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KEY WORDS

infantile G_{M2} gangliosidosis, natural history, Tay Sachs, Sandhoff, survival, lysosomal disorders, neurodegeneration

ABBREVIATIONS

G_{M2}—monosialoganglioside 2
HEXA—β-hexosaminidase A
HEXB—β-hexosaminidase B
G_{M2}A—G_{M2} activator
NTSAD—National Tay Sachs Allied Diseases Association
HSCT—hematopoietic stem cell transplant
GT—gastric tube

Drs Eichler and Tifft developed surveys at Massachusetts General Hospital and the National Institutes of Health; Mrs. Kubilus identified and recruited patients through the NTSAD database and distributed surveys, deidentified them, and forwarded them to Drs Bley and Eichler and Ms. Giannikopoulos; Drs Bley and Eichler and Ms. Giannikopoulos analyzed the data; and Mr. Hayden performed the statistical analyses of the data.

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WHAT'S KNOWN ON THIS SUBJECT: G_{M2} gangliosidosis is an autosomal recessive inherited condition of the nervous system with a heterogeneous clinical spectrum. Infants are affected most severely, but the pace and characteristics of neurologic decline and factors that affect survival have not been systematically described.

WHAT THIS STUDY ADDS: This is the largest cohort of infantile G_{M2} gangliosidosis studied to date. This article presents the first survival estimates and quantifies the gain and loss of specific developmental milestones in these patients.

abstract

OBJECTIVE: G_{M2} gangliosidoses are caused by an inherited deficiency of lysosomal β-hexosaminidase and result in ganglioside accumulation in the brain. Onset during infancy leads to rapid neurodegeneration and death before 4 years of age. We set out to quantify the rate of functional decline in infantile G_{M2} gangliosidosis on the basis of patient surveys and a comprehensive review of existing literature.

METHODS: Patients with infantile G_{M2} gangliosidosis ($N = 237$) were surveyed via questionnaire by the National Tay Sachs & Allied Diseases Association (NTSAD). These data were supplemented by survival data from the NTSAD database and a literature survey. Detailed retrospective surveys from 97 patients were available. Five patients who had received hematopoietic stem cell transplantation were evaluated separately. The mortality rate of the remaining 92 patients was comparable to that of the 103 patients from the NTSAD database and 121 patients reported in the literature.

RESULTS: Common symptoms at onset were developmental arrest (83%), startling (65%), and hypotonia (60%). All 55 patients who had learned to sit without support lost that ability within 1 year. Individual functional measures correlated with each other but not with survival. Gastric tube placement was associated with prolonged survival. Tay Sachs and Sandhoff variants did not differ. Hematopoietic stem cell transplantation was not associated with prolonged survival.

CONCLUSIONS: We studied the timing of regression in 97 cases of infantile G_{M2} gangliosidosis and conclude that clinical disease progression does not correlate with survival, likely because of the impact of improved supportive care over time. However, functional measures are quantifiable and can inform power calculations and study design of future interventions. *Pediatrics* 2011;128:e1233–e1241

Monosialoganglioside 2 (G_{M2}) gangliosidoses represent a heterogeneous autosomal recessive group of disorders caused by deficiency of the lysosomal enzyme β hexosaminidase.[1] The resulting accumulation of ganglioside G_{M2} occurs primarily in neuronal cells and coincides with a progressive broad spectrum of neurologic deterioration. The classic infantile form is known to lead to death between 3 and 5 years of life, but the rate of functional decline remains poorly defined. The juvenile- and adult-onset variants of the hexosaminidase deficiencies have later onset, slower progression, and more variable neurologic findings.[2,3]

