GM2DR – The Tay Sachs and Sandhoff Disease Multinational Patient Reported Data Registry

Why a multinational registry is key to better understanding and improving outcomes of patients suffering from Tay Sachs and Sandhoff diseases

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INTRODUCTION

The GM2 gangliosidoses are a group of autosomal recessive lysosomal storage disorders that cause a progressive deterioration of nerve cells.[1] These disorders include Tay-Sachs (TS) and Sandhoff disease (SD), caused by mutations in the *HEXA* and *HEXB* genes, respectively, leading to a deficiency of the hexosaminidase A (*HEXA*) enzyme in both diseases and hexosaminidase B (*HEXB*) in SD. Mutated enzymes are no longer able to break down GM2 gangliosides and other molecules, which will then accumulate in the neurons of the brain and spinal cord to toxic levels.

TS and SD are clinically indistinguishable and present as progressive loss of central nervous system function.[1,2] Both disorders are fatal.

There are three variants of each disorder that are characterized by the age of onset: infantile, juvenile, and adult forms.[2]

The infantile form 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.[3,4]

Juvenile and adult forms are more variable in the age of onset and symptomatology range. Both display slower progression. However, whilst the adult form may never compromise central nervous system functions fully, the juvenile form most often leads to development of life-threatening complications before adulthood.

TS and SD are rare disorders with incidences of one in 320,000[2] and one in 300,000[5], respectively. Many barriers exist to effectively study such rare disorders, hindering the advancement of knowledge of disease progression and development of treatment options.

In response to this knowledge and research gaps, the charities Cure & Action for Tay Sachs (CATS) and the Foundation and Acción y Cura para Tay-Sachs (ACTAYS) partnered with the Open App registry system to create the GM2 gangliosidoses disease registry (GM2DR), the first centralized GM2 database.

OBJECTIVES

The objective of the GM2DR was to gather information on multinational European TS and SD patients in order to serve as a research platform of real-world data for epidemiological and translational research, and to contribute to a better understanding of the longitudinal progression of disease.

METHODS

Registry Design

- The GM2DR was designed using a meticulous and collaborative multi stakeholder approach following an initiative of the United Kingdom (UK)-based CATS Foundation and the Spanish-based ACTAYS with the support of the European Tay-Sachs and Sandhoff Charity Consortium (ETSCC) member organizations.
- A high volume of data per patient was collected and, as a result, the GM2DR houses a rich data set containing information about TS and SD that can be made available for research.
- The registry went live on June 3, 2015; the first patient was enrolled on that day.

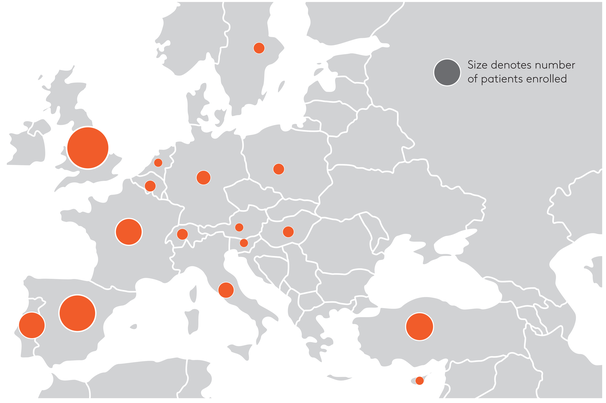
Patients and eligibility criteria

- Patients (n=114; 85 TS and 29 SD) were identified through the ETSCC, via referrals at diagnosis centers, and through social media.
- Inclusion criteria were as follows:
  - Diagnosed with TS or SD after 2015 or diagnosed prior to 2015 but still alive at the time of enrollment
  - European national or domiciled in Europe
- Patients (n=8) or their caregivers (n=106) provided informed consent.

Data collection and management

- Data is collected via a secure web-based platform and is managed by the Open App registry system. Data is protected and stored in the Open App registry system.
- 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.
- Data have been collected from European patients residing in the following countries: Austria, Belgium, Cyprus, France, Germany, Hungary, Italy, Netherlands, Poland, Portugal, Slovenia, Spain, Sweden, Switzerland, Turkey, UK, as well as from ex-EU residents in the United States and Australia. See **Figure 1**.

