ARTICLE

Variation in cognitive function over time in Gaucher disease type 3

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Abstract

Objective

To identify relevant efficacy parameters essential in designing clinical trials for brain-penetrant therapies for Gaucher disease, we evaluated cognitive function longitudinally in 34 patients with Gaucher disease type 3 seen at the NIH Clinical Center.

Methods

Individuals were tested with age-appropriate Wechsler Intelligence Scales administered between 1 and 18 times over 29 years. Variation in all IQ domains was not linear with time and was best characterized with the coefficient of variation (SD/mean) for each individual. Mixed-effects regressions were used to determine whether IQ was associated with clinical features. Models were controlled for variation in test version, participant identification, and test administrator.

Results

Mean verbal, performance, and full-scale IQs were 81.77, 75.98, and 82.02, respectively, with a consistent discrepancy between verbal and performance IQs. Mean (SD) verbal, performance, and full-scale coefficient of variations were 0.07 (0.04), 0.09 (0.05), and 0.06 (0.02), respectively. IQ varied about a mean, with no clear trajectory, indicating no clear patterns of improvement or decline over time. EEG lateralization and behavioral issues were consistently associated with IQ.

Conclusions

The observed variation in IQ in Gaucher disease type 3 across the cohort and within single individuals over time may be characteristic of other neuronopathic diseases. Therefore, to reliably use IQ as an efficacy measure in any clinical trial of neurotherapeutics, a normal variation range must be established to assess the clinical relevance of any IQ change.

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Glossary

ADD/ADHD = attention-deficit disorder/attention-deficit/hyperactivity disorder; **CI** = confidence interval; **CV** = coefficient of variation; **ERT** = enzyme replacement therapy; **FSIQ** = full-scale IQ; **GD** = Gaucher disease; **MANOVA** = multivariate analysis of variance; **PIQ** = performance IQ; **VIQ** = verbal IQ; **WAIS** = Wechsler Adult Intelligence Scale; **WISC** = Wechsler Intelligence Scale for Children; **WPPSI** = Wechsler Preschool and Primary Scale of Intelligence.

Gaucher disease (GD) is an autosomal recessive lysosomal storage disorder caused by mutations in *GBA1*, leading to a deficiency of the enzyme glucocerebrosidase. Phenotypic presentations vary widely, encompassing visceral, hematologic, skeletal, and neurologic symptoms.[1] Individuals with GD type 3 (GD3) exhibit a spectrum of neurologic manifestations, which may include myoclonic epilepsy, generalized seizures, ataxia, and cognitive dysfunction.[2–8] However, the hallmark and defining feature is slowing, looping, or absence of horizontal saccadic eye movements.[9,10]

Enzyme replacement therapy (ERT) and substrate reduction therapy are widely used therapies that dramatically improve the nonneurologic, systemic complications of GD.[4,7,8] Although no formulation has been proven to affect the neurologic aspects of GD, brain-penetrant substrate reduction therapy, gene therapy, and small-molecule chaperones are being explored.[4] However, because of the general efficacy of existing treatments, patients who would have succumbed to visceral disease in the pretreatment era are now living longer with fewer complications. With prolonged longevity, a new generation of ERT-treated individuals with GD3 are redefining the course of the disease, reporting additional, often subtle, neurologic symptoms.

A major challenge in developing novel therapeutics for neurologic disorders is the establishment of relevant efficacy parameters before initiating a clinical trial. To define a biomarker, a thorough natural history assessment must be performed, evaluating changes over time. In light of the increasing need for brain-penetrant therapy, we aimed to characterize the neurologic and neuropsychological aspects of GD3 through retrospective analysis of 34 patients with GD3 followed at the NIH Clinical Center from 1988 to 2017.

Methods

Standard protocol approvals, registrations, and patient consents

Thirty-four English-speaking patients with a clinical and molecular diagnosis of GD3 were enrolled in studies (NCT00001215, NCT00001289) approved by the National Human Genome Research Institute or the National Institute of Neurologic Disorders and Stroke Institutional Review Board, respectively, at the NIH between 1988 and 2017. Written informed consents/assents were signed by the legal guardian and/or patient as appropriate.

Study population

Patients were evaluated by members of the study team at the NIH Clinical Center. Studies performed included a physical and neurologic examination, abdominal MRI, skeletal x-rays, bone density scans (dual-energy x-ray absorptiometry), EEG, somatosensory and brainstem evoked potentials, neuro-ophthalmologic evaluations, and neurocognitive testing. The specific evaluations performed at each visit varied as clinically indicated, and not all studies were conducted at every visit. Details of these assessments have been previously reported.[2,3,11]

Molecular analyses

Samples were collected for clinical and research assays, as well as for DNA extraction. Genotypic analyses were performed by sequencing all exons of the *GBA1* gene as previously described.[12]

Neuropsychological evaluations

Participant were evaluated with the age-appropriate Wechsler IQ Scale at the time of visit. The Wechsler IQ Scales are the standard metric for evaluating intelligence. Participants 3 to 5 years of age were assessed with the Wechsler Preschool and Primary Scale of Intelligence (WPPSI), specifically test versions WPPSI-R and WPPSI-III. Participants 6 to 16 years of age were assessed with the Wechsler Intelligence Scale for Children (WISC), test versions WISC-R, WISC-III, and WISC-IV. Participants ≥17 years of age were assessed with the Wechsler Adult Intelligence Scale (WAIS), test versions WAIS-R, WAIS-III, and WAIS-IV.[3,13–18] Most individuals were tested with version III of each test. Although versions were updated over time, scores across versions have been shown to be comparable.[3,13–18] The Wechsler scales assess 3 IQ domains: verbal (VIQ), performance (PIQ), and full-scale (FSIQ) IQ. The VIQ and PIQ scores are derived from subtests assessing different domains of cognition. These include verbal comprehension, working memory, perceptual organization, processing speed, and executive functioning, among others. The subtests are scored on a z scale derived from age-matched controls with a mean score of 10 ± 3. The VIQ and PIQ are combined to give the FSIQ and are reported as z-scaled scores, relative to age-matched controls, with a mean score of 100 ± 15. All 3 IQ scores are considered to be stable across time in a control population.[19] Tests were administered by 2 neuropsychologists.

