RESEARCH REPORT

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Neurocognitive profile of adults with the Norrbottnian type of Gaucher disease

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Abstract

Introduction: Gaucher disease (GD) is a monogenic, lysosomal storage disorder, classified according to the presence of acute (type 2), chronic (type 3), or no (type 1) neurological manifestations. The Norrbottnian subtype of neuronopathic GD type 3 (GD3) is relatively frequent in the northern part of Sweden. It exhibits a wide range of neurological symptoms but is characterized by extended life expectancy compared to GD3 in other countries. The aim of our study was to describe the cognitive profile of adult patients with Norrbottnian GD3.

Materials and Methods: Ten patients with GD3 (five males and five females) underwent neurocognitive testing with the Repeatable Battery for Assessment of Neuropsychological Status (RBANS). RBANS consists of different short tests that assess Immediate Memory, Visuospatial and Constructional function, Language, Attention, and Delayed Memory. General neurological symptoms of the patients were assessed with the modified severity scoring tool.

Results: Patients (median age 41.5 range 24–57) performed lower than average in all cognitive domains. The overall index score was low (median 58.5, Interquartile range [IQR] 25.5), with the most profound deficit in attention (median 57, IQR 32.5) and immediate memory (median 76.5, IQR 13). Higher scores were found in language (median 83, IQR 21.5), delayed memory (median 81, IQR 41), and visuospatial/constructional function (median 86, IQR 32.35).

Conclusion: Norrbottnian GD3 patients showed a unique neurocognitive profile with low overall performance, mostly derived from low scores in attention and memory domains whereas language and visuospatial/constructional ability were relatively spared.

KEYWORDS

attention, cognition, glucocerebrosidase, memory, neuronopathic Gaucher disease

Synopsis

Norrbottnian Gaucher type 3 patients show deficits in attention and immediate memory but have a relatively spared language and visuospatial/constructive ability.

1 | INTRODUCTION

Gaucher disease (GD) is caused by decreased glucocerebrosidase (GCase) activity that leads to the accumulation of glucosylceramide in monocytes and macrophages.[1,2] Three clinical subtypes are described: a non-neuronopathic form (type 1), an acute (type 2), and a chronic neuronopathic form (type 3).[2] All subtypes are characterized by hematological, visceral, and bone manifestations, whereas the clinical phenotypes of GD2 and 3 also present with gaze palsy, and may include symptoms from the central nervous system (CNS).[2-5] Other neurological features like ataxia, myoclonus, epilepsy, and dystonia-like hyperkinetic symptoms may vary among patients.[6] There is a relatively high prevalence (1:17.500) of a GD3 subtype in northern Sweden, the Norrbottnian type of GD3.[7] Most of these patients are homozygotes for the missense mutation L444P (c.1448T > C) in the glucosylceramidase beta gene (*GBA*),[8] they receive enzyme replacement therapy (ERT) and have an extended life expectancy, not only compared to other GD3 patients when left untreated,[9] but also probably due to the availability and good response to treatment.[10]

The pathophysiology of CNS involvement in neuronopathic GD is poorly understood. Glucosylceramide accumulates rarely in neurons[2] but the perivascular accumulation of Gaucher cells[11] and the role of glucosylsphingosines has been studied.[2,12] Interestingly, glucosylsphingosines in the brain are involved in neuronal development and axonal growth.[13] The role of gangliosides in neuronal repair and plasticity has previously been discussed and their abnormal accumulation in the CNS has been related to neurodevelopmental diseases and neurodegeneration.[14] Neuronal loss in the hippocampal CA2-4 area and the cerebral cortical layers 3 and 5 have been described in a series of seven patients with neuronopathic GD.[11] The current therapeutic options include ERT and substrate reduction therapy (SRT), none of which is efficacious against neurological symptoms, although some SRT crosses the blood–brain barrier.[1,2] Allogeneic hematopoietic stem cell transplantation (allo-HSCT) has been implemented in a few GD2 and GD3 cases,[15] but it is not part of the standard care.

