Atypical Gilles de la Tourette Syndrome With β-Mannosidase Deficiency

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Background: β-Mannosidosis is a rare inborn error of metabolism with various phenotypes, including mental retardation, behavioral problems, hearing loss, and recurrent airway infections in childhood. To our knowledge, there is no published description of Gilles de la Tourette syndrome in association with this enzymatic deficiency.

Objective: To describe a unique case of Gilles de la Tourette syndrome associated with β-mannosidosis.

Setting: University hospital.

Patient: An 18-year-old man exhibited motor and vocal tics since childhood, attention-deficit/hyperactivity disorder, impulsivity, and aggressiveness compatible with Gilles de la Tourette syndrome. A screen for inborn errors of metabolism was made because of the atypical association with slight mental retardation and bilateral perceptual hypoacousia.

Results: Urinary analysis showed disacchariduria, and leukocyte analysis revealed a profound deficit in β-mannosidase activity. Two novel mutations in the β-mannosidase gene were found: a new splice mutation in one allele, and a unique 10-base-pair insertion in the other.

Conclusions: This case illustrates the phenotypic variability of inborn errors of metabolism in adults and demonstrates the need to screen inborn errors of metabolism in atypical Gilles de la Tourette syndrome.

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Gilles de la Tourette syndrome (GTS) is characterized by motor and phonic tics that wax and wane in severity.1 Although a genetic cause is suspected, the biological mechanisms leading to GTS remain unknown. β-Mannosidase is a lysosomal enzyme that plays a role in the last step of oligosaccharide breakdown.2 Its deficiency leads to the pathological accumulation of disaccharides composed of mannose and N-acetylglucosamine. The 14 cases of β-mannosidosis reported so far exhibited various phenotypes, including mental retardation, behavioral disturbances, hearing loss, and recurrent airway infections.3,4 Here, we report the first case, to our knowledge, of GTS in association with β-mannosidosis.

The male proband was the second child of unrelated parents of French ancestry. His parents and sister were healthy. He was born in 1985 after an uncomplicated pregnancy and delivery. Early psychomotor development was considered normal. He walked at age 12 months and spoke his first words at age 18 months. He then began to suffer from recurrent upper airway infections as well as a right hip osteochondritis that required surgery. At age 3 years, an audiogram revealed a mild bilateral perceptual hearing loss. A delay in speech acquisition was noticed. At age 9 years, he learned to write and read, though with difficulty.

From ages 5 to 18 years, he had difficulty in fixing his attention, was hyperactive, and was aggressive with other children. He began to exhibit abnormal movements, the severity of which was variable with time and exacerbated by anxiety. These movements were sudden and repetitive, and they could be suppressed voluntarily: the patient rapidly turned his head to the right or left; he often scraped his scalp; while walking in the street, he touched the pavement with his fingers; and in the subway, he blocked the door closure with his foot. He broke glasses with his teeth while drinking, knocked his jaw with his fist, and pushed people while...
walking in the street. He also made vocal noises mimicking grunting, and he had obsessive-compulsive–like behaviors such as washing his hands dozens of times per day. He had no copropraxia or coprolalia. In brief, these abnormal behaviors were suggestive of simple and complex motor and vocal tics associated with hyperactivity, obsessive-compulsive disorder, autoaggressiveness, and heteroaggressiveness.

At age 18 years, he was referred to our department because his new physician suspected GTS. His weight was 120 kg (height, 186 cm). Neurological examination results were normal except for a 50-dB bilateral hearing loss. Dysmorphology and organomegaly were absent. Neuro-psychological evaluation revealed a dysexecutive syndrome with attention difficulties, especially for verbal material, but instrumental functions were normal. The Mini-Mental State Evaluation score was 21 out of 30, the Mattis Dementia Rating Scale score was 119 out of 144, and the progressive matrix 38 score was 69 out of 100. Results of a cerebral computed tomographic scan were normal (magnetic resonance imaging could not be done because of severe claustrophobia). Auditory evoked potentials revealed a slow conduction at the level of the pons. Standard radiographs revealed a slight scoliosis with hyperlordosis, cervical vertebral osteophytes, hemisacralization of the right L5 vertebra, and flatness of the right femoral head. Electroencephalography, ophthalmologic examination, and karyotyping results were normal.

