A view into the Tay Sachs variants' populations using the GM2 Disease Registry

Lewi D[1]; Furegato M[2] ; Brignoli L[2] ; Matos JE[3]
[1] CATS, Founder & CEO, London, UK; [2] Kantar Health, Paris, France; [3] Kantar Health, New York, NY, USA

INTRODUCTION

Tay Sachs (TS) is a rare neurodegenerative lysosomal storage disorder resulting from a mutation in the HEXA gene. Given the need of the HEXA protein for the degradation of the GM2 ganglioside, its absence leads to accumulation of this ganglioside in the brain, leading to neurodegeneration and death.[1]

Patients can be diagnosed with adult (aTS), juvenile (jvTS), or infantile TS (iTS). The infantile variant is the most common and is characterized by an almost complete lack of enzyme activity. Initial symptoms appear within the first half year of life and the disease typically progresses rapidly, resulting in significant mental and physical deterioration.[2,3]

Patients with iTS can be further categorized into classical infantile (ciTS) and late infantile or B1 variant (B1TS).

The incidence of TS is very low (one in 320,000[4]), making it a challenge the study of this rare disorder.

OBJECTIVES

The goal of this study was to use the data available in the GM2 Disease Registry (GM2DR) to characterize each of the TS variants and the iTS subpopulation.

METHODS

Registry design

- The GM2DR is a multinational European registry established by the Cure & Action for Tay Sachs (CATS) Foundation and Acción y Cura para Tay-Sachs (ACTAYS), with the support of the European Tay-Sachs and Sandhoff Charity Consortium (ETSCC) member organizations.
- Self-reported data has been collected from patients or their caregivers via a web-based platform since 2015.
- Data on sociodemographic and disease-related characteristics including variant of the disease, age at diagnosis, symptomology, feeding dependence, type of diet, treatments, genetic mutations and eventually date of death, were collected upon enrollment and yearly thereafter.

Patients and eligibility criteria

- Patients were invited to enroll in the registry via referrals at diagnosis centers and through social media, according to the following inclusion criteria:
  - Diagnosed with TS after 2015 or diagnosed prior to 2015 but still alive
  - European national or domiciled in Europe
  - Provided an informed consent

Statistical analysis

- Outcomes are here reported as means and standard deviations (SD) for continuous variables and as counts and proportions for categorical variables.
- Kaplan Meier curves were used to compare rates of progression between the variants of the disease.

RESULTS

- As of April 2020, 85 patients with TS had been enrolled in the registry, among which 7 aTS, 12 jvTS and 66 iTS. The proportion of female with the adult variant is higher (85.7%) compared to the other variant: 33.3% for jvTS and 51.5% for iTS. Among the iTS, which can be further subdivided into B1TS and ciTS, there were 17 and 49 patients, respectively.
- Amongst the 46 patients who were still alive at the time of the study, the mean age was 5.3±3.4 years old for iTS, 18.2±7.5 years old for jvTS and 38.0±5.0 years old for aTS **(Table 1)**.

Table 1. Patient demographic characteristics

	Adult TS (n=7)	Juvenile TS (n=12)	Total Infantile TS (n=66)	B1 variant TS (n=17)	Classical Infantile TS (n=49)
Gender, n (%)					
Female	6 (85.7)	4 (33.3)	34 (51.5)	11 (64.7)	23 (46.9)
Male	1 (14.3)	8 (66.7)	32 (48.5)	6 (35.3)	26 (53.1)
Alive, n (%)					
Yes	5 (71.4)	12 (100.0)	29 (43.9)	10 (58.8)	19 (38.8)
No	2 (28.6)	0 (0.0)	37 (56.1)	7 (41.2)	30 (61.2)
Current Age					
Alive patients	(n=5)	(n=12)	(n=29)	(n=10)	(n=19)
Mean (SD)	38.0 (5.0)	18.2 (7.5)	5.3 (3.4)	8.3 (3.6)	3.7 (2.0)

- Time from first symptoms to diagnosis was longer in jvTS and aTS patients: jvTS were diagnosed at (mean±SD) 8.9±5.5 years old after experiencing first symptoms at 4.3±3.2 years old, and aTS were diagnosed at 28.7±6.4 years old and showed first symptoms at 18.0±8.0 years old.
- Children with iTS developed their first symptoms at the youngest age (0.6±1.1 years old) and were then diagnosed at 1.6±1.9 years old **(see Figures 1a and 1b)**.
- A similar pattern was observed for the age of death: iTS were 4.0±2.0 years old at death, while aTS were 51.0±4.2 years old. All jvTS patients were alive at the time of the study. **(Figure 1c)**

