Clinical Burden of GM2 Gangliosidoses in the United States (US): A Retrospective Observational Cohort Study Using Electronic Health Records (EHRs)

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Background

- GM2 gangliosidoses (primarily Tay–Sachs and Sandhoff diseases) are rare, autosomal recessive disorders characterized by progressive neurodegeneration and caused by deficient activity of lysosomal enzyme β-hexosaminidase A or A/B.[1,2]
- The clinical phenotypes associated with GM2 gangliosidoses vary widely. Based on age of symptom onset and rate of disease progression, these phenotypes are typically classified as acute infantile, subacute juvenile, and chronic adult, with the latter two being the late-onset forms.[2,3]
- Currently, there are no disease-modifying therapies approved for this condition, and palliative care is used to alleviate clinical manifestations.[4,5]
- Data on clinical burden and unmet medical need in patients with GM2 gangliosidoses are limited; therefore, an evidence gap exists.

Objective

- This retrospective, comparative cohort study aimed to describe clinical burden among patients with GM2 gangliosidoses and compare them to patients without GM2 gangliosidoses in the Unites States (US).

Methods

Data source

- Patients with GM2 gangliosidoses were identified (between 01 October 2015 and 30 September 2021) from the Optum® de-identified Market Clarity data, which comprises electronic health records (EHRs) and medical claims data for over 100 million people in the US, including those with commercial health plans, Medicare, Medicaid coverage, and uninsured patients receiving healthcare across all 50 states.

Study eligibility criteria and outcomes

- Patients with GM2 gangliosidoses aged ≥2 years who had ≥2 healthcare provider encounters in the EHRs with a GM2-related International Classification of Diseases, Tenth Revision (ICD-10) code (E75.0/E75.00/E75.01/E75.02/E75.09) or one encounter and two administrative claims with GM2-related ICD-10 codes on different days were included.
- Patients were excluded if they had <183 days of EHR activity prior to meeting selection criteria. Each patient with GM2 gangliosidoses was age- and sex-matched at the index date with 10 randomly selected patients without GM2 gangliosidoses (referent group).
- For the referent group, patients with a GM2 gangliosidoses diagnosis code or claim in all available data (pre- and post-index) were excluded.
- The variables assessed included demographics (age, gender, race, insurance status, and region), clinical manifestations of GM2 gangliosidoses, and other comorbidities (cognitive/executive function, neurological, psychiatric, and conditions affecting other systems). An iterative process was used to select GM2 gangliosidoses manifestations and conditions of interest from the published literature, which were further validated with internal medical experts.

Statistical analyses

- Patient demographics were reported using descriptive statistics, such as mean (standard deviation [SD]), median (interquartile range [IQR]) and proportions (*n*, %) for continuous and categorical variables as appropriate.
- Clinical conditions and symptoms were evaluated using ICD-9/10 codes and terminologies in physician notes obtained from medical records in EHR data and reported as proportion (*n*, %) of patients meeting the specified criteria.
- Comparative burden was summarized using relative measures, such as difference in proportions, risk ratios and rate ratios (95% confidence interval [CI]). Difference in proportions was calculated using generalized linear models with identity link. Risk ratios were measured as ratios of prevalence of a condition in patients with GM2 gangliosidoses vs. the referent group. Mean (SD) annualized rates were calculated as mean (SD) count of medical encounters with relevant diagnoses codes per patient per year (PPPY) in both groups.
- Clinical characteristics were assessed in all available data prior to patient identification.
- Results were stratified by age groups (pediatric: 2 to <18 years; adult: ≥18 years).

Results

- A total of 115 patients with GM2 gangliosidoses (mean [SD] baseline observability for adult and pediatric patients: 6.3 [3.5] and 2.6 [2.7] years, respectively) were matched to 1,150 patients without GM2 gangliosidoses (mean [SD] baseline observability for adult and pediatric patients: 7.1 [3.6] and 4.1 [3.1] years, respectively) (**Table 1)**.

