Is the Symptomatology of Infantile Tay-Sachs and Infantile Sandhoff Disease Identical? Data from an International Registry

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Introduction

GM2-Gangliosidosis are rare and neurodegenerative lysosomal storage disorders characterized by GM2 ganglioside accumulation into the lysosome. This accumulation is caused by a deficiency of the enzyme β-hexosaminidase(s). GM2-Gangliosidosis include Tay-Sachs (TS) and Sandhoff disease (SD). TS is characterized by mutations in the HEXA gene resulting in deficiency of the β-hexosaminidase A. Whereas SD is caused by mutations of the HEXB gene leading to both β-hexosaminidase A and β-hexosaminidase B deficiency. [1,2]

TS affects 1 in 320,000 people and SD 1 in 300,000 people.[3]

Three forms of each disorder have been described: Infantile, Juvenile, and Adult or Late-onset. These three forms are determined by age of onset.

The most common form is the infantile form and is characterized by almost no enzyme activity, which lead to more severe clinical signs and symptoms. The onset of the infantile form is usually around 3 to 6 months with a rapid progression and gradual loss of skills and seizures. Children usually died between the age of 2 and 5 years old.[4,5]

The TS infantile form can be subcategorized into the classical infantile (ciTS) and the B1 variant (B1iTS), both are different in terms of disease onset and disease progression. Literature on the B1iTS and how these patients differ from ciTS is very limited.

Objective

To compare the symptomatology of infantile forms of TS (iTS) and SD (iSD) using the GM2 Disease Registry (GM2DR).

Methods

Registry design

- The GM2DR has been launched in 2015 by the Cure and Action for Tay-Sachs (CATS) Foundation and the Accion y Cura para Tay Sachs (ACTAYS). This initiative was supported by the European Tay-Sachs and Sandhoff Charity Consortium (ETSCC) member organizations.
- Patients or caregivers were invited to participate in the registry via patient associations, referrals at diagnosis centers and via social media.
- Patients or caregivers needed to meet the following inclusion criteria to be enrolled:
  - Diagnosed with TS or SD after 2015 or diagnosed prior to 2015 but still alive
  - European national or domiciled in Europe at the time of the enrollment
  - Provided informed consent

Data collection and management

- Data is collected via a secured online-platform.
- Data is self-reported by the patients or caregivers at enrollment and updated on a yearly basis.
- The registry is collecting data on sociodemographic, family history, and disease related information such as diagnosis, symptoms, comorbidities, treatments, and impairment.

Statistical analyses

- Chi-2/Fisher exact tests have been used to evaluate the statistical differences between the different forms of iTS and iSD.

Results

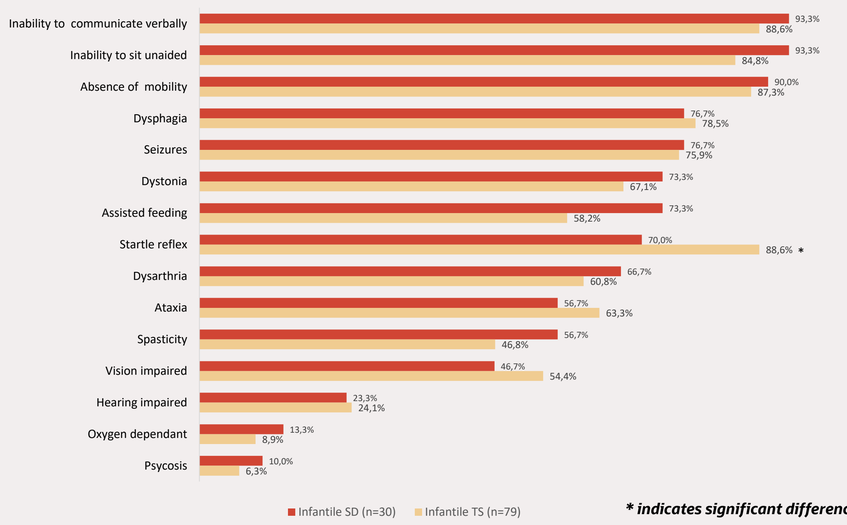
In February 2023, **109 patients** with an infantile form were enrolled in the registry: 30 with iSD and 79 with iTS. Amongst the iTS, 18 were categorized as B1iTS and 61 as ciTS. Their demographic characteristics are described in **Table 1.**

