

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

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Background

- GM2 gangliosidosis (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 gangliosidosis 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 gangliosidosis are limited; therefore, an evidence gap exists.

Objective

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

Methods

Data source

Patients with GM2 gangliosidosis 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 gangliosidosis 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 gangliosidosis was age- and sex-matched at the index date with 10 randomly selected patients without GM2 gangliosidosis (referent group).
- For the referent group, patients with a GM2 gangliosidosis 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 gangliosidosis, and other comorbidities (cognitive/executive function, neurological, psychiatric, and conditions affecting other systems). An iterative process was used to select GM2 gangliosidosis 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 gangliosidosis 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 gangliosidosis (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 gangliosidosis (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 gangliosidosis at baseline

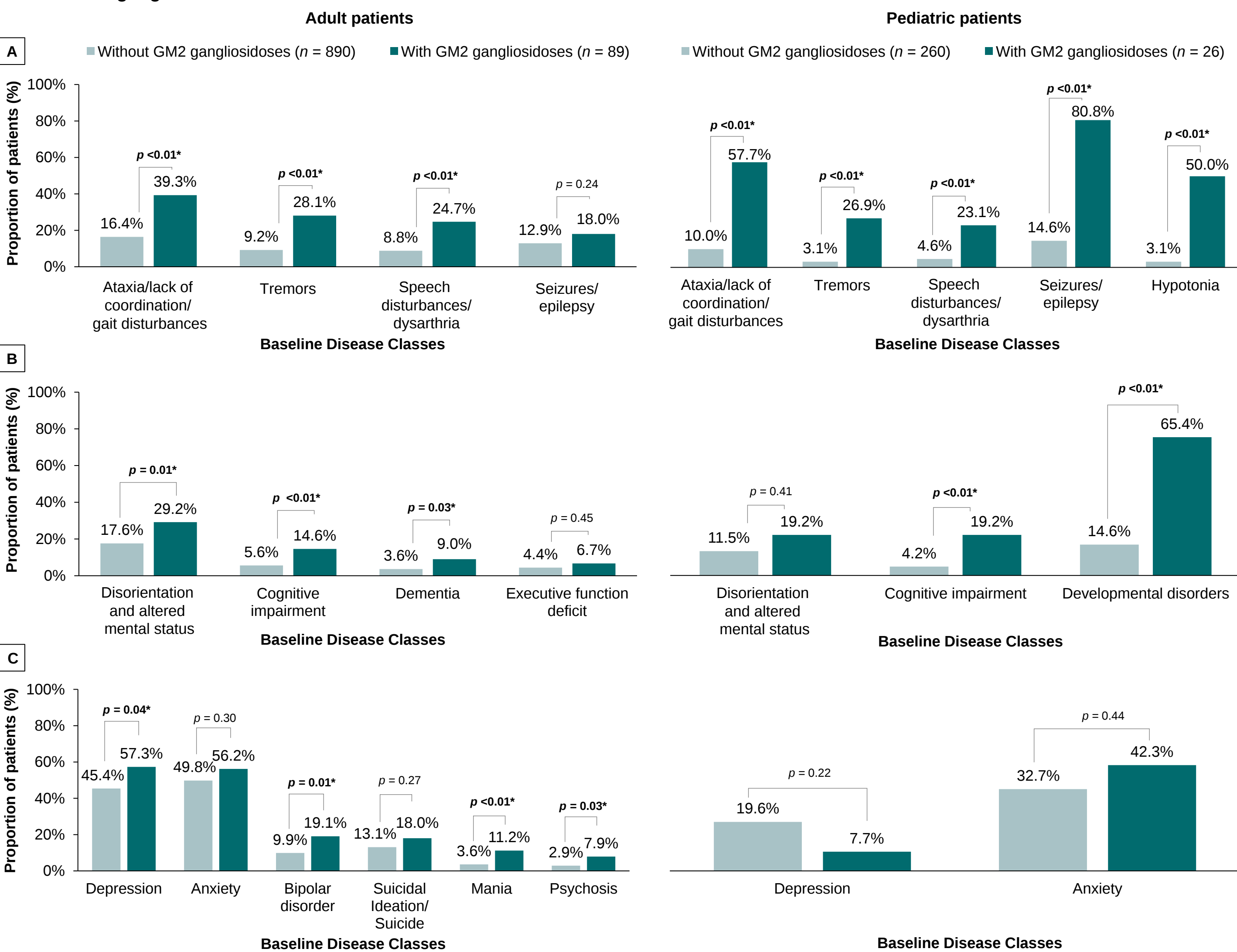
	Pediatric patients (2 to <18 years)			Adult patients (≥ 18 years)		
	Patients without GM2 gangliosidosis (N = 260)	Patients with GM2 gangliosidosis (N = 26)	p-value	Patients without GM2 gangliosidosis (N = 890)	Patients with GM2 gangliosidosis (N = 89)	p-value
Age (years), mean (SD)	5.1 (3.7)	5.1 (3.7)	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 gangliosidosis

- 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 gangliosidosis 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 gangliosidosis vs. the referent group (Figure 1).
- There was a high prevalence of depression (57.3%) and anxiety (56.2%) in patients with GM2 gangliosidosis, albeit being prevalent in the referent group (depression: 45.4%; anxiety: 49.8%) (Figure 1).

