CLINICAL/SCIENTIFIC NOTE OPEN ACCESS

Globus Pallidus Lesion With Iron Deposition and Dopaminergic Denervation in a Patient With a Pathogenic *SLC6A1* Variant

A Case Report

Victoire Leclert, MD, Chloe Laurencin, MD, Roxana Ameli, MD, Marc Hermier, MD, PhD, Anthime Flaus, MD, PhD, Stephane Prange, MD, PhD, Gaetan Lesca, MD, PhD, and Stephane Thobois, MD, PhD

Correspondence
Dr. Thobois
stephane.thobois@chu-lyon.fr

Neurol Genet 2024;10:e200136. doi:10.1212/NXG.0000000000200136

Abstract

Objectives

SLC6A1-related disorders encompass heterogeneous neuropsychiatric manifestations through GABAergic dysregulation, without any specific abnormalities on brain MRI, nor evidence of dopaminergic cell loss on I^{123}-FP-β-CIT SPECT. We report here a case of globus pallidus lesions and dopaminergic denervation in a patient with a pathogenic *SLC6A1* variant.

Methods

A 26-year-old female patient with intellectual disability, behavioral, and psychiatric disorders treated by neuroleptics for many years developed a parkinsonian syndrome associated with mild hand dystonia and chorea. A 3T brain MRI and I^{123}-FP-β-CIT SPECT were performed.

Results

MRI of the brain found bilateral pallidal lesions consistent with neurodegeneration with iron accumulation. The I^{123}-FP-β-CIT SPECT showed bilateral striatal presynaptic dopaminergic denervation. Whole-genome sequencing revealed a pathogenic *SLC6A1* de novo variant. No additional variant was found in any of the genes responsible for Neurodegeneration with Brain Iron Accumulation (NBIA).

Discussion

This is a description of dopaminergic denervation and globus pallidus lesions with iron accumulation related to a *SLC6A1* pathogenic variant. These findings expand the phenotype of *SLC6A1*-related disorder and suggest that it could be considered as a differential diagnosis of NBIA.

MORE ONLINE

Video

Introduction

SLC6A1 encodes chloride-dependent and sodium-dependent γ-aminobutyric acid (GABA) transporter 1 (GAT-1), one of the major GABA transporters of the human CNS.[1] GAT-1 is expressed primarily in the nerve terminals of GABAergic interneurons, especially in the neocortex and cerebellum, and has been shown to be crucial for the reuptake of GABA from synapses and for its clearing from the extracellular space.[2] Clinical manifestations due to

From the Department of Neurology C (V.L., C.L., S.P., S.T.), Expert Parkinson Center NS-PARK/FCRIN, Hospices Civils de Lyon, Pierre Wertheimer Neurological Hospital, Bron; Lyon Neuroscience Research Center (C.L., A.F.), UMR5292, INSERM U1028/CNRS; Department of Neuroradiology (R.A., M.H.); Nuclear Medicine Department (A.F.), Hospices Civils de Lyon, Pierre Wertheimer Neurological Hospital; Marc Jeannerod Cognitive Neuroscience Institute (S.P., S.T.), CNRS, UMR 5229, Bron; Faculté de Médecine et Maïeutique Lyon Sud Charles-Mérieux (S.P., G.L., S.T.), Université de Lyon, Université Claude-Bernard Lyon I; Department of Genetics (G.L.), Hospices Civils de Lyon, Mother Child Hospital, Bron; and Physiopathology and Genetics of Neurons and Muscles (G.L.), UMR5261, U1315, Institut NeuroMyoGène, Lyon, France.

Go to Neurology.org/NG for full disclosures. Funding information is provided at the end of the article.

The Article Processing Charge was funded by the authors.

SLC6A1 pathogenic variants are primarily caused by an excessive inhibition phenomenon induced by an increase in GABA in the synaptic cleft because of defective GAT-1 function.

