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Cognitive Impairment and Its Clinical and Neuroimaging Correlates in Fabry Disease: A Single-Center Retrospective Cross-Sectional Study

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Research Article

Keywords: Fabry disease, cognitive impairment, neuroimaging, subjective memory complaints, cognitive screening

Posted Date: September 28th, 2026

DOI: https://doi.org/10.21203/rs.3.rs-11029100/v1

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Additional Declarations: No competing interests reported.

Title Page

Cognitive Impairment and Its Clinical and Neuroimaging Correlates in Fabry Disease: A Single-Center Retrospective Cross-Sectional Study

Running title: Cognitive Impairment in FD

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Funding: Key Program of National Natural Science Foundation of China (12231018), National Natural Science Foundation of China (82401636).

Conflict of interest: None.

Abstract

Background: To characterize the prevalence and profile of cognitive impairment in Fabry disease (FD) and examine its clinical, neuroimaging, and biomarker correlates.

Methods: In this single-center retrospective cross-sectional study, we included 57 patients with FD who underwent standardized cognitive assessment; primary analyses were restricted to 50 adults. Clinical characteristics, neuroimaging (ARWML and Fazekas scores), and biomarkers (α-Gal A activity and plasma Lyso-Gb3) were evaluated in relation to cognitive impairment using age-adjusted and multivariable analyses.

Results: Cognitive impairment was present in 19 of 50 adults (38.0%), predominantly involving delayed recall, visuospatial/executive function, attention, and language. Subjective memory decline was strongly associated with objective cognitive impairment (82.4% vs. 42.9%; OR = 6.22, 95% CI 1.45–26.64). Cognitively impaired adults were older (46.7 vs. 37.3 years, P = 0.005), had longer disease duration (32.8 vs. 22.9 years, P = 0.033), and had higher Mainz Severity Score Index (MSSI) scores (21.0 vs. 10.0, P = 0.008). Greater white matter lesion burden was associated with poorer cognitive performance after age adjustment ($r = -0.40$ to -0.74; all $q < 0.05$), whereas α-galactosidase A activity and Lyso-Gb3 levels were not (all $q = 0.83$). Higher MSSI scores remained independently associated with cognitive impairment (OR = 1.08 per point, 95% CI 1.01–1.16).

Conclusions: Cognitive impairment was common in adults with FD, predominantly involving memory and executive-attentional domains. Systemic disease severity and white matter lesion burden were associated with cognitive impairment and poorer cognitive performance, whereas the measured biomarkers were not. Subjective memory complaints may provide a practical indication for formal cognitive assessment.

Keywords: Fabry disease; cognitive impairment; neuroimaging; subjective memory complaints; cognitive screening

1. Background

Fabry disease (FD) is a rare X-linked lysosomal storage disorder caused by pathogenic variants in the GLA gene, resulting in deficient or absent α-galactosidase A (α-Gal A) activity and progressive accumulation of globotriaosylceramide (Gb3) and its deacylated metabolite globotriaosylsphingosine (Lyso-Gb3) in multiple tissues

and organs [1,2]. Clinically, FD is commonly categorized into classic and later-onset phenotypes, although disease expression varies substantially according to sex, genotype, residual enzyme activity, and other modifying factors [3]. With advances in disease-specific therapies and improvements in the long-term management of FD, greater attention has been directed toward cognitive function and quality-of-life outcomes.

Cognitive dysfunction is increasingly recognized as a clinically relevant but incompletely characterized manifestation of FD. Reported prevalence and domain-specific cognitive profiles vary substantially across cohorts [4-7], and cerebral white matter lesion burden has been proposed as a contributing mechanism [6,8], but the relative contributions of clinical disease severity, neuroimaging abnormalities, and biomarkers to cognitive outcomes remain unclear.

Despite growing interest in the neurological manifestations of FD, several important knowledge gaps remain. Many previous studies were limited by relatively small sample sizes, focused primarily on global cognitive screening scores, or evaluated only selected cognitive domains [4-7]. Data from Asian populations, particularly Chinese patients, are also limited. Furthermore, few studies have comprehensively examined cognitive impairment together with clinical characteristics, disease severity, neuroimaging findings, and circulating biomarkers within a single cohort. Therefore, we aimed to characterize the prevalence and profile of cognitive impairment in a Chinese cohort with FD and to examine its clinical, neuroimaging, and biomarker correlates.

2. Methods

2.1 Study Design and Participants

This single-center retrospective cross-sectional study included patients with a confirmed diagnosis of Fabry disease (FD) who were evaluated at Peking University First Hospital between January 2021 and December 2025. The diagnosis of FD was established according to the Chinese expert consensus and relevant international recommendations[9]. Eligible patients had undergone standardized cognitive assessment using the Mini-Mental State Examination (MMSE), the Beijing version of the Montreal Cognitive Assessment (MoCA), or both, and had sufficient clinical data available. Patients were excluded if reliable cognitive assessment could not be completed.

A total of 57 patients met the eligibility criteria. Seven patients (12.3%) were younger than 18 years (range, 7-15 years). Because the education-adjusted MMSE and MoCA thresholds used to define cognitive impairment were validated for adults and no pediatric-specific reference standard was available, these patients were excluded from all primary inferential analyses and are reported descriptively in Supplementary Table S6. The primary analytic cohort therefore comprised 50 adults (age range, 18-62 years). As a robustness analysis, the primary prevalence and multivariable regression analyses were repeated in the full cohort of 57 patients, including the pediatric subgroup.