β hexosaminidase consists of 2 major isoenzymes: β-hexosaminidase A (HEXA) and β-hexosaminidase B (HEXB); it needs a noncatalytic G_{M2} activator for G_{M2} ganglioside hydrolysis. Isoenzyme HEXA has the structure $\alpha\beta$, and isoenzyme HEXB consists of a $\beta\beta$ structure. Subunit α is encoded by the gene *HEXA*, subunit β is encoded by *HEXB*, and *$G_{M2}A$* encodes the G_{M2} activator. Mutations in these 3 genes result in the 3 major forms of G_{M2} gangliosidoses: (1) Tay Sachs disease, caused by mutations of *HEXA* that result in a deficiency of HEXA but normal HEXB activity; (2) Sandhoff disease, caused by mutations of *HEXB* that result in a deficiency of both isoenzymes HEXA and HEXB; and (3) the AB variant, caused by mutations in *$G_{M2}A$* that result in detectable activities of HEXA and HEXB but an inability to form a functional ganglioside G_{M2}/G_{M2}A complex. The incidence of the Tay Sachs variant in the general population is estimated to be 1 in 222 000 live births[4]; Sandhoff-variant incidence has been reported at 1 in 422 000.

Recently, correction of the gene and enzyme has been achieved in animal models of GM gangliosidoses with gene delivery of the lysosomal enzymes using adeno-associated viral vectors.[5–7] The observed benefits are encouraging and support the development of human clinical trials. We set out to quantify functional status and its variability over time and establish a scoring system that could be applied to future clinical trials. The study was facilitated by access to patients through the National Tay Sachs & Allied Diseases Association (NTSAD), an advocacy organization.

METHODS

Identification and Recruitment of Patients

A survey was developed at Massachusetts General Hospital (MGH) and the National Institutes of Health (Drs Eichler and Tifft) (see Supplemental Appendix). Patients were identified and recruited through the NTSAD database. This database included contact information for families of 237 patients with infantile G_{M2} gangliosidosis. Surveys were distributed to these families and returned to the NTSAD, where they were deidentified. Anonymized surveys were received and analyzed at MGH (by Drs Bley, Giannikopoulos, and Eichler). The study was approved by the MGH institutional review board, which granted a waiver of written consent (because replying to the NTSAD and completing questionnaires provided implied consent). Patients who had received an experimental treatment such as a hematopoietic stem cell transplant (HSCT) were evaluated separately. Data from patients whose families did not respond but for whom life-span data were available were also analyzed. In addition, we searched PubMed with key words "Tay Sachs" (1597 resulting articles) and "G_{M2} gangliosidosis not Tay Sachs" (412 resulting articles) for articles from 1946 onward, and additional references of review chapters provided literature dating back to 1881. Articles in English, German, Spanish, French, Italian, and Portuguese were screened for case reports with a description of the life span of children with infantile G_{M2} gangliosidosis. Inclusion criteria were a confirmed diagnosis of Tay-Sachs disease/Sandhoff disease/G_{M2} gangliosidosis with a compatible clinical description of the clinical course of the disease and/or description of a cherry red spot within the older literature.

Statistics

We performed descriptive statistical calculations to summarize the clinical findings from our survey patients. Patients who had received an HSCT were analyzed separately. The median survival rate was calculated by using the Kaplan-Meier method. Survival curves among survey patients, patients from the NTSAD database, and patients from the literature were compared by using the log-rank test.

From the clinical information in the surveys, the life span of patients with symptoms in the first 6 months of life was compared with that of the patients with later symptom onset. We also compared the life span of patients who had received a gastric tube (GT) to that of the patients who had not. G_{M2} variants and gender were compared with a Student's *t* test.

A Spearman rank correlation was performed for the most commonly reported symptoms. For the correlation analysis, missing data were mean-imputed, and the month of functional loss was set to 0 (the worst possible outcome) for patients who never attained the function. A Cox proportional hazards model was used to determine independent predictors of survival.

RESULTS

Patient Population

Survey data were available for 97 patients (41% of contacted families). The majority (85%) of the surveys were com-

pleted by the patient's mother. Life-span data on an additional 103 patients (88 deceased, 15 alive) were obtained from the NTSAD database. Life-span data on 121 patients (all deceased) was extracted from the literature.[8–75] Information from the survey, the NTSAD database, and the literature was used to report on survival. Information from surveys alone was used to report on symptoms and functional domains.