Current knowledge on CNS involvement is mainly based on epidemiological studies. Neurological signs are often present early in utero and infancy in GD2, while in GD3 they present later in life.[1] Previous studies on the psychomotor and intelligence quotient (IQ) scores of pediatric GD3 patients have shown that overall intellectual delay is not common early in the disease course, but increases through childhood and adolescence and may be aggravated by splenectomy.[16] However, a more thorough, longitudinal evaluation of cognition in GD3 patients, both children and adults, showed that the variation of IQ in GD3 is not linear, and shows no clear trajectory.[17] In a series of adult GD3 patients, only mild cognitive impairment was reported in the subgroup of those with concurrent epilepsy, as assessed with the montreal cognitive assessment screening tool.[4,6,16]

The objective of this study was to assess the cognitive profile of Norrbottnian GD3 patients in Sweden with the Repeatable Battery for Assessment of Neuropsychological Status (RBANS).

2 | MATERIALS AND METHODS

This was a cross-sectional study including 10 patients with GD3 diagnosis who are followed at the Department of Medicine, Sunderby Regional Hospital of Norrbotten County in Luleå, Sweden. All participants provided oral and written informed consent in accordance with the Helsinki Declaration and the study was approved by the local ethics committee (DNR 2016/19-31/1 and 2017/1957-32/1, Regionala Etikprövningsnämnden). Information on age, gender, clinical history (genotype, age at diagnosis, epilepsy, surgical treatment) as well as past and current treatments were recorded. The patients underwent clinical evaluation with the modified severity scoring tool which has been developed for the assessment of neurological manifestations in neuronopathic GD patients.[18] Additionally, the patients underwent cognitive testing with the RBANS battery that comprises five subtests assessing immediate memory (list learning, story memory), visuospatial and constructional function (figure copy, line orientation), language (picture naming, semantic fluency), attention (digit span, coding) and delayed memory (list recall, list recognition, story recall, figure recall). Each sum score generates an index score which is scaled according to age. Index values were acquired from normative data from healthy populations, where a mean value of 100 and a SD of 15 are established as the normal range.[19] Index score values of 90–109 are classified as average, 80–89 as the lower part of the average, 70–

TABLE 1 Demographic and clinical characteristics of patients, and index scores in cognitive domains as assessed with RBANS

	Sex	Age	GBA genotype[a]	Age at Dx	SPC/ Age	Epilepsy/ Age at Dx	Therapy/ Age	mSST	Immediate Memory	Visuospatial/ Constructional	Language	Attention	Delayed Memory	Total Index Score
1	F	32	c.[1448 T > C];[1448 T > C]	2	Y/2	Y/16	allo-HSCT/2	7.5	71	90	82	59	52	56
2	F	39	c.[1448 T > C];[1448 T > C]	7	Y/10	N	ERT/13	5	75	56	82	67	80	58
3	M	29	c.[1448 T > C];[1448 T > C]	2	Y/3	Y/17	ERT/5	11.5	86	102	95	55	91	79
4	M	52	c.[1448 T > C];[1448 T > C]	5	Y/13	Y/45	ERT/27	14	98	82	88	77	105	85
5	F	44	c.[1448 T > C];[1448 T > C]	2	Y/8	Y/23	allo-HSCT/9	18	40	67	58	40	40	40
6	M	30	c.[1448 T > C];[1448 T > C]	3	N	Y/14	ERT/4	15	75	90	60	40	85	55
7	F	51	c.[1448 T > C];[1448 T > C]	1	Y/19	N	ERT/26	5.5	78	70	95	40	80	59
8	F	57	c.[1448 T > C];[1448 T > C]	3	Y/3	N	ERT/32	12.5	81	98	84	74	82	76
9	M	51	c.[1448 T > C];[1448 T > C]	1	Y/10	N	ERT27	13.5	64	40	98	40	44	40
10	M	24	c.[1138G > A];[1448 T > C]	1	N	N	ERT/1	1.5	78	96	78	72	91	75
Median (IQR)		41.5 (21.5)		2 (3)	9 (7)			12 (8.88)	76.5 (13)	86 (32.25)	83 (21.5)	57 (32.5)	81 (41)	58.5 (25.5)

Abbreviations: allo-HSCT, allogeneic hematopoietic stem cell transplantation; Dx, diagnosis; ERT, enzyme replacement therapy; F, Female; M, Male; mSST, modified severity scoring tool; N, no; SPC, splenectomy; Y, yes.

