RESEARCH REPORT

Cognitive Impairments and Subjective Cognitive Complaints in Fabry Disease: A Nationwide Study and Review of the Literature

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Abstract Fabry disease is a rare progressive X-linked lysosomal storage disorder which leads to neuropathic pain, organ dysfunction and cerebral pathology. Few studies have investigated cognitive impairment in Fabry disease and these previous studies are difficult to compare due to heterogeneous methodological designs and small cohorts. The objective was to investigate the frequency of cognitive impairment in the Danish nationwide cohort of Fabry patients. Further, we examined if subjective cognitive complaints were associated with objective cognitive performances in this patient group. Neuropsychological tests (17 measures) and evaluation of subjective complaints with the Perceived Deficits Questionnaire (PDQ) were applied in 41 of 63 patients. According to an a priori definition, 12 patients (29.3%) were cognitively impaired. Tests tapping psychomotor speed, attention and executive functions had the highest frequency of impairment. In general, disease related variables as Mainz Severity Score Index, enzyme activity and years since onset and depression did not have a significant impact on the categorisation of patients as being cognitively impaired or non-impaired. Thus, cognitive impairment in Fabry disease does not seem to occur solely by having symptoms for many years or by having high disease burden. However, impaired neuropsychological test results were significantly more common in patients with cerebrovascular disease. Only three patients had scores in the abnormal range of the PDQ scale and subjective perceptions of cognition were not associated with cognitive performances. The levels of subjective cognitive complaints were generally very low in the studied patients demonstrating that the absence of subjective cognitive complaints does not exclude the presence of objective cognitive problems.

Introduction

Fabry disease is a rare progressive X-linked lysosomal storage disorder. Due to deficient or absent lysosomal α-galactosidase enzyme activity caused by a mutation in the α-galactosidase A (*GLA*) gene (Rolfs et al. 2010), the disease leads to accumulation of glycosphingolipids in lysosomes of all cells, resulting in cellular dysfunction (Germain 2010). This leads to severe morbidity including neuropathic pain, cerebral pathology in both white and grey matter and organ dysfunction such as ophthalmologic, angiokeratomas, renal disease, cardiovascular and gastrointestinal dysfunction (Zarate and Hopkin 2008). As the defective gene is located on the X-chromosome, there is gender difference in the manifestations of symptoms of Fabry disease. Men with Fabry disease lack the enzyme completely or have very reduced concentrations, while women's enzyme deficiency is of varying degree (Zarate and Hopkin 2008), possibly related to different X-chromosome inactivation (Echevarria et al. 2016). Nevertheless, both genders display a partly unexplained heterogenous phenotypic pattern.

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Previous studies have indicated that cognitive impairments can occur in Fabry disease. In Table 1, we have summarised the findings from the previous studies in the field. In general, the studies show cognitive impairment in psychomotor speed, attention and executive functions while the remaining cognitive functions remain preserved (Segal et al. 2010; Longato et al. 2011; Schermuly et al. 2011; Elstein et al. 2012; Sigmundsdottir et al. 2014; Wadley et al. 2015). However, few studies have examined the predictors of cognitive impairment in Fabry disease. Postischaemic abnormalities and white matter lesions have been associated with cognitive deficits (Low et al. 2007; Schermuly et al. 2011; Sigmundsdottir et al. 2014; Lelieveld et al. 2015), while disease severity and pain have not (Low et al. 2007; Schermuly et al. 2011; Elstein et al. 2012; Sigmundsdottir et al. 2014; Wadley et al. 2015). Possible gender differences in cognition have only been investigated in few studies, showing mixed results (Elstein et al. 2012; Sigmundsdottir et al. 2014; Wadley et al. 2015). Subjective cognitive complaints in relation to cognitive impairment in Fabry disease have not been investigated.

The previous studies had several limitations and were difficult to compare due to heterogeneous methodological designs and small cohorts. Thus, how frequently cognitive impairments do occur in Fabry disease and which disease related variables that may have a significant impact on cognitive deficits seem unresolved. The aim of the present study was to investigate the frequency of cognitive impairment based on a large neuropsychological test battery in the Danish nationwide cohort of Fabry patients (Prabakaran et al. 2014; Fledelius et al. 2015; Korsholm et al. 2015; Madsen et al. 2017). Further, we wished to examine if subjective cognitive complaints were associated with objective cognitive performances in this patient group.