Statistical analyses

All analyses were performed with R (version 3.3.3)[20] in RStudio (version 1.0.136; R Foundation for Statistical

Computing, Vienna, Austria).[21] To account for within-participant correlation, group-wise descriptive statistics were calculated from the individual means for that variable. For each individual, the mean for each parameter was calculated across all of the individual's visits. The mean across all 34 values was then taken, excluding missing values (table 1). Analysis revealed an effect of test version on FSIQ. Therefore, to control for individual and test-related variation, FSIQ means were derived with a mixed-effects regression, with test version and participant identification as random effects. The individual FSIQ means are the intercept values for each participant (table 2). The reported FSIQ mean is the intercept of this regression model (table 3). The coefficient of variation (CV), defined as the SD divided by the mean, was calculated for each individual to assess change over time. To control for individual and test-related variation in FSIQ, individual CVs and CV means were derived from a mixed-effects regression, with test version and participant identification as random effects. The individual FSIQ CVs are the intercept values for each participant (table 2 and figure 2). The reported FSIQ CV mean is the intercept of the full regression model (figure 2). To evaluate the relationship between IQ and clinical and demographic variables, mixed-effects regressions were performed with the *lme4* package.[22,23]

The *p* values for the full regression models were obtained by a likelihood ratio test compared to the null model (intercept and random effects only). Ninety-five percent confidence intervals (CIs) were calculated via the *lme4* basic bootstrap method on 1,000 iterations.[22,24]

Data availability

Anonymized data will be shared by request from any qualified investigator.

Results

Sample demographics

Thirty-four individuals 3 to 34 years of age evaluated at the Clinical Center of the NIH between 1988 and 2017 were included in this retrospective analysis (table 1). Of those, 2 individuals were never able to complete testing, while 2 others were unable to complete testing in a single instance but did so at others. Summary statistics for the full cohort are shown in table 3. Nineteen male and 15 female participants were evaluated. The ethnicities reported included non-Hispanic white (n = 16), Hispanic (n = 11), black (n = 5), Asian (n = 1), and Native American (n = 1). Genotypes were available on 32 individuals, and the majority (n = 26) carried the L444P/L444P (p.L483P/L483P) genotype. Four patients carried complex alleles that arose from recombination with the *GBA1* pseudogene, together with a missense mutation on the second allele. The average age at symptom onset was 15.6 months, with an average age at diagnosis of 21.7 months. Organomegaly was consistently present at diagnosis. Of the 134 visits, there were 8 visits in 6 patients in which the individual was not on enzyme replacement therapy (ERT). The average duration of ERT treatment at the time of visit was 6.77 years. Of the 32 patients who completed testing, 19 had at least 2 evaluations, and 12 had ≥2 . The length of follow-up ranged from 0 years (single visit) to 23 years, with an average length of follow-up of 5.7 years.

IQ scores

IQ scores for each individual are presented in table 2. The reported score is the mean of all assessments performed. FSIQ scores were additionally controlled for test version. Scores in all 3 domains varied widely across the cohort (table 3) with a mean VIQ of 81.77, a mean PIQ of 75.98, and a mean FSIQ of 82.02. All 3 IQ means fall in the below-average to borderline range. Remarkably, the VIQs ranged from 46 to 147, and PIQs ranged from 46 to 122. We noted a consistent discrepancy between VIQ and PIQ, with a mean difference of 5.99 in favor of VIQ. Analysis of the core subtests of these 2 domains was performed to identify specific areas of weakness (table 3). It should be noted that subtests vary with test version, so the numbers of individuals tested are not equal. Verbal subtests include items from the Verbal Comprehension Index and Working Memory Index of the version IV Wechsler tests. Performance subtests include items from the Perceptual Organization Index and Processing Speed Index of the version IV Wechsler tests. Mean subtest scores were within a normal range of 10 ± 3 for 3 of 7 verbal and 1 of 5 performance subtests. The lowest subtest mean for the verbal items was 5.41 for Arithmetic. The lowest subtest mean for the performance items was 4.97 for Digit Symbol Coding. The low scores in the performance subtests were found primarily in timed subtests designed to test visuospatial skills.[13–18]

Longitudinal assessment of IQ

To better evaluate the individual test results for each participant over time, we constructed per-participant IQ trajectories, showing IQ scores relative to the age at evaluation (figure 1). Across all 3 IQ domains, individuals showed marked internal variation in IQ over time. No clear pattern of change was evident, and no trends were appreciated. There were no patterns of either improvement or decline. The IQ changes in our cohort were not linear with time, making a regression analysis or multivariate analysis of variance (MANOVA) inappropriate. Instead, the CV was used to evaluate change over time. CV was calculated for each individual by dividing the SD in IQ by the mean IQ for that individual. For FSIQ, CV was calculated by test version within each participant. A mixed-effects regression was performed to obtain controlled estimates of CV per participant and CV mean. Figure 2 shows scatterplots of the CV for each participant across the 3 IQ domains. The CV mean ± SD (range) values for VIQ, PIQ, and FSIQ were 0.066 ± 0.04 (0.00–0.18), 0.085 ± 0.05 (0.00–0.21), and 0.061 ± 0.02 (0.03–0.13), respectively. Subtests also did not vary linearly with respect to time. CVs were computed for each of the subtest scores and found to be higher than the composite score CVs (data not shown).