Clinical presentation is heterogeneous and may consist of developmental delay, intellectual disability, autism spectrum disorders, epilepsy, behavioral disorders (aggressiveness, irritability), psychiatric manifestations (schizophrenia, bipolar disorders, anxiety), attention deficit hyperactivity disorder, hypotonia, cerebellar ataxia, movement disorders (tremor, dystonia, tics and stereotypies, chorea), sleep abnormalities, gastrointestinal symptoms (constipation, diarrhea), and ophthalmologic issues (myopia, strabismus).[3-8]

Brain imaging is described as normal or with aspecific abnormalities, such as nonspecific T2/FLAIR hyperintensities.[3-8]

We report here a patient with *SLC6A1*-related disorder, who presented with severe bilateral globus pallidus lesions and dopaminergic denervation.

Case Report

We report the case of a 26-year-old woman. She is the youngest of 2 siblings from unrelated parents. There is no reported family history of epilepsy, neurologic issues, or psychiatric disorders. She presented in early childhood with developmental delay and behavioral and neuropsychiatric disorders including aggressiveness, communication disorders, social isolation, and relationship difficulties and was diagnosed with autism spectrum disorder. She had no history of seizures. No brain MRI was performed during childhood.

In 2012 when she was 15 years, behavioral disorders became more severe, with verbal and physical violence, angry outburst, and the appearance of hallucinations (probably already preexisting but not yet verbalized). These hallucinations were visual and auditory (she heard voices, saw imaginary people, talked to them, gave them first names). In this respect, the first neuroleptic treatment was introduced in July 2012, and since then, she successively received tiapride, pipamperone, aripiprazole, risperidone, paliperidone, and, finally olanzapine from June 2019. The changes of neuroleptics were justified by a lack of efficacy. In November 2019, olanzapine was replaced by haloperidol because of significant weight gain and hypercholesterolemia. Haloperidol was discontinued one month later because of nausea and vomiting and suspected drug-induced hepatitis. Then, her psychiatrist decided to interrupt all neuroleptics. This led to sudden resurgence of delusions, with incoherent speech, hallucinations, and oromandibular and facial dyskinesias, after 1 week.

Resumption of olanzapine 7.5 mg/d led to the reduction of dyskinesias, but she developed hypophonia with a whispered voice associated with gait and balance disorders, apathy, and depression. In July 2019 and January 2020, MRI of the brain was performed showing bilateral pallidal lesions considered by the radiologist as calcifications without any other abnormalities. Finally, the treatment was replaced by sertraline and clozapine in October 2020, with good tolerance and complete disappearance of hallucinations since.

In February 2020, at the age of 23 years, she was referred to our movement disorders clinic at the Pierre Wertheimer University Neurological Hospital to investigate these gait disturbances and hypophonia. Neurologic examination showed an akinetic-rigid parkinsonian syndrome predominating on the right side with mild right ante and laterocolis and oromandibular dyskinesias, choreic left hand movements, and bilateral hand dystonia (see Video 1). There was no tremor nor pyramidal or cerebellar syndrome. A levodopa treatment was introduced (50 mg 3 times daily), without significant improvement after 3 months.

Neuropsychological assessment confirmed mild intellectual disability, with an IQ of 52 on the WAIS-IV scale and revealed disorders of visuo-spatial organization and reasoning abilities, abnormalities of executive functions, and attentional difficulties. Comprehension and memory were preserved. The VINELAND scale showed a low level of adaptation for daily life skills, communication, socialization, and behavior, with little autonomy and a tendency to impulsivity. Theory of mind and social cognition were correct, going against the diagnosis of autism.

