Basal ganglia calcification - “Fahr’s disease”

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Abstract

Brain calcification is often detected incidentally, but basal ganglia calcification has a wide differential diagnosis, including genetic and acquired causes. Primary familial brain calcification (PFBC; formerly “Fahr’s disease”) refers to neurological disorders characterised by bilateral, symmetrical deposition of calcium-hydroxyapatite crystals in the basal ganglia and other encephalic regions, with a presumed genetic basis. Its clinical picture encompasses motor, cognitive and psychiatric manifestations in various combinations. Seven genes have been linked to PFBC since 2012, with either autosomal dominant (*SLC20A2*, *PDGFRB*, *PDGFB*, *XPR1*) or recessive (*MYORG*, *JAM2*, *NAA60*) mode of inheritance. Mendelian gene discovery has provided critical insights into the pathogenesis of PFBC. Dyshomeostasis of inorganic phosphate, impaired endothelial functions and disrupted blood–brain barrier integrity has been identified as converging pathomechanisms, which could highlight targets of potential disease-modifying treatments. We provide a state-of-the-art overview on phenotypic features, diagnosis, aetiopathogenesis and management of PFBC.

Introduction

Brain calcification is a common and often incidental neuroradiological finding. Despite it being considered physiological in several locations, basal ganglia calcification (BGC) is often a pathological finding. The prevalence of BGC is probably between 0.28% to 12.5%, peaking in older age.[1] In 15–20% of cases, it is found in asymptomatic individuals, whereas in elderly patients it is more commonly associated with movement disorders or cognitive impairment.[1,2]

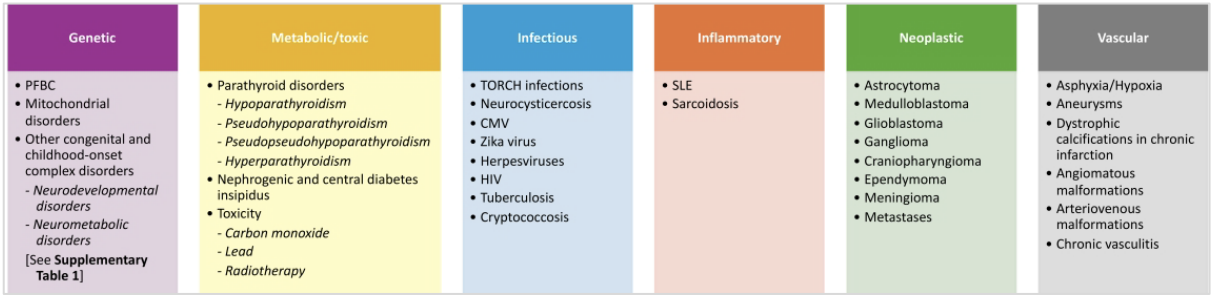
The BGC syndrome is often named after the late German pathologist Karl Theodore Fahr.[3] However, the "ossification of brain capillaries" in a 56-year-old man with "stiffness and weakness of lower extremities with tremor" was first reported by Delacour during the 19th century.[4] Inherited BGC was recognised in 1977, when Boller described nine people from one family with this condition.[5] Since then, at least 35 equivalent names have been used in the literature to describe idiopathic basal ganglia calcification (IBGC), which is now the term used to identify early genetic findings in this field.

From a genetic perspective, IBGC was initially linked to several loci (IBGC 1-3; Table 1) before candidate genes were identified several years later.[6-8] Until recently, it was assumed to be inherited in an autosomal dominant fashion, justifying the term "primary familial brain calcification" (PFBC).[9-12] However, widespread availability of next-generation sequencing has also enabled the identification of BGC-related genes with an autosomal recessive pattern of inheritance.[13-15]