[a]GBA genotyping performed in 2015 (DNA extraction, PCR and sequencing of all coding exons and flanking intronic regions) with the exception of two patients who underwent allo-HSCT. Median scores and IQR are computed.

79 as clearly below average, and ≤69 significantly below average. The scores were computed according to the manufacturer's scoring sheet and compared to the normative data for the Swedish population. RBANS has previously been used in studies on neurodegenerative[20] and neurovascular diseases[21,22] with relatively good reliability. It is easy to administer, takes approximately 30 min to complete, and the measurements provide a scaled-score profile adjusted for age and education.

Eye-tracking parameters including latency, gaze, and velocity (average and peak) of horizontal and vertical saccades, and antisaccades, as well as antisaccadic error rate, were measured with EyeBrain T2 as previously described[5] and were available in eight patients.

2.1 | Statistical analysis

Continuous variables are reported in medians and interquartile ranges, and categorical variables in percentages and absolute numbers. The Mann–Whitney U test was used for between-group comparisons of continuous variables, and the significance level was 0.05. IBM SPSS Statistics 25 software was used for statistical analysis.

3 | RESULTS

The GD3 cohort included five males and five females that were, all but one, homozygotes for the L444P mutation. Overall demographic and clinical characteristics of patients, as well as index scores in cognitive domains as assessed with RBANS, are summarized in Table 1. No siblings were included in the group, neither any close family relationship was reported among participants. The

heterozygote (L444P/A341T) presented with milder symptoms and a better cognitive profile. In the neuropsychological assessment, patients scored at the lower part of the average in visuospatial/constructional, language, and delayed memory domains. Immediate memory score was clearly below average whereas attention, as well as the total index score, were significantly below average (Table 1 and Figure 1).

Comparisons of cognitive performance between patients with and without splenectomy did not show statistically significant differences. With regard to treatment, all cognitive domain scores were lower in patients that had undergone allo-HSCT compared to those treated

TABLE 2 Saccade's characteristics in Norrbottnian Gaucher disease type 3 patients

Latency (ms)	Median (IQR)
Step horizontal	293.75 (77.94)
Step downward	276.25 (63,13)
Step upward	266 (0)
Gap horizontal	251.5 (98.75)
Antisaccades (with gap)	261 (27.25)
Gain	
Step horizontal	0.86 (0.09)
Step downward	0.9 (0.09)
Step upward	0.86 (0.26)
Gap horizontal	0.88 (0.14)
Antisaccades error rate	0.375 (0.54)

Note: Median and Interquartile ranges (IQR) of eye-movement parameters. Latency is computed in milliseconds. The gain describes the amplitude of the saccades relative to the amplitude of the visual target which was presented 20° lateral of a central fixation cross.
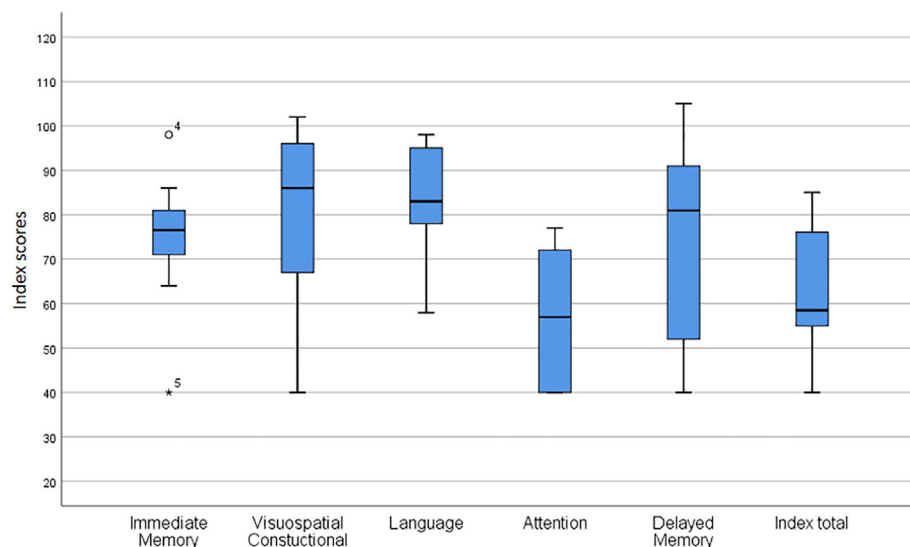
FIGURE 1 Boxplots of the RBANS index scores in five cognitive domains for the GD3 cohort. The boxplots represent the minimum, first quartile, median, third quartile and maximum of the RBANS subscores. The asterisk (*) represents an extreme outlier while the circle (o) represents a mild outlier

with ERT (Table 2), especially immediate (median 55.5 vs. 78; $p = 0.09$) and delayed memory (median 46 vs. 83.5; $p = 0.09$). Differences did not reach statistical significance presumably due to lack of power. Finally, no statistically significant difference was found in the RBANS scores between patients with and without a diagnosis of epilepsy.