Our survey included 49 boys (50%) and 48 girls (50%). Twenty-two patients (23%) had infantile Sandhoff disease, and 75 (77%) had infantile Tay-Sachs disease. All responding patients with the AB variant had onset later than in infancy and were excluded from our analysis. Of the 97 patients, 78 (80%) were deceased. Five of the 97 patients (5%) had undergone an HSCT and were evaluated separately. Hence, 92 patients formed the basis of our analysis (Tables 1–5).

TABLE 1 Ethnic Background of the Patients With Infantile G_{M2} Gangliosidosis

Ethnicity	Percentage of Survey Population
Mixed	51
Unknown	23
Jewish	17
British	2
Indian	2
Hispanic	1
German	1
Filipino	1
Black/African American	1
Cajun	1

Ethnicity

Details of ethnicity as determined by the ethnic background of the 4 grandparents are shown in Table 1. Only 17% were of 100% Jewish ancestry, and another 10% had some Jewish ancestry. Patients of Jewish ancestry had no difference in survival rate or rate of functional decline.

Survival

The median life span of patients increased over time in all 3 groups analyzed (surveys, NTSAD database, literature) (Fig 1). The literature included only deceased patients, and their life span was shorter than that in the survey data. Kaplan-Meier curves for patients in the surveys and the NTSAD database are shown in Fig 2. Patients with Tay Sachs disease had an identical median life span compared with that of patients with Sandhoff disease (47 months). There was a trend for improved survival rates in patients who had had a

TABLE 2 Characteristics of the Patients With Infantile G_{M2} Gangliosidosis

Group	Total ($N = 92$)	Tay Sachs Disease ($n = 72$)	Sandhoff Disease ($n = 20$)
Variants			
Age at disease onset, mean ± SD, mo	5.0 ± 3.3	5.2 ± 3.2	4.4 ± 3.5
Age at diagnosis, mean ± SD, mo	13.3 ± 5.3	13.1 ± 4.7	14.0 ± 7.1
Male/female, *n*/*n*	46/46	36/36	10/10
Clinical features at onset, *n* (%)[a]			
Not making milestones	76 (83)	58 (81)	18 (90)
Exaggerated startle response	60 (65)	46 (64)	14 (70)
Low muscle tone	55 (60)	42 (58)	13 (65)
Fine motor problems	39 (42)	28 (39)	11 (55)
Visual problems	38 (41)	28 (39)	10 (50)
Seizures	38 (41)	28 (39)	10 (50)
Loss of motor skills	36 (39)	27 (38)	9 (45)
Decreased responsiveness	36 (39)	27 (38)	9 (45)
Failure to thrive	24 (26)	15 (21)	9 (45)
Sleep disturbance	19 (21)	12 (17)	7 (35)
Screaming episodes	15 (16)	12 (17)	3 (15)
Irritability	15 (16)	12 (17)	3 (15)
Abnormal movements	14 (15)	8 (11)	6 (30)

[a] In decreasing order of prevalence.

TABLE 3 Developmental Milestones in Infantile G_{M2} Gangliosidosis: Gain and Loss