Table 1 Participant characteristics

Participant	Sex	Genotype[c]	Age at symptom onset	Presenting symptoms	Other clinical features
1	M	Rec*Nci*I/N188S	17 mo	OM, anemia, DD	Splenectomy
2	F	L444P/L444P	12 mo	OM, FTT, fatigue	—
3	M	L444P/L444P	18 mo	OM, anemia	Seizures
4	F	G377S/Y205C	4 y	OM, TCP	Seizures, myoclonus
5	M	P122S/P122S	18 mo	DD, bone crisis	Seizures, myoclonus
6	M	L444P/L444P	23 mo	OM	—
7	F	L444P/L444P	9 mo	OM	—
8	F	—	24 mo	OM, anemia	Splenectomy
9	F	L444P/L444P	18 mo	OM, FTT	Splenectomy
10	F	L444P/L444P	14 mo	OM, anemia, TCP, GA	—
11	M	L444P/L444P	6 mo	OM, anemia, TCP, cough, DD	—
12	F	L444P/L444P	12 mo	OM	Splenectomy
13	M	L444P/L444P	30 mo	OM	Autism
14	M	L444P/L444P	6 mo	OM	Splenectomy, seizures
15	M	L444P/L444P	13 mo	OM	Splenectomy (9)[b]
16	M	L444P/L444P	16 mo	OM, DD	—
17	M	N188S/Rec7	24 mo	OM, FTT	Myoclonus
18	F	R463C/Rec*Nci*I + Rec7	4 y	OM, anemia, TCP, bone pain	Splenectomy
19	M	L444P/L444P	5 mo	OM, anemia, TCP, GA	—
20	M	Rec*Nci*I/V458G	3 y	OM, TCP	Seizures
21	M	L444P/L444P	15 mo	OM, anemia, RD	Myoclonus
22	M	L444P/L444P	16 mo	OM, anemia, FTT	—
23	F	L444P/L444P	6 mo	OM, TCP	Seizures
24	M	L444P/L444P	15 mo	OM, anemia, lethargy	—
25	F	L444P/L444P	9 mo	OM, GA	—
26	F	L444P/L444P	3 y	OM, anemia, bone pain	Splenectomy, seizures (18)[b]
27	F	L444P/L444P	3 mo	OM, GA	Splenectomy, seizures
28[a]	F	L444P/L444P	6 mo	OM, anemia	—
29[a]	F	L444P/L444P	birth	Affected sibling	—
30	M	—	4 mo	OM, GA	Myoclonus
31	F	L444P/L444P	14 mo	OM	—
32	M	L444P/L444P	7 mo	OM, anemia, TCP	Splenectomy
33	M	L444P/L444P	birth	OM	Seizures (6)[b], autism (6)[b]
34[a]	M	L444P/L444P	2 mo	Affected sibling	Autism

Abbreviations: DD = developmental delay; FTT = failure to thrive; GA = gaze abnormality; OM = organomegaly; RD = respiratory distress; TCP = thrombocytopenia.
[a] Siblings.
[b] Age (years) first documented.
[c] Numbering of the mutant amino acid does not include the 39 amino acid leader sequence in *GBA1*.

Table 2 Individual IQ scores

Participant	Age at follow-up in years (No. of assessments)	Mean VIQ (SD), CV	Mean PIQ (SD), CV	Mean FSIQ (SE), CV[a]
1	5–7 (2)	75.5 (13.4), 0.18	71.5 (4.9), 0.07	72.9 (4.9), NA
2	6–8 (3)	74.3 (4.5), 0.06	68.7 (5.1), 0.07	71.5 (4.2), 0.06
3	8–9 (2)	49.0 (4.2), 0.09	54.0 (11.3), 0.21	49.9 (4.9), 0.13
4	31–33 (5)	73.8 (4.6), 0.06	NC	NC
5	14–15 (3)	46.0 (0.0), 0.00	46.0 (0.0), 0.00	43.1 (4.2), 0.03
6	6 (1)	83.0 (NA), NA	116.0 (NA), NA	93.3 (6.8), NA
7	9–27 (6)	136.2 (9.7), 0.07	107.5 (11.8), 0.11	125.0 (3.1), 0.08
8	33–34 (2)	89.5 (2.1), 0.02	76.5 (0.7), 0.01	81.5 (5.3), 0.04
9	11 (1)	100.0 (NA), NA	80.0 (NA), NA	90.9 (6.6), NA
10	10–12 (3)	73.3 (5.8), 0.08	63.7 (6.7), 0.10	67.9 (4.2), 0.8
11	8 (1)	NC	NC	85.3 (6.7), NA
12	14–15 (2)	88.5 (6.4), 0.07	89.0 (8.5), 0.10	88.9 (4.9), 0.03
13	9 (1)	NC	NC	126.1 (6.7), NA
14	8–15 (6)	67.2 (5.3), 0.08	66.7 (10.4), 0.16	64.9 (3.1), 0.08
15	5–15 (9)	56.8 (5.9), 0.10	62.4 (12.1), 0.19	58.6 (2.9), 0.11
16	3–15 (7)	93.0 (0.0), 0.00	115.3 (5.0), 0.04	97.2 (3.0), 0.06
17	8–10 (3)	64.3 (6.4), 0.10	48.7 (2.9), 0.06	55.0 (4.2), 0.05
18	28 (1)	85.0 (NA), NA	89.0 (NA), NA	85.3 (6.7), NA
19	6–16 (4)	101.0 (NA), NA	81.0 (NA), NA	86.0 (3.7), 0.05
20	6 (1)	NC	NC	108.0 (6.7), NA
21	12–14 (3)	78.7 (4.5), 0.06	55.3 (3.5), 0.06	67.3 (4.2), 0.06
22	7–10 (3)	124.7 (2.1), 0.02	104.0 (4.0), 0.04	116.6 (4.2), 0.04
23	3–23 (12)	95.9 (8.4), 0.09	81.6 (6.5), 0.08	89.3 (2.4), 0.05
24	3–17 (18)	97.2 (6.9), 0.07	93.2 (10.1), 0.11	96.7 (2.2), 0.08
25	5–28 (11)	115.2 (8.0), 0.07	100.9 (7.5), 0.07	109.1 (2.4), 0.04
26	9–20 (4)	66.0 (7.4), 0.11	76.0 (7.2), 0.09	68.7 (3.7), 0.06
27	19–21 (2)	72.5 (3.5), 0.05	63.0 (1.4), 0.02	65.9 (5.0), 0.05
28[b]	10–19 (5)	72.0 (1.4), 0.02	57.5 (7.8), 0.14	63.1 (3.3), 0.05
29[b]	5–12 (2)	59.0 (NA), NA	63.0 (NA), NA	67.7 (5.0), NA
30	5 (1)	64.0 (NA), NA	70.0 (NA), NA	NC
31	9–15 (2)	NC	NC	91.1 (5.1), 0.05
32	9–15 (4)	88.0 (4.5), 0.05	59.0 (2.8), 0.05	73.7 (3.7), 0.05
33	6–13 (3)	NC	NC	NC
34[b]	14 (1)	NC	NC	NC

