Natural History and Burden of Disease among Patients with Juvenile GM2 Gangliosidoses in France

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**Sarah Ba was an employee of Sanofi at the time of the study conduct*

Poster Number
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Background

- GM2 gangliosidoses (Tay–Sachs disease [TSD], Sandhoff disease [SD], and GM2 activator protein [GM2AP] deficiency or AB variant) are rare, autosomal recessive, potentially life-threatening lysosomal storage disorders characterized by progressive neurodegeneration.[1]
- Clinically, GM2 gangliosidoses are classified into infantile,[2] juvenile,[3] and late-onset[4] forms based on the age at symptom onset.
- Currently, there are no approved therapeutic options for the treatment of this disease.[5] Evidence on the clinical burden and progression of GM2 gangliosidoses, especially the juvenile form, is lacking, and limited primarily to case reports or case series.[6,7]

Objective

- To address the evidence gap regarding the clinical burden and progression of juvenile GM2 gangliosidoses in France.

Methods

Study design and participants

- This retrospective, non-interventional, longitudinal study was conducted in France with patients (alive/deceased) diagnosed with juvenile GM2 gangliosidoses, confirmed using genetic testing and/or enzymatic assays.

Data collection and statistical analyses

- Data on demographics, neurological and non-neurological manifestations, and disease impact were abstracted retrospectively using medical charts (chart review) from 2009 to 2022 and analyzed to estimate the burden of illness using descriptive statistics.
- All analyses were conducted as per the statistical analysis plan using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

Results

Baseline characteristics

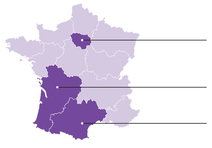
- The study included a total of 10 patients with juvenile GM2 gangliosidoses (TSD [70.0%, *n* = 7]; SD [10.0%, *n* = 1]; GM2AP deficiency [10.0%, *n* = 1]; and unknown [10.0%, *n* = 1]; aged 2–10 years at symptom onset); the majority were female (60.0%, *n* = 6) (**Table 1**).
- Patients with juvenile GM2 gangliosidoses were recruited at three academic sites in France, with the majority of patients (*n* = 8) being recruited at Assistance Publique–Hôpitaux de Paris Trousseau (**Figure 1**).

Table 1: Demographic characteristics of patients with juvenile GM2 gangliosidoses

Demographic characteristic	Patients with juvenile GM2 gangliosidoses (*N* = 10)
Phenotype, *n* (%)	
TSD	7 (70.0)
SD	1 (10.0)
GM2AP deficiency/AB variant	1 (10.0)
Unknown	1 (10.0)
Sex, *n* (%)	
Female	6 (60.0)
Male	4 (40.0)
Patient status, *n* (%)	
Alive	6 (60.0)
Deceased	4 (40.0)
Age, median (IQR), years	
At diagnosis	7.5 (6.0–13.0)
At data collection or enrollment	14.2 (11.9–25.6)
At death	13.0 (7.9–25.8)
Other relevant medical histories, *n* (%)	
Misdiagnosis	2 (20.0)
Genetic ataxia*	1 (50.0)
Schizophrenia	1 (50.0)

*Autosomal recessive or dominant.
GM2AP, GM2 activator protein; IQR, interquartile range; *N*, total number of patients; *n*, number of patients in each group; SD, Sandhoff disease; TSD, Tay–Sachs disease

Figure 1: Academic sites recruiting patients in France



Paris	AP-HP Trousseau, Pediatric Neurology Department (*n* = 8)
Limoges	CHU Neurogenetic (*n* = 1)
Toulouse	CHU Toulouse, Neurology, Epilepsy, Sleep and Movement Disorders (*n* = 1)

AP-HP, Assistance Publique–Hôpitaux de Paris; CHU, Centre Hospitalier Universitaire; *n*, number of patients in each group

- Four deaths related to juvenile GM2 gangliosidoses were reported, with a median (interquartile range [IQR]) age of 13.0 [7.9–25.8] years at death (**Table 1**). The cause of death was respiratory illness in one (25.0%) patient and unknown in three (75.0%) patients. The median (IQR) age at the last follow-up was 13.4 (10.0–25.6) years for the six alive patients.