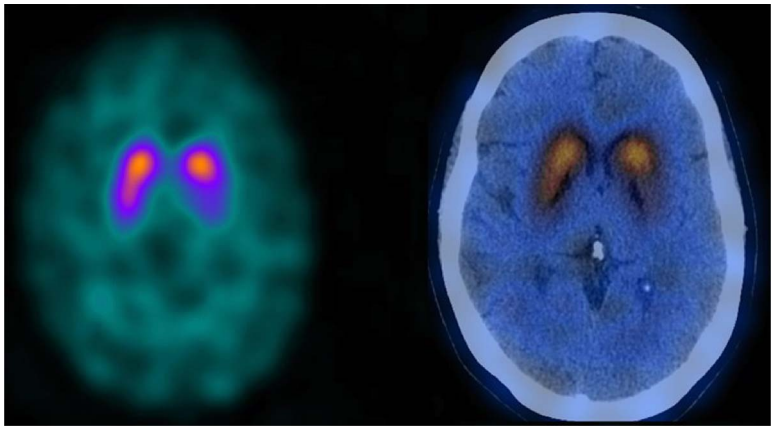
Routine biological tests revealed normal blood counts, ionogram, liver and kidney functions, C-reactive protein, thyroid-stimulating hormone, calcium levels, and iron levels. The cupric panel showed slight increase in ceruloplasmin and total serum copper but normal exchangeable copper and normal urine copper excretion. Blood lactic acid, pyruvic acid, and ketone bodies were normal.

A I^{123}-FP-β-CIT SPECT was performed and revealed bilateral striatal presynaptic dopaminergic denervation more severe on the left side (Figure 1). A 3T brain MRI with T2, T2 FLAIR, susceptibility-weighted imaging (SWI), and diffusion sequences was obtained, showing bilateral pallidal lesions that appeared hyperintense at T2 FLAIR and hypointense at SWI consistent with degeneration with iron accumulation without significant calcifications (Figure 2). There was also an abnormal SWI hypointensity of caudate nuclei and locus niger. The putamen, thalami, and cortex showed no anomaly. The presence of calcifications was also excluded by a CT scan (Figure 3).

Whole-genome sequencing analysis was performed in trio (with samples from the patient and her parents) within the framework of the DEFIDIAG project (data available upon request). The human study was approved by the local ethics committee of the DEFIDIAG project (the pilot project of the Plan France Genomique 2025).

A missense variant was found in exon 3 of *SLC6A1*: NM_003042.3:c.187G>A. It was not found in the parent's DNA, suggesting a de novo occurrence. The variant was located in the first transmembrane domain which is highly intolerant to missense variants (Metadome Tolerance score = 0.09). *In silico* predictions were in favor of a deleterious effect (REVEL = 0.932, AlphaMissense = 0.994). It was absent from

Figure 1 I^{123}-FP-β-CIT SPECT-CT Axial Slices



(A) SPECT images showing asymmetrical bilateral striatal reduction of tracer uptake. (B) Images coregistered with CT (SBR value: left striatum 1.95; right striatum: 2.18).

the population database gnomAD_V3. It has been reported in patients from the literature[9] as well as in ClinVar. All these data were suggestive of pathogenicity according to ACMG classification guidelines (PMID: 25741868). No additional pathogenic variants were found in genes responsible for NBIA or in any other gene that could be related to the clinical and radiologic phenotype.

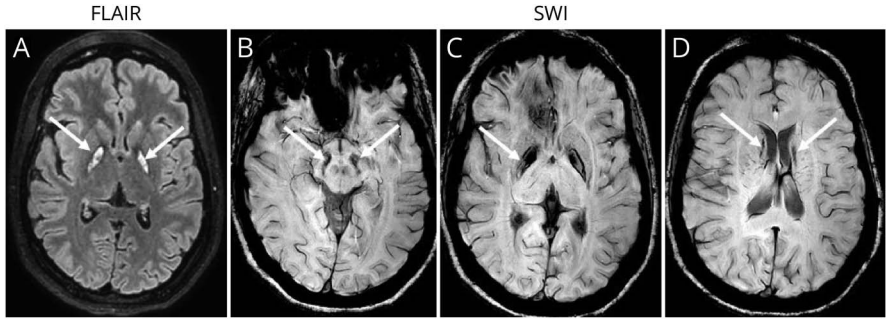
Discussion

We herein report abnormal brain MRI and dopaminergic deficit using I^{123}-FP-β-CIT SPECT in a 26-year-old female patient with neuropsychiatric and hyperkinetic movement disorders carrying a pathogenic *SLC6A1* variant.