Abbreviations: CV = coefficient of variation; FSIQ = full-scale IQ; NA = not available; NC = Not completed; PIQ = performance IQ; VIQ = verbal IQ.
[a] Calculated via mixed-effects regression.
[b] Siblings.

Table 3 Sample characteristics

	Mean (range)[a]
Female, n (%)	15 (44.1)
Age at evaluation, y	12.77 (3–34)
Race/ethnicity, n (%)	
Non-Hispanic white	16 (47.1)
Hispanic	11 (32.4)
Black	5 (14.7)
Asian	1 (2.9)
Native American	1 (2.9)
Genotype, n (%)	
Not reported	2 (5.9)
G377S/Y205C	1 (2.9)
L444P/L444P	26 (76.5)
N188S/Rec7	1 (2.9)
P122S/P122S	1 (2.9)
R463C/Rec*Nci*I + Rec7	1 (2.9)
V458G/Rec*Nci*I	1 (2.9)
N188S/Rec*Nci*I	1 (2.9)
Age at onset, mo	15.59 (0, 48)
Age at diagnosis, mo	21.71 (1, 48)
Duration of ERT at time of visit, y	6.77 (0, 24)
VIQ (n = 111)	81.77 (46, 147)
PIQ (n = 107)	75.98 (46, 122)
FSIQ (n = 121)	82.02 (40, 139)
VPIQ (n = 106)	5.99 (−33, 38)
Verbal subtests[b]	
Vocabulary (n = 80)	7.10 (1, 19)
Similarities (n = 79)	7.77 (1, 17)
Information (n = 69)	6.58 (1, 19)[c]
Comprehension (n = 33)	6.37 (1, 18)[c]
Arithmetic (n = 65)	5.41 (1, 18)[c]
Digit span (n = 65)	6.97 (1, 19)[c]
Letter-number sequencing (n = 16)	7.29 (1, 15)
Performance subtests[b]	
Picture completion (n = 62)	6.67 (1, 18)[c]
Block design (n = 80)	5.94 (1, 14)[c]
Matrix reasoning (n = 28)	8.02 (1, 14)
Digit symbol-coding (n = 72)	4.97 (1,12)[c]
Symbol search (n = 44)	6.37 (1, 13)[c]

Abbreviations: ERT = enzyme replacement therapy; FSIQ = full-scale IQ; PIQ = performance IQ; VIQ = verbal IQ; VPIQ = VIQ-PIQ.
[a] Unless otherwise noted.
[b] Cohort scores for the core subtests of the Wechsler scales; standard scores 10 ± 3.
[c] Scores fall >1 SD from the mean.

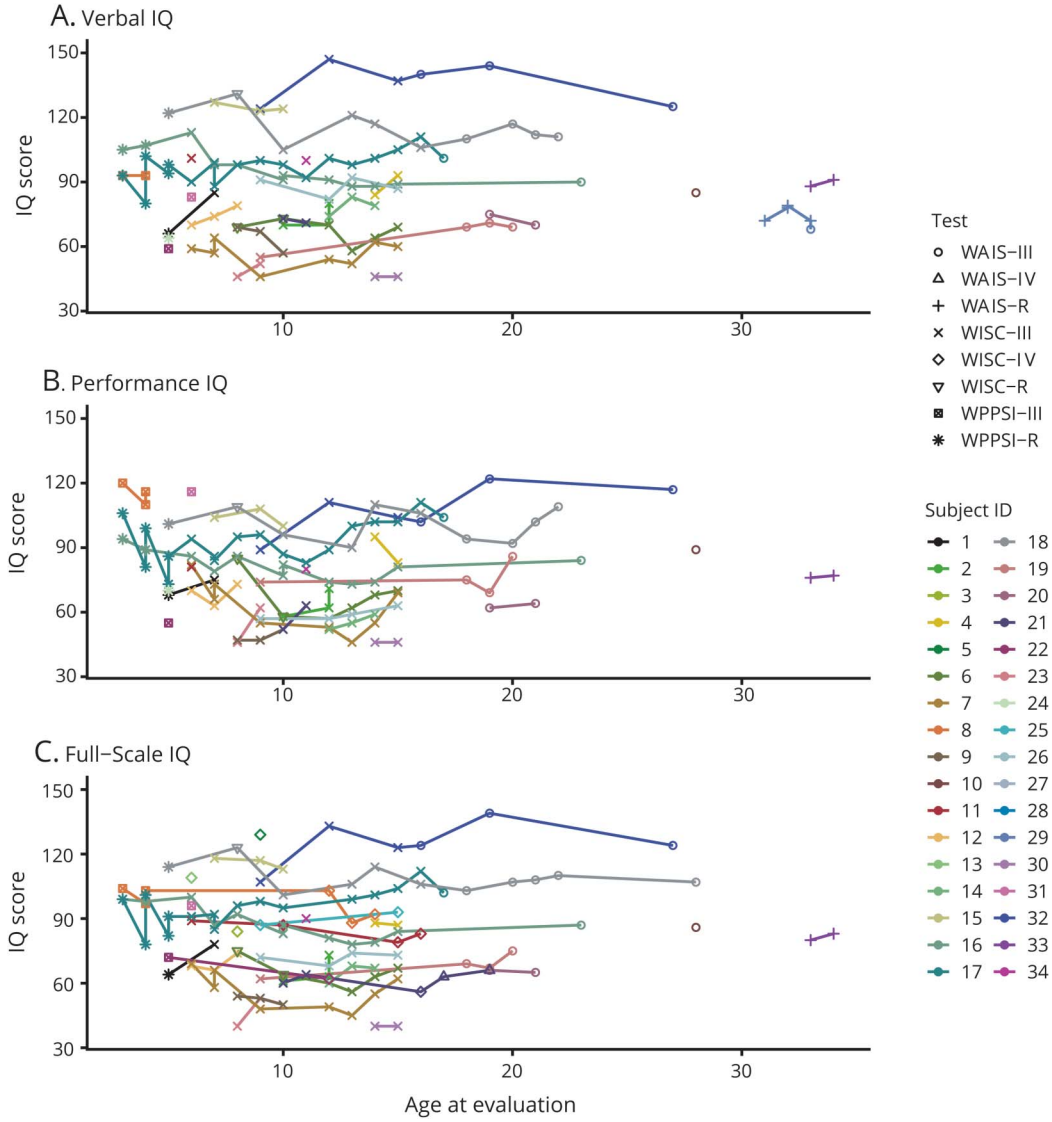
Correlation of clinical features with IQ

