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The Natural History of Juvenile or Subacute GM2 Gangliosidosis: 21 New Cases and Literature Review of 134 Previously Reported

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Abstract

OBJECTIVE—Juvenile GM2 gangliosidosis is a group of inherited neurodegenerative diseases caused by deficiency of lysosomal β-hexosaminidase resulting in GM2 ganglioside accumulation in brain. The purpose of this study was to delineate the natural history of the condition and identify genotype-phenotype correlations that might be helpful in predicting the course of the disease in individual patients.

METHODS—A cohort of 21 patients with juvenile GM2 gangliosidosis, 15 with the Tay-Sachs variant and 6 with the Sandhoff variant, was studied prospectively in 2 centers. Our experience was compared with previously published reports on 134 patients. Information about clinical features, β-hexosaminidase enzyme activity, and mutation analysis was collected.

RESULTS—In our cohort of patients, the mean (±SD) age of onset of symptoms was 5.3 ± 4.1 years, with a mean follow-up time of 8.4 years. The most common symptoms at onset were gait disturbances (66.7%), incoordination (52.4%), speech problems (28.6%), and developmental delay (28.6%). The age of onset of gait disturbances was 7.1 ± 5.6 years. The mean time for progression

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to becoming wheelchair-bound was 6.2 ± 5.5 years. The mean age of onset of speech problems was 7.0 ± 5.6 years, with a mean time of progression to anarthria of 5.6 ± 5.3 years. Muscle wasting (10.6 ± 7.4 years), proximal weakness (11.1 ± 7.7 years), and incontinence of sphincters (14.6 ± 9.7 years) appeared later in the course of the disease. Psychiatric disturbances and neuropathy were more prevalent in patients with the Sandhoff variant than in those with the Tay-Sachs variant. However, dysphagia, sphincter incontinence, and sleep problems occurred earlier in those with the Tay-Sachs variant. Cerebellar atrophy was the most common finding on brain MRI (52.9%). The median survival time among the studied and reviewed patients was 14.5 years. The genotype-phenotype correlation revealed that in patients with the Tay-Sachs variant, the presence of R178H and R499H mutations was predictive of an early onset and rapidly progressive course. The presence of either G269S or W474C mutations was associated with a later onset of symptoms along with a more slowly progressive disease course.

CONCLUSIONS—Juvenile GM2 gangliosidosis is clinically heterogeneous, not only in terms of age of onset and clinical features but also with regard to the course of the disease. In general, the earlier the onset of symptoms, the more rapidly the disease progresses. The Tay-Sachs and Sandhoff variants differed somewhat in the frequency of specific clinical characteristics. Speech deterioration progressed more rapidly than gait abnormalities in both the Tay-Sachs variant and Sandhoff variant groups. Among patients with the Tay-Sachs variant, the *HEXA* genotype showed a significant correlation with the clinical course.

Keywords

juvenile GM2 gangliosidosis; β-hexosaminidase deficiency; Tay-Sachs disease; Sandhoff disease; lysosomal storage disease

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Juvenile gm2 gangliosidosis (jGM2), also called subacute GM2 gangliosidosis (Online Mendelian Inheritance in Man [OMIM] No. 230700), is a rare and heterogeneous autosomal recessive disorder characterized by progressive neurologic deterioration that mainly affects motor and spinocerebellar function. It is a lysosomal storage disease caused by deficiency of β-hexosaminidase A, combined deficiency of β-hexosaminidases A and B, or deficiency of the noncatalytic GM2 activator. The enzyme β-hexosaminidase is comprised of 2 major isoenzymes, β-hexosaminidase A and β-hexosaminidase B. β-Hexosaminidase A is made up of 2 nonidentical subunits, α and β, that are encoded by the genes *HEXA* (15q23-q24) and *HEXB* (5q13), respectively, which are associated into the heterodimeric isoenzyme. It catalyzes the removal of the β-*N*-acetylgalactosamine residue from the nonreducing terminal of the oligosaccharide of GM2 ganglioside. β-Hexosaminidase B comprises 2 identical β subunits (β_2). It does not catalyze the degradation of GM2 ganglioside. Mutations of the *HEXA* gene encoding the α subunit cause deficiency of the β-hexosaminidase A and result in the well-known form of GM2 gangliosidosis called Tay-Sachs disease (OMIM No. 272800). Mutations of the *HEXB* gene, encoding the β-subunit, cause deficiency of both enzymes (β-hexosaminidase A and β-hexosaminidase B), leading to Sandhoff disease (OMIM No. 268800), which is, in clinical aspects, virtually indistinguishable from Tay-Sachs disease. Deficiency of the GM2 activator protein, which mediates the interaction between the water-soluble β-hexosaminidase A and its membrane-embedded substrate, GM2 ganglioside, causes the AB variant of GM2 gangliosidosis (OMIM No. 272750).[1,2]

In the general population, the Tay-Sachs variant (TSV) of GM2 gangliosidosis is rare, with a prevalence of 1 in 201 000 live births and incidence of 1 in 222 000 live births.[3] The Sandhoff variant (SV) prevalence and incidence rates have been reported as 1 in 384 000 and 1 in 422 000 live births, respectively.[3] The TSV carrier frequency is much higher in the Ashkenazi Jewish (1 in 30) and eastern Quebec French Canadian (1 in 14) populations compared with that in the general population (1 in 300).[4] Community-based TSV carrier screening programs in these at-risk populations have had a dramatic effect on birth prevalence, which is now lower than that in the general population.[5,6]

The classical infantile form of GM2 gangliosidosis is characterized by the onset of symptoms before the age of 6 months and progresses rapidly to death by 3 to 5 years of age.[7] Juvenile or subacute and the adult, also called late-onset or chronic, subtypes of this condition present later in childhood or in adulthood and progress more slowly.[1,8–22] The juvenile and adult forms of GM2 gangliosidosis differ from each other primarily by the impact of the disease on intelligence, which is minimal through much of the course of the adult or chronic variant.

Several case reports and a small number of case series have been reported.[11,13,20,21] However, few studies have provided accurate descriptions of the natural clinical course of jGM2 in larger groups of patients.[21,23] We report here a series of 21 cases of juvenile or subacute GM2 gangliosidosis followed at 2 medical centers. We also review a collection of 134 previously reported cases of jGM2.* The focus of our analysis is on initial symptomatology, age of onset, and severity of symptoms during the course of the disease. We also report on the spectrum of *HEXA* and *HEXB* mutations identified in patients with the TSV and SV, respectively, and make some generalizations concerning genotype-phenotype correlations.

STUDY OBJECTIVE

The objectives for this study were to (1) elucidate the clinical course of jGM2, (2) determine the extent to which the clinical phenotypes of the TSV and SV differ from each other, and (3) determine the value of specific genotypes in predicting the clinical course of the disease in individual patients.

METHODS

We used a combined retrospective and prospective collection of clinical, laboratory, molecular genetic, and imaging data from our own cohort of 21 patients with jGM2, supplemented by a review of 134 cases of the disease reported in medical literature from 1968 to January 2006. The mean prospective follow-up period was 8.4 years (range: 1.1–23.5 years). Clinical information about the symptoms at onset and its progression until the diagnosis was gathered retrospectively from parents through a detailed clinical protocol.