No significant correlations between the total and the subtest scores of the RBANS and the eye-movement parameters were identified. Saccades' characteristics have been described in detail in a previous publication of our group,[5] and are summarized in Table 2. In short, horizontal saccades were characterized by reduced gain, peak, and average velocity compared to healthy controls while during downwards vertical saccades, the average velocity was decreased. Latencies during both vertical and horizontal saccades were prolonged.

4 | DISCUSSION

Here, we report the presence of significant cognitive deficits in adult patients with Norrbottnian GD3, more profound in the domains of attention and immediate memory, and milder in visuospatial/constructional function, language, and delayed memory, as assessed with the RBANS test. These results are partly in accordance with a previous study[23] that has shown that nonverbal skills were typically affected in young patients with GD3. The study population examined presented with slow processing speed and poor performance in visuospatial, and perceptual organization skills, whereas language skills were spared. Similarly, in our population, we report a profound attention deficit and average language performance. Contrary to this study, we report relatively good performance in visuospatial and constructional tasks. This discrepancy may be due to differences in the age and genetic background of the investigated populations or might be attributed to different methodologies and cognitive assessment tools used. Additionally, results from the largest, longitudinal study on GD3, where both children and adults were extensively evaluated with age-appropriate cognitive tests, has also highlighted a low performance in attention, as measured with digit span and coding.[17] Moreover, the researchers highlight better scores in verbal tests compared to performance items, and indicate that this could be attributed to the fact that some of the performance subtests where timed, along with the disadvantage of impaired fine motor skills and horizontal gaze tracking. Despite the different study-design compared to our cohort, a similar cognitive profile was observed. However, the only timed subtest in RBANS is coding (part of the performance IQ assessment in the

aforementioned study), which is combined with digit span (part of the verbal IQ assessment) in order to provide a common index score for attention. Therefore, direct comparison between the studies' results is hard to be made.

There have been reports that splenectomy is associated with lower IQ and a worsening of neurological symptoms and cognitive profile in GD3 patients, probably due to accumulation of glycosylceramide in various tissues and the brain.[16,23] Our study could not confirm any statistically significant differences between the patients who had undergone splenectomy and those who had not, neither in the cognitive domains examined by RBANS nor in the total score. It has to be pointed out though that only two of the patients in our cohort were not splenectomized, while one of them is not homozygotic for the L444P mutation but has a unique genotype of L444P/A431T and a somehow milder phenotype. The results should, therefore, be interpreted with caution.

With regard to the effect of treatment on cognitive performance, patients who had undergone allo-HSCT had more pronounced memory impairment than those who received ERT. Previous studies have not confirmed a beneficial effect of ERT against neurological manifestations of GD,[24] however, based on smaller studies, a possible positive effect of ERT in cognitive outcome has been suggested.[25-27] Also, allo-HSCT is not common in clinical praxis and has, so far, been performed in a limited number of GD3 patients, with questionable effects on the neurological outcome.[28] On the contrary, allo-HSCT is indeed shown to affect cognition and lead to cognitive impairment in patients with hematologic malignancies.[29] Given that treatment options are based on symptom severity, among other factors, it is difficult to draw conclusions on the nature of the relationship between treatment and outcome within such a small group of patients.

Half of the patients were treated with antiepileptic drugs, however, no significant differences were found in the cognitive performance of those with versus without epilepsy, as it was also shown in a previous study.[17] This observation opposes previous case reports,[30,31] and a longitudinal cohort of 12 Norrbottnian GD3 patients, where three out of four patients with MoCA score lower than the cut-off for cognitive impairment had epilepsy.[6] Although evidence suggests that cognitive deficits are common features in patients with epilepsy and sometimes present early or before epilepsy onset,[32] there are no systematic studies on the association of epileptic features in GD with cognitive performance.

