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Clinical Observations

GM1 Gangliosidosis, Late Infantile Onset Dystonia, and T2 Hypointensity in the Globus Pallidus and Substantia Nigra

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ABSTRACT

BACKGROUND: GM1 gangliosidosis is a rare disease due to mutations in the *GLB1* gene and autosomal recessive deficiency of β-galactosidase. There is considerable overlap between classical phenotypes and clinical and imaging findings, which are often difficult to interpret. **PATIENT:** The patient in this study had dysmorphism, dysostosis, progressive dystonia, and T_2 hypointensity in the basal ganglia. Partially similar clinical and radiologic findings were described previously in two reports. **CONCLUSIONS:** T_2 hypointensity in the globus pallidus should, in the appropriate clinical setting, lead to consideration of the diagnosis of GM1 gangliosidosis.

Introduction

GM1 gangliosidosis is a rare disease with an incidence estimated between 1 in 100,000 or 200,000 live births. Autosomal recessive deficiency of β-galactosidase due to a mutation in the *GLB1* gene is present not only in this disorder but also in Morquio type-B disease [1].

Classically, GM1 gangliosidosis is divided into subtypes with different ages of onset and diverse neurological and systemic features. However, a significant number of patients can share characteristics of different types. There may also be overlap between GM1 gangliosidosis and Morquio phenotypes [1-3]. Neuroimaging in GM1 gangliosidosis has been reported in a limited number of patients [2,4-6].

Nonspecific white matter hyperintensity, thalamic hypointensity on T_2-weighted imaging, delayed myelination, and T_2 hyperintense signal in the putamina were reported previously.

Two reports previously described T_2 hypointensity in the globus pallidus [5,6].

Case Report

This 12-year-old boy born of healthy, nonconsanguineous parents had a history of slowly progressive psychomotor regression and involuntary movements since the age of four.

On neurological examination he was microcephalic and had convergent strabismus, severe orofacial dystonia, dysarthria, and limb and trunk dystonia. He exhibited facial dysmorphism (frontal bossing, wide nasal root, large and low set ears), pectus carinatum, short stature, and dorsal kyphosis. Corneal opacities were not present, nor were the liver and spleen enlarged.

Skeletal radiographies showed osteonecrosis of the femoral head and hypoplastic body of the tenth dorsal vertebra.

Magnetic resonance imaging revealed a hypointense T_2 signal in the substantia nigra and in the globus pallidus, with marked hypointensity in susceptibility-weighted imaging and slight T_2 hyperintensity in the posterior part of the putamen (Figs 1 and 2). Brain calcifications were not seen on computed tomography scan (not shown).

Beta-galactosidase deficiency was demonstrated subsequently (8 nm/hr/mg protein; reference value: 73-585) and a homozygous mutation in the *GLB1* gene: c.1313G>A; (p.G438E), exon 13.

Discussion

Dysmorphism and dysostosis are features of type-1 (infantile) and of Morquio type-B disease, while slowly

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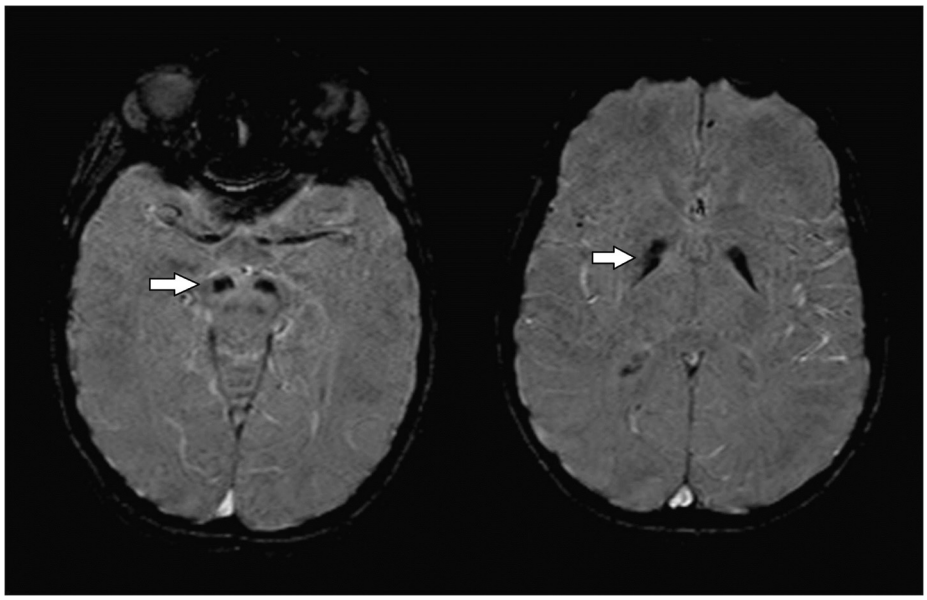

Figure 1. Susceptibility weighted imaging showing hypointense T_2 signal in the substantia nigra (right) and in the globus pallidus (left) (arrows).

progressive dystonia is seen in type-3 (adult) GM1 gangliosidosis; nevertheless, individual patients often have clinical and imagiologic features that overlap between the classical phenotypes [1].