Neurological and non-neurological manifestations

- All patients had at least one neurological and one non-neurological manifestation (**Table 2**).
- The median (IQR) number of neurological and non-neurological manifestations were 6.5 (4.0–9.0)/patient and 1.0 (1.0–2.0)/patient, respectively (**Table 2**).

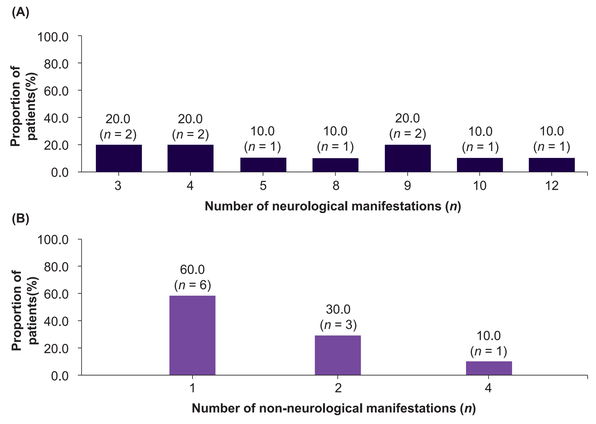
Table 2: Characteristics of neurological and non-neurological manifestations in patients with juvenile GM2 gangliosidoses

Characteristics of manifestations	Patients with juvenile GM2 gangliosidoses (*N* = 10)
Neurological manifestations	
Patients with at least one neurological manifestation, *n* (%)	10 (100.0)
Neurological manifestations/patient, median (IQR)	6.5 (4.0–9.0)
Non-neurological manifestations	
Patients with at least one non-neurological manifestation, *n* (%)	10 (100.0)
Non-neurological manifestations/patient, median (IQR)	1.0 (1.0–2.0)

IQR, interquartile range; *N*, total number of patients; *n*, number of patients in each group

- Overall, six (60.0%) patients reported at least five neurological manifestations, with two (20.0%) patients having at least 10 neurological manifestations (**Figure 2A**).
- Moreover, four (40.0%) patients presented at least two non-neurological manifestations, while one (10.0%) patient had four non-neurological manifestations (**Figure 2B**).

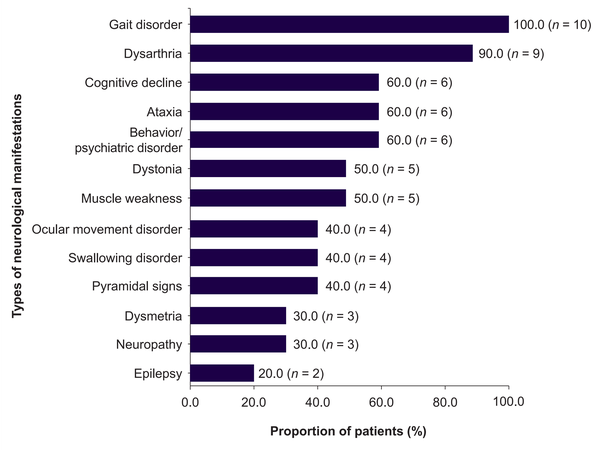
Figure 2: Number of (A) neurological and (B) non-neurological manifestations in patients with juvenile GM2 gangliosidoses



Numbers above the bar graphs represent the proportion of patients (%) with (A) neurological and (B) non-neurological manifestations.
n, number of patients in each group

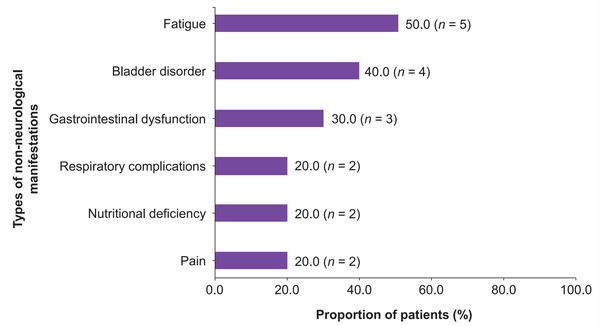
- **Figure 3** represents different types of neurological and non-neurological manifestations reported in patients with juvenile GM2 gangliosidoses.
- Among all neurological manifestations reported, gait disorder was observed in all patients, followed by dysarthria (90.0%, *n* = 9), cognitive decline, ataxia, and behavior/psychiatric disorder (60.0%, *n* = 6 each) (**Figure 3A**).
- In case of all non-neurological manifestations, fatigue was the most reported non-neurological manifestation in half of the patients, followed by bladder disorder (40.0%, *n* = 4) and gastrointestinal dysfunction (30.0%, *n* = 3) (**Figure 3B**).