The study was approved by the Ethics Committee of Peking University First Hospital (approval no. 2024-173-002) and was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants or their legal guardians.

2.2 Clinical and Neuropsychological Assessment

Demographic and disease-related information, including age, sex, educational attainment, age at disease onset, disease duration, clinical phenotype (classic or late-onset), *GLA* genotype (truncating or non-truncating), Mainz Severity Score Index (MSSI), and multi-organ clinical manifestations, was extracted from the electronic medical record. The following clinical manifestations were compared between patients with and without cognitive impairment: cerebral infarction, hypertension, hypertrophic cardiomyopathy, renal insufficiency, tinnitus, palpitations, sleep disturbance, and subjective memory decline. The complete list of recorded manifestations and additional exploratory comparisons is provided in Supplementary Tables S1 and S2.

Patients were additionally classified according to the occurrence of severe clinical events, defined as at least one of the following: (1) a cardiac event (angina pectoris, arrhythmia, congestive heart failure, myocardial infarction, cardiac device implantation, or a significant cardiac procedure); (2) a renal event (initiation of chronic dialysis for more than 40 days, or renal transplantation); (3) a cerebrovascular event (hemorrhagic or ischemic stroke); or (4) death. Patients without any of these events were classified as having a mild clinical course.

Cognitive function was assessed using the MMSE and the Beijing version of the MoCA. Cognitive impairment was defined as a score below the education-adjusted threshold on either instrument: MMSE <20 for illiterate participants, <23 for those with elementary education, and <27 for those with secondary education or above; MoCA ≤13, ≤19,

and ≤24, respectively. These thresholds were applied to the adult primary cohort. Pediatric patients were characterized descriptively and did not contribute to inferential analyses.

To compare domain-specific performance across instruments, MMSE domain scores (orientation, immediate recall, attention/calculation, language, and delayed recall) and MoCA domain scores (visuospatial/executive function, naming, attention, language, abstraction, delayed recall, and orientation) were normalized to a 0-100 scale by dividing the observed score by the maximum possible score and multiplying by 100. Patient-reported subjective memory decline was compared with objectively defined cognitive impairment using a 2 × 2 contingency table.

2.3 Neuroimaging and Laboratory Assessment

Cerebral white matter lesion burden was assessed using the Age-Related White Matter Changes (ARWML) scale and the Fazekas scale. ARWML scores included the total score and bilateral regional subscores, which were summarized into five anatomical regions for analysis: frontal, parieto-occipital, temporal, basal ganglia, and infratentorial/cerebellar regions. Fazekas scores included the total score and separate periventricular and deep white matter lesion scores. Brain MRI of adequate quality was available for 29 adults, including 10 with cognitive impairment; therefore, neuroimaging analyses were restricted to this adult MRI subcohort. Alpha-galactosidase A (α-Gal A) activity and plasma globotriaosylsphingosine (Lyso-Gb3) levels were evaluated as biochemical markers. Analyses were conducted using available-case data without imputation.

2.4 Statistical Analysis

All tests were two-sided; effect estimates and 95% CIs were prioritized over P values. Continuous variables were summarized as mean ± SD or median [IQR], as appropriate, and categorical variables as counts and percentages. Cognitive impairment prevalence was estimated with an exact binomial CI. Between-group comparisons used Welch's t test or the Mann–Whitney U test for continuous variables and Fisher's exact test for categorical variables; effect sizes were reported as Hedges' g or odds ratios with 95% CIs. Comparisons of selected clinical manifestations (Table 3) were not prespecified or corrected for multiple testing and were therefore considered exploratory. Age-adjusted partial correlations were used to assess associations between cognitive scores and neuroimaging or biomarker measures. Associations of MSSI and ARWML scores with cognitive impairment were evaluated in

separate age-adjusted Firth penalized logistic regression models, because their available data did not fully overlap and including both in a single model would have substantially reduced the sample size. Benjamini–Hochberg false discovery rate correction was applied within prespecified families of multiple comparisons. Analyses used available-case or complete-case data without imputation and were performed in Python 3.12; software details are provided in Supplementary Methods. Primary analyses were restricted to adults, with the full cohort examined in sensitivity analyses.

3. Results

3.1 Study Population and Data Availability

A total of 57 patients with a confirmed diagnosis of Fabry disease were included. Seven patients (12.3%), ages 7–15 years, were younger than 18 and were excluded from the primary analytic cohort because the education-adjusted MMSE/MoCA cutoffs used to define cognitive impairment (Section 2.2) are validated for adults; these patients are described separately below and in Supplementary Table S6. The primary analytic cohort therefore comprised 50 adults (18–62 years), 31 (62.0%) of whom were male (Figure 1). Baseline characteristics of this cohort are summarized in Table 1, using each variable's available-case denominator and without between-group comparison.

Among the 7 excluded pediatric patients (ages 7, 9, 10, 11, 11, 14, and 15 years), MMSE ranged from 25 to 30 and MoCA from 20 to 30. None of the 7 pediatric patients met the adult-based threshold for cognitive impairment; however, these classifications were considered descriptive only because the thresholds have not been validated in pediatric populations (Supplementary Table S6). Genotype, MSSI, and MRI data were available for a subset of these patients but are reported descriptively only, given the small number of cases.

