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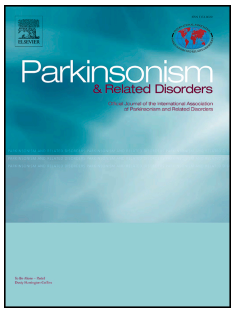

Deep brain stimulation in a Parkinson's disease patient with calcifications and a mutation in the SLC20A2 gene

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Deep brain stimulation in a Parkinson's disease patient with calcifications and a mutation in the SLC20A2 gene.

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Abstract

A patient with Parkinson's disease (PD) who was examined as a candidate for DBS was initially rejected due to extensive brain calcifications. Upon second opinion and planning of trajectories she underwent successful surgery. Genetic analyses identified a mutation in *SLC20A2,* a gene known to cause brain calcifications, but no mutation known to cause PD was found.

Correspondence

Neuroimaging of patients with neurodegenerative diseases sometimes reveal abnormal brain-calcifications, most commonly in the basal ganglia that presents as idiopathic basal ganglia calcifications (IBGC). The clinical picture is diverse, including neuropsychiatric and motor symptoms including parkinsonism, dystonia, tremor and ataxia [1]. Here we report a patient clinically diagnosed with Parkinson's disease (PD) with extensive cerebellar and basal ganglia calcifications. At the age of 45 she started experiencing increasing stiffness in her left shoulder and arm in addition to left hand clumsiness and problems executing tasks. Besides the removal of a fibroadenoma she had normal antecedent history.

The diagnosis of PD was based on neurological examination which revealed bradykinesia and rigidity on the left side both in upper and lower extremity but with no resting tremor. She had a slightly stooped posture and reduced left arm swing while walking. The patient responded very well to levodopa and dopamine agonist treatment but developed severe on/off episodes and dyskinesias within a few years after disease onset. Due to the calcifications, the patient had previously been rejected from deep brain stimulation (DBS). She came to our hospital for a second opinion work-up. Her brain CT confirmed calcifications consistent with IBGC. Her serum Ca^{2+} levels were normal, and she had normal parathyroid hormone functions.

Trajectory planning of a potential DBS treatment was performed. The calcifications were considered a severe risk factor due to potential dragging of adjacent parenchyma and subsequent trauma to blood vessels. However, these lesions proved not to be of significant hindrance, and DBS was performed after automatic trajectory planning. A frontal burr hole was made, and incision carried out throughout the parenchyma in the hemisphere, trajecting lateral to the caudate nucleus, penetrating the internal capsule and reaching STN (Fig C). The implantation of STN DBS electrodes procedure was performed under generalized anaesthesia and was without complications. She was able to resume her work less than 3 months after implantation.

At 6 months follow-up post surgery her dyskinesias were significantly reduced. Her dopaminergic medication was reduced to a moderate amount compared to preoperative levels. She was very satisfied with the outcome and commented that her sleep had improved. Her stimulation parameters were 1.7V left and 2.4V right STN, monopolar stimulation, 60ms, 130 Hz.

Genetic analyses by means of multiplex ligation-dependent probe amplification (MLPA) and a Whole-exome sequencing (WES) revealed a heterozygous mutation (c.C1703T [p.Pro568Leu]) in Solute Carrier Family 20 Member 2 (*SLC20A2*) gene. See supplementary methods for details. No known genetic causes of PD were found. This mutation is predicted damaging (CADD score = 24.8), affects a highly conserved amino acid (Gerp score = 5.28) and is only found in three alleles in 3 out of the 246,960 alleles (MAF = 1.21e-5) available through the Genome Aggregation Database (gnomAD; http://gnomad.broadinstitute.org/).

IBGC – also known as familial idiopathic basal ganglia calcification (FIBGC) or Fahr's disease - is a neurodegenerative disorder proceeding from symmetric calcium deposits in the basal ganglia or other brain regions. IBCG is identified through neuroimaging screenings such as computerized tomography, and exclusion of other causes of secondary calcification is necessary to get diagnosed. It is an uncommon, heterogenous, autosomal dominantly transmitted disease, characterized by a variety of motor symptoms [1].

The most common genetic causes of IBGC are now thought to be mutations in the *SLC20A2* gene. A recent study by Chan et al, has shown that mutations in the *SLC20A2* gene are indeed highly associated with FIBGC, and present in as many as 41 % of patients [1]. *SLC20A2* p.Pro568Leu has previously been associated with basal ganglia calcifications in patients without any movement disorder [2, 3], in a patient with dopa-responsive parkinsonism [1] and in a patient with paroxysmal dystonia [4]. These patients originate from US, Norway, and China. However, a further three heterozygotes present in gnomAD are Swedish *(8-42287588-G-A | gnomAD v2.1.1 | gnomAD (broadinstitute.org)., 05.01.22)*, suggesting that this mutation might be more common in Scandinavia. Our reported patient developed dyskinesias, something that we have not been able to find in previous patients with parkinsonism and mutations in *SLC0A2*. However, this is likely due to insufficient reporting.

Patients with PD have been reported with calcifications [5]. Nonetheless, a connection between the extent and location of calcifications and the risk of developing PD remains unknown. However, successful alleviation of movement disorders in this report, and previously [6, 7], propose this to be a suitable treatment in patients with basal ganglia calcifications and movement disorders.

