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The Natural History of Late Onset Tay-Sachs Disease

Padmaja Yerramilli-Rao, MB BS, PhD [1]; Ourania Giannikopoulos, BS. [1]; Kim Kubilus, BS [2]; Jessica Pan, BS [1]; Florian Eichler, MD. [1]

(1) Department of Neurology, Massachusetts General Hospital, Harvard Medical School, Boston, MA
(2) National Tay-Sachs & Allied Diseases Association, Boston, MA

Objectives and Introduction

- In contrast to the classic infantile form of Tay-Sachs disease, late onset Tay-Sachs (LOTS) is characterized by disease manifestation after the 1st year of life, has a more protracted course, and is divided into juvenile- and adult-onset phenotypes, albeit poorly defined.
- In this large survey we attempt to achieve better definition of juvenile- and adult-onset phenotypes focusing on initial presenting symptoms, symptom latency and variability in functional decline.

Methods

- Identification and recruitment of patients was performed by the National Tay-Sachs & Allied Diseases Association (NTSAD).
- Retrospective data on symptom onset and progression was acquired using detailed surveys from 55 anonymous LOTS patients.
- Prospective data was also acquired in 15 LOTS patients who were examined as part of a prospective natural history study of GM2 gangliosidosis at the Massachusetts General Hospital.

Results

Retrospective Analysis

- We received 55 completed surveys (45 adult, 10 juvenile) showing a heterogeneous population with overlap in age of onset.
- Comparison with previously published data (Maegawa 2006, Neudorfer 2005) confirms the nature and characteristics of early symptoms in our retrospective cohort, but places them earlier in onset than previously recognized. (**Tables 1, 2**).
- This may be due in part to the hindsight of patient/family reporting, but also confounding of "mild" mutations, thereby pushing the onset into later years.
- The most common initial symptoms were the same in both juvenile and adult LOTS (**Figs 1, 2**).
- The median symptom latency from onset to becoming wheelchair-bound is 4 years (juveniles) compared to 26 years (adults) (**Table 3**).
- Juvenile-onset patients lose the ability to climb stairs in the 1st decade and are wheelchair-bound by the 2nd decade.

Table 1: Comparison with previously published data for Juvenile-onset LOTS

	Age (years), mean ± SD (range)					
N=	At disease onset	At diagnosis	N=	At gait disturbance	N=	At speech problems onset
Our data (10)	2.1 ± 1.1 (1 to 4)	5.6 ± 4.0 (0.42 to 15)	6	5 ± 2 (2 to 8)	4	4 ± 3 (1 to 7)
Maegawa et.al. 2006 (21)	5.3 ± 4.1 (1.5 to 15)	12.3 ± 10.7 (2.5 to 36.9)	21	7.1 ± 6.9 (1.5 to 27)	21	7.0 ± 5.6 (2 to 19)
Previously published cases (134)	5.4 ± 4.0 (1 to 17)	Not reported	118	11.0 ± 7.0 (1 to 39)	104	8.4 ± 7.9 (1 to 40)

Table 2: Comparison with previously published data for Adult-onset LOTS

	Age (years), mean ± SD (range)					
N=	At disease onset	At diagnosis	N=	At gait disturbance onset	N=	At speech problems onset
Our data (45)	12.8 ± 9.5 (1 to 40)	26.8 ± 10.5 (10 to 47)	29	13.5 ± 8 (5 to 35)	27	18 ± 12 (3 to 43)
Neudorfer et.al. 2005 (21)	18.1 ± 7.2 (8 to 36)	27.0 ± 10.4 (14 to 47)	21	Late childhood/teens	21	Teens/middle-age

Figure 3: Severity in Motor Decline in Juvenile and Adult-Onset LOTS is distinctly different