Data completeness was high among the 50 adults: MMSE was available for all 50 (100%) and MoCA for 47 (94.0%). Genotype was available for 46 (92.0%), MSSI for 41 (82.0%), and brain MRI for 29 (58.0%). α-Gal A enzyme activity was available for 42 (84.0%) and Lyso-Gb3 for 40 (80.0%), with both measures available for 39 patients (78.0%) (Figure 1). The full cohort of 57, including the 7 pediatric patients, is retained as a robustness check (Supplementary Figure S2).

Table 1. Baseline Characteristics of the Primary Analytic Cohort (Adults, N = 50)

Characteristic	Value	n (available)
Demographics		
Age, years	40.9 ± 11.5	50
Sex		50
Male	31 (62.0%)	
Female	19 (38.0%)	
Education		49
Elementary or below	5 (10.2%)	
Secondary school or above	44 (89.8%)	
Disease Characteristics		
Age at onset, years	13.1 ± 11.4	42
Disease duration, years	26.9 ± 14.2	42
Phenotype		50
Classic	30 (60.0%)	
Late-onset	20 (40.0%)	
Genotype		46
Non-truncating mutation	28 (60.9%)	
Truncating mutation	18 (39.1%)	
MSSI score	12.0 [5.0–21.0]	41
Severe clinical events	23 (51.1%)	45
Major Organ Involvement and Comorbidities		
Cerebral infarction	5 (11.1%)	45
Hypertension	8 (17.8%)	45
Hypertrophic cardiomyopathy	21 (46.7%)	45
Renal insufficiency	16 (35.6%)	45

Characteristic	Value	n (available)
Selected Clinical Symptoms		
Tinnitus	21 (47.7%)	44
Palpitations	16 (41.0%)	39
Sleep disturbance	16 (38.1%)	42
Subjective memory decline	26 (57.8%)	45
MRI and Biomarkers		
Brain MRI available (ARWML/Fazekas)	29 (58.0%)	50
α-Gal A enzyme activity	0.7 [0.4–1.4]	41
Lyso-Gb3, ng/mL	20.1 [6.5–86.8]	40

Values are mean ± SD, median [IQR], or n (%); normality was assessed with the Shapiro-Wilk test. Percentages use each variable's available-case denominator (the n (available) column); no imputation was performed. One patient's disease-duration entry, originally recorded as asymptomatic, was coded as 0 years.

Data completeness ranged from 100% for age, sex, and phenotype to 78% for palpitations. MRI lesion scores were available for 29 of 50 adults (58.0%). See the n (available) column for each variable's denominator.

Abbreviations: ARWML, Age-Related White Matter Changes scale; α-Gal A, α-galactosidase A; IQR, interquartile range; Lyso-Gb3, globotriaosylsphingosine; MSSI, Mainz Severity Score Index; SD, standard deviation.

3.2 Prevalence of Cognitive Impairment

Cognitive impairment was present in 19 of 50 adults, corresponding to a prevalence of 38.0% (95% exact binomial CI, 24.7%–52.8%).

Among the 47 adults with both MMSE and MoCA available, 8 (17.0%) were abnormal on both instruments, 7 (14.9%) were abnormal on the MoCA only, 2 (4.3%) were abnormal on the MMSE only, and 30 (63.8%) were normal on both. An additional 3 adults had only the MMSE available; of these, 2 were MMSE-abnormal and 1 was MMSE-normal.

Overall, cognitive impairment was present in 38.0% of adults. Among patients who completed both instruments, abnormal results were more frequently identified by the MoCA than by the MMSE.

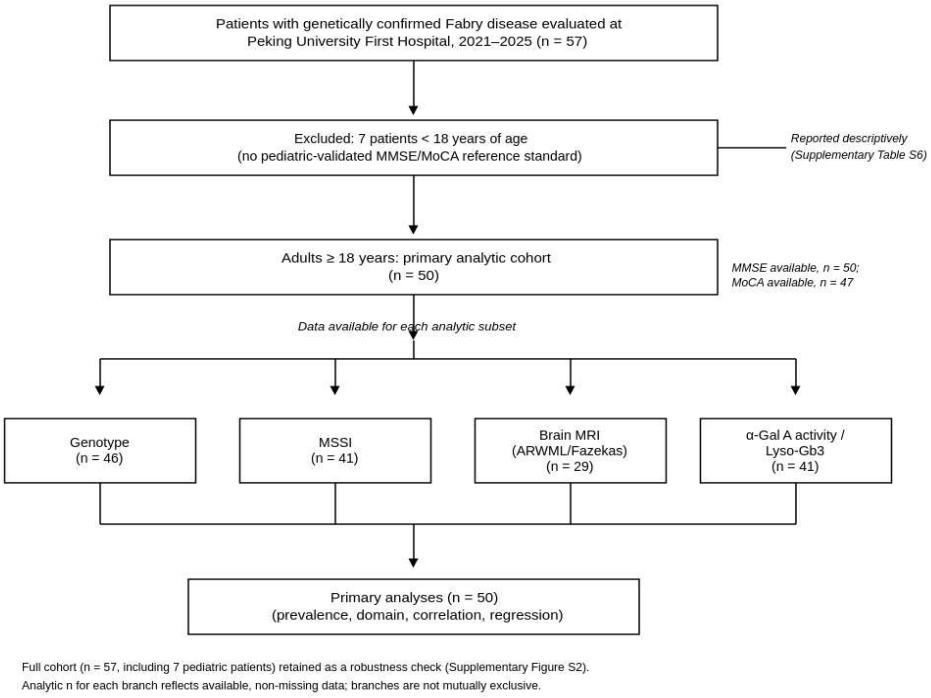


Figure 1. Patient flow: primary analytic cohort (adults, n = 50) and pediatric exclusion. The full cohort (n = 57) is retained as a robustness check (Supplementary Figure S2).

