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RESEARCH ARTICLE

Neurocognitive Functioning of Pediatric and Young Adult Patients with Gaucher Disease, Type 1

Andrea G. Alioto[1,3], Seymour Packman[2], Rowena Gomez[1], James Moses[1], Wendy Packman[1]

[1] Palo Alto University, Department of Clinical Psychology
[2] University of California, San Francisco, Department of Pediatrics
[3] Current Affiliation: Kaiser Permanente Santa Clara Medical Center

* aalioto@paloaltou.edu

ABSTRACT

This exploratory study aimed to evaluate the cognitive and executive functioning of sixteen pediatric and fifteen young adult (ages 5 through 30) patients with Gaucher disease, Type 1. The neurocognitive functioning of children with Gaucher disease, Type 1 was based on self- and parent-proxy reports while neurocognitive functioning in young adults was based on self-report only. Results showed that pediatric participants with Gaucher disease, Type 1 on self-report demonstrated a trend toward weaker cognitive functioning than healthy children. Parent proxy-reports did not show significantly different cognitive functioning of children with Gaucher disease, Type 1 compared to healthy peers. Young adults with Gaucher disease, Type 1 self-reported no significant differences in cognitive functioning from healthy young adults. No group differences in executive functioning were observed for child or young adult samples. Parent-reported disease severity was not associated with cognitive outcomes among the pediatric or young adult samples. Results suggest possible mild cognitive weaknesses among children with Gaucher disease, Type 1 while cognition in young adults appears relatively well preserved. This is the first independent examination of cognitive functioning among children and young adults with GD1. Additional studies in younger patients with Gaucher disease, Type 1 are needed to identify possible cognitive dysfunction and elucidate underlying mechanisms.

Keywords: Gaucher disease, pediatric, neurocognitive functioning, inborn error of metabolism

Introduction

Gaucher disease (GD), one of the most common lysosomal storage disorders, is caused by recessive mutations in the glucocerebrosidase gene (*GBA*). Mutations lead to reduced activity of the enzyme beta-glucocerebrosidase (GCase) and the progressive accumulation of the substrate glucocerebroside in cells and tissue macrophages throughout the body.[1] GD is classified into two broad groups: neuronopathic GD (GD types 2 and 3) and non-neuronopathic GD (GD type 1). Type 1 GD (GD1) is the most common presentation in individuals of European and Ashkenazi Jewish heritage, accounting for roughly 94% of cases in the Gaucher Registry.[2] Clinical manifestations of GD1 include hepatomegaly, splenomegaly, anemia and thrombocytopenia.[3] Skeletal disease (osteopenia, lytic or sclerotic lesions, and osteonecrosis) and growth retardation with delayed puberty are common. [3] GDI is heterogenous in terms of presenting clinical features. GD1 with childhood onset is associated with more severe disease and faster progression of symptoms.[4]

GD1 had historically been associated with the absence of nervous system involvement. However, recent studies have recognized a subset of patients with GD1 who develop neurological manifestations. In this context, and given phenotypic heterogeneity in Types 1 and 3 Gaucher disease, it is reasonable to consider that there is a spectrum or continuum of neurologic manifestations between these disorders.[5,6] Several studies have described peripheral as well as central nervous system symptoms in patients diagnosed with GD1.[5, 7-9] In addition, individuals with GD1 and carriers of *GBA* mutations show an increased risk for Parkinson's disease (PD) and related neurodegenerative disorders such as Lewy body disease.[10] Additional work has suggested abnormal microstructural[11,12] as well as functional[13] brain magnetic resonance imaging (MRI) findings in children classified as having GD1. A magnetic resonance spectroscopy study[14] reported neurochemical abnormalities in individuals with GD1 under stable GD therapy. Further research is needed to replicate these observations, and to distinguish primary manifestations from those due to concurrent medical problems.[15] Nonetheless, given the presence of neurological and possible brain changes among individuals diagnosed with GD1, there are reasonable grounds for the study and characterization of cognitive function in GD1.

Previous studies of neurocognition in GD1 have involved adult patients. One study demonstrated mild deficits in visuospatial functioning in a sample of patients diagnosed with GD1, but not in memory, attention, executive functioning or language skills.[16] Biegstraaten and colleagues examined neurocognitive functioning within an adult sample (n= 84; ages 18-75) and found deficits in domains of attention and speed of memory retrieval among adults with GD1 relative to age-matched healthy controls.[17] This latter study also showed an association between symptom severity and cognitive performance on a neuropsychological battery, suggesting that individuals with more severe GD1 symptoms show poorer concentration skills compared to patients with a milder symptom presentation.[17] Moreover, a series of studies examining neurological functioning (ages 33 - 64) among adults with GD1 found more prominent cognitive impairment among adults with GD1 with concomitant parkinsonism[18] and a higher rate of cognitive decline and dementia than in sporadic PD.[19]

While there is at least one study of neuropsychological functioning in children and young adults with GD,[20] that investigation is of patients with GD type 3 (GD3). There have been few investigations on the cognitive or neuropsychological functions of younger patients with GD1. A neurophysiological study of fifty-six children and adolescents with GD discovered electrophysiological abnormalities in the brainstems, as well as impairment on tests of intellectual functioning (IQ), of patients who were considered to have types 1 and 3.[21] Notably however, this study did not report results by genotype, making it difficult to determine whether patients with GD1 showed evoked potential or IQ abnormalities, or whether these findings were found only in those with a Type 3 genotype. As such, the neurocognitive functioning among pediatric populations with GD1 has yet to be adequately described. Importantly, no prior study has evaluated the cognitive functioning within the young adult GD1 population.