Causes of brain calcification

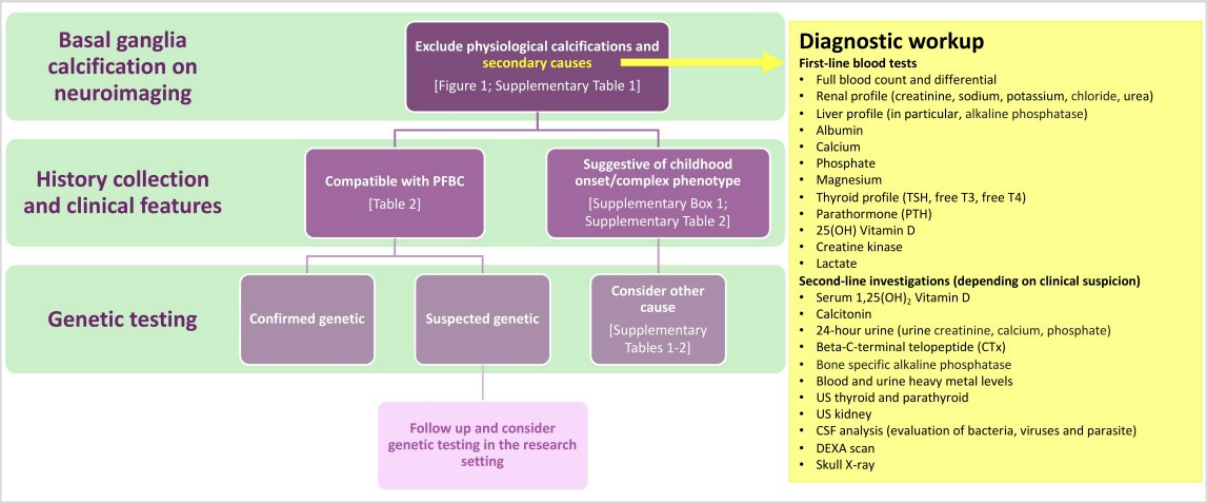
The diagnostic workup of brain calcification aims to differentiate PFBC from physiological, age-related calcification and other genetic or acquired causes (Figures 1-2). Most of these alternative disorders present with characteristic clinical features and radiological findings in addition to calcifications, which helps distinguish them from PFBC (Supplementary Box 1 and Table 2). Furthermore, the localisation (intracranial, intra- or extra-parenchymal) and pattern of brain calcification can point towards certain causes (Supplementary Table 1).

Figure 1. Main genetic and acquired causes of intracranial calcifications



Legend: CMV = cytomegalovirus; HIV = human immunodeficiency virus; PFBC = primary familial brain calcification; SLE = systemic lupus erythematosus; TORCH = congenital infections of toxoplasmosis, others (syphilis, hepatitis B), rubella, cytomegalovirus (CMV), and herpes simplex.

Figure 2. Diagnostic approach to basal ganglia calcification in the clinic setting



Legend: CSF = cerebrospinal fluid; DEXA = dual energy X-ray absorptiometry; PFBC = primary familial brain calcification; T3 = triiodothyronine; T4 = thyroxine; TSH = thyroid-stimulating hormone; US = ultrasound.

Among genetic causes, there are seven causative genes linked to PFBC (Table 1). In addition, brain calcifications detected during childhood have a wide differential diagnosis, including miscellaneous developmental and neurometabolic disorders.

Table 1. Genes, proteins and mode of inheritance of Primary Familial Brain Calcification

Phenotype OMIM #	Causative gene	Locus	Mode of inheritance	Gene product	Proportion of genetically confirmed PFBC[16]
213600	***SLC20A2***	IBGC 1-3 (8p11.21)	AD	Type III Na^+-dependent inorganic phosphate (Pi) transporter 2 (PiT2)	~60%
615007	***PDGFRB***	IBGC 4 (5q32)	AD	Receptor for platelet-derived growth factor with subunit beta	~5%
615483	***PDGFB***	IBGC 5 (22q13.1)	AD	Platelet-derived growth factor with subunit beta	~12%
616413	***XPR1***	IBGC 6 (1q25.3)	AD	Xenotropic and polytropic retrovirus receptor 1	~6%
618317	***MYORG***	IBGC 7 (9p13.3)	AR	Myogenesis-regulating glycosidase	~13%
618824	***JAM2***	IBGC 8 (21q21.3)	AR	Junction adhesion molecule 2	~2%
620786	***NAA60***	IBGC 9 (16p13.3)	AR	N-alpha-acetyltransferase 60 (NatF)	?

Legend: AD = autosomal dominant; AR = autosomal recessive; IBGC = idiopathic basal ganglia calcification; OMIM = Online Mendelian Inheritance in Man; PFBC = primary familial brain calcification; Pi = inorganic phosphate. See also Figure 3.

Table 2. Differential diagnosis of intracranial (intra- and extra-parenchymal) calcifications based on neuroradiological findings