3.3 Cognitive Profile Across MMSE and MoCA Domains

Across the adult cohort, the lowest normalized score was observed for MoCA delayed recall (59.6 ± 29.0), followed by MoCA visuospatial/executive function (74.5 ± 27.3), MoCA abstraction (81.9 ± 27.1), MMSE recall (84.0 ± 25.5), and MoCA language (85.1 ± 21.4) (Table 2; Figure 2). In contrast, orientation (both instruments), MMSE immediate recall, and MoCA naming all had mean normalized scores at or above 92.

As a secondary analysis, cognitive domain scores were compared between the cognitive impairment (CI) and normal-cognition groups within each domain (Table 2). After Benjamini–Hochberg false discovery rate (FDR)

correction across all 12 domain comparisons, six domains remained statistically significant: MoCA delayed recall (Hedges' g = −1.60, 95% CI −2.26 to −0.93), MoCA attention (g = −1.53, 95% CI −2.19 to −0.87), MMSE attention/calculation (g = −1.47, 95% CI −2.10 to −0.84), MoCA visuospatial/executive function (g = −1.28, 95% CI −1.91 to −0.64), MMSE language (g = −1.27, 95% CI −1.88 to −0.66), and MoCA language (g = −0.72, 95% CI −1.32 to −0.12; q = 0.023).

Table 2. Normalized Cognitive Domain Scores by Cognitive Status (Adults)

Rank	Domain (instrument)	n (tot/CI/norm)	Overall	CI	Normal	P (raw)	q (FDR)	Hedges' g [95% CI]
1	**Delayed recall (MoCA)**	**47/17/30**	**59.6 ± 29.0**	**35.3 ± 27.0**	**73.3 ± 21.4**	**<0.001**	**<0.001**	**−1.60 [−2.26, −0.93]**
2	**Visuospatial/executive (MoCA)**	**47/17/30**	**74.5 ± 27.3**	**54.1 ± 30.6**	**86.0 ± 17.9**	**<0.001**	**<0.001**	**−1.28 [−1.91, −0.64]**
3	Abstraction (MoCA)	47/17/30	81.9 ± 27.1	73.5 ± 31.2	86.7 ± 23.6	0.106	0.159	−0.46 [−1.05, 0.13]
4	Recall (MMSE)	50/19/31	84.0 ± 25.5	80.7 ± 27.9	86.0 ± 24.3	0.471	0.566	−0.21 [−0.77, 0.36]
5	**Language (MoCA)**	**47/17/30**	**85.1 ± 21.4**	**74.5 ± 27.7**	**91.1 ± 13.6**	**0.011**	**0.023**	**−0.72 [−1.32, −0.12]**
6	**Attention/calculation (MMSE)**	**50/19/31**	**86.0 ± 28.0**	**64.2 ± 38.1**	**99.4 ± 3.2**	**<0.001**	**<0.001**	**−1.47 [−2.10, −0.84]**
7	**Attention (MoCA)**	**47/17/30**	**89.0 ± 16.2**	**74.5 ± 22.9**	**97.2 ± 5.9**	**<0.001**	**<0.001**	**−1.53 [−2.19, −0.87]**
8	Immediate recall (MMSE)	50/19/31	92.0 ± 25.8	94.7 ± 22.9	90.3 ± 27.5	0.595	0.649	0.16 [−0.41, 0.72]
9	Orientation (MMSE)	50/19/31	93.2 ± 9.4	89.5 ± 13.1	95.5 ± 5.9	0.076	0.130	−0.61 [−1.19, −0.04]
10	**Language (MMSE)**	**50/19/31**	**94.0 ± 9.9**	**87.1 ± 12.4**	**98.2 ± 4.4**	**<0.001**	**<0.001**	**−1.27 [−1.88, −0.66]**
11	Orientation (MoCA)	47/17/30	97.9 ± 6.5	97.1 ± 8.8	98.3 ± 5.0	0.820	0.820	−0.19 [−0.77, 0.40]
12	Naming (MoCA)	47/17/30	99.3 ± 3.8	98.0 ± 8.1	100.0 ± 0.0	0.199	0.266	−0.40 [−0.99, 0.19]

Domain scores were linearly normalized to a 0–100 scale to facilitate descriptive comparison across domains with different maximum possible scores. Normalization was used only for descriptive ranking and visualization. Statistical comparisons

between the CI and normal-cognition groups were performed within each domain and are unaffected by this linear transformation. Domains are ranked by the overall normalized mean score (rank 1 = lowest mean score, i.e., most impaired). The CI-vs-normal comparison is a secondary analysis (Mann-Whitney U; Hedges' g with 95% CI; Benjamini-Hochberg FDR across all 12 domain comparisons). Bold indicates q < 0.05. MoCA domains: n = 47 (17 CI, 30 normal); MMSE domains: n = 50 (19 CI, 31 normal). Excludes the 7 pediatric patients.