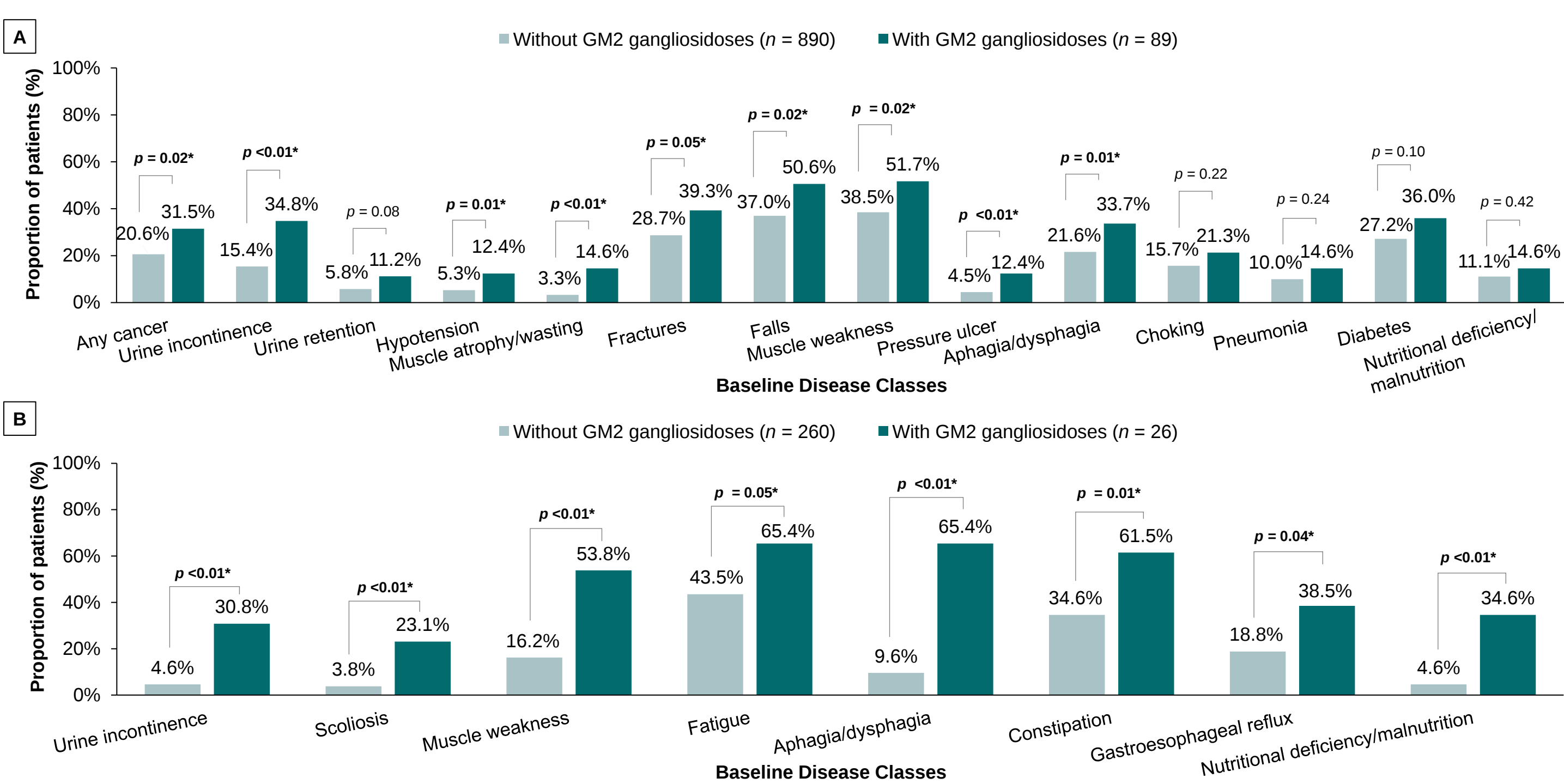
Figure 1. Baseline (A) neurological, (B) cognitive/executive and (C) psychiatric disease burden in adult and pediatric patients with and without GM2 gangliosidosis



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 gangliosidosis 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 gangliosidosis 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 gangliosidosis vs. the referent group (Figure 2A).

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



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 gangliosidosis 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 gangliosidosis 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 gangliosidosis

- 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 gangliosidosis 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 gangliosidosis vs. the referent group (Figure 1).
- Pediatric patients with GM2 gangliosidosis 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 gangliosidosis 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 gangliosidosis 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 gangliosidosis 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 gangliosidosis at baseline