The objective of this exploratory study was to describe the neurocognitive aspects of GD1 among pediatric and young adult patients. We present data from a sample of GD1 patients ages 5-30 who were evaluated for the presence of general cognitive and executive dysfunction. To our knowledge, this is the first study of neurocognitive functioning in youth with GD1 using psychometrically valid assessment measures of cognitive function.

Materials and Methods

Participants and Procedures

Information describing the study purpose and invitations to participate were posted on internet

forums and message boards comprised of individuals with GD and their family members. Forums and message boards included the National Gaucher Foundation website, the Yahoo! Gaucher Disease group, and the Gaucher Community Alliance Facebook group. Recruitment flyers were also distributed to physicians and genetic counselors at medical centers who treat patients with GD. Eligible participants included pediatric (5-17 years) and young adult (18-30 years) individuals with a self- and/or parent- reported diagnosis of GD1 who were fluent in English. One consenting parent completed parent measures. Based on information from parents, we were able to document that 81% of the pediatric participants had at least one N370S allele (See Table 1). Approximately forty percent of the young adult participants self-reported having at least one N370S allele on genotype analysis (See Table 2). Parental informed consent and child assent forms were obtained and age-appropriate measures were provided in person or by mail. Participants were recruited between 2014 and 2018. The study was approved by the Institutional Review Board (IRB) at Palo Alto University.

Table 1. Background Characteristics of Pediatric Participants with Gaucher Disease, Type 1 and their Families

	Frequency	Percentage[a]
Gender (*n* = 16)		
Male	8	50.0
Female	8	50.0
Age (*n* = 16)		
5 – 8 years	4	25.0
9 – 11 years	6	37.5
12 – 14 years	5	31.25
15 – 17 years	1	6.25
Genotype (*n* = 13)		
N370S/N370S	2	15.38
N370S/L44P	6	46.15
N370S/AD4GG	2	15.38
N370S/c.599T>A	1	7.69
N370S/Rec L44P+84GG+IVS2	2	15.38
Race/Ethnicity of parents (*n* = 32)		
Caucasian	18	56.25
Ashkenazi	9	28.13
Latino (Latin American, Hispanic)	4	12.50
Asian	1	3.13
Education of parents (*n* = 32)		
Some High School	2	6.25
High school diploma (or equivalent, e.g., GED)	2	6.25
Some college	3	9.38
Associate's degree	6	18.75
Bachelor's degree	6	18.75
Master's degree	12	37.5
Doctoral degree	1	3.13
Family history (*n* = 16)		
Parent with GD	0	0.0
Sibling with GD	10	62.5
Family history of Parkinson's disease	6	37.5
Current or past symptoms endorsed by parents of children with GD1 (parents selected as many as applied; *n* = 16)		
Enlarged spleen	13	81.25
Enlarged liver	11	68.75
Low platelet count	11	68.75
Fatigue	9	56.25
Nose bleeds	8	50.0
Bone pain	7	43.75
Growth retardation	5	31.25
Osteoporosis/bone fractures	4	25.0
Bruising	3	18.75

Respiratory problems	2	12.5
Joint pain/arthritis	2	12.5
Headaches	2	12.5
Gastrointestinal	2	12.5
Delayed puberty	1	6.25
GD1 Treatment (*n* = 16)		
Imiglucerase	11	68.75
Velaglucerase alpha	5	31.25
Severity of current GD1 Symptoms (*n* = 16)		
None	2	12.5
Little/Some	6	37.5
Moderate	6	37.5
Considerable	1	6.25
Extreme	1	6.25
Age in years when child started treatment (*n* = 16)		
0 – 4 years	6	37.5
5 – 8 years	5	31.25
9 – 12 years	5	31.25
Time away from school during the current school year because of GD1 complications (*n* = 16)		
None	5	31.25
1 Week or Less	5	31.25
1 – 2 Weeks	0	0.0
More than 2 Weeks, Less than 1 Month	1	6.25
1 – 2 Months	4	25.0
2 – 3 Months	1	6.25
GD1 interferes with extracurricular activities, such as sports (*n* = 16)		
None	2	12.5
Little	7	43.75
Moderate	7	43.75
Considerable	0	0.0
Extreme	0	0.0

Note. [a]Percentage refers to available *n*.

