

# Early onset left hemichorea-parkinsonism with POLG mutation without external ophthalmoplegia responsive to pallidal DBS

F. Garrì<sup>1</sup>, D. Calandrella<sup>1</sup>, S. Bonvegna<sup>1,2</sup>, F. Del Sorbo<sup>2</sup>, G. Sacilotto<sup>2</sup>, M. Zini<sup>2</sup>, C. Bolliri<sup>1</sup>, V. Cereda<sup>1</sup>, V. Ferri<sup>1</sup>, M. Barichella<sup>1,2</sup>, Isaias IU<sup>2</sup>, G. Pezzoli<sup>1</sup>

<sup>1</sup>Fondazione Grigioni per il Morbo di Parkinson, Milan, Italy; <sup>2</sup>Parkinson Institute, ASST G. Pini-CTO, Milan, Italy

## BACKGROUND

**POLG gene** have been associated with a wide phenotypic spectrum, including parkinsonism, usually in combination with external ophthalmoplegia. We present a case of subacute onset of left hemichorea-parkinsonism with POLG mutation, successfully treated with pallidal DBS.

## CASE PRESENTATION

A 36 year-female experienced pain in the left upper limb, followed by the appearance of involuntary movements in the left upper limb and, to a lesser extent, in the left lower limb and mouth. Moreover, she complained of deflection of mood with apathy, anhedonia and insomnia.

Her **past medical history** was unremarkable, except for an itchy lesion of the lower limb about a month earlier, associated with low-grade fever, due to an insect bite, which disappeared after taking antibiotic therapy.

Her **family history** was notable for severe depression in her mother and his brother who died by suicide.

The **neurological examination** revealed rapid, unpredictable and irregular movements in the left side of the body, mainly in the upper limb with milder involvement of mouth and left lower limb and mild bradykinesia, while no plastic rigidity or tremor was detected (Video 1).

**Laboratory tests**, including blood count, glucose, renal and liver function, electrolytes, thyroid function, iron, transferrin, ferritin, ceruloplasmin, urinalysis, tumor markers were in the normal range. Anti-streptolysin-O antibody, acanthocytes, cryoglobulins, LAC, anti-cardiolipin, anti-ds-DNA, anti-nucleus antibodies, anti-basal ganglia antibodies were also negative.

**Paraneoplastic antibody panel** (anti Hu, Yo, Ri, GAD65, Ma2, CV2, Amphiphysin, Tr, ANNA-3, PCA) and **autoimmune encephalitis antibody panel** (anti NMDAR, AMPA1, AMPA2, LGI1, CASPRA2, GABAb, DPPX, IgLON5, mGluR5, MOG) were negative.

The most common **Infectious diseases**, including syphilis (VDRL, TPHA), borrelia, HIV were ruled out.

**CT scan of chest/abdomen** ruled out any findings suspicious for tumors.

A **lumbar puncture** performed after some months from the onset ruled out infectious causes (borrelia screening, VZV, rickettsia, bartonella, other relevant pathogens, all negative). Tau, phospho-tau and beta-amyloid resulted in the normal range,

**Neuropsychological tests** revealed normal cognitive function with minimal alterations in working and visuospatial memory emerge.

**Genetic panel for Huntington disease/HDL conditions** resulted negative.

**Genetic panel con Parkinson disease** (SNCA, PRKN, UCHL1, PINK1, DJ-1, LRRK2, GBA, VPS35, SLC30A10, HGSNAT, ATP13A2, EIF4G1, OmiHTRA2, POLG, DNAJC13, VPS13C, DNAJC6, ATP7B, PANK2, FBXO7, PLA2G6, ATP6AP2, SPG11, SINJ1, GRN, MAPT, TARDBP, TAF1, GCH1, TH, SPR, ATP1A3, SGCE, PRKRA) showed two variants in POLG gene (c.2492 A>G), p. (Y831C) in coding exon 16 and c.3708G>T p.(Q1236H) coding exon 23.

