Hyperkinesias and Echolalia in Primary Familial Brain Calcification

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Brain calcifications are in most cases acquired conditions caused by hypoparathyroidism, chronic kidney failure, in utero infections, toxoplasmosis, and advanced age among other causes.[1] In some cases, brain calcifications occur in association with complex genetic syndromes but also as nonsyndromic conditions as illustrated in the following case.

A 72-year-old woman was admitted due to falls, involuntary movements, and echolalia. Her past medical history included asthma, osteoporosis, total replacement arthroplasty of the right shoulder, and recurrent depression episodes. Upon examination, oromandibular dystonia and other movement abnormalities were found (Video S1; Fig. E). This recording was made when the patient was 73 years old. Oromandibular dystonia, dysarthria, and a hesitant gait are evident. Reduced arm swing associated with dystonic posturing on the right side is also evident (prior right-shoulder arthroplasty may also contribute to reduced arm swing). In addition, the video shows mild dysmetria, impaired dexterity, saccadic intrusions, and reduction in vertical saccades. There were no signs of rigidity, bradykinesia, or pyramidal signs. In addition, marked deficits were found mainly in executive functions. The patient's mother was also affected by involuntary perioral movements. A brain computed tomography (CT) scan in our patient revealed widespread and confluent symmetric brain calcifications in the basal ganglia and cerebellum (Fig. A–D). Assessment of this CT scan with total calcification score (TCS)[1] yielded 62 points (range = 0–80 points) and remained unchanged 2 years later. Biomarkers for dementia in the cerebrospinal fluid (CSF) were otherwise normal. Abnormal parathyroid hormone levels and other etiologies for acquired brain calcifications were ruled out. Phosphate in the CSF (CSF Pi) was elevated (0.69mmol/l), suggesting a mutation in solute carrier 20 family member 2 (*SLC20A2*), which encodes a phosphate transporter. Targeted sequencing revealed the new variant c.262_266del (M88Wfs*4) in *SLC20A2*; bioinformatic tools predicted this variant as pathogenic. Taking the observations together, primary familial brain calcification (PFBC) was diagnosed. Elevated CSF Pi was found first in mouse models for PFBC-*SLC20A2* and later in patients with *SLC20A2* variants.[2]

Pathogenic variants in *SLC20A2* are the most common form of autosomal dominant PFBC.[3] Heterozygous variants in *PDGFB*, *PDGRB*, and *XPR1* are also associated with PFBC, whereas both heterozygous and biallelic variants in *MYORG* are also associated with PBFC.[4] Recently, a second autosomal recessive PFBC syndrome was reported to be associated with variants in *JAM2*.[5] The clinical manifestations for PFBC are very variable and include movement disorders, psychiatric symptoms,

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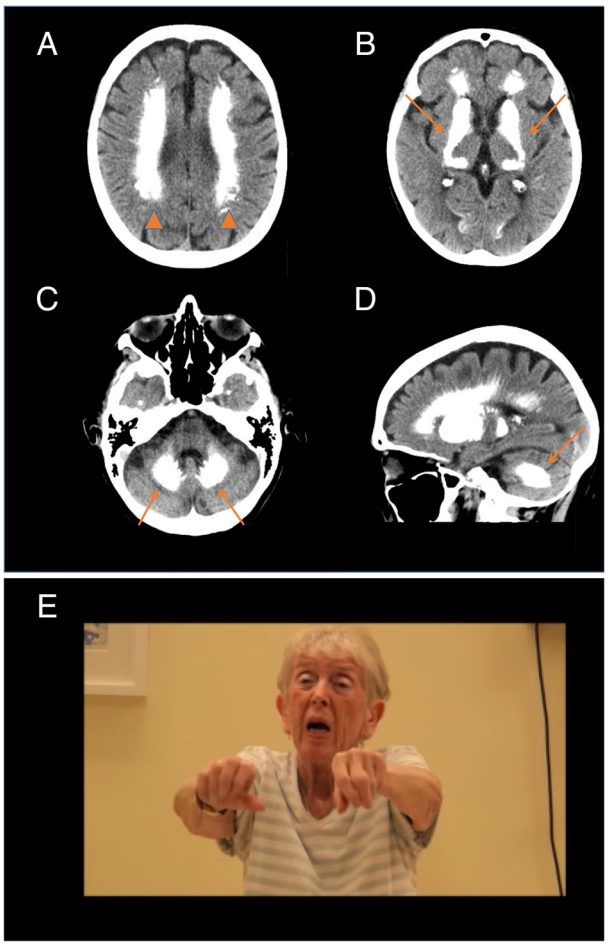

FIGURE: Widespread brain calcifications. (A–D) Axial brain computed tomography (A–C) and paramidsagittal sections (D) with the patient at age 72 years display widespread and confluent calcifications mainly in the gray matter (*arrows*). The affected areas are all the basal ganglia, thalamus, dentate nuclei, and vermis. The white matter is affected to a lesser degree (*arrowheads*). Total calcification score was 62 (range = 0–80) and remained unchanged 2 years later. (E) Oromandibular dystonia is evident in the still image. The patient provided consent to use a photograph of her face. [Color figure can be viewed at www.annalsofneurology.org]

and/or cognitive impairment.[1] Nevertheless, the clinical penetrance is reduced and estimated to be around 60% for the autosomal dominant forms of PFBC, whereas the radiological penetrance is high.[1] In contrast, both clinical and radiological penetrance in association with biallelic variants in *MYORG* and *JAM2* is very high.[4,5] Treatment for all forms of PFBC is largely symptomatic. Finally, widespread brain calcifications with high TCS scores[1] and elevated CSF Pi strongly suggest PFBC-*SLC20A2*. However, this potential biomarker needs to be evaluated in larger PFBC cohorts and particularly in patients with variants in *MYORG* and *JAM2*.

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Author Contributions

All authors contributed to the conception and design of the study; the acquisition and analysis of data; and drafting the text and preparing the figure.

Potential Conflicts of Interest

Nothing to report.

References

1. Nicolas G, Pottier C, Charbonnier C, et al. Phenotypic spectrum of probable and genetically-confirmed idiopathic basal ganglia calcification. Brain 2013;136:3395–3407.

2. Hozumi I, Kurita H, Ozawa K, et al. Inorganic phosphorus (pi) in CSF is a biomarker for SLC20A2-associated idiopathic basal ganglia calcification (IBGC1). J Neurol Sci 2018;388:150–154.

3. Wang C, Li Y, Shi L, et al. Mutations in SLC20A2 link familial idiopathic basal ganglia calcification with phosphate homeostasis. Nat Genet 2012;44:254–256.

4. Grangeon L, Wallon D, Charbonnier C, et al. Biallelic MYORG mutation carriers exhibit primary brain calcification with a distinct phenotype. Brain 2019;142:1573–1586.

5. Cen Z, Chen Y, Chen S, et al. Biallelic loss-of-function mutations in JAM2 cause primary familial brain calcification. Brain 2020;143:491–502.