Table 2. Background Characteristics of Young Adult Participants with Gaucher Disease, Type 1 and their Families

	Frequency	Percentage[a]
Gender (*n* = 15)		
Male	1	6.66
Female	14	93.33
Age (*n* = 15)		
18 – 21 years	2	13.33
22 – 25 years	8	53.33
26 – 30 years	5	38.46
Genotype (*n* = 6)		
N370S/N370S	3	42.86
N370S/L44P	2	33.33
N370S/84GG	1	16.66
Race/Ethnicity of parents (*n* = 16)		
Caucasian	6	37.50
Ashkenazi	6	37.50
Latino (Latin American, Hispanic)	2	12.50
Asian	2	12.50
Education of parents (*n* = 16)		
Some High School	0	0.00
High school diploma (or equivalent, e.g., GED)	0	0.00
Some college	1	6.25
Associate's degree	0	0.00
Bachelor's degree	4	25.00
Master's degree	9	56.25

Doctoral degree	2	12.50
Family history (n = 8)		
Parent with GD	2	25.00
Sibling with GD	4	50.00
Family history of Parkinson's disease	2	25.00
Current or past symptoms endorsed by parents of young adults with GD1 (parents selected as many as applied; n = 8)		
Spleen Enlargement	7	87.50
Fatigue	7	87.50
Liver Enlargement	6	75.00
Low platelet count	6	75.00
Bone pain	6	75.00
Nose bleeds	5	62.50
Bruising	4	50.00
Gastrointestinal	3	37.50
Muscular complications	2	25.00
Joint pain/arthritis	2	25.00
Osteoporosis/bone fractures	2	25.00
Growth retardation	1	12.50
Delayed puberty	1	12.50
Respiratory problems	1	12.50
Headaches	0	0.00
GD1 Treatment (n = 15)[c]		
Imiglucerase	6	40.00
Velaglucerase alpha	1	6.66
Eliglustat (Cerdelga)	8	53.33
Severity of current GD1 Symptoms as endorsed by parents of young adults with GD1 (n = 8)		
None	3	37.50
Little/Some	2	25.00
Moderate	1	12.50
Considerable	2	25.00
Extreme	0	0.00
Age in years when started treatment (n = 13)		
0 – 4 years	5	38.46
5 – 8 years	3	23.08
9 – 12 years	2	15.38
13 – 17 years	1	7.69
18 – 30 years	2	15.38

Note. [a]Percentage refers to available n

Assessment Measures

Peds QL Cognitive Functioning Scale. The Peds QL ™ Cognitive Functioning Scale (PedsQL CFS) is a 6-item self-and parent-proxy assessment of memory and attention/concentration.[22] The instrument has been used with children and young adults with chronic illnesses and has excellent validity and reliability for self-report and parent-proxy forms.[22-24] Scores on the PedsQL CFS correlate strongly with performance on the Behavior Rating Inventory of Executive Functioning (BRIEF)[24,25] and are associated with head computed tomography (CT) findings among children with intracranial injury.[26] Higher PedsQL CFS scores reflect better cognitive functioning.

Behavior Rating Inventory of Executive Functioning. The BRIEF measures executive functioning in the home and school environments via parent and self-report.[27,28] The BRIEF is comprised of 75-86 items in which participants and parents answered on the basis of whether each behavior is "never a problem," "sometimes a problem," or "often a problem" within the past six months. Psychometric properties show good internal consistency (α = .80-.98) and test-retest reliability (r = .76-.94).[27,28] BRIEF composite scales include the Behavioral Regulation Index (BRI), Metacognition index (MI), and Global Executive Composite (GEC). Parents of pediatric participants completed BRIEF and young adult participants with GD1 completed the Behavior Rating Inventory of Executive Functioning for Adults (BRIEF-A). Higher BRIEF scores reflect poorer executive functioning skills.

Background Questionnaire. Parents of pediatric and young adult participants with GD1 completed a background questionnaire which contained information about demographics, educational, psychological, and family history. The form also gathered information about the participants' GD symptoms, age of diagnosis, and treatment history.

Analyses

Group differences in neurocognitive functioning were analyzed using Wilcoxon signed-rank tests.[29] Cognitive functioning scores on the PedsQL CFS were based on child self-report and parent-proxy report for pediatric participants and on self-report for young adult participants. PedsQL CFS scores of children with GD1 were compared to the scores of age-matched healthy children.[24] PedsQL CFS scores of young adults with GD1 were compared to those of healthy peers.[23] Executive functioning scores on the BRIEF and the BRIEF-A were based on parent-proxy report for pediatric participants and on self-report for young adult participants. Composite scores on the BRIEF and the BRIEF-A were compared with normative sample means derived from the instrument manuals.[27,28] The alpha level was set at .05.

