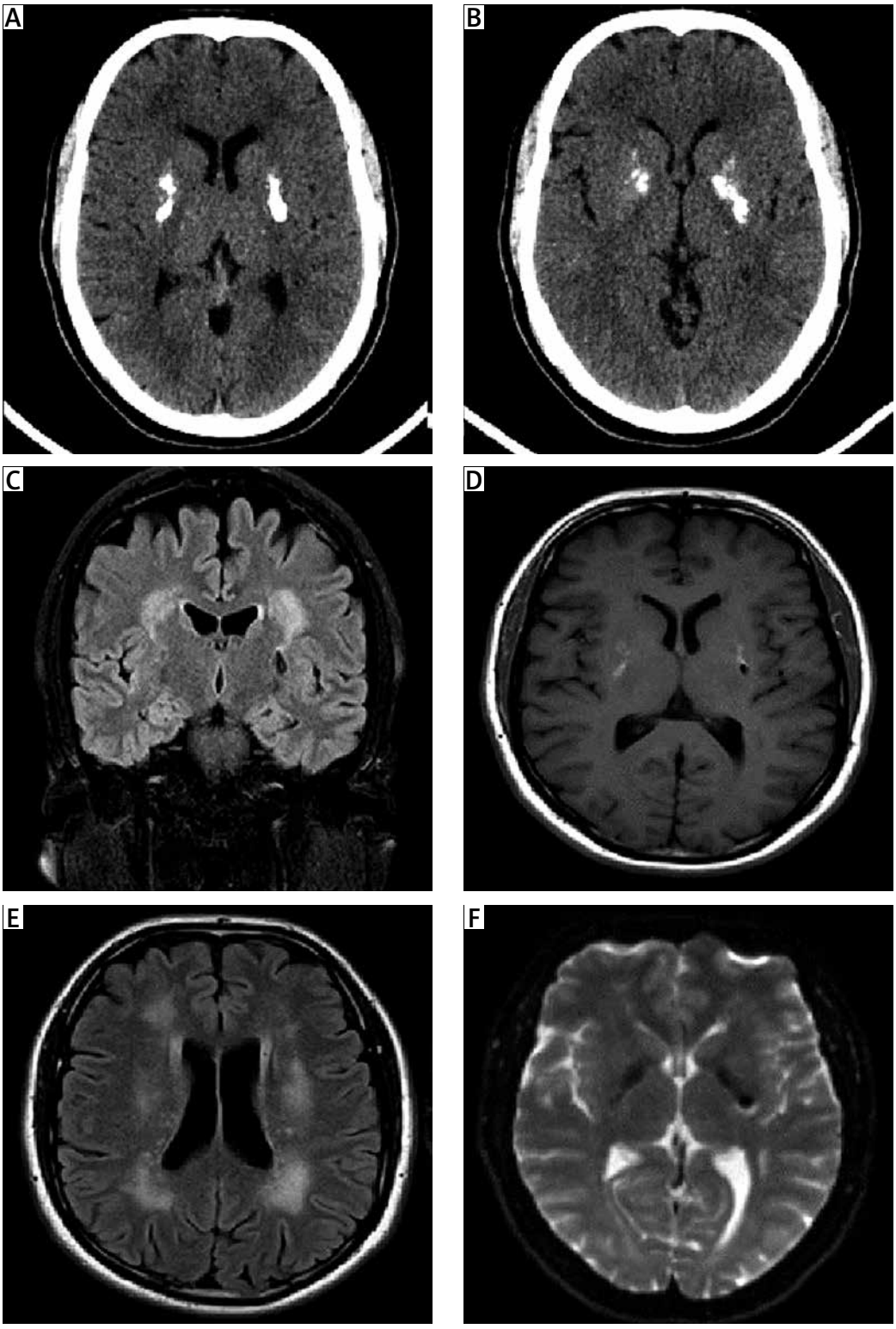

Fig. 3. Computed tomography (CT) and magnetic resonance imaging (MRI) findings in patient 2: brain CT shows a striking high density area in the basal ganglia (**A, B**); MRI calcified areas show hypersignals on FLAIR sequence (**C**), high- or low-intensity signals on MRI T1-weighted images (**D, E**) and dark spots are noted on diffusion weighted imaging (DWI) (**F**).