The clinical presentation of the patient, including intellectual disability, behavioral disorders, dystonia, and choreic movements, was consistent with the classic description of *SLC6A1*-related disorders'.[3-8]

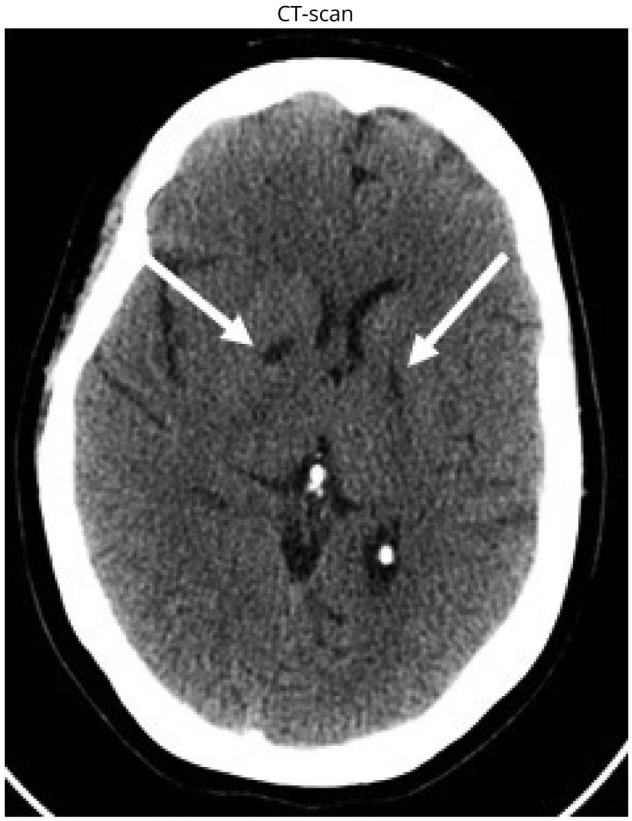
However, our case clearly differs from the literature in terms of imagery, with the presence of bipallidal degeneration with iron accumulation and presynaptic dopaminergic degeneration, which have not been reported to date. This demonstrates that, in SLC6A1-related disorder, the parkinsonian syndrome may be neurodegenerative and not drug-induced, as demonstrated by the reduction of I123-FP-β-CIT uptake.[10] In patients with *SLC6A1*-related disorder, MRI of the brain is usually described as normal or with aspecific abnormalities such as frontal enlargement of the lateral ventricles, malrotation of the left hippocampus, nonspecific T2/FLAIR hypersignals, enlargement of the subarachnoid spaces and cortical sulci with frontotemporal predominance, diffuse and nonspecific white matter loss, arachnoid cysts, mild vermal hypoplasia, or periventricular gliosis.[3-8] In our patient, MRI findings were similar to what is observed in NBIA.[11,12] Indeed, in the various forms of NBIA, MRI shows iron deposition predominantly in basal ganglia (mostly in the globus pallidus), whereas other regions, such as substantia nigra, red nucleus, dentate nucleus, thalamus, cerebellum, or cortex, are more variably affected, depending on the subtype of NBIA.[11,12] In the present case, iron accumulation predominated in the globus pallidus, whereas caudate nuclei and locus niger were less involved, and thalami, putamen, and cortex were unaffected. Of interest, clinical presentation in NBIA is variable but overlaps with that seen in *SLC6A1*-related disorder, including symptoms of dystonia-parkinsonism, cerebellar ataxia, intellectual disability

Figure 2 3T Brain MRI



(A) T2 FLAIR sequence showing bilateral globus pallidus hyperintensities with a peripheral hypointense rim. (B–D) Susceptibility-weighted imaging (SWI) sequences showing bilateral abnormal hypointensity of globus pallidus, and, more slightly, of caudate nuclei and locus niger. Putamen, thalami, and cerebral cortex are normal.