In secondary analyses, we explored the relationship between symptom severity and neurocognitive functioning in children and young adults with GD1. Parents of children and young adult participants ranked their child's current GD1 symptoms ranging from 1 (None) to 5 (Extreme) using a 5-point Likert scale. Severity scores were then correlated with parent and participant responses on the PedsQL CFS and with composite scores on the BRIEF and BRIEF-A using Spearman's Rho correlations.

Results

Tables 1 and 2 contain the demographic and clinical characteristics of the participants. A total of 31 patients with GD1 participated and completed study measures. The pediatric sample was comprised of 16 children with GD1 between the ages of five and 17 (*M* age = 10.25, SD=3.36), while the young adult sample included 15 young adults between the ages of 18 and 30 (*M* age = 24.20, SD=3.03). Fourteen total study participants were siblings. Twenty-four parents completed parent-proxy measures. Participants resided in the United States (n= 28), Israel (n = 1), Tunisia (n = 1), and Turkey (n = 1). Seventy-four percent of the sample was undergoing ERT and 26% (all in the young adult sample) were taking eliglustat (Cerdelga®) at the time of the study. All participants were receiving GD1 treatment at the time of the study and denied prior interruption or discontinuation of treatment. Results of the background questionnaire indicated that approximately 44% of pediatric participants and 13% of young adult participants with GD1 had a family history of PD.

Cognitive Functioning: Peds QL Cognitive Functioning Scale

Children with GD1. On self-report, children with GD1 demonstrated a trend toward poorer cognitive functioning relative to healthy age peers (p = 0.058). From the parents' perspective, there were no differences in cognitive functioning on the PedsQL CFS between children with GD1 relative to healthy peers (p = 0.10; Table 3).

Young Adults with GD1. On self-reported PedsQL CFS scores, young adults with GD1 did not demonstrate significantly different cognitive functioning scores than healthy age peers (p = 1.0) ; Table 4).

Table 3. Comparison Between Healthy and Gaucher Disease Samples on the PedsQL Cognitive Functioning Scale Child Self-Report and Parent Report

	Healthy Sample*			Gaucher Disease Sample					GD v. Healthy	
PedsQL CFS	*n*	M	SD	*n*	M	Median	SD	IQR	*d*	p
Child Self-Report	177	82.08	16.97	16	73.17	68.75	16.46	29.17	*.80*	.06
Parent Report	113	90.05	14.66	16	80.99	83.33	18.82	28.31	*.40*	.10

*PedsQL 4.0 CFS healthy sample comparisons.[24]
p = *p*-value for Wilcoxon-signed rank test.
d = effect size for Wilcoxon-signed rank test.
Note. PedsQL scores range from 0 – 100, with higher scores indicating better functioning.

Table 4. Comparison Between Healthy and Gaucher Disease Samples on the PedsQL Cognitive Functioning Scale Young Adult Self-Report

	Healthy Sample*			Gaucher Disease Sample					GD v. Healthy	
PedsQL CFS	*n*	M	SD	*n*	M	Median	SD	IQR	*d*	p
Young Adult Self- Report	391	70.88	18.15	15	69.64	77.08	25.76	43.74	.28	1.0

*PedsQL 4.0 CFS healthy disease sample comparisons.[23]
p = *p*-value for Wilcoxon-signed rank test.
d = effect size for Wilcoxon-signed rank test.
Note. PedsQL scores range from 0 – 100, with higher scores indicating better cognitive functioning.

Executive Function: BRIEF

On the BRIEF, parents of children with GD1 did not demonstrate significant differences in their child's executive functioning relative to the normative sample on any of the BRIEF Composite Scales (all *p*'s > 0.05; Table 5). Young adults also showed no significant differences on the BRIEF-A composite scales relative to normative standards, including BRI (*p*= 0.89), the MI (*p* = 0.93), or the GEC (*p* = 0.92; Table 6), indicating no reported problems with executive functioning.

Table 5. Comparison Between Normative and Gaucher Disease Sample for the BRIEF Parent Report

					GD v Normative	
BRIEF Scales	M	Median	SD	IQR	*d*	*p*
Behavioral Regulation Index (BRI)	50.00	49.00	5.79	7.00	.12	.77
Metacognition Index (MI)	47.33	47.00	8.73	10.00	.32	.20
Global Executive Composite (GEC)	48.20	49.00	8.44	9.00	.11	.31

p = *p*-value for Wilcoxon-signed rank test.
d = effect size for Wilcoxon-signed rank tests
Note. Normative mean = 50, SD = 10. Higher BRIEF scores reflect poorer executive functioning skills.

Table 6. Comparison Between Normative and Gaucher Disease Sample for the BRIEF Young Adult Report

					GD v Normative	
BRIEF Scales	M	Median	SD	IQR	*d*	*p*
Behavioral Regulation Index (BRI)	50.31	48.00	13.26	23.00	.17	.89
Metacognition Index (MI)	49.77	50.00	11.33	19.00	.00	.93
Global Executive Composite (GEC)	51.69	47.00	15.43	16.00	.27	.92

p = *p*-value for Wilcoxon-signed rank test.
d = effect size for Wilcoxon-signed rank tests
Note. Normative mean = 50, SD = 10. Higher BRIEF scores reflect poorer executive functioning skills.

