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Abnormal DaTscan in GM1-gangliosidosis type III manifesting with dystonia-parkinsonism

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GM1-gangliosidosis is a rare lysosomal storage disorder caused by biallelic *GLB1* variants leading to β-galactosidase deficiency.[1,2] Level of residual enzymatic activity at least partly explains its phenotypic heterogeneity, including variability in age at symptom onset, clinical severity, and progression rate.[1-3] Three phenotypes are described, including infantile-onset (type I) and late infantile/juvenile-onset (type II) forms, which are lethal in early childhood, and late-onset form (type III), which manifests between late childhood and the third decade.[1,2] GM1-gangliosidosis type III, whose milder phenotype usually permits survival into adulthood,[2] manifests as a complex syndrome featuring skeletal dysplasia, corneal opacities, progressive generalized dystonia with prominent oromandibular and bulbar involvement, akinetic-rigid parkinsonism, and cognitive decline in later stages.[1]

Despite neuropathology demonstrates selective deposition of glycosphingolipids (i.e., the substrate of β-galactosidase) in the basal ganglia leading to prominent striatal neuronal loss,[4,5] *in vivo* evidence suggesting nigrostriatal degeneration is extremely scant.[6]

We report abnormal presynaptic dopaminergic imaging and long-term follow-up of a case of GM1-gangliosidosis type III whose genotype and biochemical analysis were previously reported.[7]

Case report

A 32-year- old White British female was born prematurely at 32 gestational weeks. She had normal perinatal and neurodevelopmental history. She started experiencing running difficulty at age 5, followed by gait difficulty with unsteadiness and progressive dysarthria. One year later, she was noticed to take longer to swallow food and started experiencing painful spasms of her left lower limb. At age 10, she developed mild kyphoscoliosis and rapidly progressive visual impairment, with detection of corneal opacities on ophthalmological assessment. She subsequently developed progressive generalized dystonia with prominent oromandibular involvement and intermittent facial grimacing, which evolved into akinetic–rigid parkinsonism. Her speech progressively deteriorated, and she became anarthric by age 16. She was PEG-fed since age 20. At age 20, her verbal IQ was 90, and her performance IQ was 92 (WAIS test). Her past medical history was otherwise unremarkable. The patient's unrelated parents, one older sister and one half-brother were in good health. On examination (age 32), she was anarthric and could effectively communicate using a tablet. Pursuit and saccades were unremarkable. She had generalized dystonia, with blepharospasm, facial grimacing, tongue involvement, left torticollis, hand deformities with cubital deviation of her fingers, and bilateral foot inversion. There was severe generalized bradykinesia. Tendon reflexes were brisk throughout. There were no cerebellar signs. Brain and spine MRI showed mild global cerebral white matter atrophy, faint bilateral putaminal clefts (Figure 1A), mild cervicothoracic scoliosis, and abnormal cervical vertebral body morphology with irregularity

of the endplates and intervertebral discs. DaTscan showed reduced tracer uptake in both striata (putamen>striatum; Figure 1B). Single-gene testing and segregation analysis (Figure 1C) revealed the patient was compound heterozygote for a paternally inherited pathogenic variant NM_000404.4(*GLB1*):c.245C>T p.(Thr82Met) and maternally inherited pathogenic variant NM_000404.4(*GLB1*):c.335A>C p.(His112Pro). Biochemical analyses detected very low β-galactosidase activity in leukocytes of 5.0nmol/hr/mg protein (range in GM1 homozygotes: 0.78-8.0)[7] and galactose-containing oligosaccharides in urine. She received baclofen 25mg three times daily, gabapentin 300mg three times daily, and botulinum toxin injections with benefit, whereas miglustat and levodopa were not tolerated due to intractable diarrhoea and sinus tachycardia, respectively.

Discussion

GLB1 encodes β-galactosidase, a lysosomal hydrolase which cleaves the terminal β-galactose from ganglioside substrates and other glycoconjugates.[8] This enzyme plays a critical role in the catabolism of GM1 ganglioside and the recycling of its subunits to the lysosomal salvage pathway.[9] Genetically determined deficiency of β-galactosidase causes toxic accumulation of its substrates (including β-linked galactose-containing glycolipids GM1 ganglioside, GA1 ganglioside, and other glycoconjugates) in lysosomes. This ultimately accounts for disruption of the autophagy lysosomal pathway and neuronal damage, which has increasingly been recognized as a pathophysiological mechanism underlying Parkinson's disease and other neurodegenerative disorders.[8,9] Against this background, substrate reduction therapy with the N-alkylated sugar miglustat, which inhibits the enzyme glucosylceramide synthase and ultimately glycosphingolipid biosynthesis, has been proposed for the treatment of GM1 gangliosidis based on proven efficacy in reducing disease progression in other lysosomal storage disorders (i.e., Gaucher disease type 1, Niemann-Pick disease type C) as well as in reducing GM1 ganglioside in the central nervous system of a mouse model of GM1 gangliosidosis and patients' cultured skin fibroblasts.[1]