Figure 3A: Types of neurological manifestations in patients with juvenile GM2 gangliosidoses



Numbers beside the bar graphs represent the proportion of patients (%) with neurological manifestations.

Figure 3B: Types of non-neurological manifestations in patients with juvenile GM2 gangliosidoses

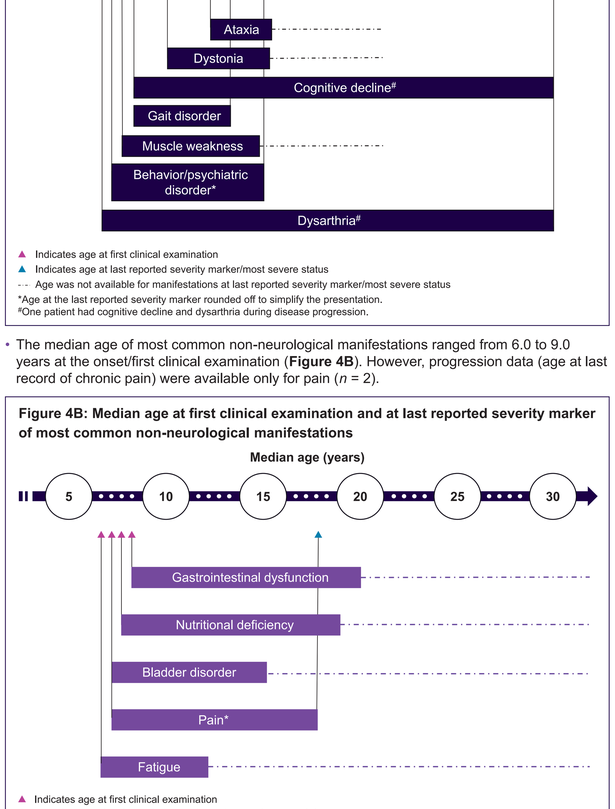


Numbers beside the bar graphs represent the proportion of patients (%) with non-neurological manifestations.

Disease progression

- Disease progression in patients with juvenile GM2 gangliosidoses is demonstrated in **Figure 4**.
- For most common neurological manifestations, the median age ranged from 6.0 to 12.0 years and 14.0 to 30.0 years at first clinical examination and last reported severity marker/disease progression, respectively (**Figure 4A**). Among these manifestations, disease progression data were reported for gait disorder (*n* = 3), dysarthria (*n* = 1), cognitive decline (*n* = 1), and behavior/psychiatric disorder (*n* = 2).

Figure 4A: Median age at the first clinical examination and at last reported severity marker/disease progression of most common neurological manifestations



▲ Indicates age at first clinical examination
▲ Indicates age at last reported severity marker/most severe status
--- Age was not available for manifestations at last reported severity marker/most severe status
*Age at the last reported severity marker rounded off to simplify the presentation.
#One patient had cognitive decline and dysarthria during disease progression.

- The median age of most common non-neurological manifestations ranged from 6.0 to 9.0 years at the onset/first clinical examination (**Figure 4B**). However, progression data (age at last record of chronic pain) were available only for pain (*n* = 2).

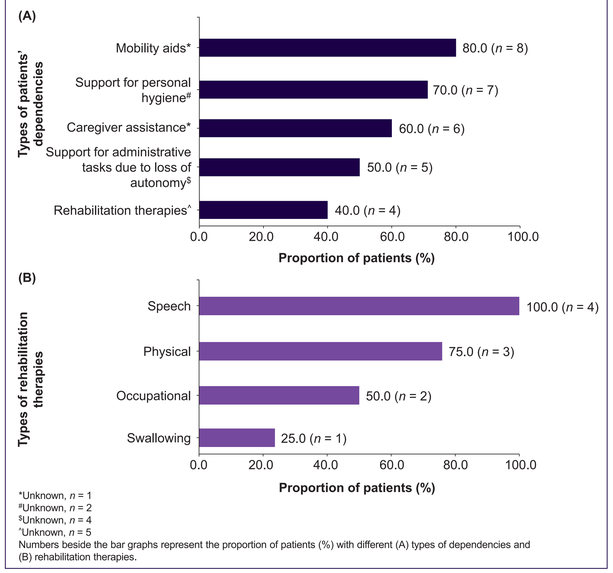
Figure 4B: Median age at first clinical examination and at last reported severity marker of most common non-neurological manifestations

▲ Indicates age at first clinical examination
▲ Indicates age at last reported severity marker/most severe status
--- Age was not available for manifestations at last reported severity marker/most severe status
*Age at the last reported severity marker rounded off to simplify the presentation.