Table 1. Demographic characteristics of adult and pediatric patients with and without GM2 gangliosidoses at baseline

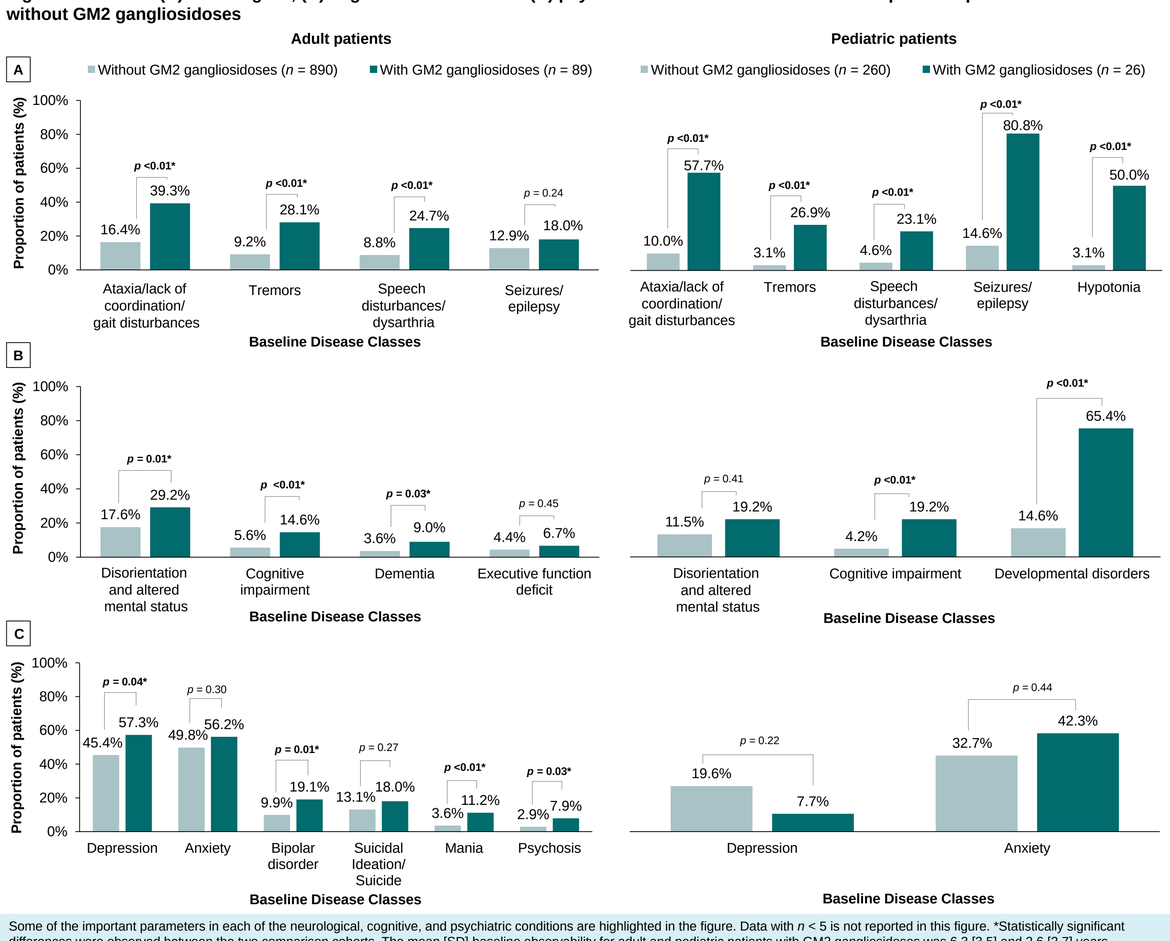
	Pediatric patients (2 to <18 years)			Adult patients (≥18 years)		
	Patients without GM2 gangliosidoses (*N* = 260)	Patients with GM2 gangliosidoses (*N* = 26)	*p*-value	Patients without GM2 gangliosidoses (*N* = 890)	Patients with GM2 gangliosidoses (*N* = 89)	*p*-value
Age (years), mean (SD)	5.1 (3.7)	5.1 (3.7)	1.00	47.6 (17.0)	47.6 (17.1)	1.00
Gender, male, *n* (%)	110 (42.3%)	11 (42.3%)	1.00	390 (43.8%)	39 (43.8%)	1.00
Race, *n* (%)						
White	204 (78.5%)	16 (61.5%)	0.09	718 (80.7%)	76 (85.4%)	0.35
Black	15 (5.8%)	NR*	–	97 (10.9%)	6 (6.7%)	0.30
Asian	6 (2.3%)	NR*	–	14 (1.6%)	0	0.47
Other/Unknown	35 (13.5%)	8 (30.8%)	**0.04**	61 (6.9%)	7 (7.9%)	0.89
Insurance- EHR, *n* (%)						
Commercial only	143 (55.0%)	13 (50.0%)	0.78	402 (45.2%)	44 (49.4%)	0.51
Medicaid only	44 (16.9%)	6 (23.1%)	0.61	52 (5.8%)	7 (7.9%)	0.60
Medicare only	0	0	–	104 (11.7%)	10 (11.2%)	1.00
Other payer type only	7 (2.7%)	0	0.86	8 (0.9%)	0	0.78
None/Uninsured	NR*	0	–	24 (2.7%)	0	0.23
Other insurance combinations^	33 (12.7%)	6 (23.0%)	–	150 (16.8%)	22 (24.7%)	–
Unknown/Missing	31 (11.9%)	1 (3.8%)	0.36	150 (16.9%)	6 (6.7%)	**0.02**
Region, *n* (%)						
Northeast	39 (15.0%)	8 (30.8%)	0.07	116 (13.0%)	22 (24.7%)	**<0.01**
Midwest	164 (63.1%)	8 (30.8%)	**<0.01**	524 (58.9%)	39 (43.8%)	**<0.01**
South	32 (12.3%)	5 (19.2%)	0.49	134 (15.1%)	20 (22.5%)	0.09
West	17 (6.5%)	NR*	–	75 (8.4%)	5 (5.6%)	0.47
Other/Unknown	8 (3.1%)	3 (11.5%)	0.11	41 (4.6%)	3 (3.4%)	0.79