*Refs 1, 8, 9, 11–14, 18, 20, 22, and 24–82.

Clinical Observations

Clinical observations were documented according to a fixed protocol, with special attention paid to clinical observations recorded in the original medical charts and from interviews with the parents, especially concerning the initial symptomatology, along with the timing of the appearance of different symptoms and their evolution during the course of the disease. The protocol was based on most common symptoms/signs encountered in patients affected with this condition. It included a full physical examination comprising general and neurologic examinations. During the prospective component of the study, the complete protocol was performed by at least 1 of the authors. Of the 21 studied patients, 17 had at least 1 brain MRI or computed tomography (CT) scan.

Diagnosis of jGM2

The gold-standard method for diagnosis of GM2 gangliosidosis is the measurement of β-hexosaminidase activity in plasma, serum, and/or fibroblasts determined with the use of the synthetic uncharged substrate, 4-methylumbelliferyl-β-*N*-acetyl glucosaminide (MUG), as well as with the sulfated substrate, 4-methylumbelliferyl-β-*N*-acetylglucosaminide-6-sulfate (MUGS), as described previously.[5,83] Through heat-denaturation assay with the use of MUG as substrate, we are able to measure β-hexosaminidase B activity and then impute the β-hexosaminidase A percent contribution of total β-hexosaminidase activity. The MUGS substrate was used to measure specific β-hexosaminidase A activity and diagnose a B1-variant phenotype of TSV. Molecular characterization of the *HEXA* and *HEXB* mutations was performed by direct sequencing of the entire coding region and intron/exon boundaries by using genomic DNA. In some patients (patients 7, 8, and 20), complementary DNA was obtained and sequenced from patient fibroblasts as described previously.[84–90]

Identification and Recruitment of Patients

The subjects were recruited from among patients affected with jGM2 who were treated and followed at 2 centers: the genetic metabolic clinic at the Hospital for Sick Children ($n = 13$) and the pediatric neurology clinic at Centro do Genoma Humano, University of Sao Paulo ($n = 8$). All recruited patients had onset of symptoms between 1 and 18 years of age. The recruitment was performed with informed-consent and assent forms approved by the relevant research ethics boards.

Review of the Literature

The review of the literature included all indexed publications that reported clinical findings in patients diagnosed with GM2 gangliosidosis whose age of onset of symptoms was between 1 and 18 years of age and covered the period from 1968 to January 2006. A PubMed search was performed with the key words “juvenile GM2 gangliosidosis,” “juvenile Tay-Sachs disease,” “juvenile Sandhoff disease,” “Tay-Sachs disease,” “Sandhoff disease,” and “GM2 gangliosidosis.”

Statistics

Descriptive statistical calculations were performed to summarize the clinical findings in our series of 21 patients and the 134 patients reported in the literature. For comparisons, the χ^2

test was used for nominal data and a 2-tailed Student's *t* test was used for analysis of continuous data.

In terms of the 134 previously reported cases, only the data provided in each anecdotal case report or small case series were used for this analysis. Clinical descriptions usually consisted of positive clinical findings in reported patients. Negative symptoms and signs were rarely, if ever, reported. Therefore, the variables from previously reported cases (described in Tables 1, 2, and 3) were based exclusively on the positive clinical findings found in those reports. In addition, we are unable to conclude that a nonreported clinical variable was invariably absent or missed by us. Comparisons of contiguous variables were made by using conventional parametric statistical methods. Categorical data were analyzed by using standard nonparametric methods. Kaplan-Meyer survival analysis was performed by taking as censored cases the 21 patients from our studied group and 30 patients previously reported who were reported after they had died.

RESULTS

Patient Population

The 21 patients reported here were from 15 unrelated families and included 10 males and 11 females. Fifteen patients (71.4%) presented with the TSV of jGM2, and 6 had SV (28.6%). The mean age of patients when they were recruited and had their first assessment was 19.3 ± 12.5 years (range: 2.7–37.2 years). The mean age at diagnosis was 12.3 ± 10.7 years. Among the 21 patients, a wide ethnic background was observed, including 5 Brazilian-Portuguese, 4 North American white, 3 Brazilian-Ashkenazi Jewish, 2 East Indian, 2 mixed Italian and French Canadian, 2 German-Dutch, and single patients of mixed black and North American white, Pakistani, and West Indian extraction. Consanguinity was seen in only one case, the parents in which were first cousins.

Our review of the literature yielded clinical descriptions of 134 individuals (70 males [52.2%] and 64 females [47.8%]). The proportions with the TSV and SV were similar to what we observed in our cohort: 96 (71.6%) had TSV, and 27 (20.1%) had SV disease.

It should be noted that 2 cases of the AB variant form of jGM2[1] and 9 with uncharacterized variants of jGM2[24,25,29–32,34] were also included among the 134 previously reported cases. Those 9 cases (6.7%), which dated from 1968 to 1973, had been diagnosed by pathologic findings of GM2 accumulation in several tissues at autopsy.[24–26,29–32,34,91] The mean age of the 134 reported patients was 16.1 ± 11.2 years (range: 1.75–43 years). Most patients were of European origin (56.3%). Patients of Ashkenazi Jewish ancestry accounted for 22.6% (30 of 134) of the total, and Portuguese patients, among the European-origin patient group, accounted for another 11.9% (16 of 134). A small but significant proportion of those described were Pakistani (9), East Indian (6), Lebanese (5), Puerto Rican (4), and French Canadian (4). Ethnic background was not reported for 9 of the patients. Parental consanguinity was reported in 32 cases (23.9%).

Enzyme Assay and Molecular Genetic Studies

All patients had residual activity of either β-hexosaminidase A, among the patients with the TSV, or total β-hexosaminidase, among the patients with the SV[5,83] (Table 4).

In the 15 patients with the TSV, we found 11 different mutations in the *HEXA* gene, with 3 groups of siblings (cases 1 and 2, 9 and 10, and 16, 17, and 18) sharing the same mutations. The most common was 1278insTATC, which accounted for 7 *HEXA* alleles. Other common alleles were R499H ($n = 5$) and R178H ($n = 5$). One novel mutation was found, Y277X, that produces a stop codon in exon 7. Only 1 patient was homozygous for any of the 11 *HEXA* mutations found (R178H/R178H).

Among the 6 patients with the SV, 5 different mutations were found. Only 2 mutations, IVS12-26G→A and R505Q, were reported previously;[7,12,92,93] all the others represent novel mutations described here for the first time (Table 2). Each of the novel mutations predicts a major alteration in the hexosaminidase β subunit. The C137Y mutation, for instance, predicts a change in a cysteine residue located at one extremity of the unique disulfide bond in domain I.[94] The Y266D mutation results in a major change in amino acid class (aromatic to acidic) in a conservative region located close to critical regions for subunit dimerization.[94] The G353R mutation found in 1 of the patients (patient 20) is located in a conserved amino acid sequence, GGDE, found in all members of the family of 20 glycoside hydrolases, to which human lysosomal β-hexosaminidase belongs.[95]

In the vast majority of the 134 case reports published previously, mutation data are incomplete. Therefore, the related data concerning molecular investigation in this group of patients are not included here.