Milestones of Normal Development	Patients Who Gained Function, *n* (%)	Patients Who Lost Function, *n*/*N* (%)	All Patients ($n = 92$), Age of Gain, Mean ± SD, mo	All Patients ($n = 92$), Age of Loss, Mean ± SD, mo	Tay Sachs Disease ($n = 72$), Age of Gain, Mean ± SD, mo	Sandhoff Disease ($n = 20$), Age of Gain, Mean ± SD, mo	Normal Age of Gain (DDST II), Mean, mo
All study children							
Head control	82 (89)	55/82 (67)	4.1 ± 2.2	15.3 ± 9.7	4.2 ± 2.4	4.0 ± 1.6.0	3.5
Ability to vocalize	74 (80)	63/74 (85)	4.4 ± 3.6	14.2 ± 5.9	4.4 ± 3.8	4.4 ± 1.8	1.9/5[a]
Reach for object	86 (93)	79/86 (92)	4.8 ± 1.8	16.0 ± 8.1	5.0 ± 1.9	4.3 ± 1.2	4.6
Transfer from hand to hand	66 (72)	53/66 (80)	6.5 ± 2.4	13.6 ± 8.1	6.2 ± 1.9	7.4 ± 3.3	6.0
Sitting without propping	51 (55)	51/51 (100)	6.8 ± 1.5	13.1 ± 6.7	7.0 ± 1.5	6.1 ± 1.4	5.9
5 study children with HSCT[b]							
Head control	5 (100)	4/5 (80)	4.0	24.0 ± 17.0	—	4.0	3.5
Ability to vocalize	4 (80)	3/4 (75)	2.0 ± 1.0	9.0 ± 4.2	1.0	2.5 ± 0.7	1.9/5.0[a]
Reach for object	4 (80)	79/86 (92)	4.0 ± 2.0	13.3 ± 9.5	6.0	3.0 ± 1.4	4.6
Transfer from hand to hand	66 (72)	53/66 (80)	4.5 ± 2.1	15.0 ± 12.7	—	4.5 ± 2.1	6.0
Sitting without propping	0 (0)	—	—	—	—	—	—

DDST II indicates Denver Developmental Screening Test II.

[a] Average age for vocalizing is listed for both squealing (1.9 months) and imitating sounds (5 months).

[b] The 5 patients (3 with Tay Sachs disease, 2 with Sandhoff disease) who had undergone an HSCT showed no significant differences, and no milestones were gained after the procedure.

TABLE 4 Caregivers Reporting on Developmental Milestones

Milestones of Normal Development	Caregivers Reporting on Gain, *n*/*N* (%)	Caregivers Reporting on Loss, *n*/*N* (%)	Caregivers Reporting on Age of Gain, *n*/*N* (%)	Caregivers Reporting on Age of Loss, *n*/*N* (%)
Head control	88/92 (96)	60/82 (73)	48/88 (55)	33/60 (55)
Ability to vocalize	90/92 (98)	74/74 (100)	48/92 (52)	47/74 (64)
Reach for object	92/92 (100)	86/86 (100)	59/92 (64)	46/86 (53)
Transfer from hand to hand	90/92 (98)	65/66 (98)	36/90 (40)	24/65 (37)
Sitting without propping	89/92 (97)	51/51 (100)	44/89 (49)	41/51 (80)

TABLE 5 Prevalence and Timing of Neurologic Signs and Symptoms of Infantile G_{M2} Gangliosidosis

Symptoms[a]	Patients, *n* (%)	All Patients (*n* = 92), Age at Onset, Mean ± SD, mo	Tay Sachs Disease (*n* = 72), Age at Onset, Mean ± SD, mo	Sandhoff Disease (*n* = 20), Age at Onset, Mean ± SD, mo
Exaggerated startle response	90 (98)	7.9 ± 6.6	8.1 ± 6.4	7.2 ± 7.4
Seizures	90 (98)	17.4 ± 5.9	16.8 ± 5.5	19.5 ± 7.0
Diminished eyesight	78 (85)	17.9 ± 11.3	18 ± 11.6	17.6 ± 11.0
Hypotonia	63 (68)	10.9 ± 3.9	10.8 ± 3.6	11.3 ± 5.0
No eyesight	63 (68)	28.4 ± 14.7	30 ± 14.8	16 ± 7.2
Spasticity	56 (61)	16.3 ± 11.4	17.4 ± 13.2	13.4 ± 4.5
Decreased hearing	45 (49)	22.8 ± 15.1	24.1 ± 13.7	19 ± 21.9
Loss of hearing	31 (34)	23.8 ± 17.3	23.8 ± 17.3	—
Screaming episodes	31 (34)	13.9 ± 8.6	13.7 ± 8.9	14.6 ± 8.4
Dyskinesia	21 (23)	18.6 ± 11.5	18.3 ± 10.0	19.5 ± 17.2
Ataxia	11 (12)	16.3 ± 10.1	13.8 ± 6.9	37

[a] In decreasing order of prevalence.