Figure 3 CT Scan Showing Bilateral Hypodense Globus Pallidus Lesions Without Calcifications



or cognitive deterioration, and psychiatric disorders.[13] In the present case, we did not find any evidence for an additional pathogenic variant that could be responsible for the brain MRI abnormal features, which is important as ~2% of patients with a genetic diagnosis actually have a dual diagnosis.[14] Of interest, 15 genes have been identified as causative for NBIA, but only 2 of them are directly associated with iron homeostasis, while all the other causative genes codify for proteins not involved in iron management, which is also the case for *SLC6A1* gene.[15]

In conclusion, this observation expands the clinico-radiologic spectrum of *SLC6A1*-related disorders and suggests that this diagnosis should be considered in the differential diagnosis for NBIA.

Study Funding

The authors report no targeted funding.

Disclosure

The authors report no relevant disclosures. Go to Neurology.org/NG for full disclosures.

Publication History

Received by *Neurology: Genetics* October 18, 2023. Accepted in final form January 19, 2024. Submitted and externally peer reviewed. The handling editor was Associate Editor Raymond P. Roos, MD, FAAN.

Appendix Authors

Name	Location	Contribution
Victoire Leclert, MD	Department of Neurology C, Expert Parkinson Center NS-PARK/FCRIN, Hospices Civils de Lyon, Pierre Wertheimer Neurological Hospital, Bron, France	Drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data
Chloe Laurencin, MD	Department of Neurology C, Expert Parkinson Center NS-PARK/FCRIN, Hospices Civils de Lyon, Pierre Wertheimer Neurological Hospital, Bron; Lyon Neuroscience Research Center, UMR5292, INSERM U1028/CNRS, France	Drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data
Roxana Ameli, MD	Department of Neuroradiology, Hospices Civils de Lyon, Pierre Wertheimer Neurological Hospital, Bron, France	Major role in the acquisition of data; analysis or interpretation of data
Marc Hermier, MD, PhD	Department of Neuroradiology, Hospices Civils de Lyon, Pierre Wertheimer Neurological Hospital, Bron, France	Major role in the acquisition of data
Anthime Flaus, MD, PhD	Lyon Neuroscience Research Center, UMR5292, INSERM U1028/CNRS; Nuclear Medicine Department, Hospices Civils de Lyon, Pierre Wertheimer Neurological Hospital, Bron, France	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
Stephane Prange, MD, PhD	Department of Neurology C, Expert Parkinson Center NS-PARK/FCRIN, Hospices Civils de Lyon, Pierre Wertheimer Neurological Hospital; Marc Jeannerod Cognitive Neuroscience Institute, CNRS, UMR 5229, Bron; Faculté de Médecine et Maïeutique Lyon Sud Charles-Mérieux, Université de Lyon, Université Claude-Bernard Lyon I, France	Drafting/revision of the manuscript for content, including medical writing for content
Gaetan Lesca, MD, PhD	Faculté de Médecine et Maïeutique Lyon Sud Charles-Mérieux, Université de Lyon, Université Claude-Bernard Lyon I; Department of Genetics, Hospices Civils de Lyon, Mother Child Hospital, Bron; Physiopathology and Genetics of Neurons and Muscles, UMR5261, U1315, Institut NeuroMyoGène, Lyon, France	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data
Stephane Thobois, MD, PhD	Department of Neurology C, Expert Parkinson Center NS-PARK/FCRIN, Hospices Civils de Lyon, Pierre Wertheimer Neurological Hospital; Marc Jeannerod Cognitive Neuroscience Institute, CNRS, UMR 5229, Bron; Faculté de Médecine et Maïeutique Lyon Sud Charles-Mérieux, Université de Lyon, Université Claude-Bernard Lyon I, France	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data