Impacts of the disease

- Several disease-associated dependencies were reported in patients.
  - To maintain the activities of daily living, mobility aids were required by 80.0% (*n* = 8) of patients (**Figure 5A**), with more than half of the patients needing wheelchairs (62.5%, *n* = 5), while 37.5% (*n* = 3) and 12.5% (*n* = 1) of patients required support for mobility and home adaptation, respectively (data not shown).
  - Also, support for personal hygiene, caregiver assistance, and support for administrative tasks due to loss of autonomy were reported by 70.0% (*n* = 7), 60.0% (*n* = 6), and 50.0% (*n* = 5) of patients, respectively (**Figure 5A**).
  - Among the different rehabilitation therapies needed (40.0%, *n* = 4) (**Figure 5A**), speech therapy was reported by all patients (100.0%, *n* = 4), followed by physical (75.0%, *n* = 3), occupational (50.0%, *n* = 2), and swallowing (25.0%, *n* = 1) therapies (**Figure 5B**).
- Moreover, fine motor function loss and frequent falls were reported in 30.0% (*n* = 3) of patients each, with incidence of injury, emergency room visit at hospital, and other consequence (*n* = 1 each).

Figure 5: Types of (A) dependencies and (B) rehabilitation therapies in patients with juvenile GM2 gangliosidoses



*Unknown, *n* = 1
#Unknown, *n* = 2
§Unknown, *n* = 4
^Unknown, *n* = 5
Numbers beside the bar graphs represent the proportion of patients (%) with different (A) types of dependencies and (B) rehabilitation therapies.

STRENGTHS AND LIMITATIONS:

- The study included limited number of patients from established study centers/sites in France; representativeness of this sample size may be evaluated using SNDS/claims data.
- Despite the small sample size, this longitudinal study was able to delineate the disease manifestations, its progression, and impact in patients with juvenile GM2 gangliosidoses.
- This small sample size might limit the generalizability of findings associated with the impact of juvenile GM2 gangliosidoses in patients.

CONCLUSIONS:

- The study highlighted a substantial burden of illness and high impact of the disease on the activities of daily living, resulting in progressive functional impairments and motor function limitations in patients.
- The study further emphasized an unmet need for an effective disease-modifying therapy that could improve the health outcomes of patients with juvenile GM2 gangliosidoses.

References:

1. Regier DS, *et al. Pediatr Endocrinol Rev.* 2016; 13(Suppl 1):663–673.
2. Bley AE, *et al. Pediatrics.* 2011;128(5):e1233–1241.
3. Leal AF, *et al. Int J Mol Sci.* 2020;21(17);6213.
4. Xiao C, *et al.* In: Adam MP *et al.* (Eds.), GeneReviews®. Seattle (WA), 1993. https://www.ncbi.nlm.nih.gov/books/NBK1116/.
5. Lyn N, *et al. Orphanet J Rare Dis.* 2020;15(1):92.
6. King KE, *et al. Mol Genet Metab Rep.* 2020;25:100676.
7. Maegawa GH, *et al. Pediatrics.* 2006;118(5):e1550–1562.

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Conflicts of interest
DNM is an employee of Sanofi and may hold stocks and/or stock options in the company.
SB was an employee of Sanofi during the study conduct and may hold stocks in the company.
SP has received honoraria from Sanofi and Biomarin; travel fees and accommodation from Sanofi, Biomarin, and Takeda.
LW has received consultancy fees for this study from Sanofi as well as Pfizer and HEVA for other works.
LAS, SBK, CB, and **PV** are employees of Oracle Life Sciences, which received consultancy fees from Sanofi for conducting this study.
YN has received consultancy fees from Sanofi for conducting this study.

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