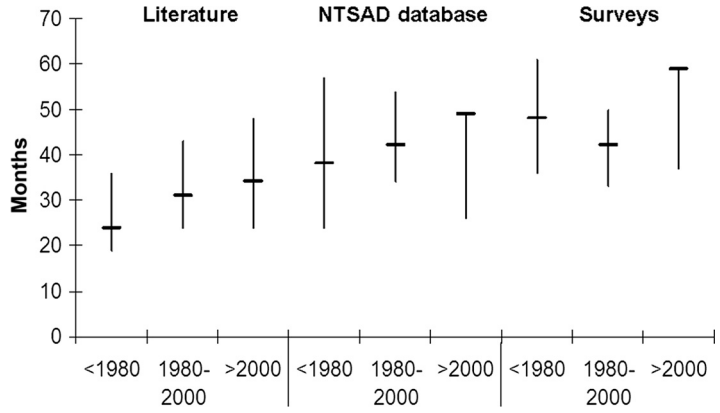

FIGURE 1
Mortality data according to cohort and birth year for patients with infantile G_{M2} gangliosidosis. Shown are the median and interquartile range.

GT placed (hazard ratio: 0.597; P = .0687), which indicates that within any given month their probability of dying was ~60% compared with those patients without a GT.

Onset of Disease

The mean age at onset of the earliest symptom was 5.0 ± 3.3 months (Table 2). The average age at diagnosis of our patients with G_{M2}-gangliosidoses was 13.3 ± 5.3 months. Patients who had an onset of symptoms between 0 and 6 months of age had the same life span as patients who had their first symptoms thereafter. The most common initial symptoms were developmental arrest (83%), abnormal startle response (65%), and low muscle tone (60%). Data from 62 of the patients (67%) indicated that the finding of a cherry-red spot by an ophthalmologist triggered testing that led to the diagnosis.

Developmental Milestones and Neurologic Symptoms

The majority of infants were able to acquire at least some developmental milestones. Those that gained milestones acquired them at the appropriate age according to the Denver Developmental Screening Test II (Fig 3, Tables 3–5). More caregivers answered the inquiries on gain and loss of milestones (~90%–100%) than on exact timing of those gains and losses (~40%–60%) (Table 4).

More infants gained earlier milestones than later milestones. For example, 93% of those in our cohort learned to reach for an object. They gained this skill at an average age of 4.8 ± 1.8 months, which is slightly later than the normal range (2.5–4.0 months on the Denver Developmental Screening Test II [DDST II]). The mean time span for retaining this ability was 12.1 ± 8.7 months. Seventy-two per-

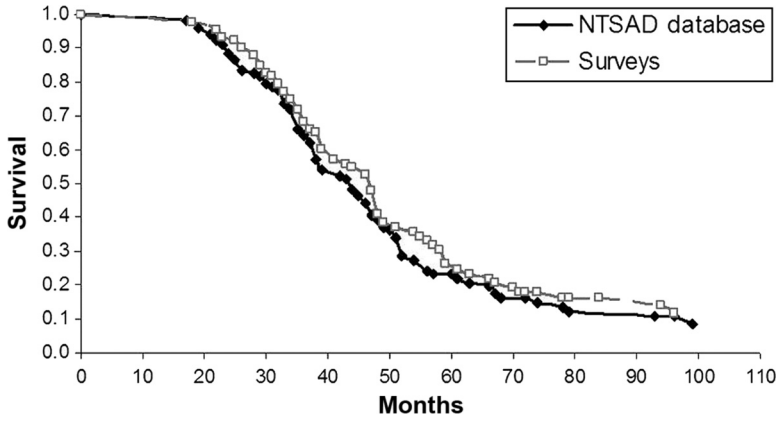

FIGURE 2
Survival curves for patients with infantile G_{M2} gangliosidosis.