Aetiologies	Intracranial localisation of calcifications	Calcification pattern
Physiological calcifications	Pineal gland, choroid plexus, habenula, falx cerebri, cerebellar tentorium, basal ganglia	Coarse and compact, punctate, curvilinear
Aicardi-Goutières syndrome	Basal ganglia, deep white matter of both frontal and parietal lobes	Symmetrical, spot-like
Cockayne syndrome	Basal ganglia with or without gyral calcifications	Bilateral rock or spot
Leukoencephalopathy with calcifications and cysts (Labrune syndrome)	Cerebral white matter or deep grey nuclei, rarely in the cerebellum	Small punctate foci or larger confluent areas asymmetrically scattered associated with diffuse bilateral cerebral white matter T2 hyperintensity and surrounding cysts
Krabbe disease	Internal capsule, corona radiata	Non-specific
3-hydroxyisobutyric aciduria	Frontal, subependymal and periventricular regions	Non-specific
Pseudo-TORCH syndrome-1	White matter, basal ganglia, cerebellum, brainstem	TORCH-like with cortical dysgenesis
TORCH infections	Periventricular regions, basal ganglia	Thick and chunky (periventricular), faint punctate (basal ganglia)
Neurocysticercosis	Brain parenchyma, subarachnoid spaces	Eccentric calcified nodule within peripherally calcified cyst
Neurofibromatosis	Cerebellum and periventricular region and disproportionately in choroid plexus	Nodular
Mycobacterium tuberculosis	Brain parenchyma and leptomeninges	Tuberculomas may calcify in the centre giving the appearance of a pathognomonic target sign
Cryptococcus neoformans	Brain parenchyma and leptomeninges	Punctate calcifications
Meningioma	Leptomeninges (variable)	Sand-like, sunburst, rim and globular
Craniopharyngioma	Pineal gland	Thin and circumferential or chunky
Pineal tumours	Pineal gland	Peripheral exploded pattern
Hypoparathyroidism	Basal ganglia	Punctate or compact calcifications
Systemic lupus erythematosus	Cerebellum (mostly)	Non-specific
Sarcoidosis	Suprasellar region, hypothalamus, cerebellum	Granulomas
Sturge-Weber syndrome	Brain parenchyma	Gyriform
Tuberous sclerosis	Subependymal	Nodular
Lead and carbon monoxide	Basal ganglia, periventricular regions	Punctiform, curvilinear, speck-like and diffuse

Legend: TORCH = congenital infections of toxoplasmosis, others (syphilis, hepatitis B), rubella, cytomegalovirus (CMV), and herpes simplex.

Clinical features and differential diagnosis of Primary Familial Brain Calcification

Since the first description of BGC cases caused by monoallelic *SLC20A2* variants,[17] our understanding of clinical manifestations of PFBC has rapidly evolved (Table 3).

Brain calcification in children can accompany a variety of disorders. The major difference between these disorders and genetically confirmed PFBC is that most childhood-onset diseases are associated with neurodevelopmental and radiological abnormalities, including retinal disorders, systemic manifestations (e.g. gonadal dysgenesis, organomegaly, skin disorders) and hypomyelination. Patients with *NAA60* and *JAM2* variants can, however, present with dysmorphic features and seizures at an early age.

Table 3. Common clinical manifestations of Primary Familial Brain Calcification and relative frequency[12,14,15,18-21]

Gene	Movement disorders	Cognitive/Neurobehavioural manifestations	Other manifestations
SLC20A2	Bradykinesia (21.5%) Rigidity (16.8%) Tremor (15.2%) Dystonia (13.6%) Ataxia (5.8%) Chorea (3.7%)	Cognitive deficits (30.4%) Psychosis (9.4%) Anxiety (5.8%)	Headache (28.8%) Speech disturbance (14.1%) Seizures (4.7%)
PDGFRB	Bradykinesia (16.7%)	Cognitive deficits (25%)	Headache (33.3%)
PDGFB	Ataxia (14.5%) Chorea (12.7%) Tremor (12.7%) Bradykinesia (9.1%) Dystonia (9.1%) Rigidity (6.7%)	Cognitive deficits (34.5%) Depression (23.6%) Psychosis (14.5%) Anxiety (10.9%)	Headache (41.8%) Speech disturbance (6.7%) Seizures (6.7%)
XPR1	Bradykinesia (14.3%) Tremor (14.3%) Ataxia (14.3%)	Cognitive deficits (38.1%) Psychosis (9.5%) Anxiety (9.5%)	Speech disturbance (28.6%)
MYORG	Bradykinesia (45%) Ataxia (36.7%) Rigidity (23%) Tremor (10%) Dystonia (6.7%)	Cognitive deficits (43.3%) Depression (18.3%) Psychosis (6.7%)	Speech disturbance (78.3%)
JAM2	Bradykinesia (80%) Rigidity (60%) Ataxia (60%) Dystonia (50%)	Cognitive deficits (50%)	Speech disturbance (40%) Seizures (30%)
NAA60	Ataxia (50%) Pyramidal (50%) Bradykinesia (40%) Dystonia (20%)	Cognitive deficits (100%) Psychosis (40%)	Seizures (30%) Dysmorphic features (50%)

Age of onset is generally a key anamnestic factor to consider in the differential diagnosis of inherited disorders with brain calcification, since certain causes are associated with childhood onset whilst others are more common in adults. Mean (standard deviation) age of onset for most cases of PFBC is around 27.9 (22.3) years, specifically 22.2 (16.0) years for men and 33.6 (26.0) years for women.[21]

Neuroradiological features and differential diagnosis of Primary Familial Brain Calcification

Calcium is a diamagnetic substance and has a very low magnetic susceptibility compared with surrounding tissue.[22] It can be difficult to identify mineral deposition on neuroimaging correctly, particularly with MRI. Iron, copper and manganese can have similar appearances based on MRI sequences used, although MRI SWI filtered phase images may help to distinguish paramagnetic blood products from diamagnetic calcifications. Hyperdensity on CT scanning is quite characteristic for calcium. In a systematic review including 46 imaging studies, there was inconsistency in identifying iron probably because of changes in its paramagnetic properties during its degradation. Iron appeared consistently hypointense only on T2*-weighted MRI and, along with calcified areas, hyperattenuated on CT. The appearance of copper, calcium and manganese, although consistently reported as hyperintense on T1-weighted MRI, was only confirmed histologically in few studies. On T2-weighted imaging, calcified areas were always reported as hypointense, whilst the appearance of iron depended on its concentration, location and degradation stage.[23] Table 4 provides a simplified overview of the appearance of mineral deposits based on CT and MRI sequences used.