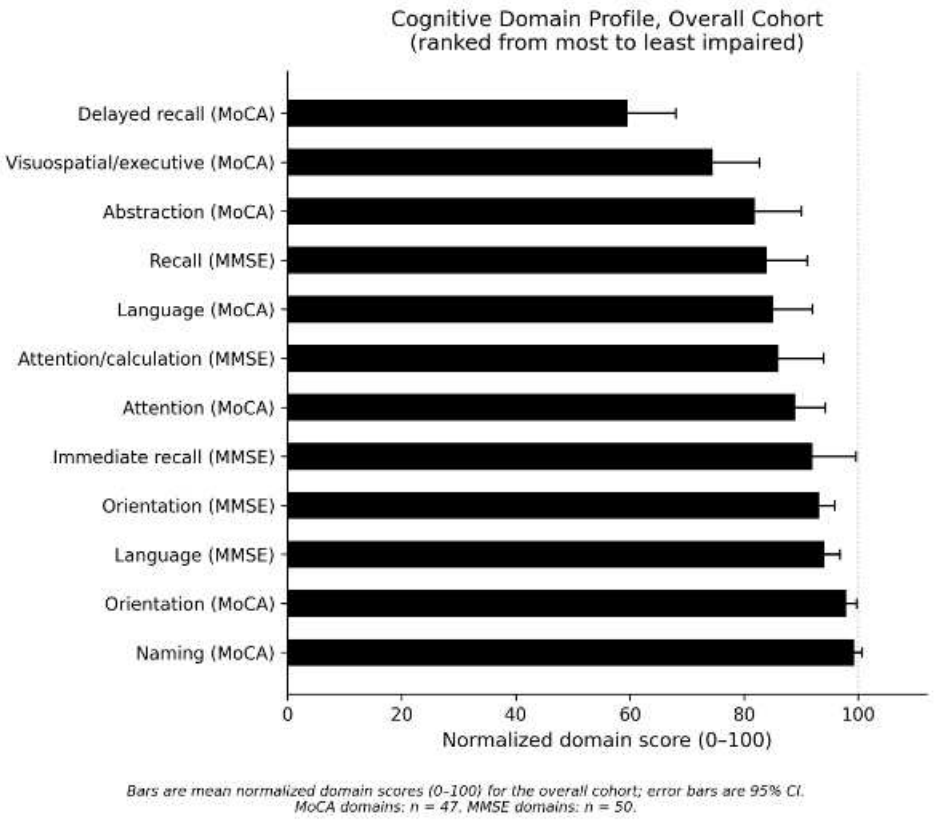


Figure 2. Adult-cohort cognitive domain profile: normalized MMSE and MoCA domain scores, ranked from most to least impaired. Error bars are 95% CI.

3.4 Clinical Characteristics Associated with Cognitive Impairment

Univariable comparisons between adults with and without cognitive impairment are summarized in Table 3.

Adults with cognitive impairment (CI) were older, had a longer disease duration, and had higher Mainz Severity Score Index (MSSI) scores, indicating greater disease severity, than those with normal cognition, with moderate-to-large standardized effect sizes (age: 46.7 ± 11.3 vs. 37.3 ± 10.3 years, P = 0.005, Hedges' g = 0.87, 95% CI 0.28–

1.46; disease duration: 32.8 ± 15.1 vs. 22.9 ± 12.3 years, P = 0.033, g = 0.72, 95% CI 0.08–1.35; MSSI, median 21.0 [13.3–29.0] vs. 10.0 [4.5–14.0], P = 0.008, g = 1.01, 95% CI 0.35–1.68) (Table 3).

Subjective memory complaints were the most frequently endorsed symptom distinguishing the two groups (82.4% vs. 42.9%, P = 0.013, OR = 6.22, 95% CI 1.45–26.64), followed by sleep disturbance (60.0% vs. 25.9%, P = 0.047, OR = 4.29, 95% CI 1.12–16.44), tinnitus (70.6% vs. 33.3%, P = 0.029, OR = 4.80, 95% CI 1.29–17.88), and palpitations (73.3% vs. 20.8%, P = 0.0022, OR = 10.45, 95% CI 2.31–47.31).

Among vascular and organ-specific comorbidities, hypertension was more frequent in the CI group (38.9% vs. 3.7%, P = 0.004, OR = 16.55, 95% CI 1.81–150.94), whereas cerebral infarction (22.2% vs. 3.7%, P = 0.141), hypertrophic cardiomyopathy (64.7% vs. 35.7%, P = 0.073), and renal insufficiency (50.0% vs. 25.9%, P = 0.122) did not reach significance in this adult-only comparison.

Table 3. Univariable Comparison of Clinical Characteristics by Cognitive Status

Characteristic	CI (n=19)	Normal (n=31)	P (raw)	Effect size [95% CI]
Age, years	46.7 ± 11.3	37.3 ± 10.3	0.005	g = 0.87 [0.28, 1.46]
Disease duration, years (n=17/25)	32.8 ± 15.1	22.9 ± 12.3	0.033	g = 0.72 [0.08, 1.35]
MSSI score (n=14/27)	21.0 [13.3–29.0]	10.0 [4.5–14.0]	0.008	g = 1.01 [0.35, 1.68]
Subjective memory decline (n=17/28)	14 (82.4%)	12 (42.9%)	0.013	OR = 6.22 [1.45, 26.64]
Sleep disturbance (n=15/27)	9 (60.0%)	7 (25.9%)	0.047	OR = 4.29 [1.12, 16.44]
Tinnitus (n=17/27)	12 (70.6%)	9 (33.3%)	0.029	OR = 4.80 [1.29, 17.88]
Palpitations (n=15/24)	11 (73.3%)	5 (20.8%)	0.002	OR = 10.45 [2.31, 47.31]
Hypertension (n=18/27)	7 (38.9%)	1 (3.7%)	0.004	OR = 16.55 [1.81, 150.94]
Cerebral infarction (n=18/27)	4 (22.2%)	1 (3.7%)	0.141	NS
Hypertrophic cardiomyopathy (n=17/28)	11 (64.7%)	10 (35.7%)	0.073	NS
Renal insufficiency (n=18/27)	9 (50.0%)	7 (25.9%)	0.122	NS