Clinical Features

Current Patient Series—The mean age of onset of the earliest symptom was 5.3 ± 4.1 years (range: 1.5–15 years). The frequency of each symptom reported at onset is illustrated in the histogram in Fig 1. Most patients were reported to have 3 symptoms (15 of 21 [71.4%]) at disease onset; 6 (28.6%) had 2 symptoms, and 5 (23.5%) had a single problem. The clinical features observed in the 21 studied patients are summarized in Table 2. As the disease progressed, gait and speech disturbances were experienced by all patients, and the majority of patients (95.3%) developed incoordination along with intellectual impairment (80.9%). An eye examination was performed on all patients. Two of our patients developed some degree of optic atrophy, and 1 patient developed optic atrophy associated with macular degeneration, which was noted along with the progression of the disease. The classical “cherry-red spot,” seen in infantile GM2 gangliosidosis, was noted in only 1 patient (patient 14) at 3.4 years of age.

Previously Published Cases—The mean age of first symptoms in the 134 previously reported patients was 5.4 ± 4.0 years (range: 1–17) (Table 2). Seventy patients (52.2%) were reported to have at least 2 symptoms, and 13 (9.7%) had at least 3 symptoms at disease onset. The most common symptom at onset was gait disturbances (58.2%), followed by speech problems (37.3%), incoordination (36.5%), intellectual impairment (29.1%), and

behavior or psychiatric disturbances (11.9%), similar to what we observed in our cohort (Fig 1). Optic atrophy was described in 10 patients during the course of the disease (15.4%).[11,13,24,35,36,38,42,64] Two patients had optic atrophy and macular alterations.[34,36] Four patients (4.6%) presented with macular alterations described as cherry-red spots.[1,18,34,65,70]

Clinical Comparison Between TSVs and SVs

The 2 major variants of jGM2, TSV and SV, are generally considered to be clinically indistinguishable.[7] However, in the studied cohort of patients, the age of onset for dysphagia and incontinence of sphincters was significantly earlier in patients with the TSV ($P < .001$) (Table 3). In addition, the age of onset for sleep problems appeared later in those with the SV ($P < .05$). The prevalence of behavioral problems was found to be statistically higher in patients with the SV ($P < .05$) (Table 3). In the previously reported jGM2 patient group, a significant male prevalence was seen in the TSV group. Consanguinity was more common among parents of patients with the SV in the previously reported cases. Muscle wasting was one of the clinical features that differed between the patients with the TSV and SV, in whom the mean age of onset was significantly earlier among patients with the SV. Diarrhea/constipation and sleep problems were also significantly more prevalent in patients with the SV (Table 3).

Disease Progression

Of the cohort of 21 patients reported here, 20 were alive at the end of this study; 1 patient died of pneumonia at age 20. The mean age at diagnosis was 12.3 ± 10.7 years (range: 2.5–36.9 years). The mean time from the initial presenting symptoms to the diagnosis was 7.5 ± 8.3 years (range: 0.3–26.8 years). The interval between the age of onset of the first symptoms of disease and the development of any additional symptom related to jGM2 is defined here as the “symptom latency.” For instance, among the 21 studied patients, the median interval between the onset of the first symptoms of disease and the development of pyramidal signs was 3.4 years (range: 0–12 years) and was 3.5 years (range: 0–35.5 years) among the 134 in the literature-review group (Table 3).

The progression of speech deterioration was categorized into 3 stages: (1) mild dysarthria (most words were comprehensible); (2) severe dysarthria (most words were incomprehensible); and (3) anarthria (unintelligible speech). Figure 2 shows the progression of speech impairment in 12 patients (57.4%). The mean interval from the progression of mild dysarthria to severe dysarthria was 2.4 years (range: 0.5–7.0 years) and from severe dysarthria to anarthria was 3.2 years (range: 0.2–10 years). The mean time progression from mild dysarthria to anarthria was 5.6 ± 5.3 years (range: 1–14 years).

Gait disturbances were classified as (1) independent impaired gait, (2) device-dependent gait, and (3) wheelchair bound. The gait deterioration of 14 patients is shown in Fig 3. All patients progressed through at least 2 severity stages during the course of the study. The mean interval from independent gait to device-dependent gait was 3.5 years (range: 0.3–8.0 years). Among 7 patients, the mean time from device-dependent gait to becoming wheelchair bound was 2.6 years (range: 0.5–8 years). The mean time for these 7 patients to progress from independent impaired gait to the wheelchair-dependent stage was 6.2 ± 5.5

years (range: 1–16 years). One third of the studied patients became wheelchair bound during the course of the study.

Among the 134 previously reported patients, 30 patients were deceased at the time they were reported,[†] with a mean age of death of 10.5 ± 5.5 years (range: 3.9–26.0 years). One of our studied patients also died as a result of respiratory infection. The survival curve of 31 patients, including the 20 studied patients as censored cases (40%), is presented in Fig 4. The remaining 104 patients reported in the literature were not considered as censored because their status is unknown. The mean survival time was 19.0 ± 2.1 years (95% confidence interval: 14.9–23.0). The median survival time was 14.5 years (95% confidence interval: 11.7–17.3), indicating that the majority of patients died early, with a smaller number surviving with their disease for many years. The most common cause of death was respiratory tract infection (13 [43.4%]).[‡] One patient died as a result of neuroleptic malignant syndrome[8] and another as a result of complications of brain biopsy.[34] For the remaining 11 deceased patients, the cause of death was not reported.[§]

Genotype-Phenotype Correlation

As shown in Table 4, all patients had 2 mutations found in 2 alleles of either the *HEXA* gene, in patients with the TSV, or the *HEXB* gene, in patients with the SV. At least 1 of the mutations identified in each patient was a null mutation, which leads to an infantile phenotype (patients 1, 2, 3, 9–12, 14–19, and 21). Therefore, disease severity will be determined by the second mutant allele associated with a less severe phenotype. The rate of speech and gait deterioration showed a strong correlation with the genotype of the patients. Among patients with the TSV, the presence of an R178H mutation in one of the *HEXA* genes was associated with an early onset and rapid disease course (patients 12–14 and 19). The R178H is the classical B1 variant mutation at the catalytic site of β-hexosaminidase A and was originally described in the Portuguese population.[75,96,97] The mean age of disease onset was 1.8 years (range: 1.5–2.5 years), and the mean time to diagnosis was 1.4 years. The mean time from mild dysarthria to anarthria was 1.3 years (patients 13, 14, and 19), and the mean time to progress from independent impaired gait to becoming wheelchair bound was 1.2 years. Among the 7 patients who became wheelchair bound, 4 had the R178H mutation. In general, the most common symptoms/signs among patients with the R178H mutation were cerebellar symptoms, intellectual impairment, extrapyramidal and pyramidal signs, seizures, distal weakness, and poor weight gain.