Table 4. "Black and white" appearance of minerals on neuroimaging sequences

	CT	MRI - T2W	MRI - SWI/T2*	MRI - T1W
Calcium	White	Black	Black/N	Black/white (based on stage)
Manganese	N	N/White	N	White
Copper	N	White	N	White
Iron	N	N	Black	N

Legend: CT = computed tomography; MRI = magnetic resonance imaging; N = normal; SWI = susceptibility weighted imaging; T1W = T1 weighted; T2W = T2 weighted. "Black" corresponds to hypodense on CT scans and hypointense on MRI scans. "White" corresponds to hyperdense on CT scans and hyperintense on MRI scans.

Pattern of calcification in Primary Familial Brain Calcification

As with the clinical features, the radiological findings in PFBC are heterogeneous, with the most common pattern being symmetrical calcification of the globus pallidus, thalamus and dentate nucleus. Other less consistently reported brain areas of calcification include brainstem, cerebellum, cortical areas and sub-cortical white matter areas. Table 5 summarises brain areas of calcification based on causative genes identified in genetically confirmed PFBC patients.

Pattern of calcification in other causes of brain calcification

Livingston *et al*. proposed a useful systematic approach to identify distinct radiological patterns associated with intracranial calcification, which may indicate specific disease entities.[22,24] They suggested posing four primary questions:

1. Is calcification present, or could haemorrhage or iron/manganese deposition account for the appearances?
2. Is there evidence of brain malformation or atrophy/hypoplasia? If so, can this be characterised further?

3. Is the white matter abnormal? If so, can the leukoencephalopathy be characterised further and a diagnostic pattern suggested?
4. Are there other radiological features, such as the presence of contrast enhancement, cysts or vascular abnormalities that may add further diagnostic information in selected cases?

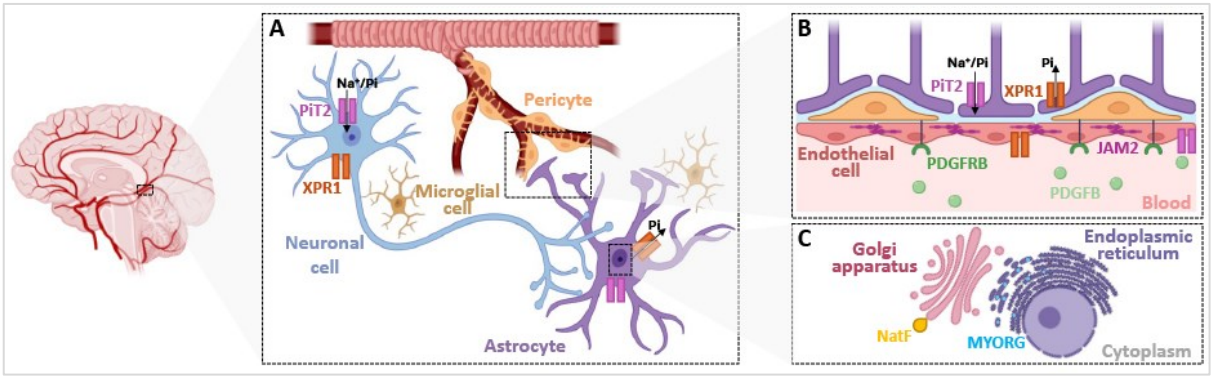
Table 2 summarises the differential to be considered based on location and pattern of brain calcification.

Table 5. Areas of brain calcification in affected patients with genetically confirmed Primary Familial Brain Calcification

Brain area	***SLC20A2***	***PDGFB***	***PDGFRB***	***XPR1***	***MYORG***	***JAM2***	***NAA60***
Basal ganglia	80%	100%	100%	71%	88%	100%	100%
Thalamus	50%	40%	100%	48%	78%	100%	NA
Cerebellum	45%	51%	67%	62%	85%	90%	60%
White matter	37%	40%	42%	19%	63%	90%	40%

Legend: NA = not available.

Figure 3. Schematic representation of Primary Familial Brain Calcification-related gene products and their localisation within the neurovascular unit.