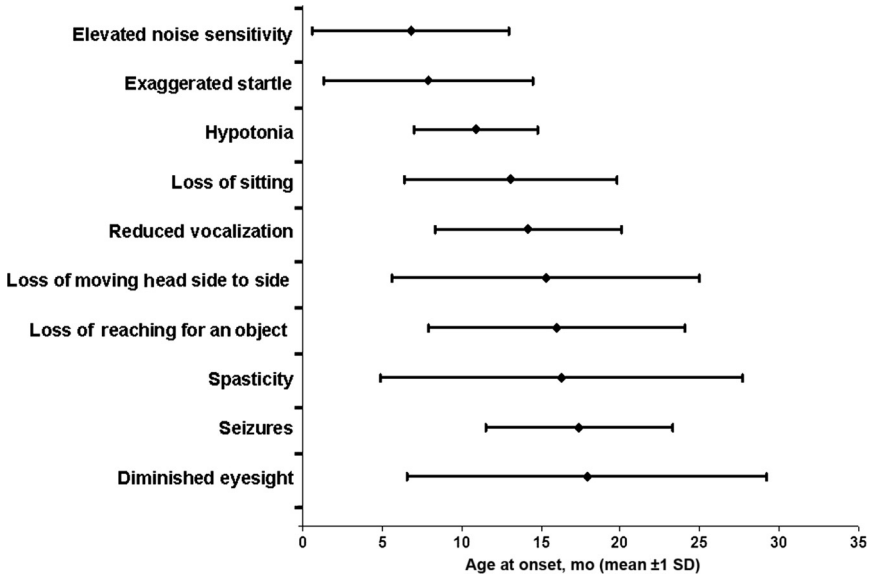

FIGURE 3
Disease progression of infantile G_{M2} gangliosidosis.

cent of those in our cohort learned to transfer an object from one hand to the other. The skill was gained at an average age of 6.5 ± 2.4 months, which is within the normal range (5–8 months on the DDST II). There was good correlation between certain functions. Patients who gained the ability to sit retained the ability to transfer an object from one hand to the other longer (11.2 ± 9.5 months) than infants who were never able to sit without propping (3.6 months ± SD). Spearman Rank correlation coefficient between time of losing ability to sit and ability to transfer from one hand to the other was $\rho = 0.464$ [$P < .0001$]. It is interesting to note that there was an excellent correlation between caregiver-reported onset of increased startle response and increased auditory sensitivity ($\rho = 0.79$ [$P < .0001$]). There was little correlation between onset of startle and onset of seizures ($\rho = 0.19$ [$P = .06$]).

Most of the patients developed seizures (98%). Most patients required multiple anticonvulsant medications for seizure control (only 23 patients required only 1 anticonvulsant versus 43 patients who required ≥2 of them). Only a few caregivers reported the use of antispasmodic medications, whereas tranquilizers and pain medications were used more frequently. The medications used by these patients are listed in Supplemental Table 7.

Medical Management

Sixty-nine patients (75%) were partially or completely fed by a GT. Seventeen infants underwent gastric surgery with fundoplication. Poor handling of mucus and respiratory congestion are common problems in patients with G_{M2} gangliosidoses. Parents and guardians of 85 of the children (92%) reported that the infants choked on mucous or oral secretions. The average age of onset was 22 months. Eighty-one infants (88%) needed regular suctioning.

Hematopoietic Stem Cell Transplant.

Of the 5 patients who had undergone an HSCT, 2 had a diagnosis of Sandhoff disease and 3 had a diagnosis of Tay Sachs disease (Table 3). Their average age of symptom onset was 3.8 ± 2.6 months. The average age at diagnosis was 8.8 ± 5.0 months. None of the infants gained the ability to sit without propping. All of them suffered from excessive startle, diminished hearing and eyesight, and spasticity. The average age of HSCT was 10.4 ± 5.8 months. After HSCT, no milestones were gained.

Of the 5 patients, 4 had died and 1 was still alive at the time of the survey. The median life span of the deceased patients was 64 months, but that was not significantly different from that of the patients who had not undergone an HSCT. One patient reportedly died from complications of the HSCT procedure, 2 died from "primary disease," and 1 died from aspiration pneumonia.

End of Life

Most of the children (60 of 74 [81%]) died at home, only 9 (12%) died in a hospital, and 5% were reported to have died in a hospice. The most common stated cause of death was primary disease (34 of 74 [46%]), followed by aspiration pneumonia (17 of 74 [23%]). Five patients (7%) died from seizures.