We were not able to identify statistically significant correlations between the eye movements and the RBANS' total score and subscores. However, since eye-tracking parameters were abnormal for all participants tested, and no

control group was included, it is difficult to make conclusive statements on the association of the Norrbottnian GD3 patients' neurocognitive and the role of gaze paralysis.

GD is strongly associated with Parkinson's disease (PD).[33,34] Cognitive impairment in PD is associated with various genetic factors,[35] and *GBA* mutations, particularly L444P, correlate with greater impairment in working memory, executive function, and visuospatial ability.[36] *GBA* mutations leading to GCase activity reduction and lysosomal dysfunction have been shown, both in vivo and in vitro, to be related to increased levels of soluble and aggregated α-synuclein. Interestingly, the accumulation of α-synuclein results in a reduction of GCase activity, the mechanism, though, is not entirely understood.[37] Although PD and GD are two distinct disease entities, studies on the role of *GBA* in well-described disease cohorts like the Norrbottnian GD3 patients could provide important insight into its function in disease processes.

Our study has several limitations, the most important of which is the small number of patients that prevents the generalizability of our findings. Also, the RBANS test does not provide a thorough neuropsychological evaluation rather than an overview of the patients' cognitive profile. However, it was considered appropriate given the practical difficulties of more time-consuming neurocognitive evaluation in patients who suffer physical limitations. Our results are in line with previous studies on GD3 patients but in contrast to most of the previous published data, it includes adult patients of a GD3 subgroup (i.e., the Norrbottnian subtype of GD3).

During the past few years, there have been attempts to build registries of neuronopathic GD patients to better describe the natural course of the disease as well as the effect of different types of treatment. Early cognitive and neurological screening and longitudinal assessment with standardized tools in large-size, multicentre cohort studies will provide valuable information on the evolution and treatment of CNS manifestations in neuronopathic GD.

In conclusion, RBANS appears to be a useful tool to assess the cognitive profile of Norrbottninan GD3 patients. However, more studies where the results of RBANS would be compared to those of a detailed neurocognitive evaluation are needed in order to examine whether the two assessments would be in accordance. RBANS has indicated that Norrbottnian GD3 patients show a unique neurocognitive profile with low overall performance, mostly derived from low scores in attention and memory domains whereas language and visuospatial/constructional ability are intact.

AUTHOR CONTRIBUTIONS

Research Project: Conception, Design, Execution; Statistical Analysis: Design, Execution, Analysis and Interpretation; Manuscript Preparation: Writing of the First Draft, Review and Critique, Drafting Tables and/or Figures: Panagiota Tsitsi. *Research Project: Conception, Design; Statistical Analysis: Execution, Analysis and Interpretation; Manuscript Preparation: Review and Critique, Drafting Tables and/or Figures.*: Ioanna Markaki. *Research Project: Conception, Design; Statistical Analysis: Analysis and Interpretation; Manuscript Preparation: Review and Critique, Drafting Tables and/or Figures*: Josefine Wardthaler. *Research Project: Conception, Design; Statistical Analysis: Analysis and Interpretation; Manuscript Preparation: Review and Critique, Drafting Tables and/or Figures*: Maciej Machaczka. *Research Project: Conception, Design, Execution; Statistical Analysis: Analysis and Interpretation; Manuscript Preparation: Review and Critique, Drafting Tables and/or Figures*: Per Svenningsson. Corresponding Author and Guarantor: Panagiota Tsitsi is guarantor for the article and accepts full responsibility for the work and the conduct of the study, had access to the data, and controlled the decision to publish.

ETHICS STATEMENT

All procedures followed were in accordance with the ethical standards of the local ethics committee (Regionala Etikprövningsnämnden Stockholm), which approved the study (DNR 2016/19-31/1 and 2017/1957-32/1), and in accordance with the Helsinki Declaration of 1975, as revised in 2000. All participants provided oral and written informed consent. Proof that informed consent was obtained is available upon request. This article does not contain any studies with animal subjects performed by the any of the authors.

DATA AVAILABILITY STATEMENT

The datasets generated and analyzed during this study are available from the corresponding author on reasonable request.

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