In 5 patients from various ethnic backgrounds with an R499H mutation in one of their *HEXA* genes (patients 1–3, 11, and 15), the mean age of onset was 2.6 years (range: 2.0–3.0 years), and the interval between onset and diagnosis was 3.0 years. The R499H mutation causes loss of stabilization between domains I and II of the α-subunit without affecting the active site of the enzyme.[98] These patients progressed from having mild dysarthria to having anarthria in a mean time of 4.8 years. The most common symptoms at onset were speech problems and developmental delay. Intellectual impairment, along with incoordination,

[†]Refs 1, 8, 11, 13, 20, 24, 25, 27, 34, 36, 38, 42, 45, 56, 65, 68–70, 74, and 91.
[‡]Refs 1, 20, 25, 27, 29, 34, 38, 42, 56, 74, and 91.
[§]Refs 13, 20, 24, 27, 28, 36, 40, 45, 56, 65, 68, and 70.

diarrhea/constipation, and incontinence of sphincters and pyramidal signs, were particularly prominent in this group of patients.

Four patients who had 1 G269S mutation (patients 16–18 and 21) in one of the *HEXA* genes showed the mildest clinical course. G269S is one of the most common mutations found in the late-onset form of TSV and is also found in 2% of the Ashkenazi-Jewish population.[4] This mutation leads to defective processing and association of α with the β chain of β-hexosaminidase A.[99] The mean age of disease onset was 9.0 years (range: 6–11 years). The mean time to diagnosis was also the longest (21.4 years). The most frequent symptoms at onset observed in these patients were behavioral or psychiatric problems, along with proximal weakness, incoordination, and diarrhea/constipation. Two patients with the W474C mutation in a heterozygous state (patients 9 and 10) were siblings who showed the onset of symptoms at 10 and 15 years of age with developmental delay, behavioral problems, and incoordination. The W474C mutation encodes an α-subunit precursor that was normally synthesized but not phosphorylated or secreted.[100] The interval between the onset of symptoms and diagnosis was relatively short at 3.9 years. No patients with G269S or W474C mutations of the *HEXA* gene progressed to having severe dysarthria. In terms of the gait progression, only 1 patient (patient 17) with a G269S mutation was wheelchair bound, and it took 16 years to reach that stage.

The number of patients with the SV in our cohort was too small to make confident generalizations about the relationship between genotype and phenotype of the condition.

Neurologic Imaging Studies

Brain imaging studies were available for 17 of the 21 patients studied. The mean age of the first brain MRI was 9.7 ± 7.9 years (range: 1.8–28.6 years). Six (35.3%) patients with a mean age of 5.1 ± 1.8 years (range: 1.8–6.9 years) showed subcortical white matter changes along with some degree of cerebral and/or cerebellar atrophy. Four patients (23.5%) showed mild cerebellar and cerebral atrophy at a mean age of 11.4 ± 7.3 years (range: 5.3–15.6 years). Five patients (29.4%) showed severe cerebellar atrophy at a mean age of 18.6 ± 6.4 years (range: 6–28.6 years). One patient had a normal brain MRI at 3.3 years of age, and another had only a head CT scan that revealed moderate cerebral and cerebellar atrophy at 5.3 years of age. Magnetic resonance spectroscopy was performed for 5 patients and showed decreases of the normal *N*-acetylaspartic acid peak in 4 at a mean age of 13.0 ± 4.2 years (range: 6.9–16.0 years).

Among the 134 patients reported in the literature, 35 had brain imaging studies at a mean age of 28.7 ± 10.7 years (range: 16–42 years). Head CT scan was the only central nervous system imaging study reported for 18 patients, and brain MRI studies were reported for 14 patients. One patient had a pneumoencephalogram.[38] The most common finding was a moderate-to-severe degree of cerebellar atrophy, which was found in 15 (42.8%) of 35 patients at a mean age of 18.0 ± 13.3 years (range: 4–42 years). Mild generalized cerebral atrophy was noted in 7 (20%) of 35 patients at a mean age of 8.2 ± 4.2 years (range: 2.5–15 years).[11,13,70] Two patients showed white matter changes on brain MRI performed at 8 and 30 years of age.[52,81] Six of 35 (17.1%) patients showed normal neuroimaging studies at a mean age of 7.5 ± 7.9 years (range: 2.7–20 years).

DISCUSSION

Despite being well known as a cause of spinocerebellar symptoms and developmental delay in childhood, jGM2 is poorly studied with regard to the initial symptomatology and clinical course of the disease. We report here a comprehensive, combined retrospective and prospective study of 21 patients with the disease, supplemented by a review of another 134 patients previously reported as case reports or small series in the medical literature.

The definition of jGM2 is not always clear. The age of onset of earliest symptoms, rather than the age at diagnosis, is generally considered to distinguish patients with jGM2, and many would restrict the diagnosis to patients who show the onset of symptoms between 2 and 10 years of age.[7] A careful review of the clinical history of many cases classified as adult onset or chronic GM2 gangliosidosis showed that symptoms actually began in childhood and adolescence.[‖] This misclassification of patients with jGM2 has the effect of biasing our understanding of the clinical course of the disease by excluding patients with early onset of symptoms but a relatively mild and slowly progressive course. For our study, we classified patients as having jGM2 when symptoms first appeared between 1 and 18 years of age, which would include, by convention, all patients in the pediatric age group.

Our patients, derived from 2 widely separated medical centers in Canada and Brazil, were from many different ethnic backgrounds. The increased number of patients of Brazilian Portuguese and Brazilian Jewish extraction is not surprising, considering that one of the centers is located in Brazil. The R178H mutation, which accounted for 5 mutant *HEXA* alleles, was common in patients of Portuguese ancestry (patients 12–14 and 19). This is a common mutation associated with the B1 TSV and has been reported previously in patients of Portuguese ancestry.[96,97] The observation that this mutation was particularly common among the Brazilian patients suggests a founder effect. The relatively small proportion of patients of Ashkenazi Jewish ancestry was somewhat surprising, considering the frequency of *HEXA* mutations in members of this ethnic group. It is interesting to note that among the patients with the TSV, the most common mutation was the 1278insTACT, which is frequently found in Ashkenazi Jews[2,4]; however, only 3 patients reported being Jewish. All patients reported with this mutation were compound heterozygous, with a second mutant allele associated with a juvenile-onset phenotype (patients 1, 2, 9, 10, 16, and 17).

This study showed that gait and speech disturbances, along with incoordination, were the most common symptoms at the onset of disease symptoms (Fig 1). Behavioral or psychiatric symptoms, muscular weakness, intellectual impairment, and extrapyramidal signs were also frequently reported symptoms at disease onset (Fig 1). In general, the age of onset and prevalence of different clinical features in our group of 21 patients were similar to those reported for the 134 patients reported previously. However, some differences were found, particularly an earlier age of onset for muscle wasting, proximal and distal weakness, and extrapyramidal signs among our own patients. In addition, diarrhea/constipation complaints, sleep problems, sphincter incontinence, poor weight gain, and acroparesthesia were more common in our series of patients (Table 2). To some extent, this may be explained by

[‖]Refs 8, 10, 39, 46, 47, 49, 52, 55, 59, 60, 67, and 76.

incompleteness of the published accounts of the cases reported in the literature. Our experience would suggest that these problems may be more common than previously thought. Failure to recognize their importance might result in inappropriate investigation and unnecessary delays in diagnosis.