Methods

Study Design and Population

A nationwide cohort of patients with Fabry disease was invited to participate in a cross-sectional study performed at departments of Neurology and Endocrinology, Copenhagen University Hospital, Rigshospitalet, and department of Psychology, University of Copenhagen. The cohort included 88 genetically and/or enzymatically verified patients with Fabry disease. Eight patients have declined contact after diagnosis. Remaining living patients above 18 years of age were eligible. Twelve patients were below 18 years of age and five patients had died at the time of study, thus sixty-three patients were invited to participate. Forty-one of sixty-three patients performed neuropsychological testing and evaluation of subjective complaints; hence, twenty-two patients did not, due to refusal ($n = 9$) or

failure of patient/interviewer (e.g. sickness, missed appointments, etc., $n = 13$). The study was performed from July 2015 to January 2016.

Neuropsychological Testing and Classification

Premorbid intellectual level was assessed by the Wechsler Adult Intelligence Scale (WAIS) Vocabulary subtest and the Danish Adult Reading Test (DART), a Danish equivalent of the National Adult Reading Test (Nelson and O'Connell 1978). Memory was assessed by the Selective Reminding Test (Buschke and Fuld 1974), both immediate recall (errors were recorded) and delayed recall (retention interval 10 min) and the Rey Complex Figure Test (RCFT) (recall 3 min) (Meyers and Meyers 1995). Psychomotor speed/Attention was assessed by Trail Making Test A and B (Reitan 1955) (only completion time used for analyses) and Symbol Digit Modalities Test (SDMT) (Smith 1982). Executive functions were assessed with the Stroop test (100 items) (Stroop 1935) and verbal fluency tests. Only performance of the incongruent version was used for the Stroop test analyses (only completion time was used). We applied three verbal fluency tests: category fluency (animals, 1 min) and lexical fluency (s-words and a-words, 1 min); these measures were analysed separately. Visuospatial functions were assessed using an RFCT, Ravens Progressive Matrices (set 1) (Raven et al. 2003) and a modified version of the Block Design Test (Mortensen and Gade 1993). The normative data for the neuropsychological tests used in this study were derived from the test results from 80 age-matched healthy subjects, retrieved from a database at the Department of Neurology, Rigshospitalet, University of Copenhagen.

For each test, expected scores were generated from factors based on regression analyses including age, years of education and general verbal intellectual level (as assessed by the Vocabulary subtest from WAIS and DART). To assess if observed scores differed from expected scores and could be categorised as impaired, the variation in residual values from the regression analyses was used. Difference scores between observed and expected scores were used to evaluate impairment (Vogel et al. 2011). Scores above the tenth percentile of the normal variation in the regression analyses were categorised as unimpaired, whereas difference scores in the lowest 10% of the normal variation were categorised as impaired. This method for classifying impairment has been used and validated in patients with Huntington's disease (Vinther-Jensen et al. 2014) and systemic lupus erythematosus (Vogel et al. 2011).

The following criteria for classifying a patient as cognitively impaired were applied: (a) if four (or more) test performances categorised as impaired or (b) if all test performances in a single domain were impaired.

Table 1 Overview of studies on cognition in Fabry disease

Authors	N	Age (years)	Sex	Tests performed	Type of analysis	Stroke (n)	Impaired cognitive domains	Limitations
Low et al. (2007)	21 P, 46 C	Mean 40.2 Range 20–62	2 F 19 M	MMSE, NUCOG	Group comparisons healthy vs. patient	9/14, MRI in 14/ 21 P	Language	Too broad and too few N-tests. No measure of premorbid or present intellectual functioning. Depression not examined
Segal et al. (2010)	16P	Mean 29 Range N/A	9 F 7 M	Comprehensive N-battery	N-test results were compared to age-based norms	1	Psychomotor speed, attention and executive functions	No measure of premorbid or present intellectual functioning. Children and adults grouped in analysis
Schermuly et al. (2011)	25 P, 20 C	Mean 36.5 Range 21–56	15 F 10 M	RAVLT, WMS-R, TAP, TMT, Part A + B, and WCST	Group comparisons healthy vs. patient	5	Attention and executive functioning (became non-significant after controlling for depression severity)	No measure of premorbid intellectual functioning
Elstein et al. (2012)	6P	Mean 41.3 Range 25–63	4 F 2 M	Mindstream's computerised cognitive battery for mild impairment	The results were compared to Norms from Mindstream's program	2	Psychomotor speed	The results are not controlled for depression
Sigmundsdottir et al. (2014)	17 P, 15 C	Mean 46.6 Range 25–60	5 F 12 M	Comprehensive N-battery	Group comparisons healthy vs. patient	4	Psychomotor speed and executive functions (only males)	
Wadley et al. (2015)	54, 216 C	Mean 55.7 Range 46–72	37 F 17 M	NINDS-CSN, CERAD	Group comparisons healthy vs. patient	6	No significant difference between patient and control group. No significant gender difference	The results are not controlled for depression. Neuropsychological assessment was made by telephone. Disease severity not stated
Lelieveld et al. (2015)	25 P	Mean 37.9 Range N/A	15 F 10 M	MMSE, AVLT, WMS-R, TMT part A + B	Comparisons between baseline and 8-year follow-up	N/A	N/A	No measure of prevalence of cognitive deficits. No control group
Current study	41 P, 80 C	Mean 47.2 Range 20–75	29 F 12 M	Comprehensive N-battery	Observed scores compared to regression based reference data	7	Psychomotor speed, attention and executive functions	Fixed categorisation of tests in cognitive domains