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Disclosure Statement
The authors have no conflicts of interest to declare

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Author Contributions
Nina Asheim Birkeland and Viel Nyborg Carlsen have contributed equally to this work, contributed to study concept and design, manuscript drafting
Sasha Gulati, MD, Data collection, manuscript drafting and critically reviewed manuscript
Emil K. Gustavsson, PhD, Data collection, genetic testing and critically reviewed manuscript.

Jan O. Aasly, MD, Conceived the idea of the study, data collection, critically reviewed the manuscript.

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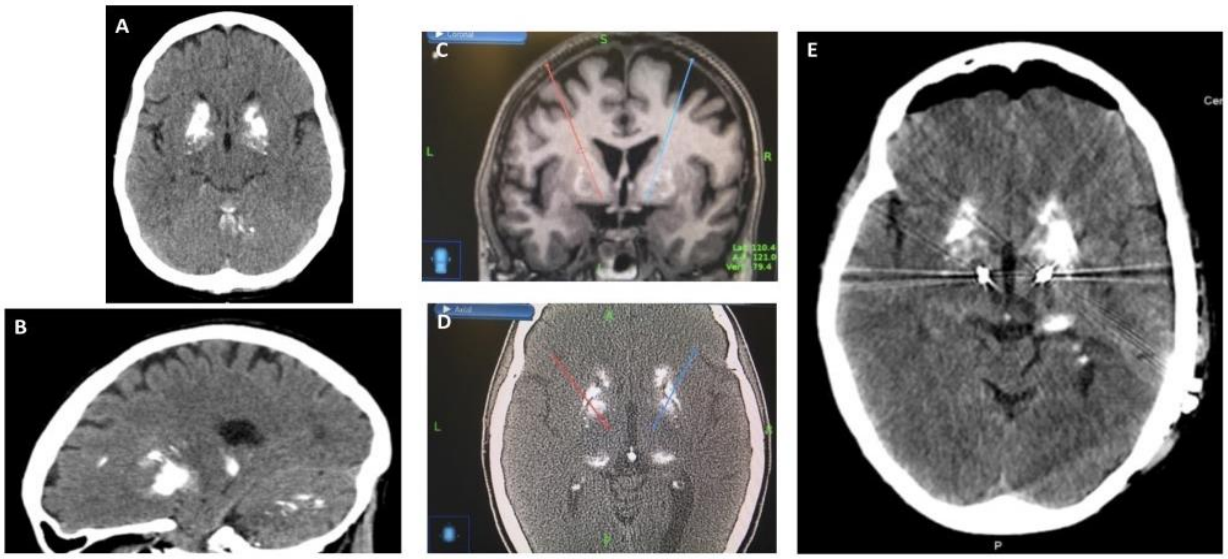
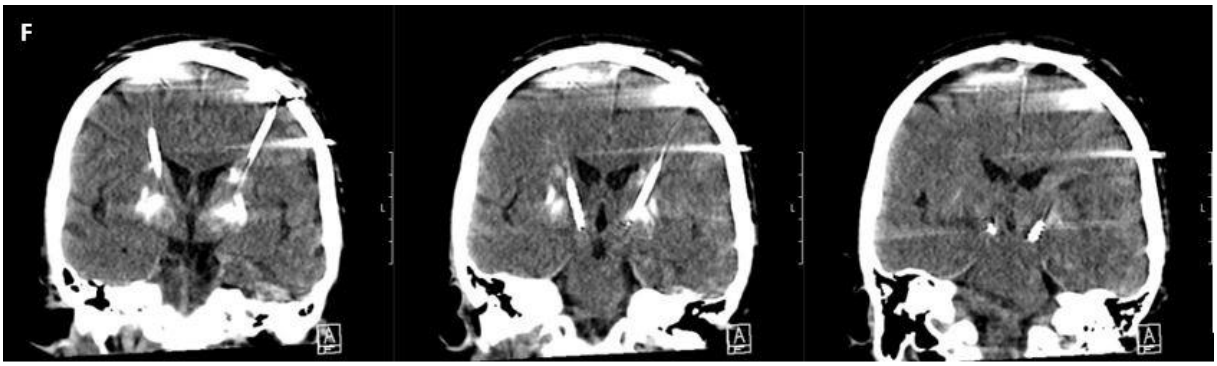
Figure legends

Figure A: Preoperative CT-scan showing extensive bilateral brain calcifications, mainly in the basal ganglia, thalamus and cerebellum
Figure B: Preoperative CT-scan showing extensive bilateral brain calcifications, mainly in the basal ganglia, thalamus and cerebellum
Figure C: Trajectory planning
Figure D: Trajectory planning
Figure E: Postoperative CT-scan showing placement of electrodes in STN bilaterally.
Figure F: Implanted electrodes surrounded by extensive basal ganglia calcifications. The white areas in the cortical regions are metal artefacts.





Highlights

- **A patient with levodopa responsive early-onset Parkinson's disease**
- **Successful deep brain stimulation surgery on patient with large brain calcifications**
- **Genetic analysis revealed calcifications likely explained by a SLC20A2 gene mutation**