Unravelling the Differences Between Infantile Tay Sachs and Sandhoff Disease 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 Division, Paris, France; [3] Kantar, Health Division, New York, NY, USA

INTRODUCTION

GM2 gangliosidoses, including Tay-Sachs (TS) and Sandhoff Disease (SD), are neurodegenerative lysosomal storage disorders caused by mutations in *HEXA* and *HEXB*. Consequent deficiency in beta-hexosaminidases A (in TS) or A and B (in SD) leads to accumulation of GM2 in the neurons of the brain and spinal cord.[1]

Clinically, TS and SD are indistinguishable and present a progressive neurodegeneration and loss of central nervous system function, eventually leading to death.[1,2]

The infantile form is the most common and is characterized by an almost complete lack of enzyme activity. Most children diagnosed with infantile TS or SD appear healthy at birth but will experience slow neurological decline after a period of normal development. Initial symptoms appear within the first half year of life and the disease typically progresses rapidly, resulting in significant mental and physical deterioration and culminating in death.[3,4]

Currently, treatments are based solely on symptom relief. There are some ongoing clinical trials but, as of yet, there is no approved treatment for cure.

Incidences of TS and SD are low; one in 320,000[2] for TS and one in 300,000[5] for SD. As with so many other rare diseases, many barriers exist to effectively investigate them, thus hindering the advancement of knowledge of disease progression and development of treatment options.

The charities Cure & Action for Tay Sachs (CATS) and the Foundation and Acción y Cura para Tay-Sachs (ACTAYS) created the GM2 gangliosidoses disease registry (GM2DR), the first centralized GM2 database, in response to this knowledge and research gaps.

This registry collects information from multinational European TS and SD patients to serve as a research platform of real-world data. Data can be used for epidemiological and translational research and contribute to a better understanding of the longitudinal progression of these diseases.

In this study, we sought to characterize the infantile forms of TS and SD and to compare them, using data obtained from the GM2DR.

OBJECTIVES

- To characterize infantile TS and SD and compare outcomes between these two diseases
- To improve the understanding of TS and SD diseases

METHODS

Registry Design

- 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, designed the GM2DR using a meticulous and collaborative multi stakeholder approach.
- The registry went live on June 3, 2015; the first patient was enrolled on that day.

Patients and eligibility criteria

- Patients were identified via referrals at diagnosis centers, social media and through the European Tay-Sachs and Sandhoff Charity Consortium (ETSCC) organizations
- Criteria for inclusion in the Registry included having been diagnosed with TS or SD after 2015 or diagnosed prior to 2015 but still alive; and European nationality or residence.
- Informed consent to participate in the Registry was provided by patients or their caregivers.
- In this study, data from patients diagnosed with the infantile variants of TS and SD were included.

Data collection and management

- Data is collected via a secure web-based platform and is managed, protected and stored by the Open App registry system.
- 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.
- 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.

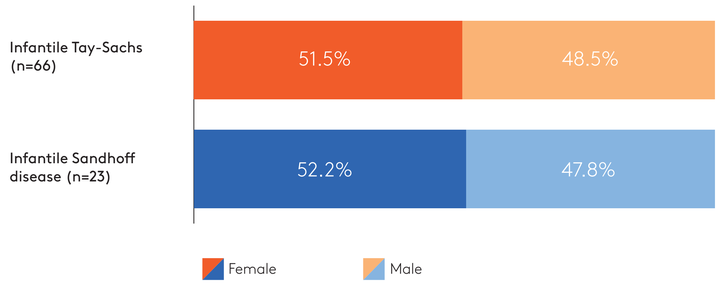
Statistical analysis

- T-test and Chi-squared tests have been used to evaluate the statistical differences for categorical and numerical variables, respectively between the infantile variants of TS and SD.
- Kaplan-Meier curves have been derived to compare the life expectancy of the infantile variants of TS and SD.

RESULTS

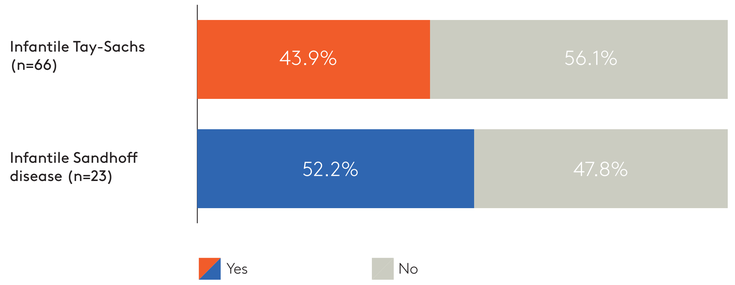
In the registry, 66 TS and 23 SD patients were identified as having the infantile variants of the diseases and included in this analysis. Approximately half were female (51.5% TS and 52.2% SD). **See Figure 1.**

Figure 1. Gender



As of April 2020, 43.9% (n=29) of the infantile TS patients, and 52.2% (n=12) of the infantile SD registered patients were still alive. **See Figure 2.**

Figure 2. Alive



The average age of the first symptoms onset was significantly lower in infantile SD patients (0.3±0.4) than in infantile TS patients (0.6±1.1, p=0.04). **See Figure 3a.**