References

1. Madsen KK, Hansen GH, Danielsen EM, Schousboe A, The subcellular localization of GABA transporters and its implication for seizure management. *Neurochem Res.* 2015; 40(2):410-419. doi:10.1007/s11064-014-1494-9
2. Zhou Y, Danbolt NC, GABA and Glutamate transporters in brain. *Front Endocrinol (Lausanne)*. 2013;4:165. doi:10.3389/fendo.2013.00165
3. Carvill GL, McMahon JM, Schneider A, et al. Mutations in the GABA transporter SLC6A1 cause epilepsy with myoclonic-atonic seizures. *Am J Hum Genet.* 2015;96(5), 808-815. doi:10.1016/j.ajhg.2015.02.016
4. Johannesen KM, Gardella E, Linnankivi T, et al. Defining the phenotypic spectrum of SLC6A1 mutations. *Epilepsia*. 2018;59(2):389-402. doi:10.1111/epi.13986
5. Goodspeed K, Perez-Palma E, Iqbal S, et al. Current knowledge of SLC6A1-related neurodevelopmental disorders. *Brain Commun.* 2020;2:fcaa170. doi:10.1093/braincomms/fcaa170
6. Kahen A, Kavus H, Geltzeiler A, et al. Neurodevelopmental phenotypes associated with pathogenic variants in SLC6A1. *J Med Genet.* 2022;59(6):536-543. doi:10.1136/jmedgenet-2021-107694
7. Kassabian B, Fenger CD, Willems M, et al. Intrafamilial variability in SLC6A1-related neurodevelopmental disorders. *Front Neurosci.* 2023;17:1219262. doi:10.3389/fnins.2023.1219262
8. Goodspeed K, Demarest S, Johannesen K, et al. SLC6A1-Related neurodevelopmental disorder. 2023. In: Adam MP, Mirzaa GM, Pagon RA, et al., eds. *GeneReviews® [Internet]*. University of Washington, Seattle; 1993-2023. ncbi.nlm.nih.gov/books/NBK589173/
9. Liu Z, Zhang N, Zhang Y, et al. Prioritized high-confidence risk genes for intellectual disability reveal molecular convergence during brain development. *Front Genet.* 2018; 9:349. doi:10.3389/fgene.2018.00349
10. Thobois S, Prange S, Scheiber C, Broussolle E What a neurologist should know about PET and SPECT functional imaging for parkinsonism: a practical perspective, *Parkinsonism Relat Disord.* 2019;59:93-100. doi:10.1016/j.parkreldis.2018.08.016
11. Lehéricy S, Roze E, Goizet C, Mochel F MRI of neurodegeneration with brain iron accumulation, *Curr Opin Neurol.* 2020;33(4):462-473. doi:10.1097/WCO.0000000000000844
12. Lee J-H, Yun JY, Gregory A, Hogarth P, Hayflick SJ Brain MRI Pattern Recognition in neurodegeneration with brain iron accumulation. *Front Neurol* 2020;11:1024. doi.10.3389/fneur.2020.01024
13. Gregory A, Hayflick S Neurodegeneration with brain iron accumulation disorders Overview. In: Adam MP, Mirzaa GM, Pagon RA, et al, eds. *GeneReviews® [Internet]*. University of Washington, Seattle; 1993. 2013.
14. Smith ED, Blanco K, Sajan SA et al. A retrospective review of multiple findings in diagnostic exome sequencing: half are distinct and half are overlapping diagnoses. *Genet Med.* 2019;21(10):2199-2207. doi:10.1038/s41436-019-0477-2
15. Levi S, Tiranti V. Neurodegeneration with brain iron accumulation disorders: valuable models aimed at understanding the pathogenesis of iron deposition. *Pharmaceuticals (Basel)*. 2019;12(1):27. doi:10.3390/ph12010027