THE RETRIEVE STUDY: A NATURAL HISTORY STUDY OF TYPE 2 GAUCHER DISEASE, AND GM1 AND GM2 GANGLIOSIDOSES WITH EARLY ONSET

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INTRODUCTION

- GM1 gangliosidosis (GM1), GM2 gangliosidoses (GM2; Tay-Sachs, Sandhoff, and AB Variant), and Gaucher disease type 2 (GD2) are rare autosomal recessive lysosomal storage disorders (LSDs) with no approved treatment.
- GM1 is an LSD caused by deficiency in the enzyme beta-galactosidase.[1] GM1 can be classified into 3 subtypes: type I (infantile form), type II (late infantile and juvenile form), and type III (adult form).[2] The infantile form has been described as having symptom onset prior to 12 months of age, with a life expectancy of 1–5 years.3 In the late-infantile and juvenile forms, onset is between 1–3 years of age and between 3–10 years of age, respectively. Life expectancy is 5–10 years for patients with the late-infantile form, and up to the third decade in the juvenile form. In the adult form, onset of symptoms is between late childhood and the 3rd decade.[2] The life span for individuals with GM2 adult type is usually shortened compared to unaffected relatives.[1,2]
- GM2 is a group of LSDs caused by deficiency of the enzyme beta-hexosaminidase, and includes Tay-Sachs disease, Sandhoff disease, and AB Variant.[4] They are usually categorized into 3 forms: infantile, juvenile, adult. The infantile form has symptom onset prior to 6 or prior to 12 months of age,[2,3,5,6] the juvenile form between 2–10 years of age,[2] and the adult form after 10 years of age.[2] Life span in the infantile form with age at onset < 12 months has been reported to be about 4 years, with a reported range of 33–67 months.[3,5] The age at death of the juvenile form is usually by the second decade,[2] but in some cases the patient dies before 3 years of age.[3,7] It is unclear whether the adult form of disease shortens life.
- GD is an LSD caused by a deficiency of the enzyme acid beta-glucocerebrosidase. It is classically categorized into 3 types, GD Types 1, 2 and 3, based on the presence or absence of neurological manifestations and, importantly, age at onset.[8] GD Type 2 (GD2) is the aggressive neuronopathic form, with onset within the first 6 months of life and a rapidly progressing neurodegeneration, resulting in death usually before 2 years of life.[9] GD Type 3 also has neurological symptoms, but age at onset is usually at a later stage of childhood.[10] GD Type 1 (GD1), is the most common form with age at onset varying from early childhood to adulthood and is often called non-neuronopathic although neurological symptoms have been reported.[10] Neurological symptoms in GD range from Parkinson syndrome and peripheral neuropathy that can occur in GD1 through severe encephalopathy to hydrops fetalis in GD2.[10]
- Because of the specific need for more accurate, up-to-date information on disease progression and life span in these 3 LSDs that have forms with symptom onset in infancy, a single protocol (RETRIEVE study) is considered an appropriate and effective approach to collect data on disease course and survival. Patients with GM1, GM2 and GD2 will thus be included in the current observational study provided they had an «early onset», defined as onset of a neurological manifestation within the first 24 months of life.
- The aim of the RETRIEVE study is to broaden knowledge of the natural history of these three disorders. Furthermore, for future clinical trials, the RETRIEVE patient population can serve as a historical control group. The RETRIEVE study is ongoing. Here we present an interim analysis of preliminary Group A data.