This study showed few differences in the clinical phenotypes when comparing TSV and SV. Among the 21 studied patients, we observed that the age of onset of dysphagia, sleep problems, and sphincter incontinence was earlier in patients with the TSV. Among the cases previously reported in the literature, the age of onset for muscle wasting was earlier in the patients with the SV. The prevalences of diarrhea/constipation and sleep problems were higher in patients with the SV. However, all remaining clinical features analyzed in our studied group, along with the previously reported cases, showed no statistically significant differences between the SV and TSV subgroups (Table 3).

Analysis of the median of symptom latencies (Table 1) provides a summary of the disease course. The gait disturbances were the earliest symptom, followed by speech problems, incoordination, intellectual impairment, seizures, extrapyramidal signs, incontinence of sphincters, and upper motor neuron signs. Dysphagia, along with diarrhea/constipation, tended to emerge later, with a median onset of 3 to 3.5 years. Behavioral or psychiatric problems, proximal and distal weakness, and muscle wasting also tended to appear late in the disease course.

Brain imaging studies showed that the most frequent finding in our studied patients and previously reported cases has been cerebellar atrophy, followed by generalized cerebral atrophy. It is interesting to note that the white matter changes and generalized cerebral atrophy seem to precede the appearance of cerebellar atrophy, which tends to be noted in the late teen years. Magnetic resonance spectroscopy has revealed low *N*-acetylaspartate concentrations in basal ganglia as the disease progresses, which is consistent with a recent publication that reported findings on an older population of the same chronic subtype of GM2 gangliosidosis.[101,102]

The Kaplan-Meyer survival curve (Fig 4) based on the 21 studied patients and 30 previously reported deceased patients is the first published analysis of survival in patients affected with jGM2. The survival curve indicates that nearly half of the patients affected with the condition die in the first decade. It also shows that fully one quarter of patients live into the late teen years.

Results of the analysis of genotype-phenotype correlations were instructive and indicate that prediction of the disease course and longevity on the basis of age of onset alone may be inaccurate. The presence of some mutations, such as R178H in the *HEXA* gene, along with a mutation generally associated with the infantile TSV phenotype (c.1278insTATC or c.1073 + 1G→A) predicts an early onset and relatively rapid course of disease. Similarly, the R499H allele, again in combination with a severe *HEXA* mutation, is associated with early and faster disease progression. However, in the latter, gastrointestinal, incontinence of sphincters, and pyramidal signs were more prominent. In contrast, the presence of G269S or W474C mutations is apparently associated with milder and more slowly progressive disease.

Patients with 1 of these 2 mutations along with a deleterious mutation in their *HEXA* genes showed more pronounced behavioral or psychiatric problems, proximal weakness, incoordination, and gastrointestinal problems.

One limitation of our study was the lack of more detailed information and data from previously reported cases in the literature. The majority of the publications were single case reports or retrospective cross-sectional studies of small series of cases; none of them report prospective clinical data obtained over a period of time. In the vast majority of these published reports, mutation information was lacking. Therefore, information about mutation identification was not included here. The number of patients with the SV makes generalizations on disease course or genotype-phenotype correlation more speculative. In terms of the neuroradiologic data, considerable interval variation in brain MRI/magnetic resonance spectroscopy occurred among the patients who underwent >1 imaging study.

Delineation of the natural history of jGM2 is an important requirement for the evaluation of new therapies currently in development for the treatment of the disease. The details of the natural history of the disease summarized here provide direction for the identification of useful clinical end points for emerging clinical trials of the treatment of jGM2. Our data also show that mutation analysis is potentially useful for predicting the clinical course of this debilitating inherited metabolic condition in individual patients.

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Abbreviations

jGM2	juvenile GM2 gangliosidosis
OMIM	Online Mendelian Inheritance in Man
TSV	Tay-Sachs variant
SV	Sandhoff variant
CT	computed tomography
MUG	4-methylumbelliferyl-β-*N*-acetyl glucosaminide
MUGS	4-methylumbelliferyl-β-*N*-acetylglucosaminide-6-sulfate

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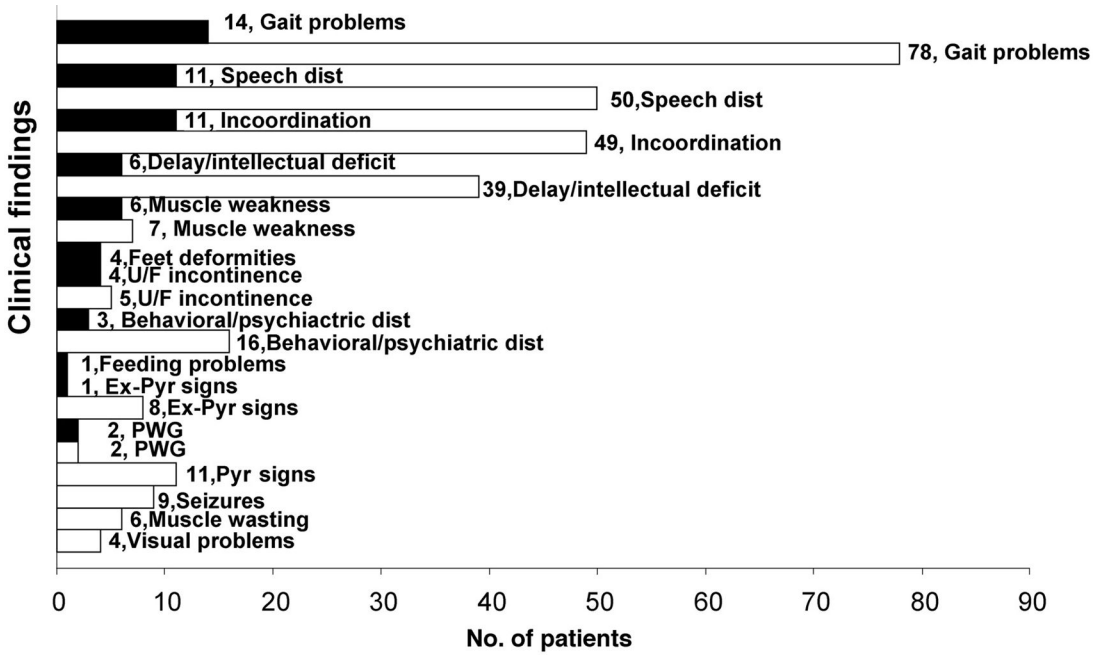

FIGURE 1.

Prevalence of clinical findings at onset in jGM2. Black bars represent number of patients from the studied group ($n = 21$); white bars represent number of patients previously reported ($n = 134$). U/F indicates urinary and fecal; dist, disturbances; Ex-Pyr, extrapyramidal; Pyr, pyramidal; PWG, poor weight gain; dist, disturbance.