test, parathyroid hormone, phosphorus/calcium, liver function tests, complete blood count, sedimentation and ionic calcium level were normal. Serologic tests for syphilis and HIV were negative. Cerebrospinal fluid (CSF) analysis was normal. Mini Mental State Examination (MMSE) score was 30/30 (Italian version); other neuropsychological tests were normal. Brain CT scan showed extensive bilateral calcifications in the dentate nuclei of the cerebellum, basal ganglia and bilateral white matter. Magnetic resonance imaging confirmed severe hypointense focal areas with a maximum diameter of about 10 x 7 mm in capsular and peritrigonal areas (Fig. 4). No therapy was administered because of slight symptomatology.

After informed consent to diagnostic genetic testing was obtained, sequencing of SLC20A2, PDGFRB, and PDGFB was performed giving normal findings.

2-year or regular follow-up disclosed no sign of disease progression.

Discussion

Bilateral striopallidodentate calcinosis is mostly associated with a disorder of calcium and phosphate metabolism, especially hypoparathyroidism (HPT) [2,20,55,60]; however, different aetiology must be considered, including infectious, metabolic, and genetic diseases [65].

Our clinical series did not reveal abnormalities in calcium, phosphate, parathyroid levels and other dysmetabolism responsible or calcium deposition.

Furthermore, there was no family history of the disease in all of the three cases reported.

Genetic analysis for SLC20A2, PDGFRB, and PDGFB genes detected no mutations.

Recent reports have highlighted novel hypothesis regarding the possible causes and etiopathological processes of PFBC [21]. In particular, mutations in 3 different genes have been identified as causative agents of PFBC. First, SLC20A2 (OMIM158378) was described in February 2012 as coding for type III sodium-dependent inorganic phosphate (Pi) transporter 2 (PiT-2). The second reported gene, PDGFRB (OMIM173410), was described in January 2013 as encoding 1 of 2 receptors for platelet-derived growth factor. The gene encoding its major ligand, PDGFB (OMIM190040), was the third gene identified in September 2013 [28]. The different mutations in all the 3 genes share loss of function as the probable cause of pathology. Mutations in the SLC20A2 gene lead to accumulation of Pi and subsequently to calcium phosphate deposition. Mutations in PDGFB and PDGFRB also result in calcification through indirect processes. Although the receptor and its ligand are also expressed in neurons, data from selective knockout studies indicate impaired recruitment of pericytes to endothelial cells, resulting in a dysfunctional blood-brain barrier and thereby contributing to brain calcification.

Disease progression is heterogeneous even within the same family. The prevalence of extrapyramidal disorders (parkinsonism, dystonia, dyskinesia) and cerebellar signs (ataxia and dysarthria) is reported; neuropsychiatric symptoms, including schizo-morphous psychosis [9], changes of personality [34], lability of mood and compulsive [18,35,40] obsessive disturbance, were evidenced. Nevertheless a progressive subcortical cognitive impairment could occur.

In a study combining 38 cases recruited through a registry and 61 cases reported in the literature, movement disorders were found as the most common manifestations of BSPDC accounting for 55% of symptomatic patients. The most common movement disorders were parkinsonism (57% of cases), chorea (19%), tremor (8%), dystonia (8%), athetosis (5%) and orofacial dyskinesia (3%).

Measurements of the total volume of calcification suggest a significantly larger amount of calcification in symptomatic patients compared with asymptomatic patients [46].