METHODS

- RETRIEVE is an international, multi-center, observational study with two groups:
  - Group A: Retrospective data collection from patients who are deceased or whose survival status is not known at enrolment.
  - Group B: Prospective data collection from patients who are alive at enrolment.
- In order to minimize the patient/data selection bias, the centers are asked to include all eligible patients from their center.
- A patient (whether Group A or Group B) must meet the following criteria to be eligible for the study:
  - Patient with GM1, GM2 (Tay-Sachs, Sandhoff, or AB Variant), or GD2
  - Diagnosis confirmed by biochemical and/or genetic tests,
  - Documented date of birth on or after January 2000,
  - Onset of the first neurological symptom within the first 24 months of life
  - Written informed consent of parent or legal guardian as required by local law.
- Data are recorded in a web-based system that includes automatic verification in real-time, e.g., checks for plausible dates.
- Date of birth is collected using month and year.
- 100% source data verification is planned to be performed for all collected data.
- Survival is determined as the time interval from date of birth to date of death or, if status is alive or unknown, to the date of last contact alive. Subjects with survival status of alive or unknown at end of study are considered censored. Survival is summarized using the Kaplan-Meier method; median survival time is estimated along with its corresponding 95% confidence interval (CI).
- The present interim analysis of the RETRIEVE study is based on preliminary Group A data only.

Table 1. Demographics

	GM1	GM2	GD2	TOTAL
Sex [n (%)]				
n	55	69	44	**168**
Male	20 (36.4)	29 (42.0)	19 (43.2)	**68 (40.5)**
Female	35 (63.6)	40 (58.0)	25 (56.8)	**100 (59.5)**
Birth decade [n (%)]				
n	55	69	44	**168**
2000 - 2009	20 (36.4)	39 (56.5)	18 (40.9)	**77 (45.8)**
2010 - 2019	35 (63.6)	30 (43.5)	26 (59.1)	**91 (54.2)**

RESULTS

- At the time of this interim analysis, 1st July 2020, 168 patients (59% females) have been included in RETRIEVE: 55 GM1, 69 GM2 and 44 GD2 (Table 1).
- 17 sites from Belgium, Brazil, France, Germany, Italy, Portugal, Spain, Switzerland, UK and US, have contributed patients to the RETRIEVE study. The highest patient number is coming from France (Figure 1).
- Not all the data for this interim analysis have been verified with source data and not all queries have been resolved at the time of the data snapshot.
- For 156 patients date of death was available. For 11 patients date of last contact alive was available. For 1 patient there is neither birth nor death date.
- 23% of patients were born in the years 2000-2004, 22.6% in 2005-2009, 34.5% in 2010-2014, and 19.6% in 2015-2019.
- Mean onset of first neurological symptom was earliest in GD2, followed by GM1 and latest in GM2 (Table 2).
- Diagnosis occurred earliest in GD2, followed by GM1 and latest in GM2 (Table 2).
- The time interval between onset of first neurological symptom and diagnosis was shortest in GD2 and longest in GM2 (Table 2).
- In all 3 LSDs, more than half of the patients were diagnosed using both enzyme activity test and genetic test (Table 2).
- Over half of the patients had received gastric-tube, with the highest proportion in GM2 (Table 3).
- First insertion of permanent enteral support was earliest in GD2, followed by GM1 and latest in GM2 (Table 2).
- In all 3 diseases, very few patients were treated with pharmacological investigational or off-label treatment (Table 3).
- The survival was longest in GM2 (median 44.0 months; 95% CI 37.0-53.0), intermediate in GM1 (median 19.0 months; 95% CI 18.0-21.0) and shortest in GD2 (median 14.1 months; 95% CI 10.0-16.0) (Figure 2).

Figure 1. Patients per country [n (%)]