Characteristic	CI (n=19)	Normal (n=31)	P (raw)	Effect size [95% CI]
Sex, male	12 (63.2%)	19 (61.3%)	1.000	OR = 1.08 [0.33, 3.52]
Classic phenotype	12 (63.2%)	18 (58.1%)	0.774	OR = 1.24 [0.38, 4.00]
Severe clinical events (n=18/27)	13 (72.2%)	10 (37.0%)	0.033	OR = 4.42 [1.21, 16.12]

Values are mean ± SD, median [IQR], or n (%). Comparisons used Welch's t-test or Mann-Whitney U (continuous) and Fisher's exact test (categorical); effect sizes are Hedges' g (continuous) or OR (categorical), both with 95% CI. P values were not corrected for multiple testing and should be interpreted as hypothesis-generating rather than confirmatory. NS = not significant (P ≥ 0.05).

** Sex, phenotype, and severe clinical events are also evaluated as part of the exploratory subgroup analysis with Benjamini-Hochberg FDR correction across 12 comparisons (Section 2.4; Supplementary Table S5); P values shown here are uncorrected and should be interpreted alongside the FDR-corrected results in Supplementary Table S5.*

3.5 Associations of Neuroimaging and Biochemical Markers With Cognitive Scores

Associations between MMSE and MoCA scores and neuroimaging or biomarker variables were assessed using age-adjusted partial correlations together with the corresponding age-adjusted regression coefficient (β) from an OLS model (cognition ~ variable + age); for a single covariate, the two approaches yield the same significance test (Section 2.4). Age adjustment was applied because age was independently associated with both cognitive performance and ARWML burden in this cohort (age vs. ARWML, r = 0.40, P = 0.033; age vs. MoCA, r = −0.54, P = 0.002) and differed significantly between the cognitively impaired and normal-cognition groups (Section 3.4), raising the possibility of confounding in an unadjusted analysis. Imaging and biomarker variables were evaluated as separate FDR families.

In the adult MRI subcohort (n = 29), higher white matter lesion burden was associated with lower MMSE and MoCA scores after adjustment for age. MoCA total score correlated with ARWML total score (age-adjusted partial r = −0.65, P < 0.001, q = 0.002; Figure 3), Fazekas total score (r = −0.57, P = 0.002, q = 0.004), periventricular score (r = −0.47, P = 0.012, q = 0.015), and deep white matter score (r = −0.53, P = 0.004, q = 0.008). MMSE total score

showed a parallel pattern (ARWML: r = −0.59, P < 0.001, q = 0.003; Fazekas: r = −0.47, P = 0.010, q = 0.015; periventricular: r = −0.43, P = 0.019, q = 0.022; deep white matter: r = −0.40, P = 0.030, q = 0.030). All 8 comparisons remained significant after FDR correction (Table 4).

Table 4. Cognition–Neuroimaging Correlations (Adults, MRI Subcohort)

Variable	n	r	P	Adjusted P (q)	Age-adjusted β
MoCA (age-adjusted partial correlation)					
ARWML total	**28**	**−0.65**	**<0.001**	**0.002**	**−0.44**
Fazekas total	**28**	**−0.57**	**0.002**	**0.004**	**−1.30**
Deep white matter	**28**	**−0.53**	**0.004**	**0.008**	**−1.98**
Periventricular	**28**	**−0.47**	**0.012**	**0.015**	**−1.98**
MMSE (age-adjusted partial correlation)					
ARWML total	**29**	**−0.59**	**<0.001**	**0.003**	**−0.25**
Fazekas total	**29**	**−0.47**	**0.010**	**0.015**	**−0.69**
Periventricular	**29**	**−0.43**	**0.019**	**0.022**	**−1.19**
Deep white matter	**29**	**−0.40**	**0.030**	**0.030**	**−0.99**

r = age-adjusted partial Pearson correlation (residual method); β = coefficient from OLS model cognition ~ imaging variable + age. q = Benjamini-Hochberg FDR-corrected P across these 8 comparisons. Bold indicates q < 0.05. n = 28–29, MRI subcohort excluding pediatric patients (4 of the 33 original MRI cases were pediatric).

To localize this association, ARWML subscores were summed into five bilateral regions (frontal, parieto-occipital, temporal, basal ganglia, and infratentorial/cerebellar; Section 2.3) and each was correlated with MMSE and MoCA scores, age-adjusted, as its own FDR family (5 regions × 2 instruments = 10 comparisons). All 10 region × instrument comparisons remained significant after FDR correction (Supplementary Table S3, Supplementary Figure S4), with point estimates ranging from r = −0.44 (frontal, MMSE) to r = −0.74 (infratentorial/cerebellar, MMSE). All five regions showed significant associations with cognition (r = −0.44 to −0.74, all q < 0.05). Given the small

MRI subcohort (n = 28–29) and the resulting limited degrees of freedom, these regional estimates are reported as exploratory and should be interpreted with caution pending replication in a larger sample.