Neuropsychiatric symptoms can be either the first or the most prominent manifestation ranging from mild concentration or memory impairment, personality and behaviour changes, to psychosis and dementia. About 40% of patients with basal ganglia calcification (BGC) may initially present psychiatric features [5], such as psychotic syndrome and mood changes, but even cognitive disorders are common [13]. Paranoid and psychotic features often begin in patients aged between 20 and 40 [19]. In FD two patterns of psychotic presentation are described: early onset (mean age 30.7 years) with minimal movement disorder and late onset (mean age 49.4 years) associated with dementia and movement disorders [12]. Nevertheless, all the symptoms may vary during the course of disease. Calcification extension and subarachnoid space dilatation correlate with the presence of psychiatric manifestations [41]. Other clinical findings in patients with BSPDC are cranio-cerebral trauma,

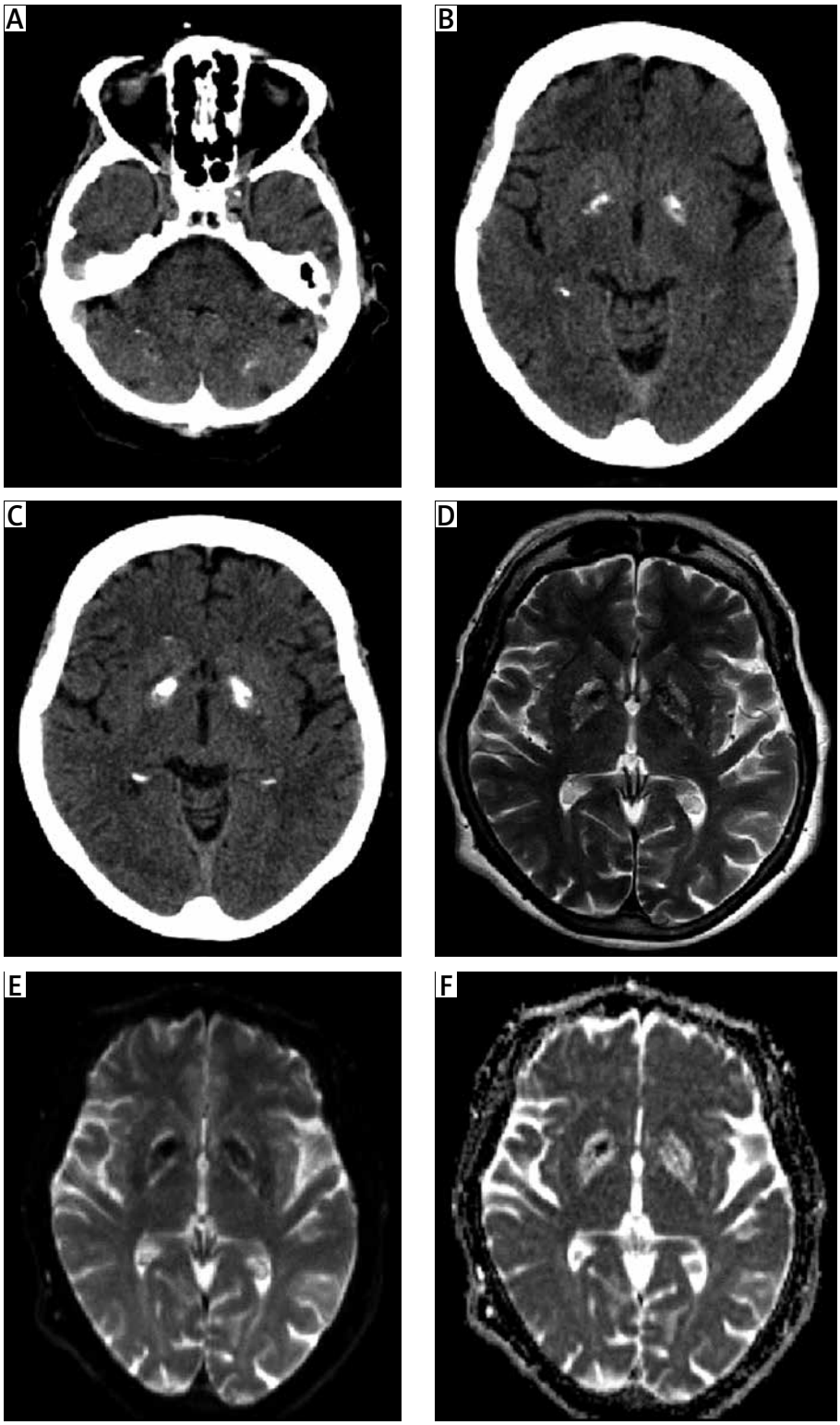

Fig. 4. Computed tomography (CT) and magnetic resonance imaging (MRI) findings in patient 3: an axial view shows a marked high density area in the basal ganglia and dentate nuclei of the cerebellum (**A-C**); MRI calcified areas show hypersignals on FLAIR sequence (**C**), high- or low-intensity signals on MRI T1-weighted images (**D**) and dark spots are noted on diffusion weighted imaging (DWI) (**E**) and the corresponding ADC map (**F**).