DISCUSSION

We report for the first time, to our knowledge, the results of a systematic analysis of milestones during the natural history of infantile G_{M2} gangliosidoses. In our comprehensive retrospective study we analyzed the neurologic symptoms of 92 patients and compared their survival rate to that of 121 cases from the literature and 103 patients from the NTSAD database.

Our study revealed that more than half of the infants with G_{M2} gangliosidoses attained initial motor developmental milestones. It was surprising that the infants with G_{M2} gangliosidoses who attained milestones did so within the standard range of normal development. The majority of infants achieved early motor milestones, such as head control, reaching, and transferring. Those who did not attain initial milestones tended not to gain that ability later in life. Hence, developmental delay is less a feature of infantile G_{M2} gangliosidosis than frank regression.

The average age at first symptom was 5.0 ± 3.3 months. However, despite the early and progressive symptoms, the diagnosis was, on average, not established until 13.3 months. Misdiagnoses listed in our surveys included cerebral palsy and mitochondrial disorders. Remediating this delay in diagnosis is crucial to therapeutic efforts, because the window for intervention might be brief and later efforts might be futile.

Hypotonia and acoustic hypersensitivity were among the most common early symptoms, followed by hypertonia/spasticity and subsequent loss of hearing. Other early signs and symptoms included a loss of manual dexterity and vocalization and diminished eyesight. Only 55% of the children in our cohort learned to sit without support, and most of those who gained this ability lost it within 1 year (see Table 3). If an infant did not gain the ability to sit by 10 months, he or she did not gain that skill thereafter. The combination of exaggerated startle response and low tone is relatively uncommon and should prompt the general practitioner and neurologist to consider G_{M2} gangliosidosis as a diagnosis.

Seizures were a late but common symptom. Early seizures seemed to be a marker of disease severity, or at least worse motor developmental outcomes. For example, those infants who had seizures within their first 12 months of life retained the ability to sit for an average of only 3.5 months, whereas some infants with seizures after 12 months retained the ability to sit for as long as 14 months. Once in an advanced stage, seizures were often the focus of clinical care, necessitating multiple anticonvulsant medications, the adverse effects of which were burdensome for the patients and caregivers. This highlights the importance of ongoing multidisciplinary care with a neurologist and palliative care specialist to help optimize symptom control and minimize drug-related morbidity.

On the basis of our findings in infants with G_{M2} gangliosidosis, we propose a clinical severity scoring system that rates disease severity according to the time at which abilities are lost or new abnormal symptoms arise (Fig 3, Tables 3–6). On our scale, earlier occurrence is scored higher than later occurrence. The less severe the disease, the longer the functions persist. The age cutoffs for loss of abilities or development of symptoms are based on the average age of symptom occurrence plus 1 SD in our population of patients with G_{M2} gangliosidosis. Patients who develop symptoms before the cutoff receive 2 points, and those who develop them at or after the cutoff receive 1 point. Because of the temporal aspect of the scoring system, some points might still be added up to 4 years of age. We are currently planning a prospective study for validation of this scoring system.

TABLE 6 Clinical Severity Score of Infantile G_{M2} Gangliosidosis

2 Points	1 Point	0 Points
Increased noise sensitivity at <14 mo	Increased noise sensitivity at ≥14 mo	No increase in noise sensitivity
Muscle hypotonia at <16 mo	Muscle hypotonia at ≥16 mo	No muscle hypotonia
Startling at <16 mo	Startling at ≥16 mo	No startling
Loss of sitting at <21 mo	Loss of sitting at ≥21 mo	Able to sit
Reduced vocalization at <21 mo	Reduced vocalization at ≥21 mo	Able to vocalize
Seizures at <24 mo	Seizures at ≥24 mo	No seizures
Loss of reaching for an object at <25 mo	Loss of reaching for an object at ≥25 mo	Able to reach for an object
Loss of moving head side to side at <26 mo	Loss of moving head side to side at ≥26 mo	Able to move head side to side
Spasticity at <29 mo	Spasticity at ≥29 mo	No spasticity
Diminished eyesight at <30 mo	Diminished eyesight at ≥30 mo	Normal eyesight

The higher the score, the more advanced the disease.