Figure 1a. Average age at first sympton onset (SD)

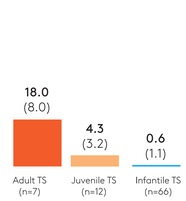


Figure 1b. Average age at diagnosis (SD)

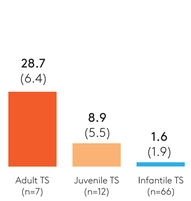
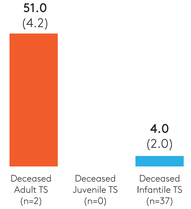


Figure 1c. Average age at death (SD)



- With regards to the 2 iTS subpopulations, patients with ciTS had an earlier onset of disease and were diagnosed much faster than those with B1TS, with an average age at first symptoms of 0.3±0.6 years old and age at diagnosis 0.8±0.7 years old, vs. 1.5±1.3 years old and 3.7±2.5 years old, respectively **(see Figures 2a and 2b)**.
- Among the deceased iTS patients, 30 were ciTS who died at a mean age of 3.5±1.8 years old suggesting a faster progression of the disease when compared to the 7 B1iTS who had an average age at death of 6.0±1.5 years old (see **Figure 2c)**.

Figure 2a. Average age at first sympton onset (SD)

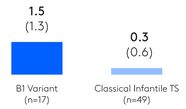


Figure 2b. Average age at diagnosis (SD)

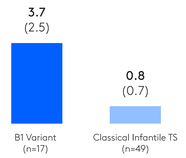
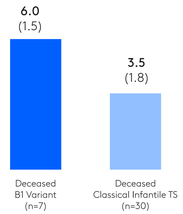


Figure 2c. Average age at death (SD)



- The Kaplan-Meier curves in **Figure 3** confirm this observation, illustrating that aTS patients experienced a slower rate of disease progression than patients with jvTS, and even slower than iTS.
- **Figure 4** illustrates how, within iTS patients, those with the B1 variant (B1TS) display a slower rate of progression of disease than the ciTS patients.

Figure 3. Kaplan-Meier survival curves for the 3 variants

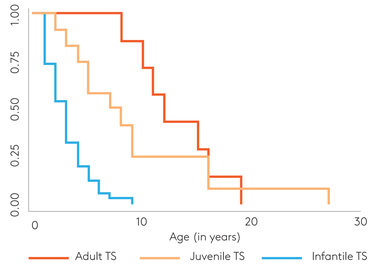
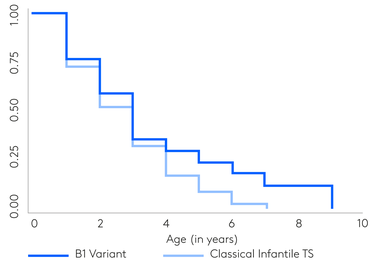


Figure 4. Kaplan-Meier survival curves for the infantile TS



CONCLUSIONS

Rare diseases are defined in Europe as those affecting less than 1 in 2000 people. The low prevalence is a barrier to effectively collect data. Disease registries such as the GM2DR are therefore crucial to the research of the longitudinal progression of rare diseases. Here, we further the understanding of the specificities of each of the TS variants, including the iTS subpopulations. Our results show clear differences not only across the three main variants but also between the two iTS subpopulations.

REFERENCES

1. Maegawa, G. H. B. et al. The natural history of juvenile or subacute GM2 gangliosidosis: 21 New cases and literature review of 134 previously reported. Pediatrics vol. 118 (2006).
2. Tay Sachs Disease - NORD (National Organization for Rare Disorders). https://rarediseases.org/rare-diseases/tay-sachs-disease/.
3. Sandhoff Disease - NORD (National Organization for Rare Disorders). https://rarediseases.org/rare-diseases/sandhoff-disease/.
4. Lew, R. M., Burnett, L., Proos, A. L. & Delatycki, M. B. Tay-sachs disease: Current perspectives from australia. Appl. Clin. Genet. 8, 19–25 (2015).5. What is Sandhoff? – The CATS Foundation. http://www.cats-foundation.org/what-is-sandhoff/.