Relationship between disease severity and Neurocognitive Functioning

For children with GD1, parent-reported disease severity was not significantly associated with child-reported cognitive functioning (r_x = 0.09, *p* = 0.76) or parent-reported cognitive functioning (r_x = 0.07, *p* = 0.81) on the PedsQL. Likewise, parent-reported disease severity was not associated with parent-reported executive functioning on the BRIEF BRI (r_x = -0.23, *p* = 0.42), MI (r_x = -0.39, *p* = 0.16), or GEC (r_x = -0.39, *p* = 0.17) composite scales.

Among young adult participants, parent-reported symptom severity was not significantly associated with young-adult reported cognitive functioning (r_x = -0.55, *p* = 0.16) or young-adult reported executive functioning on the BRIEF-A BRI (r_x = 0.32, *p* = 0.44), MI (r_x = 0.22, *p* = 0.60), or GEC (r_x = 0.32, *p* = 0.44) composite scales.

Discussion

This is the first independent investigation of the cognitive and executive functioning of youth with GD1. The neurocognitive functioning of children with GD1 was based on self- and parent-proxy reports while neurocognitive functioning in young adults was based on self-report only. The objective of this exploratory study was to examine the reported neurocognitive functioning of school-age children and young adults with GD1. Our results demonstrate possible cognitive difficulties among pediatric participants (ages 5 – 17) according to child report. Parent reports did not show statistically significant differences in cognitive or executive functioning among children with GD1 relative to healthy peers. Among young adults with GD1 (age 18 – 30), there were no significant differences in cognitive or executive functioning relative to age peers.

Cognitive Functioning

Children with GD1 demonstrated a trend toward poorer cognitive functioning relative to healthy peers. Parent-reported cognitive functioning showed no difference in cognitive functioning for children with GD1 than that of healthy peers. The cognitive scores of children with GD1 were lower than the parent reports of cognition among their children with GD1. Discrepancies between self and parent-proxy report have been described in prior studies, particularly for internal symptoms like cognition that are less visible compared to external domains such as physical functioning.[30] It is possible that children with GD1 experience cognitive difficulties in their daily lives that are of greater severity than is apparent to their parents.

For young adults, participants rated themselves as having comparable cognitive functioning to the healthy population. This finding suggests that young adults with GD1 function well from a cognitive perspective and perform similarly to healthy peers their same age.

Findings from other empirical studies of cognitive performance in adults with GD1 have generally demonstrated relatively subtle deficits.[16,17] For example, Elstein and colleagues demonstrated slight visuospatial disturbances in an adult GD1 sample.[16] Likewise, the mild deficits in attention and speed of recall reported by Biegstraaten and colleagues were felt by the study authors to be of minimal clinical significance.[17] Similar to findings in adult samples, the present findings provide support for the presence of relatively mild cognitive deficits in younger patients with GD1 overall, with greater deficits in pediatric patients. These findings suggest the need for parents and clinicians to consider evaluation of the cognitive functioning of children with GD1.

Executive Functioning

According to parent report on the BRIEF, pediatric participants with GD1 do not exhibit significant executive functioning problems relative to normative standards. Absence of significant executive functioning deficits were also observed for young adult participants on the BRIEF-A. Although children with GD1 may experience difficulties in general cognitive functioning, the GD1 sample appears to function very well in the area of executive functioning. Findings suggest that younger patients with GD1 exhibit minimal difficulties with executive functioning such that they can recruit higher-order cognitive skills that enable them to perform well in academic and other settings.

Relationship to Disease Severity

In the pediatric sample, parent-reported symptom severity was not correlated with cognitive functioning based on child self-reports and parent-proxy reports on the PedsQL CFS. Parent-reported disease severity was also not correlated with parent-reported executive functioning on the BRIEF. Similarly, in our young adult sample, parent-reported disease severity was not correlated with self-reported cognitive functioning or executive functioning of young adults. These findings suggest that in our limited sample of young people with GD1, the presence of reported cognitive symptoms may be unrelated to clinical status or severity of GD1 disease.

The cognitive functioning difficulties observed in the pediatric sample of children with GD1 are relatively subtle overall. It is important to note, however, that the functional impact of small deficits in neurocognition can be substantial. For example, children with chronic illness who present with cognitive dysfunction have poorer performance at school[31] and reduced competence in peer relationships.[32] These factors could contribute to adverse effects on academic achievement and social functioning. Cognitive dysfunction among children with chronic illness is also associated with problems effectively coping with stress.[33] Thus, neurocognitive functioning in GD1 has important implications for the lives and long-term outcomes of young patients.