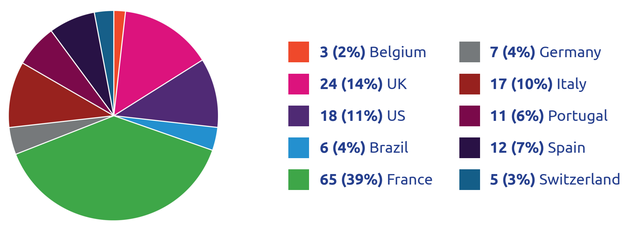


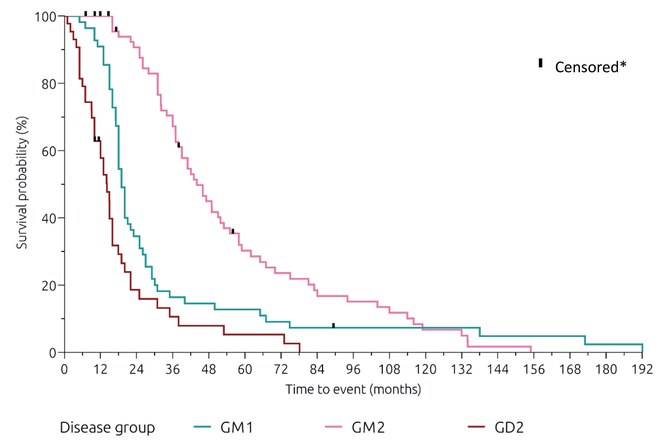
Table 2 . Onset of neurological symptoms and diagnosis. Preliminary analysis.

	GM1	GM2	GD2	TOTAL
Age at onset of first neurological symptoms (months)				
n	55	68	42	**165**
Mean	5.5	8.4	4.7	**6.5**
Median	4	8	4	**6**
Min	0	0	0	**0**
Time from onset of first neurological symptoms to diagnosis (months)				
n	55	67	41	**163**
Mean	6.0	11.6	4.0	**7.8**
Median	4.3	8.0	3.4	**5.9**
Min	-15.1	-9.9	-13.5	**-15.1**
Age at diagnosis (months)				
n	55	68	42	**165**
Mean	11.2	19.7	9.7	**14.3**
Median	10	14	7	**11**
Min	-6	0	0	**-6**
Diagnosis test [n (%)]				
n	55	69	43	**167**
Enzyme activity test	21 (38.2)	27 (39.1)	6 (14.0)	**54 (32.3)**
Genetic test	0	5 (7.2)	5 (11.6)	**10 (6.0)**
Both enzyme activity test and genetic test	34 (61.8)	37 (53.6)	32 (74.4)	**103 (61.7)**
Missing	0	0	1	**1**

Table 3. Gastric tube placement and treatments. Preliminary analysis.

	GM1	GM2	GD2	TOTAL
Gastric tube placement [n (%)]				
n	55	67	43	165
Yes	16 (29.1)	34 (50.7)	10 (23.3)	60 (36.4)
No	38 (69.1)	28 (41.8)	30 (69.8)	96 (58.2)
Unknown	1 (1.8)	5 (7.5)	3 (7.0)	9 (5.5)
Missing	0	2	1	3
Subjects with at least one pharmacologic investigational / off label treatment [n (%)]				
n	4 (7.3)	6 (8.7)	5 (11.4)	15 (8.9)

Figure 2. Kaplan-Meier plot of survival by disease. Preliminary analysis.



Number at risk

GM1	55 (0)	51 (5)	18 (36)	10 (46)	9 (47)	8 (48)	6 (50)	5 (51)	5 (51)	5 (51)	5 (51)	5 (51)	3 (52)	3 (52)	3 (52)	2 (53)	1 (54)
GM2	69 (0)	66 (0)	59 (6)	45 (21)	29 (35)	19 (44)	15 (48)	11 (52)	10 (53)	8 (55)	5 (58)	4 (59)	2 (61)	1 (62)	1 (62)	1 (62)	1 (62)
GD2	43 (0)	25 (18)	7 (33)	4 (36)	3 (37)	2 (38)	2 (38)	0 (40)	0 (40)	0 (40)	0 (40)	0 (40)	0 (40)	0 (40)	0 (40)	0 (40)	0 (40)

***Subjects with survival status of alive or unknown at end of study are considered censored**

SUMMARY AND DISCUSSION

- This interim analysis shows preliminary data from a large retrospective sample of 'early onset' GM1, GM2 and GD2 patients.
- High quality data are obtained in this study, as all subjects from a site are included, hereby reducing selection bias; all data will have source data verification.
- Median survival was longer in 'early onset' GM2, intermediate in 'early onset' GM1 and shortest in GD2.
- Survival may be a good endpoint to evaluate the efficacy of a potential new treatment in 'early onset' GM1 and GM2, and in GD2.
- The findings suggest that, it is feasible to study all 3 diseases in a single clinical trial with survival as primary endpoint.

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