P patients, C controls, F Female, M male

All cognitive tests were performed by the same rater. To assess depressive (neuropsychiatric) symptoms, the Hamilton Rating Scale for Depression-17 (HAM-D) was applied. This scale covers 17 symptom areas and was administered as a semi-structured interview by the rater (Hamilton 1960). The rater interviewed the patients and rated the different symptom areas. Thus, HAM-D is not a self-report instrument.

Disease Data, Subjective Cognitive Complaints and Self-Rating of Depression

We used four different measures to measure the individual patient's disease: The patient's α-galactosidase A enzyme activity level measured as nmol/h/mg protein, Mainz Severity Score Index (MSSI) measuring the severity level of the disease, whether the individual patient had received Enzyme Replacement Therapy (ERT) and the debut of disease symptoms measured as years since symptom onset. Cranial MRI or CT scan were performed for 40/41 participants and history of cerebrovascular disease was investigated in all patients.

Cognitive complaints were assessed with Perceived Deficits Questionnaire (PDQ) (Sullivan et al. 1990) (which is constructed and validated for the use in patients with multiple sclerosis (MS)) (Christodoulou et al. 2005). It has also been applied in patients with systemic lupus erythematosus (Vogel et al. 2011). The PDQ is a self-report measure with 20 questions to be scored in four categories: $0 =$ never, $1 =$ rarely, $2 =$ sometimes, $3 =$ often and $4 =$ almost always. Total score ranges from 0 to 80. Perceived cognitive deficits vary widely among healthy persons, with the PDQ the mean score of healthy controls is 20 (SD 10) (31). Thus, significantly more complaints than expected from normal variation was defined as a score more than 2 standard deviations (PDQ score >40) greater than previously found in healthy persons (Sullivan et al. 1990).

Statistical Analysis

The level of significance in group by group comparisons was investigated by independent sample t-test for quantitative variables with normal distribution or Mann–Whitney U Test. We used the Chi square test to examine differences in percentage of patients classified as cognitively impaired for gender and for patients with/and without vascular episodes or lesions on structural imaging. Fischer's exact test (two-sided) was applied when cells had expected counts of less than five. Associations between variables were investigated using Pearson product–moment correlations or Spearman's rho. The level of significance was set at $p \leq 0.05$.

Results

Background Data

Background data for the 41 participants are shown in Table 1. MSSI were significantly higher in the patients investigated with cognitive test (median 25 (range 1–42)) relative to patients who did not undergo neuropsychological testing (median 15 (range 3–32)) ($U = 284$, $p = 0.016$). These two groups did not differ significantly on age and enzyme activity (data not shown). For the 41 included participants, we investigated possible gender differences. Women had significantly higher enzyme activity (Mean $= 16$, SD $= 7.6$) compared to men (Mean $= 1.5$, SD 1.0); $t(39) = -0.37$, $p < 0.0001$. There were no significant gender differences on age, MSSI score, Ham-D score, years since diagnosis/symptom debut or PDQ score.

Table 2 shows the neuropsychological test results for the patients. Further, in Table 2 the percentage of patients classified as impaired in each of the cognitive tests is also shown. The results demonstrate that tests tapping psychomotor speed and attention had the highest frequency of impairment. The three most frequently impaired tests were the Stroop test, SDMT and Trail Making Test B. The patients were generally not impaired on memory test (Table 3).