*NR: Data with *n* < 5 is not reported in this table except for unknown/missing and other/unknown category. ^Other insurance combinations included commercial and Medicaid; commercial and Medicare; commercial, Medicaid, and Medicare; Medicaid and Medicare; other payer type and other; uninsured and other. EHR, electronic health record; *n*, number of patients; NR, not reported; SD, standard deviation

Disease burden among adult patients with GM2 gangliosidoses

- During the baseline period, the prevalence of **neurological conditions**, such as ataxia/lack of coordination/gait disturbances, tremors, and speech disturbances/dysarthria was >2 times more prevalent in patients with GM2 gangliosidoses vs. the referent group **(Figure 1)**.
- **Cognitive conditions**, such as disorientation and altered mental status, cognitive impairment, and dementia and **psychiatric conditions**, such as bipolar disorder, mania, and psychosis had nearly 2 times higher prevalence in patients with GM2 gangliosidoses vs. the referent group **(Figure 1)**.
- There was a high prevalence of depression (57.3%) and anxiety (56.2%) in patients with GM2 gangliosidoses, albeit being prevalent in the referent group (depression: 45.4%; anxiety: 49.8%) **(Figure 1)**.

Figure 1. Baseline (A) neurological, (B) cognitive/executive and (C) psychiatric disease burden in adult and pediatric patients with and without GM2 gangliosidoses



Some of the important parameters in each of the neurological, cognitive, and psychiatric conditions are highlighted in the figure. Data with *n* < 5 is not reported in this figure. *Statistically significant differences were observed between the two comparison cohorts. The mean [SD] baseline observability for adult and pediatric patients with GM2 gangliosidoses was 6.3 [3.5] and 2.6 [2.7] years, respectively whereas, the mean [SD] baseline observability for adult and pediatric patients without GM2 gangliosidoses was 7.1 [3.6] and 4.1 [3.1] years, respectively) *n*, number of patients

- Statistically significant differences were observed for the prevalence of **conditions affecting other systems**, such as any cancer, urine incontinence, hypotension, muscle atrophy/wasting, fractures, falls, muscle weakness, pressure ulcer, and aphagia/dysphagia with a higher prevalence reported in patients with GM2 gangliosidoses vs. the referent group **(Figure 2A)**.

Figure 2. Baseline comorbidities and clinical characteristics in (A) adult and (B) pediatric patients with and without GM2 gangliosidoses