Neither α-Gal A enzyme activity nor plasma Lyso-Gb3 level was associated with cognitive performance in adults. Age-adjusted partial correlations with MMSE were r = −0.05 (P = 0.76) for enzyme activity and r = −0.16 (P = 0.34) for Lyso-Gb3; correlations with MoCA were r = 0.03 (P = 0.83) for enzyme activity and r = 0.10 (P = 0.56) for Lyso-Gb3. None of the 4 comparisons reached significance after FDR correction (q = 0.83 for all) (Supplementary Table S4).

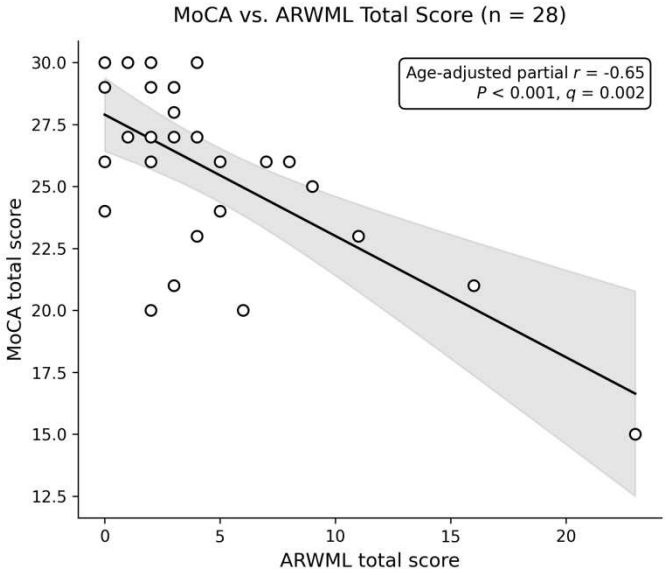


Figure 3. MoCA total score vs. ARWML total score, adult MRI subcohort (n = 28).

3.6 Multivariable Models of Cognitive Impairment

In the clinical model (age and MSSI; n = 41, 14 events), MSSI was independently associated with cognitive impairment after adjustment for age (OR = 1.08 per 1-point increase, 95% CI 1.01–1.16, P = 0.026); age was not independently significant (OR = 1.05, 95% CI 0.97–1.13, P = 0.236) (Table 5).

In the MRI model (age and ARWML total score; n = 29, 10 events), neither predictor reached significance after mutual adjustment: ARWML (OR = 1.14 per 1-point increase, 95% CI 0.96–1.36, P = 0.133) and age (OR = 1.08, 95% CI 0.97–1.20, P = 0.148) both showed confidence intervals crossing 1. Estimates from the full-cohort

robustness check (n = 57, including pediatric patients) are shown alongside these adult-only estimates in Supplementary Figure S2.

Table 5. Multivariable Logistic Regression for Cognitive Impairment (Adults, N = 50)

Variable	OR [95% CI]	P
Clinical model: age + MSSI (n = 41, 14 events, EPV = 7.0)		
Age (per 1 year)	1.05 [0.97, 1.13]	0.236
MSSI (per 1 point)	**1.08 [1.01, 1.16]**	**0.026**
MRI model: age + ARWML (n = 29, 10 events, EPV = 5.0)		
Age (per 1 year)	1.08 [0.97, 1.20]	0.148
ARWML (per 1 point)	1.14 [0.96, 1.36]	0.133

OR = odds ratio from Firth penalized logistic regression; 95% CI is Wald-type from the Firth information matrix. Bold indicates P < 0.05. EPV = events per variable. Complete-case analysis (no imputation).

3.7 Exploratory Analyses

Exploratory subgroup analyses (genotype, phenotype, sex, severe clinical events) were repeated in the adult cohort (Supplementary Table S5, updated). Before FDR correction, a difference was observed for severe clinical events (CI prevalence 56.5% vs. 22.7%, P = 0.033); a trend toward lower MoCA in males vs. females (P = 0.043) and in truncating vs. non-truncating genotype (P = 0.081) was also observed. After Benjamini-Hochberg FDR correction across all 12 comparisons, none of these differences remained significant (all $q \geq 0.139$).

Note on the pediatric subgroup and robustness check. The 7 pediatric patients excluded from the primary analysis are described in Supplementary Table S6 (descriptive only; no statistical tests). As a robustness check, prevalence and the two multivariable models were repeated in the full cohort (n = 57, including the 7 pediatric patients); prevalence and multivariable regression estimates were closely similar between the adult-only primary analysis and the full-cohort robustness check (Supplementary Figure S2).

4. Discussion

In this single-center study of 50 adults with genetically confirmed Fabry disease, cognitive impairment was identified in 38.0% of patients, indicating that cognitive dysfunction is a common and clinically relevant manifestation of the disease. Cognitive impairment was reflected in lower performance on delayed recall and visuospatial/executive function, while comparisons by cognitive status showed differences in delayed recall, attention, visuospatial/executive function, and language. Orientation and naming were relatively preserved. Cognitive impairment was associated with older age, longer disease duration, greater systemic disease severity, subjective memory decline, selected clinical manifestations, and greater cerebral white matter lesion burden. In contrast, neither α-Gal A activity nor Lyso-Gb3 level was significantly associated with cognitive performance.