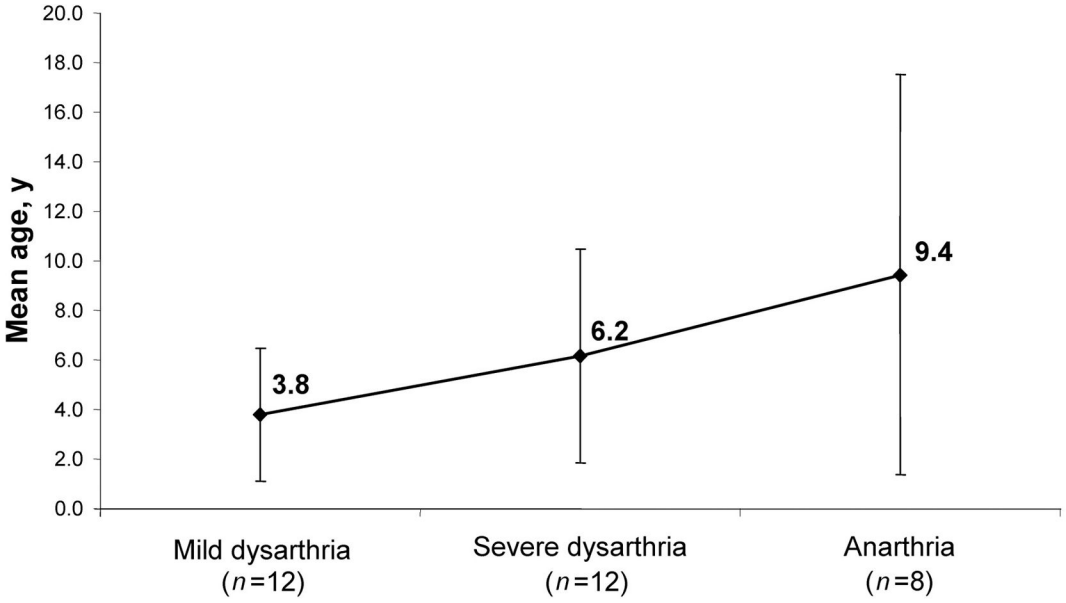

FIGURE 2.
Speech deterioration in jGM2. Shown are the means ± SDs.

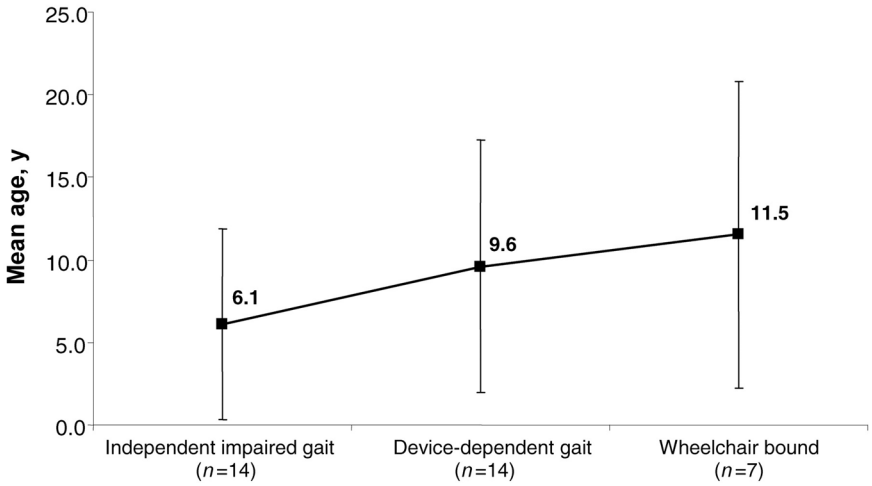

FIGURE 3.
Gait deterioration in jGM2. Shown are the means ± SDs.

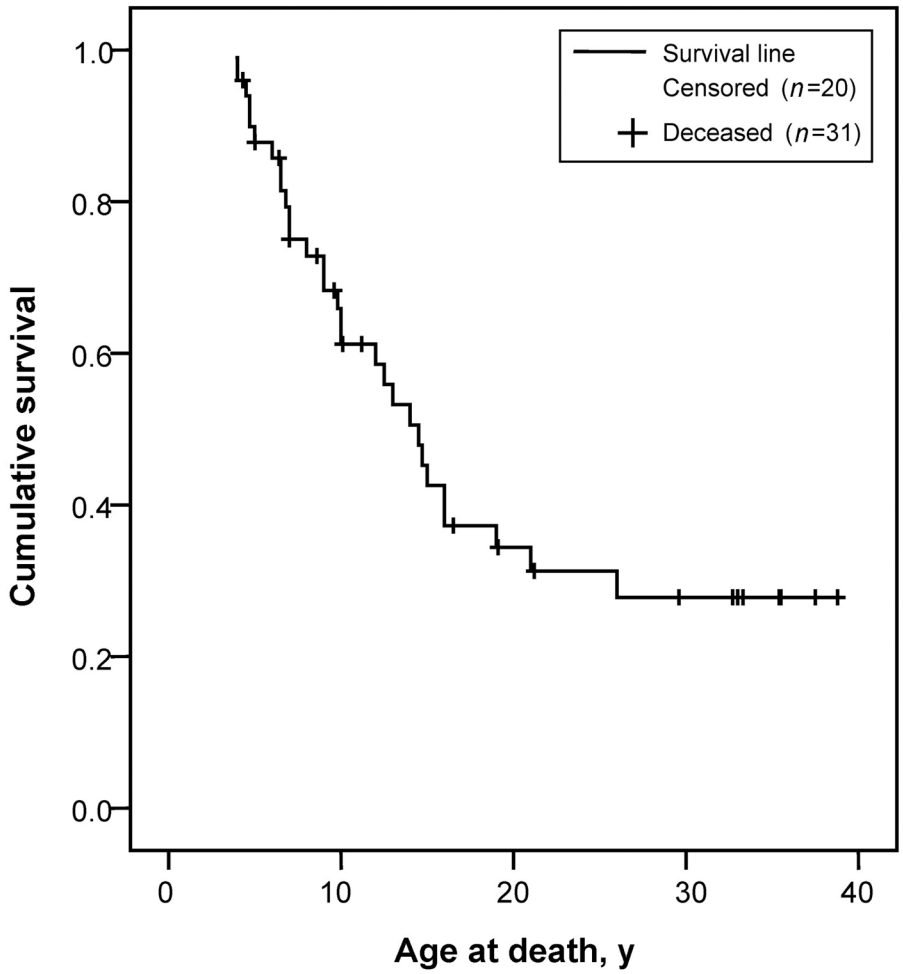

FIGURE 4.
Survival curve in jGM2.