stroke, meningitis, encephalitis, brain tumours, cerebral aneurysm, arteriovenous malformation, subdural hematoma, and mastoiditis [36]. Cases presenting with BSPDC and disturbed calcium metabolism were associated with idiopathic hypoparathyroidism, hyperparathyroidism, pseudo-hypoparathyroidism, and postoperative hypoparathyroidism. Patients having parathyroid hormone deficiencies due to thyroidectomy showed more severe mental deterioration [41]. In the three cases reported in our study, the beginning of symptomatology was different and characterised by tremor, psychiatric disorders or movement disorders. The patient with a higher quantity of calcium in TC (case 2) showed onset with predominant psychiatric symptoms, whereas the cases with less (case 2) or earlier (case 3) calcium deposition had prevailing tremor without parkinsonism signs. Besides, aetiology of calcium deposition remains mostly undetermined and no metabolic causes came up in the cases observed.

The exact pathological process responsible for the calcification of brain structures is still poorly understood; it could be secondary to a progressive metabolic or inflammatory process, which subsequently causes the neurological impairments observed [2]. Neuroradiological findings are also different in CT and MRI. The areas involved were basal ganglia, dentate nuclei of cerebellum, medial thalamic paraventricular nuclei, white matter and no correlations were found with clinical manifestations.

These data were confirmed by the literature, especially the non-specificity of lesions for localisation, extension and correlated symptoms.

Moreover, our patients were examined in regular follow-ups and all of them had no progression of symptomatology since the beginning of disease.

It is still unknown why the basal ganglia are the most vulnerable site for calcium deposition, but even in other conditions they are a favourite target, like bilirubin in kernicterus or 1-methyl-4-phenyl, 1,2,3,6-tetrahydropyridine (MPTP) and carbon monoxide causing parkinsonism.

Although correction of dysmetabolic causes, such as hypoparathyroidism or mitochondrial encephalopathy, can improve neuropsychiatric syndrome, there are no specific treatments at the moment that may limit the progression of calcification in the basal ganglia. A report of amelioration using Ca-chelators with antioxidant and Ca-antagonist has still to be confirmed [11]. Currently there is no cure for BSPDC nor is there a standard treatment. The available therapy is only symptomatic and corrections of known aetiology are admitted.

The prognosis is variable and unpredictable. There is no reliable correlation between age, extent of calcium deposits in the brain and neurological deficit. Progressive neurological deterioration generally results in disability and death.

Reduced 25-OH vitamin D_3 with normal levels of $1.25(OH)_2$ vitamin D_3, suggest an inborn error of vitamin D metabolism [47]. Further evaluation of this finding is needed so as to provide a therapeutic solution.

The treatment of BSPDC is directed to the identifiable causes [49]. Especially in HPT, an early treatment can prevent calcification and neurophysiological disorders [20,55,56].

Studies show that psychoses in BSPDC have variable and sometimes null responses to treatment [32].

The treatment targets include symptomatic support. The response to levodopa in those patients with parkinsonian features is reportedly poor. Atypical antipsychotics are preferred for psychiatric symptoms because of the coexistence of the extra pyramidal syndrome in this group of patients.

Treatment of underlying aetiology such as hypoparathyroidism has led to neuropsychiatric improvement, but there are no specific treatments limiting the progression of calcification in the basal ganglia in BSPDC, except a theoretically unconfirmed report of Ca-chelators plus antioxidant and Ca-antagonist benefits [11]. Metal binding proteins and metal-chelating agents (like ammonium tetrathiomolybdate, which is a Cu-chelating agent) have been theoretically suggested as one of the treatment options [22].

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Disclosure

Authors report no conflict of interest.

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