Legend: [A-B] Schematic of a neurovascular unit. The Na+-dependent inorganic phosphate (Pi) transporter PiT2/SLC20A2 (Na+/Pi importer) and XPR1 (Pi exporter) modulates Pi homeostasis. [B] Defects in PDGFB, PDGFRB, and JAM2 cause increased permeability of the vessels and calcium leakage. [C] Magnification of the intracellular compartment depicting MYORG as an enzyme located at the endoplasmic reticulum in astrocytes and NAA60/NatF located at the cytoplasmic face of the Golgi apparatus in neurons and astrocytes. NatF = N-alpha-acetyltransferase 60; Pi = inorganic phosphate; PiT2 = Type III Na+-dependent inorganic phosphate transporter 2.

Current understanding on PFBC pathogenesis and implications for future therapies

The pathophysiological hallmarks of PFBC are calcium-hydroxyapatite deposits at the tunica media of medium- and small-size arteries and capillaries within the basal ganglia and other encephalic regions. This deposition can precede the onset of clinical manifestations by years, as documented by radiological evidence of brain calcification in asymptomatic children belonging to families with genetically confirmed PFBC. Currently, there is no evidence that the localisation or extension of calcification is associated with type and severity of clinical manifestations. The presence of motor, cognitive and psychiatric manifestations and detection of calcification in the basal ganglia, dentate nucleus and cerebral and cerebellar white matter intuitively point towards an alteration of cortico-subcortical and cerebellar pathways.

Mendelian gene discoveries in the field of PFBC have shed light on the complex neuropathological framework that underpin it, identifying a discrete number of relevant biological pathways. Interestingly, genes linked to PFBC are implicated in inorganic phosphate homeostasis, the maintenance of endothelial functions and blood–brain barrier integrity (Figure 3).

Genetic testing and counselling for confirmed or suspected Primary Familial Brain Calcification

Genes which have been linked to PFBC are associated with either AD (*SLC20A2*, *XPR1*, *PDGFB*, *PDGFRB*) or AR (*MYORG*, *JAM2*, *NAA60*) mode of inheritance. In the UK, genetic testing for *SLC20A2*, *XPR1*, *PDGFB*, *PDGFRB* and *KIAA1161* (former name of *MYORG*) is available as NHS standard of care through whole-genome sequencing (https://nhsgms-panelapp.genomicsengland.co.uk/) with analysis of the panel "Adult neurodegenerative disorders" (R58) or "Adult onset dystonia, chorea or related movement disorder" (R56). Currently (11/2024), mutation analysis of *JAM2* and *NAA60* is available only in the research setting, which reflects their recent identification as PFBC-relates genes.

Most patients diagnosed with autosomal dominant PFBC have an affected parent identified either clinically or by neuroimaging. However, the transmitting parent can be asymptomatic throughout their life or may manifest milder or later symptoms/signs than their offspring. Non-familial (singleton) cases can be the result of *de novo* pathogenic variants, incomplete penetrance and germinal mosaicism in autosomal dominant PFBC or homozygosity or compound heterozygosity for variants in autosomal recessive PFBC-related genes. Genetic testing, physical and neurological examination, and CT scanning are recommended for the parents of a proband with an apparent *de novo* pathogenic variant. The risk to the siblings of a proband depends on the genetic status of the proband's parents. The lack of clinical symptoms in parents whose genetic status is unknown must not be used to predict risk to siblings of a proband. Each child of an individual with autosomal dominant PFBC-related pathogenic variant has a 50% chance of inheriting the pathogenic variant, whereas each child of someone with an autosomal recessive PFBC-related pathogenic variant has a 100% chance of inheriting one pathogenic variant. Genetic counselling is indicated for family members of PFBC probands. Genetic testing should be offered to symptomatic individuals regardless of age in a family with an established diagnosis of PFBC. Predictive testing of at-risk asymptomatic adults can be performed, whereas predictive testing of at-risk asymptomatic individuals younger than age 18 years should be discussed on an individual basis because of the current absence of curative or preventive treatment.

With more widespread testing and improving methods, our understanding of PFBC-related genes and their pathogenic mechanisms will likely improve in the future; we should therefore encourage the banking of DNA from probands in whom a molecular diagnosis has not been confirmed and their parents. DNA banking for PFBC is currently possible on a research basis at the National Hospital for Neurology and Neurosurgery – UCL Queen Square Institute of Neurology, London, UK (Dr Francesca Magrinelli - f.magrinelli@ucl.ac.uk).

Current treatment options for Primary Familial Brain Calcification

The mainstay of treatment for PFBC focuses on conservative measures, using patient education, support and a multi-disciplinary management approach. Following diagnosis of PFBC (not necessarily molecular), regular follow-up with a neurology and/or neuro-psychiatry team enables the

monitoring of symptoms and disease progression. In addition to genetic counselling, patient education and signposting are essential. An international patient charity dedicated to PFBC, called Fahr Beyond (https://www.fahrbeyond.org/), provides written information and downloadable leaflets for patients, carers and healthcare professionals.