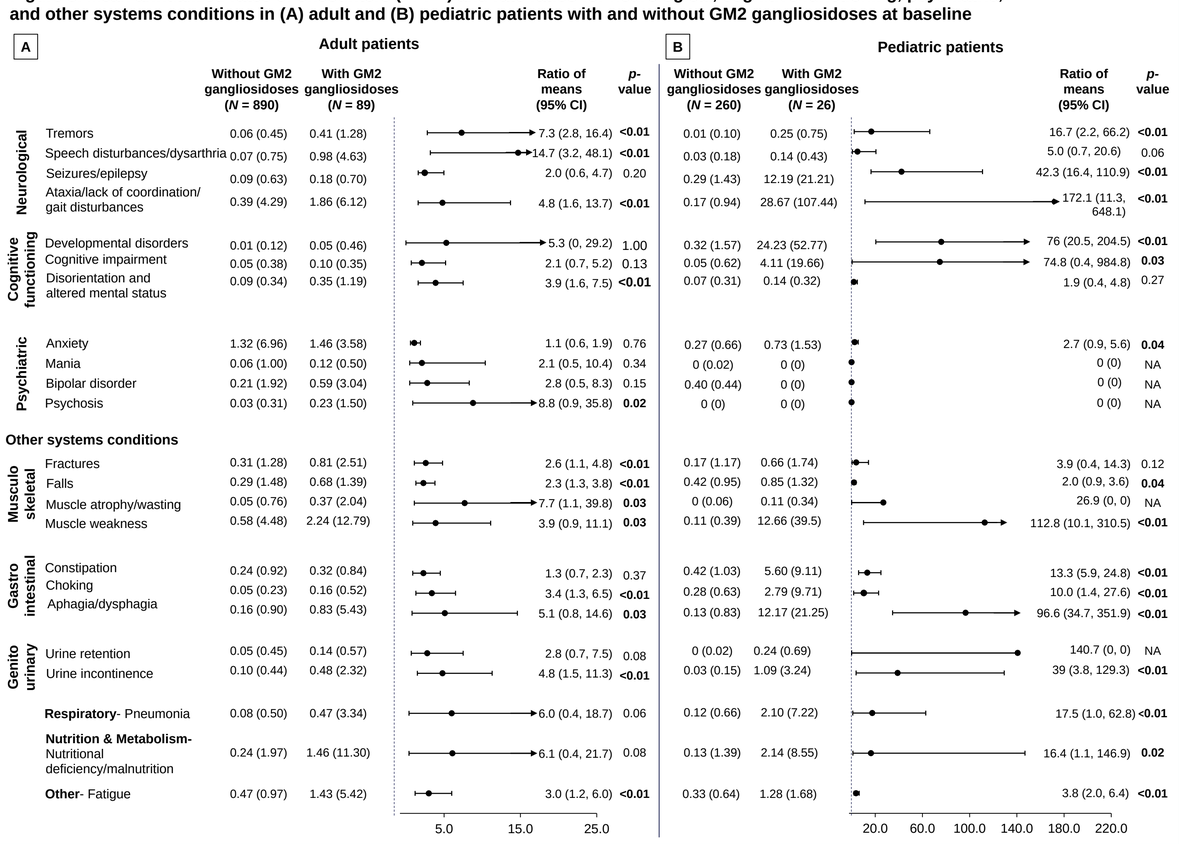
Some of the important parameters in each of the neurological, cognitive, and psychiatric conditions are highlighted in the figure. Data with *n* < 5 is not reported in this figure.
*Statistically significant differences were observed between the two comparison cohorts. *n*, number of patients

- At baseline, the mean annualized rates of encounters PPPY for a few neurological, cognitive, and psychiatric symptoms were significantly higher in patients with GM2 gangliosidoses vs. the referent group (**Figure 3A)**.
- **At 1 year follow-up from index**, larger differences were observed in the prevalence of conditions, with a higher prevalence reported in patients with GM2 gangliosidoses vs. the referent group (**neurological**: ataxia/lack of coordination/gait disturbances [34.7% vs. 8.8%, *p* <0.01], tremors [20.8% vs. 3.7%, *p* <0.01], speech disturbances/dysarthria [30.6% vs. 2.6%, *p* <0.01], seizure/epilepsy [15.3% vs. 4.0%, *p* <0.01]; **cognitive**: disorientation and altered mental status [20.8% vs. 9.1%, *p* <0.01], cognitive impairment [11.1% vs. 2.6%, *p* <0.01]; **psychiatric**: bipolar disorder [12.5% vs. 4.6%, *p* = 0.01]; **conditions affecting other systems**, such as musculoskeletal: muscle weakness [44.4% vs. 15.7%, *p* <0.01], falls [41.7% vs. 16.3%, *p* <0.01], fractures [26.4% vs. 12.5%, *p* <0.01], muscle atrophy/wasting [8.3% vs. 1.4%, *p* <0.01]; gastrointestinal: diarrhoea [26.4% vs. 15.1%, *p* = 0.02], aphagia/dysphagia [20.8% vs. 8.4%, *p* <0.01], choking [13.9% vs. 5.3%, *p* <0.01]; and genitourinary: urine retention [6.9% vs. 2.1%, *p* = 0.04]).