Previous studies explored the prevalence of akinetic-rigid parkinsonism in GM1-gangliosidosis type III, with the most methodologically robust one revealing a prevalence of 48%.[10,11] Among brain MRI findings described in GM-gangliosidosis type III, reduced SWI signal due to iron deposition in the substantia nigra and T2 hyperintensity of the posterior putamen are consistent with involvement of the nigrostriatal pathway, the latter being also observed in our case.[11,12] MRI spectroscopy in one case of GM1-gangliosidosis type III detected increased myoinositol in the striatum but not in white matter, suggesting selective gliosis in this cerebral region.[11] In keeping with this observation, autopsy cases of GM1-gangliosidosis type III revealed selective intracytoplasmic neuronal GM1 ganglioside storage, neuronal loss, and gliosis in the striatum, which reflects a higher turnover of GM1 ganglioside in this

area.[4,5] Given neuronal structures prominently affected in GM1-gangliosidosis type III, it is not surprising that presynaptic dopaminergic imaging is abnormal in this disorder. However, only one previous case reported reduced ^{123}I-Ioflupane radiotracer uptake in the basal ganglia.[6] Our case confirmed a presynaptic pattern of dopaminergic dysfunction in GM1-gangliosidosis type III, thus providing *in vivo* evidence suggestive of nigrostriatal degeneration. We suggest that this disease should be included in the differential diagnosis of young-onset dystonia-parkinsonism with abnormal DaTscan, with implications for dopaminergic treatment. Finally, our observation also opens to the potential use of deep brain stimulation (DBS) in GM1-gangliosidosis type III. This was explored in two cases treated with sequential and simultaneous stimulation of the globus pallidus internus and subthalamic nucleus (STN) by Baizabal-Carvallo et al.[13] The authors reported preliminary evidence favoring benefits of DBS-STN on akinetic-rigid dystonia associated with GM1-gangliosidosis type III, with 35% improvement of akinesia documented in one case.[13]

Author roles

1.   Research project: A. Conception, B. Organization, C. Execution.

2.   Data Analysis: A. Design, B. Execution, C. Review and Critique.

3.   Manuscript Preparation: A. Writing of the first draft, B. Review and Critique.

SKK: 1A, 1B, 1C, 2B, 3A

FM: 1A, 1B, 1C, 2B, 3A

AVM: 1C, 2C, 3B

KPB: 1C, 2C, 3B

Book of Movement Disorders (Oxford University Press, 2012), and of Case Studies in Movement Disorders–Common and uncommon presentations (Cambridge University Press, 2017). He has received honoraria/personal compensation for participating as consultant/scientific board member from Ipsen, Allergan, Merz and honoraria for speaking at meetings and from Allergan, Ipsen, Merz, Sun Pharma, Teva, UCB Pharmaceuticals and from the American Academy of Neurology and the International Parkinson's Disease and Movement Disorders Society. Shahedah Koya Kutty and Anna Vera Milner have no disclosures to declare.

Ethical Compliance Statement

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines. The authors confirm that the approval of an institutional review board was not required for this work. The authors confirm that informed consent from the patient was obtained.