	Infantile TS (iTS) (n=79)	B1 variant (B1iTS) (n=18)	Classical Infantile (ciTS) (n=61)	Infantile SD (iSD) (n=30)
Gender, n (%)				
Female	40 (50.6)	12 (66.7)	28 (45.9)	13 (43.3)
Male	39 (49.4)	6 (33.3)	33 (54.1)	17 (56.7)
Current age (if alive)				
Alive patients	n=26	n=8	n=18	n=8
Mean age (SD)	6.4 (5.2)	12.1 (6.2)	3.8 (1.4)	4.1 (2.0)

iSD and iTS

iSD and iTS patients are considered to have similar symptomology. We can see in our study that, iSD experienced on average 9.2 (SD:2.8) symptoms and 8.9 (3.1) for iTS. The most common symptoms for iSD were the inability to communicate verbally and to sit unaided (93.3%), while for iTS, there were the inability to communicate verbally and the startle reflex (88.6%). Both diseases were similar in terms of symptomatology, except for startle reflex, which was more prevalent among iTS (88.6% vs. 70.0%, p=0.04). **(see Figure 1)**

Figure 1. *Symptoms and impairments among iSD and iTS*



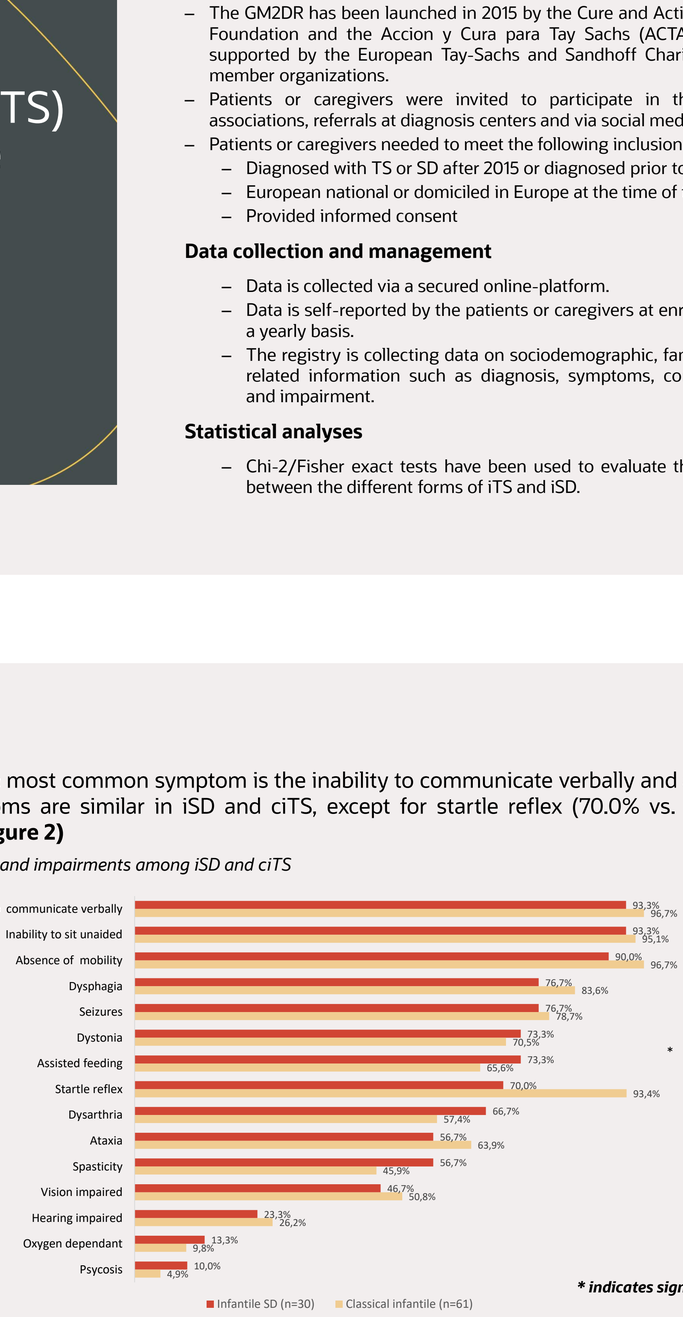
**** indicates significant difference (p<0.05)***