According to the a priori definition of cognitive impairment, 12 patients (29.3%) were cognitively impaired (all of them were impaired in at least four cognitive tests). Of the 12 patients classified as cognitively impaired 8 were men and 4 women. The percentage of males and females classified as cognitively intact/impaired was not significantly different ($p = 0.49$) using Fischer's exact test.

Of the included patients, five had verified structural lesions indicating cerebrovascular disease. Of these, only one had a history of cerebrovascular disease whereas two patients had history of cerebrovascular disease (but no vascular lesions on structural imaging). In total, seven patients had signs of cerebrovascular disease. Among these, five were classified as cognitively impaired. Thus, history of identifiable cerebrovascular lesions is significantly associated with classification of cognitive impairment ($\chi^2 = 10.4$, $p = 0.006$). To investigate if other disease related variables had a significant impact on cognitive functioning, group comparisons between cognitively impaired and cognitively intact patients were conducted for MSSI score, Ham-D score, years since diagnosis/ symptom debut and enzyme activity. There were no significant group differences in MSSI score $t(20) = -1.8$, $p = 0.08$, enzyme activity $t(39) = -0.86$, $p = 0.16$, Ham-D score $t(39) = 1.09$, $p = 0.28$ and years since diagnosis $t(39) = -1.4$, $p = 0.16$ between patients classified as

Table 2 Background data of participating Fabry patients

	Participating patients $N = 41$
Age (years)	47.2 (14.7) Range 20–75
Sex	71% female 29% male
Years since symptom onset/debut	27.6 (20.6) Range 0–69
Enzyme activity (nmol/h/mg protein)[a]	11.8 (9.3) Range 0.4–33.0
MSSI	23.3 (10.8) Range 1–42
Treatment with ERT (%)[b]	17/41 (41.5%)

Results are presented as mean (SD), unless stated otherwise
MSSI Mainz Severity Score Index, *ERT* enzyme replacement therapy
[a] Reference range 20–65 nmol/h/mg protein
[b] Current treatment is indicated

Table 3 Neuropsychological test scores and frequency of impairment in cognitive tests

Neuropsychological tests	Results mean (SD)	Frequency of impairment (%)[a]
Trail Making Test A (s)	30.0 (12.7)	22.0
Trail Making Test B (s)	82.6 (36.9)	29.3
Symbol Digit Modality Test (number correct)	45.7 (10.4)	26.8
Stroop interference (s)	135.6 (57.3)	31.7
Category verbal fluency	25.6 (6.5)	7.3
Lexical fluency, s-words	13.8 (4.8)	9.8
Lexical fluency, a-words	8.8 (3.2)	4.9
Rey's Complex Figure Test, recall	24.6 (6.4)	2.4
Rey's Complex Figure Test, copy	35.5 (1.0)	2.4
Ravens Matrices Advanced	7.9 (2.4)	14.6
Selective Reminding Test immediate recall	9.7 (8.5)	9.8
Selective Reminding Test delayed recall	8.7 (1.1)	9.8
Block design	11.2 (1.6)	24.4
Hamilton Depression Rating Scale	5.4 (4.3)	

[a] Impairment was based on comparisons between observed and expected scores. Based on regression analyses, scores in the lowest 10% of the normal variation were categorised as impaired

cognitively impaired and non-impaired. When assessing differences of single tests between patients classified as impaired and non-impaired on the specific test, a significant group difference was found for MSSI $t(39) = -2.5$, $p = 0.02$ on the Stroop test, and patients classified as cognitively impaired in the Stroop test had lived signifi-

cantly longer with the diagnosis/symptoms relative to patients without cognitive impairment $t(39) = -2.3$, $p = 0.03$.

Only three patients (7.3%) had scores in the abnormal range of the PDQ scale. Thus, subjective cognitive complaints were generally not common in this group of patients with Fabry disease. PDQ scores were significantly associated with scores of Ham D ($r = 0.55$, $p < 0.001$). Significantly lower scores on PDQ were found in patients classified with cognitive impairment (Mean = 12.5, SD = 10.8) relative to patients with no cognitive impairment (Mean = 23.2, SD = 14.5), $t(39) = -2.3$, $p = 0.03$. No significant differences in PDQ scores were found when patients with and without cognitive impairment were compared on MSSI score, enzyme activity and years living with the disease (data not shown). When analysing correlations between PDQ and the 13 cognitive measures, significant correlations were found between PDQ and copy of the RCFT ($r = 0.31$, $p = 0.04$) as well as Trail Making B ($r = -0.32$, $p = 0.04$). However, when taken the number of comparisons into consideration, the association could not be considered significant. Thus, in general subjective cognitive complaints were not frequent in this patient group, and subjective perceptions of cognition were not associated with cognitive performances.