Physiotherapy and occupational therapy are important to optimise patients' mobility and daily function. PFBC patients commonly have speech disturbance and swallowing difficulties and so may need involvement of speech and language therapists. Communication devices can significantly impact on patients' quality of life. Recurrent tongue biting from orolingual dystonia may occur, hence dental extraction or bite blocking may be necessary. Severe cases may also be affected by profound malnutrition, hence the importance of dietetic input to optimise caloric intake.

To date, there is no specific disease-modifying therapy licensed or shown to be consistently effective for PFBC in humans, and so most available treatments are aimed primarily at symptom control. However, a recent pre-clinical study in mice showed that inhibiting the cryptic-exon incorporation with splice-switching antisense oligonucleotides increased the expression levels of functional SLC20A2 in cells carrying *SLC20A2* mutations. Intracerebroventricular administration of antisense oligonucleotides also reduced CSF Pi concentrations and suppressed brain calcification in *SLC20A2* knockin mice.[25] These studies emphasise that gene-specific therapies may be highly effective treatment options for the future.

Bisphosphonates have been favoured from previous studies with very small sample sizes or descriptions of isolated cases (PMID 36469195, 26976513), showing reduction in basal ganglia calcification being associated with some clinical improvement. However, the evidence base for their use remains very limited. Disodium etidronate is currently being investigated in an ongoing clinical trial (CALCIFADE trial, EudraCT Number: 2022-003299-17).[26]

For symptom control, despite limited evidence in PFBC, levodopa has been used in parkinsonism, and trihexyphenidyl and botulinum toxin in dystonia. Antiseizure medications may be needed for those with recurrent seizures. Several patients may also require treatment for depression and anxiety. The treatment for psychosis can be complicated as first-generation antipsychotic medications may cause tardive dyskinesia, secondary parkinsonism or chorea, and should be avoided. There is no evidence for using cholinesterase inhibitors in cognitive dysfunction associated with PFBC.

PFBC patients, families, carers and healthcare professionals can liaise with the Movement Disorder clinical and research team at the National Hospital for Neurology and Neurosurgery – UCL Queen Square Institute of Neurology, London, UK (Authors).

Key points

- Brain calcification has a wide differential diagnosis, including miscellaneous genetic and non-genetic diseases.
- Age at detection, localisation and a positive family history of brain calcification are clues to certain underlying causes
- Disruption of inorganic phosphate homeostasis, endothelial function and integrity of the blood–brain barrier are possible mechanisms and potential therapeutic targets for PFBC.
- A multidisciplinary team approach is essential to PFBC patient care to address specific clinical manifestations.

Further reading

- Carecchio, M., Mainardi, M. & Bonato, G. The clinical and genetic spectrum of primary familial brain calcification. *J Neurol* **270**, 3270-3277 (2023).

- Balck, A. *et al.* Genotype-Phenotype Relations in Primary Familial Brain Calcification: Systematic MDSGene Review. *Mov Disord* **36**, 2468-2480 (2021).

Supplementary Box 1. Phenotypic features not commonly observed in Primary Familial Brain Calcification and suggestive of alternative genetic aetiologies for brain calcifications

- Choroid or retinal disorders associated with visual deficit/blindness
- Haemorrhage or arterial damage
- Hypomyelination or leukodystrophy
- Grey matter and developmental brain disorder
- Gonadal or ovarian failure
- Microcephaly
- Deafness
- Neuropathy
- Skin disorder
- Organomegaly
- Positive interferon signature
- Thrombocytopenia

Supplementary Table 1. Genetic disorders associated with complex phenotypes and brain calcifications other than Primary Familial Brain Calcification