TABLE 1

Median of Symptom Latency in jGM2

Clinical Features	Our Patients (*n* =21)			Previously Reported Patients (*n* =134)			Total (*N* =155)		
	Median Symptom Latency	Range of Symptom Latency (Mean)	No. of Patients With Latency >0	Median Symptom Latency	Range of Symptom Latency (Mean)	No. of Patients With Latency >0	Median Symptom Latency	Range of Symptom Latency (Mean)	No. of Patients With Latency >0
Gait problems	0	0–17.0 (5.4)	7	0	0–33.0 (5.1)	40	0	0–33.0 (5.2)	47
Speech problems	0	0–13.0 (3.6)	10	0.5	0–28 (5.2)	54	0.5	0–35.5 (4.4)	64
Incoordination	0	0–11.0 (3.9)	9	0	0–25.0 (4.6)	34	0	0–25.0 (4.2)	43
Intellectual impairment	0.5	0–17.0 (4.7)	11	0	0–28.0 (4.2)	31	0	0–28.0 (4.4)	42
Distal weakness	1.5	0–6.0 (2.8)	8	9.5	0–31.0 (12)	32	6.0	0–31.0 (7.4)	40
Poor weight gain	2.5	0–10 (5.9)	6	3.2	0–14.5 (7)	4	2.5	0–14.5 (6.4)	10
Seizures	2.7	0.5–5.0 (2.8)	8	2.0	0–29.5 (4.2)	36	1.4	0–29.5 (3.5)	44
Dysphagia	2.7	0.1–15.0 (5.3)	12	3.8	0–13.0 (4.7)	18	3.0	0–15.0 (5)	30
Pyramidal signs	3.4	0–12.0 (4.7)	15	3.5	0–35.5 (8.1)	63	3.4	0–35.5 (6.4)	78
Extra-pyramidal signs	3.5	0–2.0 (3.7)	7	3.0	0–33.0 (8.6)	24	3.0	0–33.0 (6.1)	31
Diarrhea/ constipation	3.7	0–17.0 (4.5)	15	3.0	0–7.0 (3.5)	10	3.0	0–17.0 (4)	25
Proximal weakness	4.0	0–16.0 (7.7)	10	8.5	0–30.0 (11.2)	39	8.5	0–30.0 (9.4)	49
Bladder/bowel incontinence	4.0	0–22.0 (10.5)	7	2.5	0–17.5 (5)	11	2.5	0–22.0 (7.7)	18
Muscle wasting	5.8	0–18.0 (6.9)	12	7.0	0–31.0 (12.4)	37	6.0	0–31.0 (9.6)	49
Visual problems	5.8	1–28 (9.3)	6	2.3	0–28 (8.3)	16	2.6	0–28 (8.8)	22
Behavioral symptoms	7.5	0–13.0 (8.4)	10	4.0	0–28.0 (9.2)	31	4.5	0–28.0 (8.8)	41

All values listed are years.

TABLE 2

Prevalence of Symptoms in jGM2

Clinical Features	Our Patients (N = 21)[a]		Previously Reported Patients (N = 134)[b]	
	n (%)	Age at Onset, Mean ± SD (Range), y	n (%)	Age at Onset, Mean ± SD (Range), y
Gait disturbances	21 (100)	7.1 ± 6.9 (1.5–27.0)	118 (88)	11.0 ± 7.0 (1.0–39.0)
Speech problems	21 (100)	7.0 ± 5.6 (2.0–19.0)	104 (77.6)	8.4 ± 7.9 (1.0–40.0)
Incoordination	20 (95.3)	6.8 ± 5.6 (1.5–20.0)	83 (62.4)	7.4 ± 6.1 (1.0–35.0)
Pyramidal signs	17 (81)	8.5 ± 4.5 (2.8–16)	73 (54.5)	12.2 ± 10.7 (2.0–40.0)
Intellectual impairment	17 (80.9)	7.8 ± 7.4 (1.6–26.0)	70 (52.2)	5.8 ± 5.6 (1.0–32.0)
Diarrhea/constipation	16 (76.2)[c]	8.6 ± 6.8 (2.0–27.0)	11 (8.2)	6.4 ± 3.0 (1.0–10.0)
Muscle wasting	14 (66.7)[d]	10.6 ± 7.4 (2.0–27.0)[c]	43 (32.3)	17.8 ± 11.2 (2.3–40.0)
Proximal weakness	13 (61.9)[d]	11.1 ± 7.7 (1.75–27.0)[d]	42 (31.3)	17.6 ± 10.4 (1.3–38.0)
Behavioral/psychiatric symptoms	13 (61.9)[d]	13.6 ± 6.0 (3.0–21.0)	47 (35.1)	12.1 ± 8.4 (1.2–35.0)
Dysphagia	12 (57.1)[c]	8.5 ± 7.4 (2.0–25)	19 (14.1)	9.0 ± 6.0 (2.1–22)
Distal weakness	11 (52.4)[d]	5.7 ± 3.0 (2.0–11.0)[c]	36 (26.9)	17.6 ± 10.2 (2.2–40.0)
Sleep problems	11 (52.4)[c]	10.9 ± 5.8 (2.0–18.0)	6 (4.5)	7.4 ± 3.9 (3.0–13.0)
Bladder/bowel incontinence	11 (52.4)[c]	14.6 ± 9.7 (5.5–28.0)	16 (11.9)	8.2 ± 5.3 (3.0–22.5)
Limb contractures	10 (47.6)[d]	8.1 ± 5.7 (1.5–17)	25 (18.6)	12.7 ± 10.7 (1.3–40.0)
Poor weight gain	9 (42.8)[c]	8.1 ± 4.1 (3.0–15.5)	6 (4.5)	8.9 ± 9.4 (2.0–27.0)
Extrapyramidal signs	8 (38.1)	6.0 ± 2.0 (2.5–8.0)[d]	32 (23.9)	10.8 ± 8.4 (1.5–40.0)
Seizures	8 (38.1)	8.0 ± 5.1 (2.0–7.5)	45 (33.6)	6.7 ± 6.4 (1.5–32.0)
Visual problems	6 (28.6)	11.9 ± 10.9 (2.5–30.0)	20 (14.9)	12.4 ± 12.2 (1.6–40.0)
Acroparestesia and/or neuropathy	3 (14.3)[c]	5.3 ± 3.1 (2.0–8.0)	3 (2.2)	17.3 ± 8.1 (10.0–26.0)

[a] Mean age at diagnosis: 12.3 ± 10.7 years.

[b] Mean age at diagnosis: 16.1 ±11.2 years.

[c] P <0.001.

[d] P <0.05.