The Kaplan-Meier survival curves (Fig 2) (based on 92 survey patients and 103 patients from the NTSAD database) are, to our knowledge, the first published analysis results of survival in patients affected by infantile G_{M2} gangliosidosis. These survival curves confirm that this is a devastating disorder; only one-quarter of patients survive to the age of 5 years. Nearly half of the patients had died by the age of 3 years. The overall life span seems to have increased over the last 50 years (Fig 1), which likely reflects improved symptomatic management such as use of antibiotics and GT placement. This result is consistent with that of our Cox proportional hazard model in which both the influence of birth decade and GT placement on survival approached significance ($P = .0544$ and .0687, respectively). The fact that life span in the literature is shorter for all decades compared to the NTSAD database may indicate the tendency to publish the most severe cases.

Receipt of an HSCT did not significantly alter survival rates but our sample size was limited ($n = 5$). Although some of the survey patients received the transplant as early as 5 months of age, no survival advantage or retention of milestones was observed. No controlled clinical trials have been conducted regarding the efficacy of HSCT for infantile G_{M2} gangliosidosis, but our series data suggest that little or no benefit is to be expected.

It is interesting to note that there was no significant difference in life span between children with an onset of symptoms before and after 6 months. (Even 2 patients who preserved the ability to sit for >2 years longer than the average did not live significantly longer than the average.) We conclude that life span is not a good marker for disease severity in children with infantile G_{M2} gangliosidoses.

For many decades, G_{M2} gangliosidoses, especially Tay Sachs, were thought to only affect Jewish children. Our results reveal that a 100% Jewish background was only present in 17% of the patients, which likely reflects the impact of carrier screening within the Ashkenazi community that began in the early 1970s.[76] As a result, the majority of patients with infantile Tay-Sachs disease currently born in North America are of non-Jewish ancestry. Therefore, we emphasize the importance of considering a diagnosis of G_{M2} gangliosidosis for any patient who presents with clinical symptoms, not just those with Jewish ancestry.

Our study revealed no gender differences and, in contrast with late-onset cases of G_{M2} gangliosidosis,[2] few differences in the neurologic phenotype when comparing Tay Sachs and Sandhoff diseases. Among the 92 studied patients, we observed that there was a tendency for seizures, visual problems, and movement abnormalities to occur earlier in patients with Tay Sachs disease.

Limitations of our study lie in its retrospective nature and the self-reporting by parents or other family members. Although our survey data revealed that caregivers can provide a detailed recollection of distinct clinical findings, many of which are often recorded in infant books, milestones might be tainted by subjective impression and cannot be verified objectively. Clinical features that are harder to isolate and define, such as vocalizing, might be more prone to misrepresentation. Reported cases from the literature and life-span data from the NTSAD database allowed for a comparison of survival rates in our survey data to that of other patients with infantile G_{M2} gangliosidosis. However, we cannot exclude recall bias, ascertainment bias, and the bias of potentially missing data for individual questions.

Our retrospective cohort could serve as a historical control for future clinical trials with recognition of important caveats. The fact that life expectancy has improved over time might lead to false-positive results, because the standard of care will have evolved since the data were acquired. If, in assessing an intervention, the expected effect size of a drug is modest, the variability in the present data might be prohibitive. Yet, the onset of certain symptoms within a narrow time frame might allow for more rapid assessment of interventions than life-span data alone and needs to be prospectively assessed.

CONCLUSIONS

Infantile G_{M2} gangliosidosis remains one of the most devastating inherited neurologic disorders despite advances in supportive care. Loss of motor milestones and late recalcitrant seizures mark the relentless disease course that poses a challenge to caregivers and specialists alike. Details on the course of regression presented here are a valuable foundation from which to choose outcome measures and design trials for future interventions.

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Natural History of Infantile G_{M2} Gangliosidosis

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