Syndrome	Clinical features	Investigations that can help diagnosis
Aicardi-Goutières syndrome	Neonatal onset with fever, seizures, hepatosplenomegaly, thrombocytopenia, anaemia with/without microcephaly. Infantile onset with irritability, fever, regression and acquired microcephaly.	Quantitative PCR analysis of RNA/cDNA for interferon signature. Thrombocytopenia and elevated liver enzymes. Genetic testing for *ADAR*, *IFIH1*, *RNASEH2A*, *RNASEH2B, RNASEH2C*, *SAMHD1*, *TREX1*.
Cockayne syndrome	Growth failure (cachectic dwarfism), shrivelled and wrinkled skin, loss of subcutaneous fat, beaked nose, dental anomalies, stooped posture, severe photosensitivity (in some patients)	Genetic testing for *ERCC6*, *ERCC8*.
Leukoencephalopathy with calcifications and cysts (Labrune syndrome)	Variable age at diagnosis with bilateral exudative retinopathy (Coats disease), skeletal abnormalities, gastrointestinal and hepatic vascular abnormalities, and cutaneous findings (e.g. sparse hair, dystrophic nails)	Genetic testing for *SNORD118*.
Krabbe disease	Infantile or early childhood onset with irritability, spasticity of lower extremities and fisting, axial hypotonia, regression, neuropathy, vision loss, esotropia, seizures	GALC enzyme activity in peripheral leukocytes. Genetic test for *GALC*.
Mitochondrial leukoencephalopathies (Kearnes-Sayre syndrome, Leigh syndrome, etc.)	Deafness, neuropathy, seizures, ataxia, movement disorders, striatal necrosis, pigmentary retinopathy that may lead to vision loss, ophthalmoplegia and/or ptosis, cardiac conduction defects	High CSF protein lactate/pyruvate ratio. Lactic acidosis. Mitochondrial genome sequencing.
Leukoencephalopathy, cystic, without megalocephaly	Seizures, microcephaly, regression, spasticity, dystonia, nystagmus, hearing loss	Genetic testing for *RNASET2*.
3-hydroxyisobutyric aciduria	Microcephaly, developmental retardation	
Pseudo-TORCH syndrome-1	Seizures, microcephaly, regression, immune abnormalities, intravascular coagulopathy	Genetic testing for *OCLN*, *USP18*.
Coats plus syndrome	Growth retardation with epilepsy, spasticity, dystonia, ataxia, retinal telangiectasia and exudates, osteopenia and fractures, gastrointestinal and hepatic bleeding, portal hypertension, bone marrow suppression	Genetic testing for *CTC1*.
Inborn errors of folate metabolism	Regression, spasticity, dystonia	Leucopenia, hypogammaglobulinaemia, megaloblastic bone marrow. Genetic testing for *FOLR1*, *SLC46A1*, *MTHFR*, *DHFR*, *MTFD1*.
Immunodeficiency 38 with basal ganglia calcification	Severe clinical disease with BCG vaccines	Gene testing for *ISG15*.
HSP (SPG47, SPG56, SPG64)	Spastic paraparesis, dystonia, cognitive impairment, macular dystrophy	Genetic testing for *AP4B1*, *CYP2U1*, *ENTPD1*.
Pseudohypoparathyroidism	Tetani, seizures, mental retardation, short stature, subcutaneous calcifications, brachydactyly	Hypocalcaemia, hyperphosphatemia, and increased serum PTH (PTH resistance). Genetic testing for *GNAS*, *PRKAR1A*, *PDE4D*, *PDE3A*.

Legend: BCG = Bacille Calmette-Guerin; cDNA = complimentary deoxyribonucleic acid; CSF = cerebrospinal fluid; GALC = galactosylceramidase; HSP = hereditary spastic paraplegia; PCR = polymerase chain reaction; PTH = parathormone; RNA = ribonucleic acid; SPG = spastic paraplegia; TORCH = congenital infections of toxoplasmosis, others (syphilis, hepatitis B), rubella, cytomegalovirus (CMV), and herpes simplex.

Figure Legends

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Legend: **[A-B]** Schematic of a neurovascular unit. The Na+-dependent inorganic phosphate (Pi) transporter PiT2/SLC20A2 (Na^+/Pi importer) and XPR1 (Pi exporter) modulates Pi homeostasis. **[B]** Defects in PDGFB, PDGFRB, and JAM2 causes increased permeability of the vessels and calcium leakage. **[C]** Magnification of the intracellular compartment depicting MYORG as an enzyme located at the endoplasmic reticulum in astrocytes and NAA60/NatF located at the cytoplasmic face of the Golgi apparatus in neurons and astrocytes. NatF = N-alpha-acetyltransferase 60; Pi = inorganic phosphate; PiT2 = Type III Na^+-dependent inorganic phosphate transporter 2.

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Legend: CT = computed tomography; MRI = magnetic resonance imaging; N = normal; SWI = susceptibility weighted imaging; T1W = T1 weighted; T2W = T2 weighted. "Black" corresponds to hypodense on CT scans and hypointense on MRI scans. "White" corresponds to hyperdense on CT scans and hyperintense on MRI scans.

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Legend: NA = not available.

Supplementary Materials

Supplementary Box 1. Phenotypic features not commonly seen in Primary Familial Brain Calcification, suggesting alternative genetic causes for brain calcifications

Supplementary Table 1. Genetic disorders associated with complex phenotypes and brain calcifications other than Primary Familial Brain Calcification

Legend: BCG = Bacille Calmette-Guerin; cDNA = complimentary deoxyribonucleic acid; CSF = cerebrospinal fluid; GALC = galactosylceramidase; HSP = hereditary spastic paraplegia; PCR = polymerase chain reaction; PTH = parathormone; RNA = ribonucleic acid; SPG = spastic paraplegia; TORCH = congenital infections of toxoplasmosis, others (syphilis, hepatitis B), rubella, cytomegalovirus (CMV), and herpes simplex.

Competing interests

None.