**Brain MRI** showed a significant atrophy in the right striatum, mainly in the caudate nucleus, along with hemosiderin deposits in the right pallidum. No vessels abnormalities were detected. Brain FDG-PET revealed hypometabolism of the right basal nuclei.

**DaTscan** showed bilateral and asymmetric striatal hypocaptation, mainly in the right side and in putamina region (Tab1).

Dopaminergic and tetrabenazine treatment were ineffective.

At the age of 37, surgery for DBS placement in right internal globus pallidus (Gpi) was performed with relevant improvement of choreic movements (Video 2).

A **second DAT scan**, performed 2 years after DBS, confirmed the bilateral striatal hypocaptation showing a slight increase in tracer uptake in the left caudate and striatum overall (Tab1).

After 4 years from the onset, the patient underwent a sudden clinical worsening with reappearance of left hemichorea due to battery failure which achieved remission after battery replacement.

## REFERENCES

- Rahman S, Copeland WC. POLG-related disorders and their neurological manifestations. Nat Rev Neurol. 2019 Jan;15(1):40-52. doi: 10.1038/s41582-018-0101-0. PMID: 30451971; PMCID: PMC68796686.
- Synofzik M, Schüle R, Schulte C, Krüger R, Lindig T, Schöls L, Asmus F. Complex hyperkinetic movement disorders associated with POLG mutations. Mov Disord. 2010 Oct 30;25(14):2472-5. doi: 10.1002/mds.23307. PMID: 20818669.