To assess the relationship between specific clinical features and IQ scores, mixed-effects regressions were performed with each of the IQ domains as the outcome variable. Participant identification, test version, and test administrator were included as a random intercept effects in all models. Participant identification accounted for a significant proportion of variance in IQ in all models; test version accounted for a proportion of FSIQ variance; test administrator did not account for variance in IQ in any model (table 4). For each IQ domain, the model was constructed with the following clinical correlates: year of evaluation (to control for generational differences), sex, splenectomy (yes/no), bone pain (yes/no), slowed saccadic eye movements (yes/no), history of seizures (yes/no), abnormal EEG (yes/no), EEG lateralization (no, left, right, both), EEG with background slowing (yes/no), abnormal brainstem auditory evoked response (yes/no), genotype, behavioral issues (yes/no), psychiatric issues (yes/no), hearing loss (yes/no), ataxia (yes/no), tremor (yes/no), myoclonus (yes/no), attention-deficit disorder/attention-deficit/hyperactivity disorder (ADD/ADHD) (yes/no), being assigned an individualized education plan at school (yes/no), skeletal issues (mild vs severe), kyphosis (yes/no), scoliosis (yes/no), interstitial lung disease (yes/no), sleep apnea (yes/no), age at symptom onset (months), duration of ERT (years), and autism (yes/no). EEG lateralization was determined by evidence of either slowing or spike and wave activity on one side more than the other. When both of these were seen but were predominant on different sides, lateralization was designated "both." Behavioral issues included outbursts and behavior problems in school or at home. Psychiatric issues were anxiety or depression. Mild skeletal issues included radiographic evidence of Erlenmeyer flask deformity, bone marrow infiltration, and alignment abnormalities. Severe skeletal involvement was defined as radiographic evidence of alignment abnormalities requiring surgical intervention, avascular necrosis, or spontaneous fractures. Interstitial lung disease was determined by radiograph and/or CT. ADD/ADHD, sleep apnea, and autism required formal diagnosis for a "yes" designation. Missing values were treated as a separate variable level in the regressions. The results of these models can be found in tables 4 and 5.

To evaluate the significance of associations between clinical variables and IQ scores, we used a basic bootstrap over 1,000 iterations to obtain 95% CIs. Intervals that do not include zero are more likely to have a true association. For VIQ, left-sided EEG lateralization was associated with an increase in VIQ of 5.88 points (95% CI 1.65–10.49) and behavioral issues with a decrease of 5.72 points (95% CI −11.28 to −0.51). A response of "not available" for interstitial lung disease also had a CI excluding zero.

For PIQ, splenectomy was associated with a decrease in PIQ of 28.61 points (95% CI −45.12 to −11.95), slow saccades with a decrease of 15.89 points (95% CI −30.17 to −0.67),

Figure 1 Variation in IQ over time is not linear



(A) Verbal IQ scores over time. Each line represents a single individual with an evaluation at that age. (B) Performance IQ scores over time. Each line represents a single individual with an evaluation at that age. (C) Full-scale IQ scores over time. Each line represents a single individual with an evaluation at that age

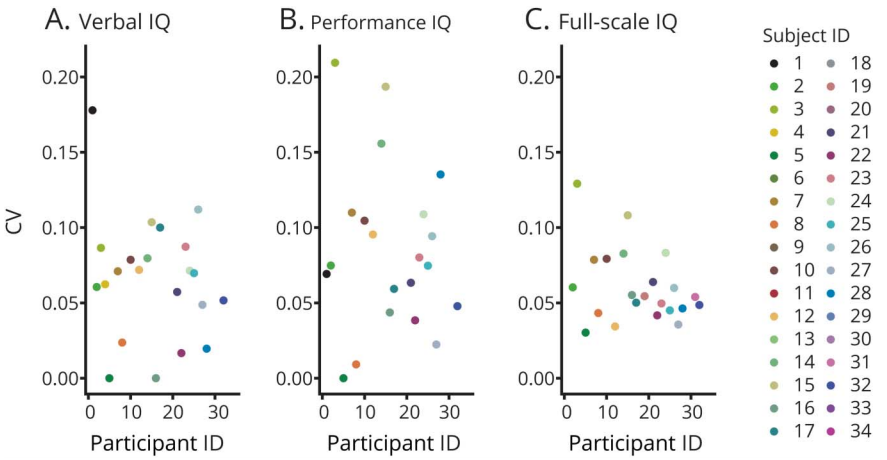
both-sided EEG lateralization with a decrease of 8.43 points (95% CI −14.90 to −1.20), and behavioral issues with a decrease of 9.91 points (95% CI −16.32 to −2.96). A response of "not available" for EEG slowing, interstitial lung disease, and sleep apnea also had CIs excluding zero, in addition to 2 with missing genotypes.