As iTS includes B1iTS and ciTS, we also investigated potential similarities and differences between those two sub-groups and iSD patients.

iSD and ciTS

Among ciTS, the most common symptom is the inability to communicate verbally and absence of mobility (96.7%). Symptoms are similar in iSD and ciTS, except for startle reflex (70.0% vs. 93.4% respectively, p<0.01). **(See Figure 2)**

Figure 2. *Symptoms and impairments among iSD and ciTS*

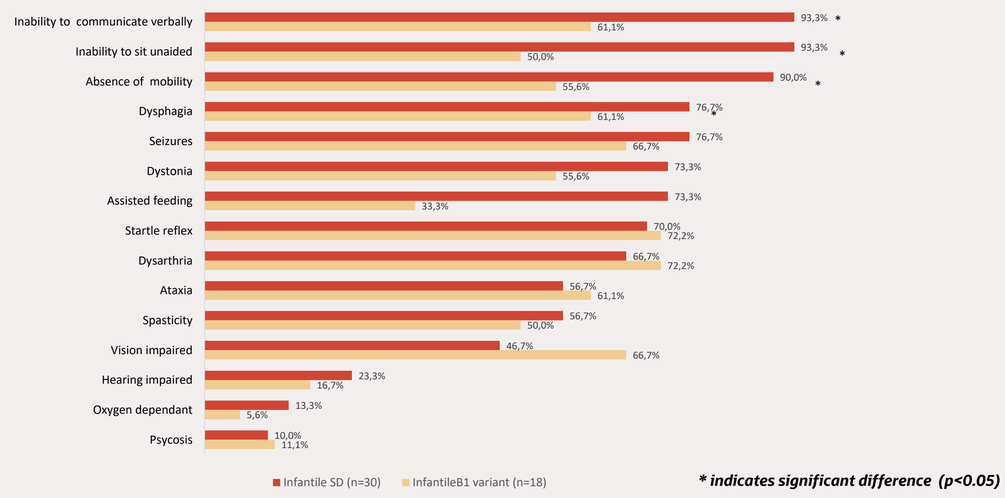


**** indicates significant difference (p<0.05)***

iSD and B1iTS

Looking at B1iTS, the most common symptoms for those patients are dysarthria and startle reflex (72.2%). Several differences were observed among B1iTS and iSD with higher prevalence of assisted feeding (73.3% vs. 33.3%, p=0.01), inability to communicate verbally (93.3% vs. 61.1%, p<0.01), inability to sit unaided (93.3% vs. 50.0%, p<0.01) and absence of mobility (90.0% vs. 55.6%, p=0.01) in iSD compared to B1iTS. **(See Figure 3)**

Figure 3. *Symptoms and impairments among iSD and B1iTS*



**** indicates significant difference (p<0.05)***

Conclusion

The clinical course of iSD and iTS are considered alike. Our results confirmed that, in terms of symptoms, iSD and ciTS are similar. Nevertheless, we highlighted symptoms specificities for B1iTS compared to iSD and ciTS, which reinforce the need to recognize B1iTS as a distinguishable form of iTS.

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