Figure 1. Number of patients enrolled in the GM2DR per country of current residence



There were also 2 patients residing in the United States and 1 patient in Australia

RESULTS

- As of April 2020, the complete dataset included 75% (n=85) of patients with TS and 25% (n=29) patients with SD. Around half (52%) were female (n=59; 44 TS and 15 SD).
- The majority resided in the UK (25%, n=28; 23 TS and 5 SD), Spain (18%, n=21; 17 TS and 4 SD), or Germany (12%, n=14; 10 TS and 4 SD). See **Table 1**.

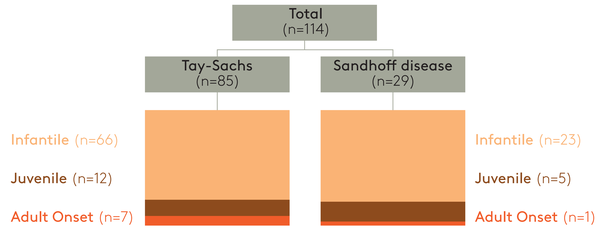
Table 1. Patient Sociodemographic Characteristics

	Total (n=114)	Tay-Sachs (n=85)	Sandhoff Disease (n=29)
Alive, n (%)			
Yes	63 (55%)	46 (54%)	17 (59%)
No	51 (45%)	39 (46%)	12 (41%)
Gender, n (%)			
Male	55 (48%)	41 (48%)	14 (48%)
Female	59 (52%)	44 (52%)	15 (52%)
Resident Country, n (%)			
United Kingdom	28 (25%)	23 (27%)	5 (17%)
Spain	21 (18%)	17 (20%)	4 (14%)
Germany	14 (12%)	10 (12%)	4 (14%)
Turkey	12 (10%)	7 (8%)	5 (17%)
Portugal	11 (10%)	11 (13%)	0 (0%)
Other*	28 (25%)	17 (20%)	11 (38%)

*Other counties include Australia (n=1), Austria (n=1), Belgium (n=2), Cyprus (n=1), France (n=7), Hungary (n=2), Italy (n=4), Netherlands (n=1), Poland (n=2), Slovenia (n=1), Sweden (n=2), Switzerland (n=2), and the US (n=2).

- There were 89 patients with the infantile form (66 TS and 23 SD), 17 patients with the juvenile form (12 TS and 5 SD), and 8 with the adult form (7 TS and 1 SD). See **Figure 2**.

Figure 2. Variant of the diseases



- Amongst the most common form, the infantile one, on average, patients were diagnosed at 1.8 years old (ranging from 1 month to 10 years old). Among patients with the juvenile form, on average, they were diagnosed at 8.6 years old (ranging from 15 months to 17 years old). Among patients with adult onset GM2, patients were diagnosed, on average, at 28.5 years old (ranging from 20 years to 38 years old). See **Figure 3**.
- More than half (55%, n=63; 46 TS and 17 SD) of registered patients were still alive. Amongst the patients with the infantile form who were still alive (n=41), the mean age was 5.3 years old. See **Figure 4**. Among those with the infantile form who died (n=48), the average age of death was 4.2 years old. See **Figure 5**.

Figure 3. Average Age of Patient at Diagnosis

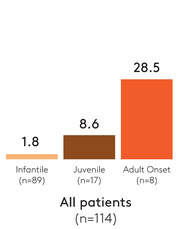


Figure 4. Average Age of Patients Currently Alive

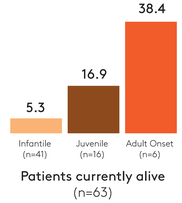
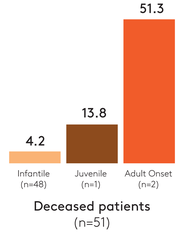


Figure 5. Average Age of Patient at Death



CONCLUSIONS

- Rare diseases cannot be studied effectively on patient groups drawn from one or a few medical centers. Disease registries are therefore key components on the research of the longitudinal progression of rare diseases and potential support for the development of new therapies.
- The GM2DR is a new resource for the TS and SD community which has the potential to increase awareness and accelerate and support clinical and basic research, thus contributing to a better understanding of the disease and providing evidence-based data to support compound development and improve patient outcomes.

REFERENCES

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