For FSIQ, splenectomy was associated with a decrease in FSIQ of 16.93 points (95% CI −30.38 to −4.17), both-sided EEG lateralization with a decrease of 6.36 points (95% CI −11.52 to −1.15), behavioral issues with a decrease of 8.92 points (95% CI −13.62 to −4.12), and psychiatric issues with an increase of 6.01 points (95% CI 0.01–12.21). Diagnosis of autism and patient genotype also had CIs excluding zero. There was no correlation between any of the IQ scores and duration of ERT treatment.

Discussion

This retrospective analysis of cognition in a neurologic disorder identified many factors to consider when IQ is used as an efficacy parameter. Our evaluation of IQ in individuals with GD3 shows that cognition is variable both among patients and within a single patient over time. Our cohort consisted primarily of individuals with the most common GD3 genotype, L444P/L444P.[25,26] Mean VIQ, PIQ, and FSIQ fell in the below-average to borderline ranges. However, this mean is not indicative of the wide spectrum of IQs seen throughout the cohort, with multiple individuals in the above-average and superior ranges. It is important to note that IQ cannot be assessed in individuals at the lowest end of the cognitive spectrum. We have included 2 such individuals (patients 33, 34) to give a more complete picture of the phenotypic variation.

Figure 2 Coefficient of variation demonstrates IQ fluctuations



(A) Coefficient of variation (CV) of verbal IQ by participant. Average variation across the cohort was 0.066 (0.04), mean (SD). (B) CV of performance IQ by participant. Average variation across the cohort was 0.085 (0.05), mean (SD). (C) CV of full-scale IQ by participant. Average variation across the cohort was 0.061 (0.02), mean (SD).

Prior studies have reported a variety of neurologic symptoms associated with GD3. While some maintain that the neurologic manifestations are stable or even improve over time, others report progressive deterioration, leaving no clear consensus.[2,3,6–8,11]

As patients with GD3 have begun to experience less visceral symptoms, an increased emphasis has been placed on cognitive function and school performance. A commonly reported measure of cognitive function is the IQ. Previous studies have looked at the IQs in patients with GD3, reporting that IQs are typically below average, although the range of these values varies widely.[2,3,11,27,28] However, most studies have been cross-sectional, and the few that are longitudinal are limited by population size or intervals of follow-up. This study evaluates the neurocognitive function in the largest GD3 cohort to date, spanning a course of 29 years.

Some of the individuals in this cohort were included in prior studies.[2,11] These studies noted a discrepancy between VIQ and PIQ scores, with higher VIQ scores.[3] This was seen in our larger cohort as well, with an average difference of ≈6 IQ points. However, the earlier studies in GD3 reported no IQ changes in their cohort over time, whereas we found a variation of 3% to 7% (VIQ), 4% to 14% (PIQ), and 4% to 8% (FSIQ). These different conclusions are likely due to the statistical methodology used. In 1 study, the investigators compared a baseline and single follow-up visit, which is a limited longitudinal analysis. Another study used MANOVA with time as a within factor. MANOVA analyses assume an underlying linearity of the data, which, given the results of our trajectory plots, is likely an invalid assumption. We propose that any longitudinal studies of IQ in neurologic diseases include an assessment of the linearity of the data before further analysis.

Our study also differs from the previous 2 studies in that we analyzed the subtest scores to probe the discrepancy between VIQ and PIQ. We found that while only 4 of 7 verbal subtest means fell >1 SD from the mean, 4 of 5 performance subtest means fell outside a single SD. Moreover, the performance subtests with the lowest scores were timed tests, incorporating fine motor skills, horizontal gaze tracking, and processing speed.[13–18] This suggests that clinical deficits in these areas may be driving performance scores down.

Mixed-effects regressions were used to assess which clinical variables were associated with each of the IQ domains. Using participant identification, test version, and test administrator as random intercept effects, we obtained 3 unique models. Participant identification accounted for variance in IQ in all models, whereas test administrator did not account for variance in any model. Test version accounted for variance in FSIQ only. Significance of the association with IQ of fixed effects was evaluated by construction of 95% CIs by basic bootstrap method on 1,000 iterations.[22,24] Significant effects are identified by CIs that exclude zero.

We found no association between IQ and year of evaluation, sex, bone pain, history of seizures, general EEG abnormality, abnormal brainstem auditory evoked response, hearing loss, ataxia, tremor, myoclonus, ADD/ADHD, having an individualized education plan in school, skeletal issues or structural abnormalities, age at disease onset, or the duration of ERT. The only clinical parameter found to be associated with all 3 IQ domains was behavioral issues, which may be indicative of compliance during testing or the degree of brain involvement. Left-sided EEG lateralization was associated with a minor increase in VIQ score, which may suggest increased activity or compensatory mechanism on the side of the brain involved with language, although EEG was not performed simultaneously with testing. Slow saccades were associated with a lower PIQ score, which corresponds with the results of the subtest analyses showing poorest performance on tests that were timed and required rapid

Table 4 Model parameters, random effects, and fixed effects show correlations between IQ, demographics, and visceral features of GD3