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References

1. Yalcin, A., Ceylan, M., Bayraktutan, O.F., Sonkaya, A.R. & Yuce, I. Age and gender related prevalence of intracranial calcifications in CT imaging; data from 12,000 healthy subjects. *J Chem Neuroanat* **78**, 20-24 (2016).
2. Carecchio, M., Mainardi, M. & Bonato, G. The clinical and genetic spectrum of primary familial brain calcification. *J Neurol* **270**, 3270-3277 (2023).
3. Fahr, T. Idiopathische Verkalkung der Hirngefäße. in *Zentralblatt für allgemeine Pathologie und pathologische Anatomie*, Vol. 50 129–133 (1930).
4. Delacour, A. Ossification des capillaires du cerveau. *Ann Med Psychol*, 458–461 (1850).
5. Boller, F., Boller, M. & Gilbert, J. Familial idiopathic cerebral calcifications. *J Neurol Neurosurg Psychiatry* **40**, 280-5 (1977).
6. 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* **65**, 764-72 (1999).
7. Volpato, C.B. *et al.* 2q37 as a susceptibility locus for idiopathic basal ganglia calcification (IBGC) in a large South Tyrolean family. *J Mol Neurosci* **39**, 346-53 (2009).
8. Dai, X. *et al.* Identification of a novel genetic locus on chromosome 8p21.1-q11.23 for idiopathic basal ganglia calcification. *Am J Med Genet B Neuropsychiatr Genet* **153B**, 1305-10 (2010).
9. Hsu, S.C. *et al.* Mutations in SLC20A2 are a major cause of familial idiopathic basal ganglia calcification. *Neurogenetics* **14**, 11-22 (2013).
10. Nicolas, G. *et al.* Mutation of the PDGFRB gene as a cause of idiopathic basal ganglia calcification. *Neurology* **80**, 181-7 (2013).
11. Keller, A. *et al.* Mutations in the gene encoding PDGF-B cause brain calcifications in humans and mice. *Nat Genet* **45**, 1077-82 (2013).
12. Legati, A. *et al.* Mutations in XPR1 cause primary familial brain calcification associated with altered phosphate export. *Nat Genet* **47**, 579-81 (2015).
13. Arkadir, D., Lossos, A., Rahat, D., Abu Snineh, M. & Meiner, V. MYORG is associated with recessive primary familial brain calcification. *Movement Disorders* **34**, S166-S166 (2019).
14. Schottlaender, L.V. *et al.* Bi-allelic JAM2 Variants Lead to Early-Onset Recessive Primary Familial Brain Calcification. *Am J Hum Genet* **106**, 412-421 (2020).
15. Chelban, V. *et al.* Biallelic NAA60 variants with impaired n-terminal acetylation capacity cause autosomal recessive primary familial brain calcifications. *Nat Commun* **15**, 2269 (2024).
16. Chen, S.Y. *et al.* The Genetics of Primary Familial Brain Calcification: A Literature Review. *Int J Mol Sci* **24**(2023).
17. Wang, C. *et al.* Mutations in SLC20A2 link familial idiopathic basal ganglia calcification with phosphate homeostasis. *Nat Genet* **44**, 254-6 (2012).
18. Chelban, V. *et al.* MYORG-related disease is associated with central pontine calcifications and atypical parkinsonism. *Neurology-Genetics* **6**(2020).
19. Balck, A. *et al.* Genotype-Phenotype Relations in Primary Familial Brain Calcification: Systematic MDSGene Review. *Mov Disord* **36**, 2468-2480 (2021).
20. Batla, A. *et al.* Deconstructing Fahr's disease/syndrome of brain calcification in the era of new genes. *Parkinsonism & Related Disorders* **37**, 1-10 (2017).
21. Tadic, V. *et al.* Primary familial brain calcification with known gene mutations: a systematic review and challenges of phenotypic characterization. *JAMA Neurol* **72**, 460-7 (2015).
22. Livingston, J.H., Stivaros, S., Warren, D. & Crow, Y.J. Intracranial calcification in childhood: a review of aetiologies and recognizable phenotypes. *Dev Med Child Neurol* **56**, 612-26 (2014).
23. Valdes Hernandez Mdel, C., Maconick, L.C., Tan, E.M. & Wardlaw, J.M. Identification of mineral deposits in the brain on radiological images: a systematic review. *Eur Radiol* **22**, 2371-81 (2012).
24. Livingston, J.H., Stivaros, S., van der Knaap, M.S. & Crow, Y.J. Recognizable phenotypes associated with intracranial calcification. *Dev Med Child Neurol* **55**, 46-57 (2013).

25. Zhao, M. *et al.* Antisense oligonucleotides enhance SLC20A2 expression and suppress brain calcification in a humanized mouse model. *Neuron* **112**, 3278-3294 e7 (2024).
26. Snijders, B.M. *et al.* The effects of etidronate on brain calcifications in Fahr's disease or syndrome: rationale and design of the randomised, placebo-controlled, double-blind CALCIFADE trial. *Orphanet J Rare Dis* **19**, 49 (2024).

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