Discussion

This study aimed to investigate the frequency of cognitive impairment in patients with Fabry disease. Based on our results, about 1/3 of the patients with Fabry disease were classified as cognitively impaired. When analysing impairment in the different cognitive domains, tests tapping psychomotor speed, attention and executive functions had the highest frequency of impairment. In general, disease related variables or depression did not have a significant impact on the categorisation of patients as being cognitively impaired or non-impaired. Thus, cognitive impairment in Fabry disease does not seem to occur solely by having symptoms for many years or by having high disease affection. Test performances in the abnormal range do not seem to be caused by depressive symptoms, which is an important point given the high rates of depression in the disease (Cole et al. 2007). This study also investigated the occurrence of subjective cognitive complaints in Fabry patients. Cognitive complaints in an abnormal range were only found in a minority of patients, and subjective perceptions of cognition were not associated with cognitive performances but were significantly associated with clinician rated depressive symptoms.

The majority of previous studies of cognitive functioning in Fabry disease has found that cognitive deficits do occur in this patient group (Low et al. 2007; Segal et al. 2010;

Longato et al. 2011; Schermuly et al. 2011; Elstein et al. 2012; Sigmundsdottir et al. 2014; Wadley et al. 2015). Only one study found no significant difference in cognitive tests when comparing performances of patients with Fabry disease to performances of healthy controls (Lohle et al. 2015). Interestingly, this is the largest study to date, including 110 Fabry patients. However, they only applied cognitive screening tools designed for measuring dementia (MMSE and Montreal Cognitive Assessment (MOCA)) which may not be sensitive to capture mild cognitive impairment. To our knowledge, the current study is the second largest study (as measured by the number of participants) worldwide including 41 patients with Fabry disease while all other studies have included 25 patients or less. The previous studies have compared test performances in patients with Fabry disease to those of healthy controls by different types of cognitive tests. By using such group comparisons, it is possible to demonstrate that a combined group of patients perform significantly worse than a group of healthy persons in different measures. However, such comparisons do not provide evaluation of which patients could be categorised as significantly impaired and therefore cannot be used to estimate the frequency of cognitive impairment. In this study, a large neuropsychological test battery was applied, and each individual observed test performance was compared to expected test performances based on age, education and premorbid verbal intelligence. The results from this study with respect to frequency of cognitive impairments seem to be valid for most Fabry populations. From the entire Danish population of Fabry patients, we were only able to examine cognitive functions in approximately 2/3 due to various reasons. If the MSSI had been higher in the non-tested group, the frequency of cognitive impairment and the relation to disease variables could potentially be underestimated. However, as the MSSI score was significantly lower in the patients not assessed by neuropsychologist relative to the tested patients, there seem to be no obvious bias concerning the reported frequency of cognitive impairment and the relationship between cognitive test scores and disease related variables.

The primary focus of the present study was not predictors of cognitive dysfunction in Fabry disease. However, our results indicated that neither depression nor disease severity, years living with Fabry symptoms and enzyme activity predicted cognitive dysfunction in our cohort. Few other group studies have examined predictors of cognitive dysfunction in Fabry patients. These studies point out that depression (Segal et al. 2010; Schermuly et al. 2011; Lelieveld et al. 2015) and ischaemia (Sigmundsdottir et al. 2014) may have an impact on the patients' cognitive functioning, while on the other hand, there has not been found any correlation between disease severity (Elstein et al. 2012) and pain (Sigmundsdottir et al. 2014) and the patients' cognitive functioning. In our study,

17% of the patients had a history of TCI/stroke or had cerebrovascular lesions on structural brain imaging. Among these 17%, the percentage of patients with cognitive impairment was significantly higher than among patients with no cerebrovascular disease. Thus, cerebrovascular disease is an important and significant risk factor for cognitive impairment but patients may have cerebrovascular episodes without impaired neuropsychological test performances. We grouped males and females together in the analysis although we had 2/3rd Fabry females in the study. Women had significantly higher enzyme activity compared to men, but apart from this we found no effect of gender on the results (the classification of cognitive impairment was not biased by gender). This does exclude that gender differences may be important in other groups, as females (even with classical mutations) may present much later with similar severity as the males or have fewer symptoms and signs.