Model Parameters	VIQ	PIQ	FSIQ
No. of observations	111	107	121
No. of participants	28	27	30
***p* Value**	0.081	0.001	0.002
Random effects (SD)			
Participant identification (intercept)	14.714	9.956	13.603
Test (intercept)	0.000	0.000	2.318
Evaluator (intercept)	0.000	0.000	0.000
Residual	5.402	6.473	5.122
Fixed Effects	**β (95% CI)**	**β (95% CI)**	**β (95% CI)**
Evaluation year	−0.88 (−2.25 to 0.35)	−0.35 (−1.58 to 0.87)	−0.52 (−1.73 to 0.70)
Male sex	−3.79 (−17.46 to 10.76)	6.48 (−4.39 to 17.44)	−1.89 (−14.93 to 12.05)
Genotype			
Not reported	−5.20 (−32.20 to 18.63)	−0.90 (−22.62 to 20.48)	8.68 (−26.58 to 43.95)
G377S/Y205C	−14.43 (−66.94 to 32.11)	NA	NA
N188S/Rec7	−12.70 (−48.01 to 23.91)	−39.59 (−72.22 to −6.94)[a]	−16.56 (−54.29 to 17.90)
P122S/P122S	−33.41 (−69.99 to 1.80)	−37.98 (−71.23 to −3.77)[a]	−35.28 (−69.33 to −2.39)[a]
R463C/Rec*Nci*I + Rec7	−5.77 (−55.83 to 41.69)	−10.49 (−50.27 to 30.20)	8.40 (−38.62 to 55.04)
V458G/Rec*Nci*I	NA	NA	23.27 (−19.74 to 63.92)
N188S/Rec*Nci*I	−29.02 (−61.59 to 8.55)	−19.25 (−51.27 to 13.81)	−16.14 (−52.17 to 16.56)
Age at onset, mo	−0.09 (−1.11 to 0.92)	0.77 (−0.11 to 1.64)	−0.16 (−1.10 to 0.82)
Duration ERT, y	0.43 (−0.88 to 1.92)	0.53 (−0.76 to 1.85)	0.29 (−0.99 to 1.55)
IEP			
Yes	3.13 (−1.27 to 7.67)	−1.52 (−7.07 to 3.90)	0.46 (−3.58 to 4.85)
NA	5.32 (−5.09 to 16.59)	4.04 (−9.34 to 16.49)	0.63 (−9.11 to 9.68)
Kyphosis			
Yes	−1.75 (−7.69 to 4.29)	−2.60 (−9.92 to 4.04)	−2.69 (−8.11 to 2.19)
NA	NA	NA	−21.67 (−58.54 to 21.55)
Scoliosis	3.26 (−2.20 to 9.09)	0.97 (−5.49 to 7.73)	3.67 (−1.12 to 8.47)
Lung disease			
Yes	−2.37 (−8.28 to 3.64)	−5.59 (−12.96 to 1.45)	−3.33 (−9.13 to 2.22)
NA	−42.24 (−76.60 to −6.22)[a]	−42.94 (−73.58 to −15.49)[a]	−7.35 (−15.92 to 1.69)
Sleep apnea			
Yes	−0.63 (−7.92 to 6.82)	−0.72 (−9.35 to 7.65)	−2.80 (−9.92 to 5.03)
NA	−3.47 (−37.21 to 30.21)	29.90 (5.25 to 55.34)[a]	13.65 (−16.98 to 44.98)
Splenectomy	−13.21 (−28.95 to 3.98)	−28.61 (−45.12 to −11.95)[a]	−16.93 (−30.38 to −4.17)[a]
Bone pain	4.39 (−3.14 to 11.87)	−1.59 (−12.76 to 8.73)	3.61 (−4.85 to 11.55)

Abbreviations: CI = confidence interval; ERT = enzyme replacement therapy; GD3 = Gaucher disease type 3; IEP = individualized education plan; NA = not available.
The *p* values are the result of a likelihood ratio test comparing the full model to a null (intercept and random effects only) model. SD indicates the amount of variance in random intercept estimates that can be explained by inclusion of that random effect.
[a] The 95% CIs that do not include zero. β Values for binary categorical variables represent a point difference in IQ score vs the "no" response. Genotype β values are vs L444P/L444P genotype. The 95% CIs were calculated via basic bootstrap method (1,000 iterations).

Table 5 Fixed effects show correlations between IQ and neurologic features of GD3

Fixed effects	VIQ β (95% CI)	PIQ β (95% CI)	FSIQ β (95% CI)
History of seizures	0.61 (−11.83 to 12.38)	5.51 (−7.24 to 16.40)	−3.64 (−13.52 to 6.22)
Abnormal EEG			
Yes	2.25 (−6.62 to 11.04)	−0.01 (−10.70 to 11.05)	2.57 (−5.46 to 10.49)
NA	6.58 (−11.40 to 23.94)	20.00 (−2.38 to 42.73)	11.47 (−1.71 to 24.94)
EEG lateralization			
Both	−5.36 (−11.29 to 0.31)	−8.43 (−14.90 to −1.20)[a]	−6.36 (−11.52 to −1.15)[a]
Left	5.88 (1.65–10.49)[a]	0.14 (−5.48 to 5.31)	2.86 (−1.49 to 7.07)
Right	2.49 (−9.91 to 14.55)	6.44 (−7.26 to 21.02)	3.48 (−4.64 to 12.39)
EEG slowing			
Yes	−5.48 (−14.89 to 4.24)	−5.97 (−18.05 to 5.19)	−5.88 (−14.76 to 2.68)
NA	−9.59 (−27.62 to 8.20)	−23.28 (−46.54 to −2.85)[a]	−13.29 (−26.46 to 0.32)
Abnormal BAER			
Yes	−1.42 (−6.40 to 3.94)	2.75 (−3.64 to 9.46)	−0.27 (−5.04 to 4.49)
NA	−1.18 (−6.31 to 3.60)	3.51 (−2.93 to 10.67)	−1.05 (−5.41 to 3.36)
Behavioral issues	−5.72 (−11.28 to −0.51)[a]	−9.91 (−16.32 to −2.96)[a]	−8.92 (−13.62 to −4.12)[a]
Psychiatric issues			
Yes	2.96 (−4.84 to 11.02)	3.40 (−5.23 to 12.21)	6.01 (0.01–12.21)[a]
NA	−2.04 (−21.35 to 16.28)	4.99 (−16.57 to 27.15)	3.29 (−13.57 to 20.94)
Hearing loss			
Yes	−2.67 (−7.63 to 1.93)	−0.02 (−5.90 to 6.03)	−3.28 (−7.78 to 1.29)
NA	−2.82 (−7.91 to 2.58)	0.97 (−5.67 to 7.36)	−2.50 (−7.06 to 2.30)
Ataxia			
Yes	−1.04 (−6.88 to 5.16)	−3.93 (−12.04 to 3.73)	0.85 (−5.11 to 5.95)
NA	20.10 (−23.83 to 64.80)	25.03 (−16.82 to 67.93)	9.73 (−32.91 to 53.20)
Tremor	−4.31 (−8.66, 0.06)	−1.12 (−7.18 to 4.81)	−3.38 (−7.75 to 0.73)
Myoclonus	−5.59 (−17.10 to 6.42)	−4.68 (−19.38 to 10.37)	−5.21 (−16.57 to 6.20)
ADD/ADHD	−1.72 (−10.46 to 6.78)	2.51 (−7.81 to 12.53)	−1.36 (−9.86 to 6.32)
Autism	NA	NA	62.84 (23.35–101.40)[a]