Similarly, patients with infantile SD were diagnosed at an earlier age (0.8±0.6, ranging from 4 months to 30 months old) than those with infantile TS (1.6±1.9, ranging from 1 month to 11 years old) (p=0.02). **See Figure 3b.**

The average age at death, amongst those patients that had died prior to April 2020, was lower in infantile SD patients (2.7±1.8) than in patients with infantile TS (4.0±2.0) (p=0.03). **See Figure 3c.**

Figure 3a. Average age at first symptoms onset (in years, SD)

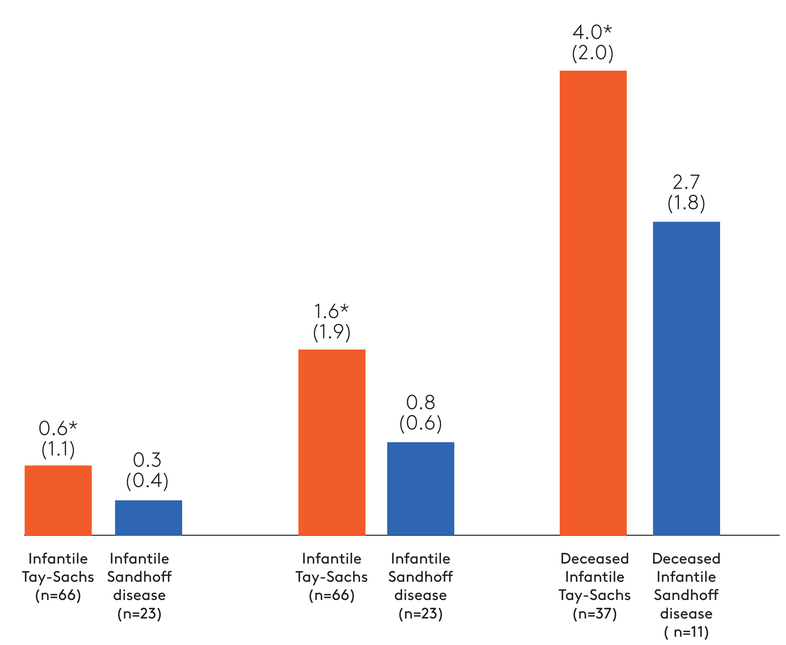


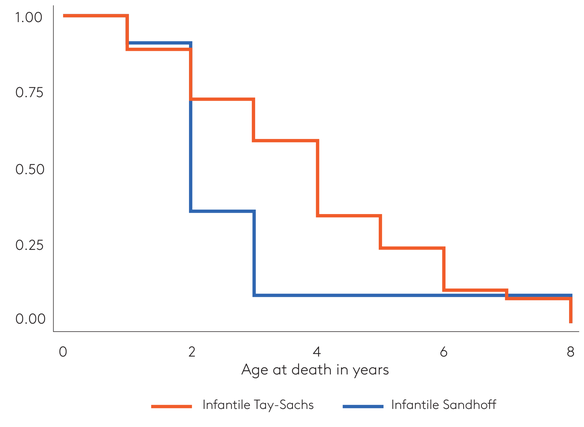
Figure 3b. Average age at diagnosis (in years, SD)

Figure 3c. Average age at death (in years, SD)

* indicates significant difference (p<0.05)

This is confirmed by the Kaplan-Meier curves where the life expectancy in the infantile TS is higher than in those with the infantile variant of SD. **See Figure 4.**

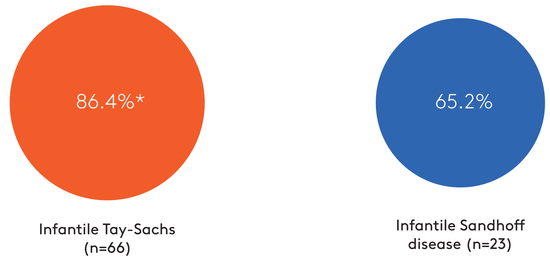
Figure 4. Kaplan-Meier estimates of survival by infantile forms of TS and SD



The prevalence of symptoms reported by the patients was similar between the two diseases for all of them: ataxia, dystonia, dysphagia, seizures, dysarthria, spasticity, and psychosis. Frequency of chest infections was also similar between infantile TS and SD.

In terms of physical impairment, patients with infantile TS were similar to those with SD to a great extent, at the exception of the startle reflex. A higher proportion of patients with infantile TS than patients with infantile SD reported startle reflex (86.4% vs. 65.2%, p=0.03). **See Figure 5.**

Figure 5. Prevalence of startle reflex



CONCLUSIONS

This study contributes to the current knowledge of the infantile variants of TS and SD. These results suggest that the infantile variant of SD typically has an earlier clinical onset and patients are diagnosed at an earlier age. Their life expectancy is lower than that for patients with the infantile variant of TS.

No significant differences are observed in the symptomatology, at the exception of the startle reflex which is reported by a higher proportion of patients with infantile TS.

This research unravels differences between SD and TS, despite very similar clinical phenotypes otherwise, which could be important for the diagnosis and management of the disease.

Disease registries such as the GM2DR may therefore have a chief role on the research of the longitudinal progression of rare diseases and in identifying phenotypical differences between similar diseases or variants of a disease or patient subgroups. A deeper knowledge can potentially open new avenues for the development of new therapies.

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