The coexistence of hearing loss, slight mental retardation, and GTS prompted us to screen for metabolic diseases. Thin-layer chromatography of the urine revealed a slight oligosacchariduria, with excretion of disaccharides pointing to a disorder of oligosaccharide breakdown. Lysosomal enzymes involved in oligosaccharide degradation, including α-mannosidase, β-mannosidase, α-fucosidase, α-glucosaminidase, and N-acetylgalactosaminidase, were measured on leukocytes. All of the enzyme levels were normal except β-mannosidase (18 U/L, with 469 U/L in the control). β-Mannosidase activity in the serum was 24 U/L in the proband, 80 U/L in his father, and 84 U/L in his mother, which is compatible with heterozygous levels in the parents (407 U/L in the control). Sequencing of 17 exons of the β-mannosidase gene in the proband was performed as previously described.3 The proband had 2 novel mutations: a 10–base-pair (bp) insertion in exon 5 from his father (562–571 dup TTAGTTGGGA), and an acceptor splice site mutation at exon 13 from his mother (1705 -1G>A). The insertion into the coding sequence immediately introduces a stop codon and makes that allele a functional “null” allele. The splice site mutation is in an invariant base, predicting that the exon carrying this mutation would be skipped.

Clinical criteria for GTS include the following: (1) the existence of both multiple motor tics and 1 or more phonic tics; (2) tics must occur intermittently throughout a period of more than 1 year; (3) the anatomical location, number, frequency, type, complexity, or severity of tics must change over time; (4) the onset must occur before age 21 years; and (5) involuntary movements and noises must not be explainable by other medical conditions.1 In addition, patients with GTS often have a variety of behavioral symptoms, particularly attention-deficit/hyperactivity and obsessive-compulsive disorders.

Chronic motor and vocal tics have been described in association with many organic disorders, including genetic diseases such as Huntington disease, neuroacanthocytosis, neurodegeneration with brain iron accumulation type 1, and Wilson disease.1 More controversial is the association between GTS and group A β-hemolytic streptococcal infections.2 Our patient had typical features of GTS, including chronic multiple motor and vocal tics since childhood that varied with time, as well as an association with attention-deficit/hyperactivity disorder, aggressiveness, and obsessive-compulsive disorder. However, the atypical association with perceptive hypoacusia, mental retardation, recurrent upper airway infections in childhood, and skeletal deformities was indicative of β-mannosidase deficiency. Among the 14 previously reported cases of β-mannosidosis, mental retardation was described in 11 patients (78%), behavioral problems including hyperactivity and/or aggressiveness in 9 (64%), hearing loss in 9 (64%), respiratory infections in 7 (53%), and dysmorphology including skeletal deformities in 5 (40%). Other signs were occasionally observed, including angiokeratoma in 3 patients,5,6,7 demyelinating polyneuropathy in 1 patient,8 and epileptic encephalopathy in 1 patient.9 To our knowledge, no previous case of GTS has been reported in association with this disorder, and we cannot exclude the possibility that early streptococcal infections have played a role in the appearance of tics in our patient.

The β-mannosidase protein is produced by a single gene that is located on chromosome 4q22-25, composed of 17 exons, and transcribed into a 3293-bp complimentary DNA encoding a peptide of 879 amino acids.10 To date, mutations in this gene have been described for 5 patients from 4 different families. These included splice site mutations, nonsense mutations, and small deletions.3,4 Our patient was a compound heterozygote with a 10-bp insertion in exon 5, which predicts the introduction of a nonsense codon and a new splice site mutation in exon 13 of the other allele that would produce an alternatively spliced mRNA and an altered protein. This finding further demonstrates the allelic and phenotypic heterogeneity of β-mannosidosis.

Family studies have provided support for a genetic basis for GTS, and the presence of a gene of major effect acting on a multifactorial background is suspected.11 The Tourette Syndrome Association International Consortium for Genetics,11 using a systematic genome screen of GTS in 76 families, described an association with locus 4q between markers D4S1644 and D4S1625. Similarly, Zhang et al12 found an association between hoarding, a clinical feature of GTS, and the locus 4q32-35. However, these genomic regions are located more than 40 megabases from the β-mannosidase gene, which makes the latter a poor candidate gene. In conclusion, this case illustrates the need to search for metabolic diseases in

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adult patients referred for GTS, especially if other subtle organic signs are present.

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