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Figure legend

Figure 1. (A) Brain MRI (age 19) showing mild global cerebral white matter volume loss and faint bilateral putaminal clefts on T2-weighted sequence. **(B)** DaTscan (age 27) showing asymmetrically reduced tracer uptake in both striata (putamen>caudate; right>left) consistent with nigrostriatal degeneration. **(C)** *Left side*. Family tree of the reported case. An arrow identifies the proband, "?" identifies healthy family members whose genotype was unknown. Half-filled symbols represent heterozygous carriers of the mutant alleles herein reported, with dark grey indicating the variant NM_000404.4(*GLB1*):c.245C>T p.(Thr82Met) and green indicating the variant NM_000404.4(*GLB1*):c.335A>C p.(His112Pro). *Right side*. Segregation analysis confirming that the two *GLB1* variants were in *trans* configuration in the proband. DNA regions of interest were amplified bidirectionally using the following primer sets (5'→3'): for *GLB1* variant c.245C>T, F-gtggacctggcttagcaatg and R-ccctcccagaacatcacact, with an amplicon size of 472 base pairs; for *GLB1* variant c.335A>C, F-tccccacgcttctttcttct and R-agctcacacacaccaggtag, with an amplicon size of 258 base pairs. Chromatograms were analyzed using the Sequencher software package. Legend: HET = heterozygote; HOM = homozygote; wt = wild type.
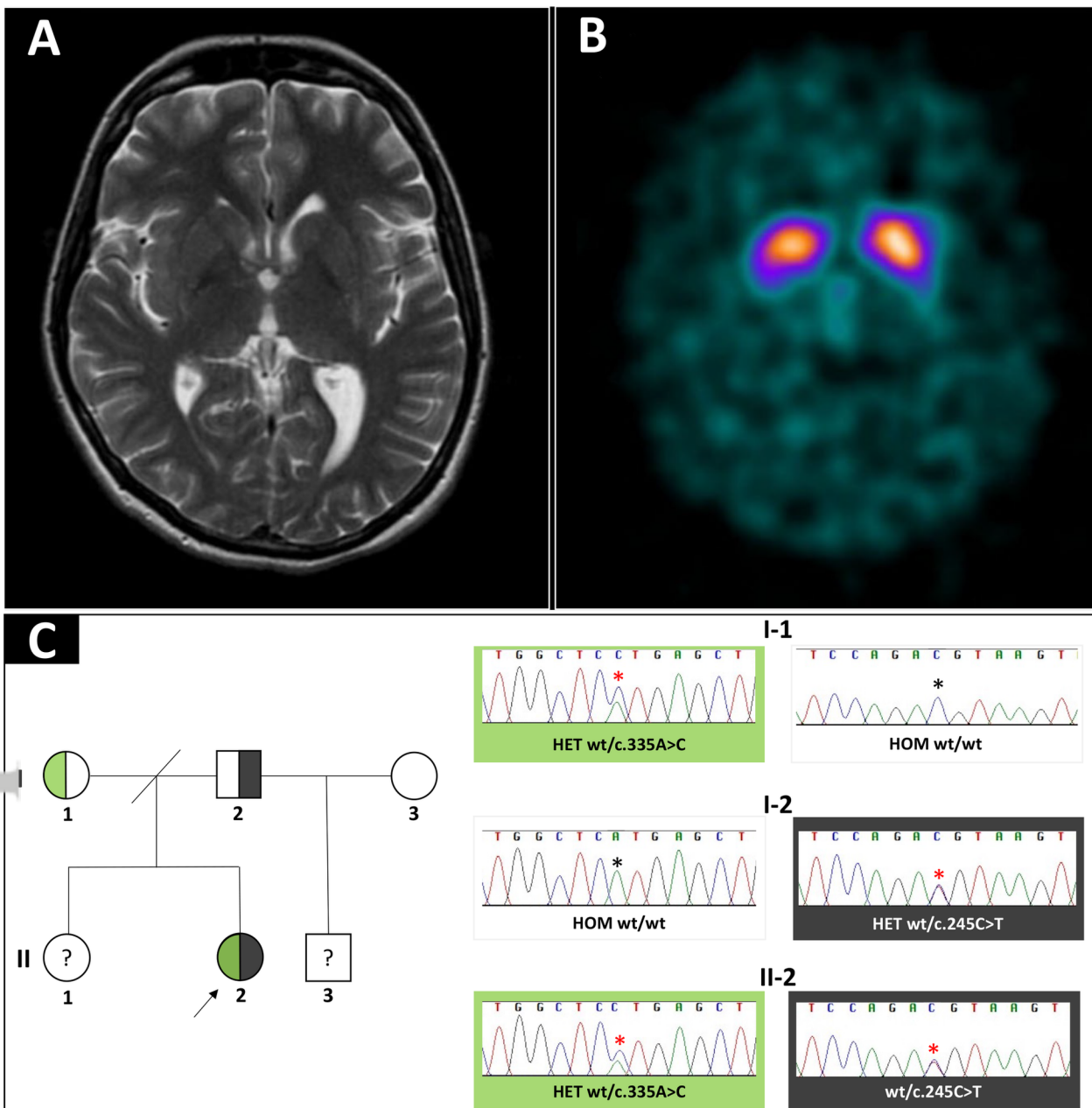
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