It is not known whether the observed trend toward decreased cognitive functioning on the PedsQL CFS in the pediatric GD1 sample results from illness during an important time of neurodevelopment, mild cognitive effects from

chronic GD1, or other factors. Some recent studies have demonstrated non-specific white matter microstructural alterations on neuroimaging[11,12] and altered brain functional networks[13] among pediatric patients with GD1. Neurobiological contributions to cognitive dysfunction cannot be ruled out. Our pediatric sample includes a higher percentage of N370S compound heterozygote participants than the young adult sample. Compound heterozygosity of the N370S mutation is associated with a more severe disease presentation with earlier age of onset than N370S homozygosity,[34,35] raising the possibility that genotype differences between our samples could account for the comparatively decreased cognition scores of our pediatric participants.

Another possible explanation is that mildly reduced cognition scores in this sample result from psychosocial distress and anxiety experienced as a result of living with a chronic and potentially progressive disease. Psychological symptoms and emotional reactivity are known contributing variables to cognitive dysfunction in children.[36,37] Further, our prior study of psychosocial functioning in young patients with GD1 indicated the presence of lower health-related quality of life HRQoL among children with GD relative to a healthy sample while young adults with GD1 showed minimal psychosocial symptoms.[38] Combined with the finding from the present study that pediatric patients with GD1 perform more poorly on cognitive measures, this may suggest that young adults possess better coping strategies for the psychological symptoms of GD1 and therefore exhibit fewer cognitive weaknesses. It is possible that maturation and the resulting improved ability to manage symptoms of GD1 may have provided the young adult participants with GD1 with protection from the cognitive weaknesses exhibited by the child sample.

Based on the finding of a trend toward decreased cognitive functioning among pediatric participants on a validated instrument of cognitive functioning (PedsQL CFS), we suggest that children with GD1 may have weaker cognitive function than age peers. This interpretation is preliminary in an exploratory study. However, our analysis certainly warrants further investigation of cognition in a broader GD1 sample and study protocol.

This investigation has several limitations. Our small sample size may have limited the statistical power of our statistical analyses. The disproportionately female makeup of the young adult sample differs from the sex distribution found in epidemiological studies of GD,[39] making the generalizability of our findings across sexes difficult. As this was an exploratory study, a standardized neuropsychological assessment battery was not administered to GD1 participants. The PedsQL CFS and BRIEF assessment measures are valid measures of cognitive function that have been correlated with gold standard neuropsychological instruments.[23-25,27,28] Our streamlined approach to data collection also meant that we did not investigate the relationships between cognitive function and disease-related factors such as length of time on ERT that would have allowed us to provide fuller explanation of our findings. We did not specifically evaluate the possible association between mood and cognitive functioning within our study, suggesting that follow-up studies are needed to better-clarify the underlying etiology of the cognitive deficits found in this study. Finally, our sample was not large enough to statistically compare the cognitive functioning of children to that of young adult participants; significant differences between age groups could provide important insights regarding the neurological and cognitive profiles of GD1.

Despite these limitations, our study advances our understanding of the neurocognitive functioning of young patients with GD1. The results underline the importance of awareness toward possible neurocognitive dysfunction in young patients with GD1, particularly in children with the condition. As the first study to explore the cognitive and executive functioning of children and young adults with GD1, these findings provide a foundation from which future research may stem. Further elucidation of the neurocognitive functioning of younger patients with GD1 and associated underlying mechanisms is needed. Because this study found possible age-related differences in cognitive outcomes, future research should more closely examine neurocognition using a longitudinal design or explicitly investigate differences in cognitive performance across the lifespan. Studies across age groups could further highlight possible variability in cognition over time. Given that treatment is associated with attenuated disease severity, it will be important for future researchers to consider the interaction between treatment for GD1, including length of time on ERT, and cognitive performance.

In summary, the findings of this study add to the available medical and neuropsychological literature of Gaucher disease. The present study shows a trend toward poorer cognitive functioning among pediatric patients with GD1 based on self-report, while parent proxy reports did not show significantly different cognitive or executive functioning of children with GD1 compared to

healthy peers. Young adults with GD1 self-reported no significant differences in cognitive functioning from healthy young adults. No group differences in executive functioning were observed for child or young adult samples. Parent-reported disease severity was not associated with cognitive outcomes among the pediatric or young adult samples. These findings should inform assessment and treatment recommendations delivered to patients with GD1 and their families by medical providers. Specifically, there is a need for healthcare professionals working with young patients with GD1 to concurrently assess the presence of physical, cognitive, and emotional symptoms. An increased knowledge of the neurocognitive functioning of GD through future research and inquiry would support a more comprehensive understanding of the spectrum of GD1 symptoms and their long-term functional effects for patients and their families.

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Conflict of Interest Statement

The authors report no conflict of interest.