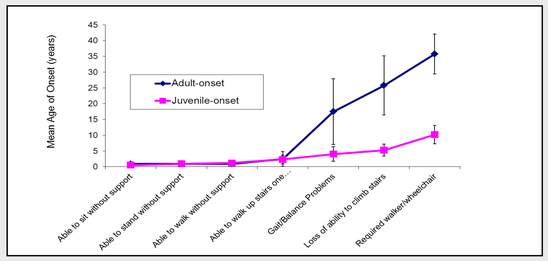

Figure 1: Most Common Presenting Symptom in Juvenile-onset

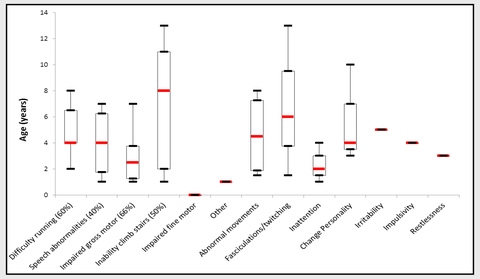

Figure 2: Most Common Presenting Symptom in Adult-onset

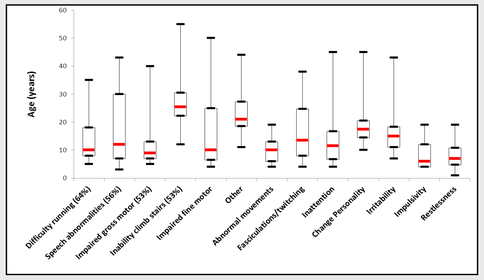

Table 3: Median Symptom Latency (Years) from Onset of First Symptom to Becoming Wheelchair-bound

		N=	Mean (± SD) Age onset	Median Latency	Range
All Patients	Adult+Juvenile	55	30.3±14.8	20	1 to 43
	Adult	45	36.3±10	26	2 to 43
	Juvenile	10	8±5.5	4	1 to 8
Patients presenting with motor disturbance	Adult+Juvenile	25	13.3±10.2	17.5	2 to 43
	Adult	21	15.5±9.7	21	2 to 43
	Juvenile	4	2.1±1.3	3.25	2 to 8
Patients presenting with speech problems	Adult+Juvenile	11	7.3±8	19	1 to 42
	Adult	9	8.7±8.2	30	12 to 42
	Juvenile	2	1.3±0.4	3	1 to 5
Patients with only motor symptoms	Adult	6	23±14.1	23	2 to 43
"Fast progressors" (those who progress in <3 yrs from 1st to 2nd symptom)	Adult+Juvenile	25	8.6±11.5	17	1 to 36
	Adult	16	12.5±13.2	20	2 to 36
	Juvenile	9	2.1±1.5	3.5	1 to 19
"Slow progressors" (those who progress in ≥ 3yrs from 1st to 2nd symptom)	Adult	24	11.4±6	29.5	6 to 43

Results (cont.)

- In adult-onset patients this does not occur until the 3rd to 4th decade of life (**Fig 3**).
- 45% presented with gait abnormalities as their first symptom, 20% with speech problems and 11% experienced only motor abnormalities without speech problems (**Table 3**).

Prospective Analysis

- Data from 15 LOTS patients (10 adult and 5 juvenile) was acquired.
- 80% (8/10) of adult-onset patients had muscle weakness and cerebellar dysfunction (range of onset 24 to 64 yrs) .
- 20% had selective lower motor neuron weakness with no cerebellar dysfunction (ages of onset 23 and 25 yrs), and no cerebellar atrophy on MRI of the brain.
- All juvenile-onset patients had gait difficulties from the 3rd year of life and 80% (4/5) were wheelchair-bound at the time of examination.

References

- Maegawa et al. The natural history of juvenile or subacute GM2 gangliosidosis: 21 new cases and literature review of 134 previously reported. *Pediatrics.* 2006.
- Neudorfer et al. Late-onset Tay-Sachs disease: phenotypic characterization and genotypic correlations in 21 affected patients. *Genet Med.* 2005.

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Discussion

- Our study confirms an overlap in age of first symptoms among juvenile and adult LOTS.
- It is clear that although the diagnosis is often not established until adulthood the first symptoms of LOTS often occur years earlier in childhood.
- Juvenile and adult LOTS patients do not differentiate by age of onset, initial symptom or by symptom latency, but by their ultimate severity of decline, as all juvenile patients are wheelchair-bound by the 2nd decade of life. This is not the case for adult LOTS patients.
- A select group of patients are spared cerebellar symptoms (dysarthria) in adolescence and/or adulthood (11% in retrospective surveys; 20% in prospective study).
- A previously published study found G269S or W474C mutations were associated with a milder and more slowly progressive form of the disease (Maegawa, 2006). This may account for the earlier symptom onset and progression seen in our study.
- A more rigorous definition of disease progression in juvenile LOTS patients is needed as their disease course may, after exclusion of select mutations, turn out to be more homogeneous than previously recognized.
- Mutation analysis of our cohort is pending, and may reveal important prognostic information for the child neurologist.