Tests tapping psychomotor speed, attention and executive functions had the highest frequency of impairment and the patients were generally not impaired on memory tests. The three most frequently impaired tests were the Stroop test, SDMT and Trail Making Test B. The impaired psychomotor speed was in accordance with most previous studies of Fabry patients (Segal et al. 2010; Longato et al. 2011; Elstein et al. 2012; Sigmundsdottir et al. 2014). However, one previous study did not find a significant impairment of the patients' psychomotor speed (Schermuly et al. 2011). In previous studies where large neuropsychological batteries were administered, attention deficits have been found (Segal et al. 2010; Longato et al. 2011; Schermuly et al. 2011). Some studies did not find significant differences between attentional performances in Fabry patients and healthy controls (Low et al. 2007; Elstein et al. 2012; Sigmundsdottir et al. 2014; Lohle et al. 2015), but all these studies but the one by Sigmundsdottir et al. (2014) used cognitive screening tests and therefore may not have had the adequate diagnostic sensitivity. In accordance with our results, some studies found impairments in executive functions in Fabry disease (Segal et al. 2010; Longato et al. 2011; Sigmundsdottir et al. 2014; Wadley et al. 2015), whereas others did not. This may be because that the disease affects only specific executive functions or that different aspects of executive functions are impaired in different patients. Comparison between studies is hampered by the use of different tests and/or division of the tests into different domains.

The previous studies on cognition in Fabry disease all had several limitations including small cohorts (Bolsover et al. 2014) and the applied cognitive tests were screening tests or tapping specific cognitive domains (Lohle et al. 2015; Wadley et al. 2015). Some studies did not include control groups (Segal et al. 2010; Longato et al. 2011; Lelieveld et al. 2015), whereas others did not include

premorbid intellectual level in the evaluation of impairment (Low et al. 2007; Segal et al. 2010; Schermuly et al. 2011; Lohle et al. 2015) or mix children and adults in the statistical analyses (Segal et al. 2010). Furthermore, some studies did not report disease severity nor the degree of depressive symptoms (Low et al. 2007; Longato et al. 2011; Elstein et al. 2012; Lohle et al. 2015; Wadley et al. 2015), despite the high frequency of depression in this patient group (Cole et al. 2007). The latter is relevant since depressive symptoms may have a negative effect on cognitive functioning.

Even though 29% of the patients with Fabry disease in the sample were classified as cognitively impaired, only 7% of the patients had cognitive complaints above normal range. In general, the study showed no association between the level of cognitive complaints and "objective" test performances. Thus, the identification of cognitive impairments cannot be based solely on patients' reports but requires cognitive testing. The lack of significant association between subjective cognitive complaints and test performances is not surprising when analysing findings from previous studies in other diseases. In Danish SLE outpatients, the level of significant subjective cognitive complaints was low even among patients with cognitive impairment (Vogel et al. 2011). Further, subjective well-being and cognitive performance was not significantly associated in patients with Graves' disease (Vogel et al. 2007). This study showed an association between subjective cognitive complaints and clinician rated depressive symptoms implicating that affective status may influence subjective experience of cognitive functions even more than cognitive functioning itself, and the absence of subjective cognitive complaints does not exclude the presence of objective cognitive impairments.

To summarise, this study showed that in accordance with most previous results cognitive impairments were found in outpatients with Fabry disease. The most common deficits occurred in the areas of psychomotor speed, attention and executive functions. Our results have indicated deficits in about 1/3 of the patients and that impaired neuropsychological test results are significantly more common in patients with cerebrovascular disease. The levels of subjective cognitive complaints were generally very low in the studied patients and even patients with cognitive deficits did not have significantly more complaints of cognitive dysfunction than healthy controls demonstrating that the absence of subjective cognitive complaints does not exclude the presence of objective cognitive problems. Thus, cognitive testing seems important when pursuing suspicion of cognitive deficits in patients with Fabry disease.

Key Message

This article provides important insight regarding the frequency and nature of cognitive impairments in a large cohort of patients with Fabry disease both as measured by a large neuropsychological battery and as experienced by patients.

Compliance with Ethics Guidelines

Conflict of Interest

Josefine Loeb declares no conflicts of interest.

Asmus Vogel declares no conflicts of interest.

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Author Contributions

AV and UFR conceptualised and designed the study. JL, CVM and AV analysed the data. JL drafted the article with major contribution from AV. All authors gave important input to the intellectual content of the manuscript, and all authors have read and approved the manuscript for submission.

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