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References

1. Stirnemann J, Belmatoug N, Camou F, et al. A review of Gaucher disease pathophysiology, clinical presentation and treatments. *Int. J. Mol. Sci.,* 2017;18(441),1-30. doi:10.3390/ijms18020441

2. Charrow J, Andersson HC, Kaplan P, et al. The Gaucher registry: Demographics and disease characteristics of 1698 patients with Gaucher disease. *Arch. Intern. Med.* 2000;160(18),2835-2843. doi:10.1001/archinte.160.18.2835

3. Rosenbloom, BE, Weinreb NJ. Gaucher disease: a comprehensive review. *Crit. Rev. Oncog.,* 2013;18(3),163-75. doi:10.1615/critrevoncog.2013006060

4. Kaplan P, Baris H, De Meirleir L, et al. Revised recommendations for the management of Gaucher disease in children. *European J. Pediatr.* 2013;172,447-458. doi:10.1007/s00431-012-1771-z

5. Capabolo JL, Saenz de Cabezón A, Fraile J, et al. Neurological evaluation of patients with Gaucher disease diagnosed as type 1. *J Neurol. Neurosurg. Psychiatry.* 2008;79(2),219-222. doi:10.1136/jnnp.2006.111518

6. Roshan Lal, T, Sidransky, E. The Spectrum of Neurological Manifestations Associated with Gaucher Disease. *Diseases,* 2017;5(1),10. doi:10.3390/diseases5010010

7. Biegstraaten M, Mengel E, Maródi L, et al. Peripheral neuropathy in adult type 1 Gaucher disease: A 2-year prospective observational study. *Brain.* 2010;133(10),2909-2919. doi:1093/brain/awq198

8. Biegstraaten M, van Schaik IN, Aerts JMFG, Hollak, CEM. 'Non-neuronopathic' Gaucher disease reconsidered. Prevalence of neurological manifestations in a Dutch cohort of type I Gaucher disease patients and a systematic review of the literature. *J. Inherit. Metab. Dis.* 2008; 31(3),337-349. doi:10.1007/s10545-008-0832-y

9. Chérin P, Rose C, de Roux-Serratrice C, et al. The neurological manifestations of Gaucher disease type 1: the French Observatoire on Gaucher disease (FROG). *J. Inherit. Metab. Dis.* 2010;33(4),331-338. doi:10.1007/s10545-010-9095-5

10. Aflaki E, Westbroek W, Sidransky E. The complicated relationship between Gaucher disease and parkinsonism: Insights from a rare disease. *Neuron.* 2017;93(4),737-746. doi:10.1016/j.neuron.2017.01.018

11. Davies EH, Seunarine KK, Banks T, Clark CA, Vellodi A. Brain white matter abnormalities in paediatric Gaucher Type I and Type III using diffusion tensor imaging. *Image in Metab. Med.* 2011;34(2),549-555. doi:10.1007/s10545-011-9288-6

12. Kang H, Zhang M, Ouyang M, et al. Brain white matter microstructural alterations in children of type I Gaucher disease characterized with diffusion tensor MR imaging. *Eur. J. Radiol.* 2018;102, 22-29. doi:10.1016/j.ejrad.2018.02.014

13. Zhang M, Wang S, Hu D, et al. Altered brain functional network in children with type 1 Gaucher disease: A longitudinal graph theory-based study. *Neuroradiology.* 2019;61,63-70. doi:10.1007/s00234-018-2104-3

14. Kartha RV, Joers J, Terluk MR, et al. Neurochemical abnormalities in patients with type 1 Gaucher disease on standard of care therapy. *J. Inherit. Metab. Dis.* 2020;43(3),564-573. doi:10.1002/jimd.12182

15. Pastores G M, Barnett NL, Bathan P, Kolodny EH A neurological symptom survey of patients with type I Gaucher disease. *J. Inherit. Metab. Dis.* 2003;26,641-645. doi:10.1023/B:BOLI.0000005623.60471.51

16. Elstein D, Guedalia J, Doniger GM, et al. Computerized cognitive testing in patients with type I Gaucher disease: Effects of enzyme replacement therapy. *Genet. in Med,* 2005;7(2),124-130. doi:0.1097/01.GIM.0000153666.23707.BA

17. Biegstraaten M, Wesnes KA, Luzy, C, et al. The cognitive profile of type 1 Gaucher disease patients. *J. Inherit. Metab. Dis.,* 2012;35,1093-1099. doi:10.1007/s10545-012-9460-7

18. Lopez G, Kim J, Wiggs E, et al. Clinical course and prognosis in patients with Gaucher disease and parkinsonism. *Neurol. Genet,* 2016;2(2),e57. doi:10.1212/NXG.0000000000000057

19. Li Y, Li P, Liang H, Zhao Z, Hashimoto M, Wei H. Gaucher-associated parkinsonism. *Cell. Mol. Neurobiol.* 2015;35,755-761. doi:10.1007/s10571-015-0176-8

20. Steward AM, Wiggs E, Lindstrom T, et al. Variation in cognitive function over time in Gaucher disease type 3. Neurology. 2019;93(24),e2772-e2283. doi:10.1212/WNL.0000000000008618