TABLE 3

Tay-Sachs and Sandhoff Comparison in jGM2

Groups	Our Patients (*n* = 21)		Previously Reported Patients (*n* = 134)	
	TSV (*n* = 15)	SV (*n* = 6)	TSV (*n* = 96)	SV (*n* = 27)
Variants				
Age of disease onset, mean ± SD, y	5.4 ± 3.5	4.8 ± 4.4	5.8 ± 4.3	5.0 ± 3.3
Age at diagnosis, mean ± SD, y	13 ± 12.6	10.5 ± 3.3	17.2 ± 11.2	15.9 ± 11.8
Male/female	1.0	1.0	1.23[a]	0.93
Consanguinity, *n* (%)	0	1 (16.7)	11 (11.4)	14 (51.8)[b]
Clinical features, *n* (%); age of onset, mean ± SD				
Gait disturbances	15 (100); 7.9 ± 7.8	6 (100); 4.8 ± 3.4	88 (91.6); 7.5 ± 6.6	20 (74.1); 7.4 ± 8.4
Speech problems	15 (100); 6.5 ± 5.7	6 (100); 8.4 ± 5.6	92 (95.8); 9.1 ± 7.9	19 (70.4); 7.5 ± 9.1
Incoordination	13 (86.7); 6.5 ± 5.9	6 (100); 7.2 ± 5.3	60 (62.5); 7.7 ± 6.2	15 (55.5); 8.0 ± 8.4
Pyramidal signs	12 (80); 7.1 ± 4.5	5 (93.4); 9.2 ± 3.8	51 (53.1); 14.2 ± 11.5	15 (55.5); 9.0 ± 7.9
Intellectual impairment	13 (86.7); 7.4 ± 7.7	3 (50); 9.2 ± 6.9	45 (46.5); 7.1 ± 6.5	15 (55.5); 3.9 ± 2.3
Diarrhea/constipation	10 (66.7); 8.8 ± 8.1	6 (100); 8.8 ± 8.0	6 (6.2); 7.6 ± 2.8	5 (18.5); 5.7 ± 3.7[a]
Muscle wasting	8 (53.3); 9.0 ± 8.5	6 (100); 12.7 ± 5.4	32 (33.4); 20.5 ± 10.9	7 (25.9); 11.1 ± 9.8[a]
Proximal weakness	9 (60); 8.7 ± 5.8	4 (66.7); 16.5 ± 9.5	33 (34.4); 18.9 ± 10.2	7 (25.9); 12.8 ± 9.6
Behavioral and psychiatric problems	7 (46.7); 15.2 ± 6.0	6 (100); 11.7 ± 5.9[a]	35 (36.4); 13.2 ± 8.2	8 (29.6); 10.1 ± 9.6
Dysphagia	8 (53.3); 4.7 ± 2.3[b]	4 (66.7); 16.1 ± 8.5	12 (12.5); 10.4 ± 6.7	4 (14.8); 7.7 ± 4.4
Distal weakness	8 (53.3); 5.0 ± 2.8	3 (50); 7.5 ± 3.5	28 (29.2); 19.4 ± 10.1	6 (22.3); 11.2 ± 6.5
Sleep problems	7 (46.7); 8.6 ± 4.8	4 (66.7); 15.0 ± 5.3[a]	2 (2.1); 5.7 ± 2.5	5 (18.5); 8.2 ± 4.6[b]
Incontinence (bowel/urinary)	7 (46.7); 3.5 ± 4.8[b]	4 (66.7); 19.5 ± 10.2	10 (10.5); 5.7 ± 3.7	5 (18.5); 9.1 ± 8.5
Limb contractures	9 (60); 7.1 ± 5.0	1 (16.7); 17	17 (17.8); 13.8 ± 11.2	6 (22.3); 11.7 ± 10.8
Poor weight gain	6 (40); 9.7 ± 4.2	3 (50); 4.8 ± 1.0	4 (4.2); 10.0 ± 11.7	NR; NR
Extrapyramidal signs	7 (46.7); 6.6 ± 1.7	2 (33.3); 4.2 ± 2.5	24 (25.0); 11.0 ± 10.6	5 (18.5); 13.3 ± 14.7
Seizures	7 (46.7); 5.2 ± 2.1	1 (16.7); 4	1 (1.0); 7.5 ± 7.4	7 (25.9); 5.4 ± 4.7
Visual problems	4 (26.7); 7.2 ± 6.8	2 (33.3); 16.7 ± 9.2	2 (2.1); 14.3 ± 12.9	3 (11.1); 5.4 ± 3.3
Acroparestesia and/or neuropathy	1 (6.7); 2	2 (33.3); 7.0 31.4[a]	2 (2.1); 26 37.0[a]	1 (3.7); 10.0

NR indicates not reported.

[a] $P < .05$.

[b] $P < .001$.

TABLE 4

Hexosaminidase Activity and Mutation Description

Patients	Diagnostic Hexosaminidase Activity				Mutations 1 and 2	Amino Acid Alteration 1	Amino Acid Alteration 2
	T Hex, nmol/mg protein per h	β-Hexosaminidase B, nmol/mg protein per h	β-Hexosaminidase B, %	β-Hexosaminidase A, %			
TSVs					*HEXA* gene		
1	2021(l)	1778(l)	88	12	c.1496G→A/c.1278insTATC	R499H	Frameshifting →stop codon
2	681(l)	646(l)	95	5	c.1496G→A/c.1278insTATC	R499H	Frameshifting →stop codon
3	739(l)	716(l)	97	3	c.1496G→A/c.1073 →1G→A	R499H	Cryptic donor splice site
9	392(l)	349(l)	89	11	c.1422G→C/c.1278insTATC	W474C	Frameshifting →stop codon
10	389(l)	334(l)	86	14	c.1422G→C/c.1278insTATC	W474C	Frameshifting →stop codon
11	1173(l)	1009(l)	86	14	c.1496G→A/c.1073 →1G→A	R499H	Cryptic donor splice site
12	798(p)	487(p)	61	39[a]	c.533G→A/c.1510delC	R178H	Frameshifting →stop codon
13	1253(p)	714(p)	57	43[b]	c.533G→A/c.533G→A	R178H	R178H
14	647(p)	355(p)	55	45[c]	c.533G→A/c.681C→G	R178H	Y227 →stop codon
15	7664(f)	7334(f)	95.7	4.3	c.1496G→A/c.1330 →1G→A	R499H	Cryptic donor splice site
16	1166(p)	1003(p)	86	14	c.805G→A/c.1278insTATC	G269S	Frameshifting →stop codon
17	1096(p)	919(p)	84	16	c.805G→A/c.1278insTATC	G269S	Frameshifting →stop codon
18	870(p)	835(p)	96	4	c.805G→A/c.1278insTATC	G269S	Frameshifting →stop codon
19	465(p)	251(p)	54	46[d]	c.533G→A/c.1495C→T	R178H	R499C
21	1202(l)	1166(l)	97	3	c.805G→A/c.672 →1G→A	G269S	Frameshifting
SVs					*HEXB* gene		
4	82(l)	ND(l)	0	100	c.1514G→A/IVS11→5G→A	R505Q	Cryptic splice site
5	51(l)	ND(l)	0	100	c.1514G→A/IVS11→5G→A	R505Q	Cryptic splice site
6	126(l)	21(l)	16.7	83.3	c.410G→A/c.410G→A	C137Y	C137Y
7	36(p)	ND(p)	0	100	c.796T→G/IVS12–26G→A	Y266D	Cryptic splice site
8	230(f)	ND(f)	0	100	c.796T→G/IVS12–26G→A	Y266D	Cryptic splice site
20	65(l)	ND(l)	0	100	c.1057G→C/IVS12–26G→A	G353R	Cryptic splice site

Patients are listed according to the order of ascertainment. T Hex indicates total hexosaminidase activity (nmol/mg protein per hour) determined in the use of the synthetic neutral substrate (MUG) on the basis of the assay conditions described in the main text. β-Hexosaminidase A, heat-labile hexosaminidase; β-hexosaminidase B, heat-stable hexosaminidase. In patients with the Tay-Sachs-B1 variant, who typically show normal β-hexosaminidase A% (patients 12, 13, 14, and 19), β-hexosaminidase A–specific activity was performed in the use of the sulfated substrate (MUGS). (p) indicates plasma (reference

range for T Hex: 2400 ± 488 nmol/mL per hour; for β-hexosaminidase B: 30%– 45%); (l), leukocytes (reference range for T Hex: 961–1576 nmol/mg protein per hour; for β-hexosaminidase B: 30%–45%); (f), fibroblasts (reference range for T Hex: 4900–21 000 nmol/mg protein per hour; for β-hexosaminidase B: 30%– 45%); ND, not detected.

a–d β-hexosaminidase A specific activity of 4.8, 14.5, 6.7, and 9.1 nmol/mg protein per hour, respectively (in leukocytes, reference range: 150–390 nmol/mg protein per hour);