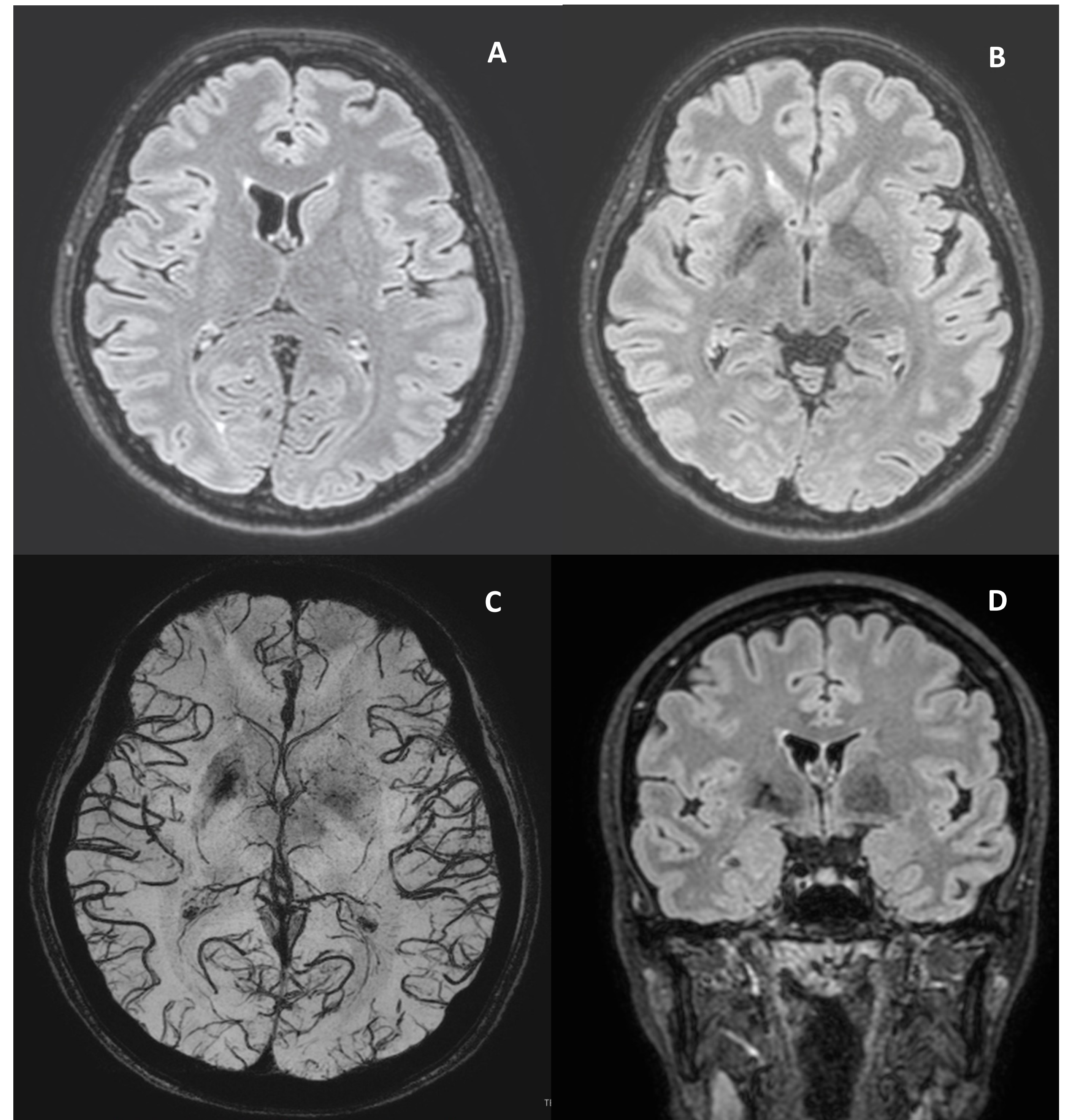


Fig1. Right caudate atrophy with enlargement of homolateral lateral ventricle (A, B, D); GPI and putamen atrophy with iron accumulation in T2 sequence (B,D); SW sequence confirming iron accumulation in the right striatum (C).

|                          | DaTscan 2017 |      | DaTscan 2019 |      | Reference range |
|--------------------------|--------------|------|--------------|------|-----------------|
|                          | Right        | Left | Right        | Left | Right/left      |
| Global striatum          | 0.58         | 0.94 | 0.60         | 1.31 | 1.5-2.9         |
| Caudate                  | 0.70         | 1.04 | 0.52         | 1.34 | 1.7-3.3         |
| Putamen                  | 0.48         | 0.88 | 0.66         | 1.30 | 1.4-3.1         |
| Putamen to Caudate ratio | 0.68         | 0.84 | 1.26         | 0.97 | >0.7            |

Tab1. Comparison between DaT scan values between 2017 (some months after clinical presentation onset) and 2019 (2 years after DBS).

## DISCUSSION AND CONCLUSION

We described a patient with POLG mutation presenting with a subacute onset of left hemichorea-parkinsonism responsive to DBS.

All possible aetiologies of acute/subacute chorea, including vascular, autoimmune, metabolic, toxic, nutritional, and infectious diseases, have been ruled out. The most common genetic causes of chorea/parkinsonism have also been excluded.

From a clinical perspective, a neurodegenerative disease seemed less probable. However, the involvement of bilateral of striatum, as showed in DAT scan, and iron accumulation in the right basal ganglia are indicative of a neurodegenerative disorder.

To the best of our knowledge a paucity of cases of chorea associated with POLG mutations have been described, suggesting as POLG mutations should be considered in the workup of complex hyperkinetic movement disorders. In most cases, POLG1 has been associated with a levodopa-responsive parkinsonism, more commonly associated with other features, including external ophthalmoplegia (1). Conversely, other movement disorders like dystonia, chorea (2) and myoclonus have been rarely mentioned, often in the context of a plethora of POLG-associated symptoms and rarely as the cardinal presentation feature (1,2).

Our case is worth of consideration for its unique clinical phenotype, characterized by the subacute onset of hemichorea, moreover it is the first case of left hemichorea/parkinsonism with POLG mutation, treated with Gpi-DBS, with long term efficacy, confirmed confirmed by the reappearance of involuntary movements due to DBS battery failure after 4 years from implantation.