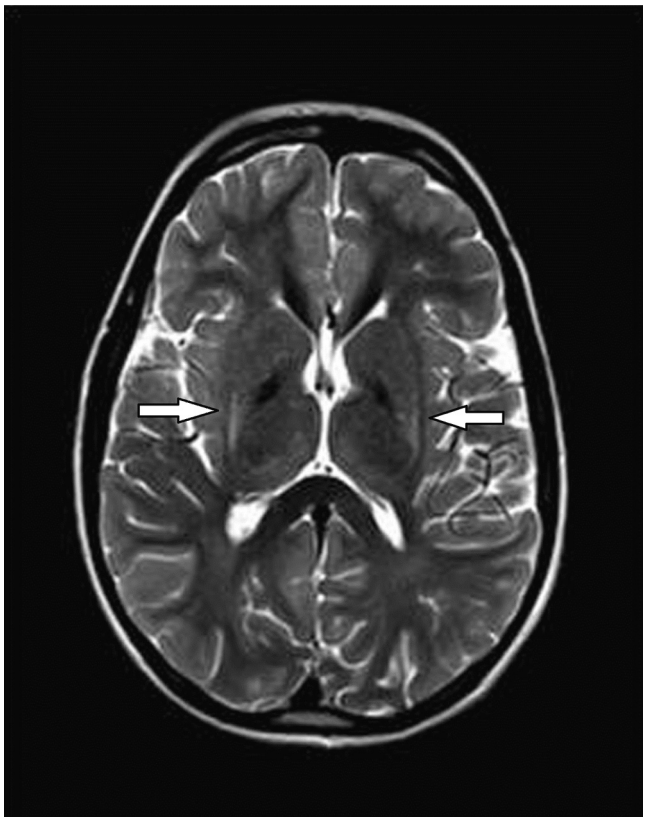

Figure 2. T_2-weighted image showing hypointense signal in the globus pallidus and slight hyperintensity in the posterior part of the putamen (arrows).

Our patient exhibited the homozygous mutation c.1313G>A; (p.G438E), which has been reported in patients with Morquio type-B and with type-3 GM1 phenotypes [1]. Caciotti et al. [1] reported one patient (patient number 20 in their series) with the same mutation and a phenotype very similar to that in this report, but they did not mention imaging findings.

Tanaka et al. [5] reported a girl with a mutation in exon 2, dysmorphism, dysostosis, and slowly progressive dystonia since early childhood. Two patients reported by De Grandis et al. [6] had dysostosis: one had dystonia and ataxia and the other dystonia and spasticity, apparently also of childhood onset, but dysmorphism was not reported. Their genotype was not reported. MRI findings in this case study and in those reported by Tanaka et al. and De Grandis et al. are identical: T_2 pallidal hypointensity and T_2 hyperintensity in the posterior putamen were seen; iron deposition in the substantia nigra was not reported.

T_2 hypointensity due to iron deposition in the basal ganglia is found in normal adults but not usually in children or adolescents. Neuronal brain iron accumulation is responsible for the shortening of T_2 relaxation time in pantothenate kinase–associated neurodegeneration, infantile neuroaxonal dystrophy, and neuroferritinopathy. In pantothenate kinase–associated neurodegeneration, hypointensity occurs besides the globus pallidus in the substantia nigra but later in the course of the disease.

In some lysosomal diseases like fucosidosis and GM1 gangliosidosis, iron overload may result from a defect in intralysosomal recycling. The Table lists the differential diagnosis for neuronal brain iron accumulation in children.

Table. Differential diagnosis of T_2 hypointensity (iron deposition) in the globus pallidus in children

Diagnosis	Clinical Features	MRI Findings
Pantothenate kinase-associated neurodegeneration (PKAN)	Dystonia, dysarthria; pigmentary retinopathy	Iron deposition in GP; eye of the tiger sign
PLA2G6-associated neurodegeneration (PLAN); Infantile neuroaxonal dystrophy (INAD)	Psychomotor regression; ataxia; hypotonia	Iron deposition in GP; cerebellar atrophy
Mitochondrial membrane protein-associated neurodegeneration (MPAN)	Spasticity, dystonia, cognitive decline	Iron deposition in GP and SN
Fatty-acid hydroxylase-associated neurodegeneration (FAHN)	Dystonia, spasticity, dysarthria	Iron deposition in GP and SN, cerebellar and brainstem atrophy, leukoencephalopathy
Kufor-Rakeb syndrome	Juvenile Parkinsonism	Iron deposition in caudate and lenticular nuclei
GM1 gangliosidosis	Dystonia; dysmorphism; dysostosis	Iron deposition in GP
Fucosidosis	Psychomotor regression, spasticity, coarse facial features	Leukoencephalopathy; T_2 hypointensity in the GP

Abbreviations:
GP = Globus pallidus
MRI = Magnetic resonance image
SN = Substantia nigra

In the clinical setting of dysostosis and dystonia, the finding of T_2 hypointense pallidal lesions should lead to consideration of GM1 gangliosidosis.

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