Abbreviations: ADD/ADHD = attention-deficit disorder/attention-deficit/hyperactivity disorder; BAER = brainstem auditory evoked response; CI = confidence interval; FSIQ = full-scale IQ; GD3 = Gaucher disease type 3; NA = not available; PIQ = performance IQ; VIQ = verbal IQ.
[a] The 95% CIs that do not include zero. Note: β values for binary categorical variables represent a point difference in IQ score vs the "no" response. The 95% CIs were calculated via basic bootstrap method (1,000 iterations).

horizontal eye tracking. Both-sided EEG lateralization and splenectomy were associated with lower PIQ and FSIQ and may be indicative of a global neurologic decline. This result should be validated in other neurologic diseases. Chart reviews indicate that all individuals who required splenectomy had severe systemic disease. In all but 1 case, splenectomy was performed before the advent of ERT. The remaining case was not responsive to ERT and continued to have severe visceral disease with life-threatening splenomegaly. We believe the association with splenectomy to be indicative of more aggressive disease.

Our analysis also revealed some associations that we do not believe to be legitimate, despite CIs that may indicate significance. A missing value for lung disease was associated with lower VIQ and PIQ. Missing values for EEG slowing and sleep apnea were also associated with PIQ changes. In cases of missing data, which were very few, this is likely not a real

association. We also believe that very small sample sizes of only a single individual are responsible for the apparent associations with genotypes (VIQ and FSIQ) and autism (FSIQ). We assert that these apparent associations should be interpreted with extreme caution and are likely artifacts due to small sample size.

Sample size was a limitation of our study, as evidenced by the artifact associations. In addition, because of our limited sample size, we were unable to include random slopes in our model. A combined random slope and random intercept approach would have been beneficial for mixed-effects regressions because random intercept alone can overestimate the significance of associations. Although the model for VIQ did not differ significantly from a null model ($p = 0.08$), IQ variation was accounted for by inclusion of random effects. Perhaps a better measure of validation for our models is the relatively low residuals, indicating that a large portion of variance is accounted for in the full models, even without the random slopes. Small sample size, while a general limitation of our study, is not uncommon in rare disease research. With respect to change in IQ over time, there is a dearth of longitudinal studies of IQ in healthy controls, limiting interpretation of the CVs. However, IQ is generally considered to be stable over time, and normalization of data at each age is designed to keep consistency.[13–18] Finally, we recognize that there is potential for selection bias because all participants were seen at the NIH Clinical Center, a tertiary referral center.

Despite these limitations, the strengths of our study include a relatively large and diverse sample considering that this is a rare disease. In fact, this is the largest longitudinal study of IQ in GD3.[2, 11] All participants underwent detailed clinical examination, allowing us to assess associations with many different clinical parameters. Careful genotyping was performed by full sequencing of all exons of *GBA1*. This study also has the longest duration, including patients followed up for up to 20 years (mean 5 years). All evaluations were performed by only 2 neuropsychologists, limiting the effects of varying interpretations. Our study is the first study of IQ in GD3 to include analyses of the subtests and the first in which the analysis was performed in a data-driven manner, with no a priori assumption of linear change over time.

Characterization of the normal range of variation in IQ in GD3 is an essential part of understanding the course of the disease. This component is important for parents, providers, and educators working with GD3, and it must be recognized that any single increase or decrease in IQ cannot be interpreted as an absolute change. Fluctuations within the range of 3% to 7% (VIQ), 4% to 14% (PIQ), and 4% to 8% (FSIQ) are to be expected, and variations outside of that range should not necessarily be cause for alarm but should prompt investigation into the appropriate associated clinical parameters. As the field moves toward trials of brain-penetrant therapies, it is essential to understand the expected baseline fluctuations. To truly assess efficacy of a treatment, it will be essential to demonstrate an effect outside of the normal variation range. Moreover, it is important that studies control for the effects of the associated clinical parameters in their interpretation. The difference in FSIQ across test versions makes it important for future studies to control for test version, ideally by using only a single test within each age group. This study demonstrates that future longitudinal studies of cognition, in both GD and other pediatric-onset neurologic disorders, must establish baseline preintervention measures of IQ, define a range of expected variation without assuming linear change, and include >1 postintervention assessment to demonstrate an effect. Such measures should be incorporated early in study design to reliably assess efficacy. While multiple baseline studies at appropriate intervals are the ideal standard, in cases in which only one can be obtained, the normal variation ranges established here would provide a guideline for indication of a clinically meaningful change in IQ for individuals with GD3. We suggest that the following equations be used to calculate a range of expected IQ variation:

1. When multiple preintervention IQs (IQ_{pre}) are obtained and an individual CV is calculated, this equation should be used:

$$\text{Expected Variation} = \text{mean}\left(IQ_{pre}\right) \pm \text{mean}\left(IQ_{pre}\right)(CV)$$

2. When only 1 preintervention IQ is obtained but a population CV range has been established, the following 2 equations apply:

$$\text{Expected Variation Min} = IQ_{pre} + \left(IQ_{pre}\right)(CV_{min})$$

$$\text{Expected Variation Max} = IQ_{pre} + \left(IQ_{pre}\right)(CV_{max})$$

A postintervention IQ score outside of these ranges would then be considered clinically meaningful. It is reasonable to assume that these findings may not be unique to GD3 and should be tested in other chronic neurologic conditions to establish normal variation ranges.

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Variation in cognitive function over time in Gaucher disease type 3

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