Disease burden among pediatric patients with GM2 gangliosidoses

- During the baseline period, the prevalence of **neurological conditions**, such as ataxia/lack of coordination/gait disturbances, tremors, speech disturbances/dysarthria, seizures/epilepsy, and hypotonia was ≥5 times higher in patients with GM2 gangliosidoses vs. the referent group **(Figure 1)**.
- The prevalence of **cognitive conditions**, such as cognitive impairment and developmental disorders was nearly 4 times higher in patients with GM2 gangliosidoses vs. the referent group **(Figure 1)**.
- Pediatric patients with GM2 gangliosidoses reported a higher prevalence of anxiety vs. the referent group pediatric patients (42.3% vs. 32.7%) **(Figure 1)**.
- Statistically significant differences were observed for the prevalence of **conditions affecting other systems**, such as urine incontinence, scoliosis, muscle weakness, fatigue, aphagia/dysphagia, constipation, gastroesophageal reflux, and nutritional deficiency/malnutrition with a higher prevalence reported in patients with GM2 gangliosidoses vs. the referent group **(Figure 2B)**.
- At baseline, the mean annualized rates of encounters PPPY for a few neurological, cognitive, and psychiatric symptoms were significantly higher in patients with GM2 gangliosidoses vs. the referent group (**Figure 3B)**.
- **At 1 year follow-up from index**, larger differences were observed in the prevalence of conditions, with a higher prevalence reported in patients with GM2 gangliosidoses vs. the referent group (**neurological**: ataxia/lack of coordination/gait disturbances [50.0% vs. 4.6%, *p* <0.01], seizure/epilepsy [85.0% vs. 8.2%, *p* = 0]; **cognitive**: disorientation and altered mental status [25.0% vs. 6.7%, *p* = 0.02]; **psychiatric**: anxiety [35.0% vs. 13.4%, *p* = 0.03]; **conditions affecting other systems**, such as musculoskeletal: muscle weakness [50.0% vs. 5.7%, *p* <0.01]; gastrointestinal: aphagia/dysphagia [60.0% vs. 4.1%, *p* <0.01], choking [60.0% vs. 4.6%, *p* <0.01], constipation [70.0% vs. 16.5%, *p* <0.01], gastroesophageal reflux [45.0% vs. 7.2%, *p* <0.01]; nutrition and metabolism: nutritional deficiency/malnutrition [35.0% vs. 2.6%, *p* <0.01]; and genitourinary: urine incontinence [40.0% vs. 3.6%, *p* <0.01]).

Figure 3. Mean annualized rates of encounters (PPPY) and rate ratios for neurological, cognitive functioning, psychiatric, and other systems conditions in (A) adult and (B) pediatric patients with and without GM2 gangliosidoses at baseline



Some of the important parameters in each of the neurological, cognitive, and psychiatric conditions are highlighted in the figure. Rate ratio = 1 (null value) indicates no difference between the two groups (GM2 gangliosidoses and referent group); rate ratio >1 indicates that frequency of encounters was higher in GM2 gangliosidoses group vs. referent group; rate ratio <1 indicates that frequency of encounters was higher in referent group compared to GM2 gangliosidoses group. CI, confidence interval; *n*, number of patients; PPPY, per patient per year

Limitations

- There are no specific ICD-9 diagnosis codes for GM2. Therefore, it was not feasible to identify GM2 gangliosidoses patients prior to 2015.
- Pediatric patients are underrepresented in the Optum® de-identified Market Clarity database.
- Some misclassification of patients is possible due to secondary use of pre-existing data and absence of a validated algorithm for patient identification. To avoid misclassification of non-GM2 as GM2 gangliosidoses patients, inclusion criteria was set to at least 2 GM2 diagnosis records or claims on different days.
- Some relevant patient/disease characteristics could have been misclassified due to different rate of capture by providers in the EHRs.
- Clinical conditions were evaluated using both ICD9/10 codes and physician notes. While some misclassification is possible, we expect it to be non-differential and reflective of un-biased relative differences.
- High prevalence of depression and anxiety was reported in the referent group patients. These findings were unexpected and would require further investigation.

Conclusions

- This study showed that patients with GM2 gangliosidoses experience substantial clinical burden encompassing a wide range of clinical manifestations, including neurological, cognitive/executive function, psychiatric, and other systems conditions.
- These findings highlight an urgent need for better diagnosis, disease-modifying treatments, and comprehensive management strategies to address the complex unmet needs of this patient population.

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CONFLICTS OF INTEREST: MBR, NP-I, IB, ALF, MF, JK, RZ, DM, and **SU** are employees of Sanofi and may hold stocks and/or stock options in the company. **CJT** has no conflict of interest.

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