21. Tantawy AA, Sherif EM, Adly AA, Hassanine S, Awad AH Evoked potentials and neurocognitive functions in pediatric Egyptian Gaucher patients on enzyme replacement therapy: A single center experience. *J. Inherit. Metab. Dis.* 2013;36(6),1025-1037. doi:10.1007/s10545-013-9597-z

22. Varni JW, Burwinkle TM, Katz ER, Meeske K, Dickinson P. The PedsQL in pediatric cancer: Reliability and validity of the Pediatric Quality of Life Inventory Generic Core Scales, Multidimensional Fatigue Scale, and Cancer

Module. *Cancer,* 2002;*94*(7),2090-2106. doi:10.1002/cncr.10428

23. Varni JW, Limbers CA. The PedsQL Multidimensional Fatigue Scale in young adults: Feasibility, reliability and validity in a university student population. *Qual. Life Res.* 2008;17(1),105-114. doi:10.1007/s11136-007-9282-5

24. Varni JW, Limbers CA, Sorensen LG, Neighbors K, Martz K, Bucuvalas JC, Alonso, EM. PedsQL Cognitive Functioning Scale in Pediatric Liver Transplant Recipients: Feasibility, reliability and validity. *Qual. Life Res.,* 2011;20(6),913-921. doi:10.1007/s11136-010-9823-1

25. McCarthy ML, Mackenzie E, Durbin D, & Aitken M. The Pediatric Quality of Life Inventory: An Evaluation of its Reliability and Validity for Children with Traumatic Brain Injury. *Arch. Phys. Med. and Rehabil.* 2005;86(10),1901-1909. doi:10.1016/j.apmr.2005.03.026

26. Swanson JO, Vavilala MS, Wang J, et al. Association of initial CT findings with quality-of-life outcomes for traumatic brain injury in children. *Ped. Radio.,* 2012;42,974-981. doi:10.1007/s00247-012-2372-8

27. Gioia GA, Isquith PK, Guy SC, Kenworthy L. *Behavior Rating Inventory of Executive Function.* PAR;2000

28. Roth RM, Isquith PK, Gioia, GA. *Assessment of Executive functioning using the Behavior Rating Inventory of Executive Function (BRIEF).* In S. Goldstein & J. A. Naglieri (Eds.), Handbook of Executive Functioning. Springer; 2005.

29. Siegel S, Castellan NJ. *Nonparametric statistics for the behavioral sciences.* 2nd ed. New York: Mcgraw-Hill Book Company; 1988.

30. Eiser C, Morse R. A review of measures of quality of life for children with chronic illness. *Arch. Dis. Child* 2001;*84*(3),205-211. doi:10.1136/adc.84.3.205.

31. Compas BE, Jaser SS, Reeslund K, et al. Neurocognitive deficits in children with chronic health conditions. *Am Psychol.* 2017;*72*(4),326-338. doi:10.1037/amp0000042

32. Schuman WB, La Greca AM. Social correlates of chronic illness. In: Brown R T (Ed.). *Cognitive aspects of chronic illness in children.* New York: Guilford; 1999.

33. Compas BE, Jaser SS, Dunn MJ, et al. Coping with chronic illness in childhood and adolescence. Annu. Rev. Clin. Psychol. 2012;8,455-480. doi:10.1146/annurev-clinpsy-032511-143108

34. Fairley C, Zimran A, Phillips M, et al. Phenotypic heterogeneity of N370S homozygotes with type I Gaucher disease: An analysis of 798 patients from the ICGG Gaucher Registry. *J. Inherit. Metab. Dis. 2008;31*(6),798-744. doi:10.1007/s10545-008-0868-z

35. Grabowski G, Kolodny EH, Weinreb N. Gaucher disease: Phenotypic and genetic variation. In Scriver CR, Beaudet AL, Valle D, et al., eds. *The online metabolic and molecular basis of inherited metabolic disease.* New York: McGraw-Hill; 2006.

36. Carthy T, Horesh N, Apter A, Edge MD, & Gross, JJ. Emotional reactivity and cognitive regulation in anxious children. *Behav. Res.Ther.* 2010.48(5),384-393. doi:10.1016/j.brat.2009.12.013

37. Wagner S, Müller C, Helmreich I, Huss M, Tadić A. A meta-analysis of cognitive functions in children and adolescents with major depressive disorder. *Eur. Child Adolesc. Psychiatry.* 2015;*24*,5-19, doi:10.1007/s00787-014-0559-2

38. Alioto AG, Gomez R. Moses J, Paternostro J, Packman S, Packman W. Quality of life and psychological functioning in pediatric and young adult patients with Gaucher disease, type 1. *Am. J. Med. Genet. Part A,* 2020;182A,1130-1142. doi:10.1002/ajmg.a.61533

39. Weinreb N, Goldblatt J, Villalobos J, et al. Long-term clinical outcomes in type 1 Gaucher disease following 10 years of imiglucerase treatment. *J. Inherit. Metab. Dis.,* 2013;*36*(3),543-554. doi:10.1007/s10545-012-9528-4