The observed cognitive profile is broadly consistent with previous studies reporting preferential involvement of executive function, attention, processing speed, and memory in Fabry disease [4,6,7]. Although language scores on the MMSE and MoCA also differed between patients with and without cognitive impairment, these brief language tasks require attention, verbal fluency, repetition, and the ability to follow multistep commands; the observed differences may therefore partly reflect broader attentional and executive demands rather than isolated language dysfunction. The complexity of the cognitive phenotype in FD is further underscored by reports of increased attention deficit and hyperactivity symptoms [10] and a high prevalence of depressive symptoms [11] in this population; in the present cohort, clinically assessed anxiety/depression did not differ significantly between cognitive groups (Supplementary Table S2), but a modest confounding contribution of mood or attentional symptoms cannot be excluded.

The combined cognitive and neuroimaging findings are compatible with involvement of distributed subcortical and cerebrovascular networks. The predominance of executive-attentional and delayed-recall abnormalities, together with relatively preserved orientation and naming, shares some features with the fronto-subcortical cognitive profile described in CADASIL and other hereditary cerebral small-vessel diseases [12,13]. Consistent with prior reports that white-matter-related cognitive impairment in FD can occur even without overt stroke [6], most cognitively impaired adults in this cohort (14 of 18 with available data) had no history of cerebral infarction, suggesting a more diffuse microvascular contribution rather than one driven primarily by macroscopic infarcts. However, the MMSE and

MoCA do not directly assess processing speed or distinguish impaired memory encoding from impaired retrieval, and the proposed network interpretation should therefore be regarded as hypothesis-generating rather than definitive.

Among adults who completed both cognitive instruments, abnormal findings were more frequently identified by the MoCA than by the MMSE. This suggests that the MoCA may be more sensitive to the visuospatial/executive, attentional, and delayed-recall domains most affected in this cohort. However, the study was not designed to formally compare the diagnostic accuracy of the two instruments, and no independent neuropsychological reference standard was available.

These findings support consideration of routine cognitive screening in adults with Fabry disease, particularly among those with greater systemic disease burden or subjective memory complaints. The MoCA may be useful for detecting the pattern of cognitive abnormalities observed in this cohort. When brain MRI is otherwise clinically indicated, assessment of white matter lesion burden may provide complementary information regarding current cognitive status. Larger longitudinal studies are needed to determine clinically meaningful age- or disease-duration thresholds and to evaluate whether targeted cognitive interventions improve patient outcomes.

Several limitations should be acknowledged. First, this was a single-center study, and the clinical and demographic characteristics of the cohort may limit the generalizability of the findings to other populations and healthcare settings. Second, the adult analytic cohort, and particularly the MRI subcohort, was modest in size, limiting statistical power and the precision of the effect estimates. MRI data were available for only 58% of adults, raising the possibility of selection bias in the neuroimaging analyses. Third, the cross-sectional design precludes causal inference and does not establish the temporal sequence among systemic disease burden, white matter injury, and cognitive impairment. Finally, residual confounding by educational attainment, mood, sleep, vascular risk factors, disease-specific treatment exposure, and other unmeasured variables cannot be excluded.

5. Conclusions

In this cohort of Chinese adults with FD, cognitive impairment was common. Cognitive impairment was reflected in lower performance on delayed recall and visuospatial/executive function, and differences between adults with and without cognitive impairment were observed for delayed recall, attention, visuospatial/executive function, and language. Cognitive performance was associated with systemic disease severity and cerebral white matter lesion

burden, whereas no significant associations were detected for α-Gal A activity or Lyso-Gb3. Subjective memory complaints may provide a practical indication for formal cognitive screening, and the MoCA may be more sensitive than the MMSE to the domains most affected in this cohort.

Declarations

Ethics approval and consent to participate: This study was approved by the Ethics Committee of Peking University First Hospital (approval no. 2024-173-002) and was conducted in accordance with the ethical standards of the institutional research committee and the Declaration of Helsinki and its later amendments. Written informed consent was obtained from all participants; for participants younger than 18 years, informed consent was obtained from a parent and/or legal guardian.

Consent for publication: All participants, or their parent and/or legal guardian for participants younger than 18 years, consented to the publication of anonymized data derived from their clinical information.

Availability of data and materials: The datasets generated and/or analysed during the current study are not publicly available due to patient privacy and institutional data protection requirements, but are available from the corresponding author on reasonable request.

Competing interests: The authors declare that they have no competing interests.

Funding: This study was supported by the Key Program of the National Natural Science Foundation of China (12231018) and the National Natural Science Foundation of China (82401636).

Authors' contributions: Siwei Chen contributed to conceptualization, methodology, investigation, formal analysis, data curation, funding acquisition, project administration, and writing of the original draft, as well as review and editing of the manuscript. Yan Zhang contributed to formal analysis, investigation, visualization, resources, data curation, and review and editing of the manuscript. Yujing Yuan contributed to formal analysis, investigation, data curation, and validation. Jingyi Huang contributed to formal analysis, data curation, validation, and review and editing of the manuscript. Lanqiu Yao contributed to methodology, software, formal analysis, and review and editing of the manuscript. Yong'an Sun contributed to project administration, supervision, validation, data curation,

funding acquisition, and review and editing of the manuscript. Wei Zhang contributed to conceptualization, supervision, project administration, validation, and review and editing of the manuscript. Yawen Zhao contributed to conceptualization, investigation, formal analysis, validation, supervision, project administration, funding acquisition, and review and editing of the manuscript. All authors read and approved the final manuscript.

Acknowledgements: Not applicable.

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