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Respiratory impairments in patients suffering from Fabry disease – A cross-sectional study

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Abstract

Background: The inherited X-linked disorder, Fabry disease, is caused by deficient lysosomal enzyme α-galactosidase A, with progressive accumulation of globotriaosylceramide in multiple organs including the upper and lower airways.

Objectives: To assess pulmonary function at the time of the first pulmonary function test (PFT) performed among the National Danish Fabry cohort and define the prevalence of affected lung function variables.

Materials and Method: A cross-sectional retrospective cohort study of 86 adult patients enrolled in one or both international patient registry databases for Fabry disease, *Fabry Registry* or *FollowME* with at least one PFT. The Mainz Severity Score Index (MSSI) was calculated to determine the disease severity. Lung function variables were examined by multivariate regression adjusted for important variables for developing airway illness.

Results: Seventeen patients (20%) showed obstructive airflow limitation and 7 (8%) a restrictive lung deficiency. Smoking status ($p = .016$) and MSSI ($p < .001$) were associated with increasing obstructive airway limitation.

Conclusion: The prevalence of affected lung function among the National Danish Fabry cohort was 28%. Patients with classic gene variants frequently developed a decrease in lung function regardless of their smoking status, with significant relationship with disease severity.

Keywords

Fabry disease, pulmonary involvement, respiratory impairment, pulmonary function test

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Introduction

Fabry disease is an inherited X-linked recessive lysosomal storage disorder, secondary to pathogenic variants in the *GLA* gene, responsible for encoding the lysosomal α-galactosidase A enzyme. The classic variants comprise the severe phenotypes in males and some females due to complete or severe loss of function of α-galactosidase A. Some females with classical variants and both males and females with late-onset variants demonstrate milder phenotypes, whereas some females are asymptomatic.[1] The deficiency of the enzyme activity results in a

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Data Availability Statement included at the end of the article

progressive accumulation of globotriaosylceramide (Gb_3) in the lysosomes of multiple organs, leading to decreased perfusion, development of fibrosis and consequently organ damage.[2] A similar mechanism is suggested to concern also the smooth muscle of upper and lower airways leading to bronchial/bronchiolar obstruction and obstructive sleep apnoea.[3–5]

Although many patients seem to complain about shortness of breath,[1] the evaluation of pulmonary function in Fabry disease has generally been neglected, probably because symptoms of dyspnoea in Fabry patients have often been ascribed to cardiac or kidney involvement or to general fatigue with low physical performance. Despite lack of clear recommendations, the clinical impression has changed over time, and currently there is increased attention to include pulmonary causes as possible explanation of shortness of breath in Fabry patients. However, in a study by Svensson et al.[1] where multiple literature studies on pulmonary involvement in Fabry disease were included the pulmonary function tests (PFT) showed various results, and consistent findings could not be documented to determine if there is an obstructive or a restrictive airflow limitation in Fabry patients due to the lack of a larger cohort. Few, if ever, have investigated lung diseases among Fabry patients in an unselected large cohort or Nationwide registry.

The current treatments of Fabry disease focus on replacing the absent or deficient α-galactosidase A by enzyme replacement therapy (ERT) (available since 2001) or chaperone (migalastat) (available since 2016), which alleviate and prevent deposits of Gb_3 in tissues.

The primary aim of the study was to assess pulmonary function at the time of the first PFT performed among the National Danish Fabry cohort and define the prevalence of affected lung function variables. The secondary aim was to classify the type of lung disease and to study the influence of smoking status and the disease severity.

Materials and method

Study design and population

The study was an investigator initiated retrospective observational study of prospectively collected data from the National Danish Fabry cohort followed at Department of Endocrinology and Metabolism, Copenhagen University Hospital, Rigshospitalet in collaboration with other specialist departments in the Danish Fabry Team. All enrolled Danish Fabry probands and their affected family members were genetically verified. Data was included from the introduction of the first PFT as routine in 2007 (except 2 now deceased patient with PFTs in 2002 and 2003) until datalock June 2021, including data from deceased Fabry patients. Part of the data from the Fabry cohort has been published previously.[6] Patients aged 18 years and older, with at least one PFT and enrolled in one of two international patient registry databases for Fabry disease, *Fabry Registry*® (Genzyme-Sanofi) and *FollowME*® (Amicus), were included (Figure 1). Fifty percent of the patients were on ERT and 50% were not on ERT (by indication or own choice) nor migalastat (not licenced) at the time of the first PFT. The study was approved by the Danish Health and Medicine Authority (3-3013-667/1/), the Regional Health Research Ethics Committee (H-3-2014-FSP8) and the Danish Data Protection Agency 2014–641-0055 and 2013-41-1949.

Pulmonary function test

All PFT were performed using the same equipment (Jaeger®), half of which (n = 45) were conducted at the Department of Respiratory Medicine, Bispebjerg Hospital, Copenhagen, Denmark, and in the periods 2007–2012 and 2020–2021 the other half (n = 41) PFTs at the Department of Clinical Physiology, Nuclear Medicine and PET, Copenhagen University Hospital Rigshospitalet, Copenhagen, Denmark. All tests were completed according to American Thoracic Society's and European Respiratory Society's standards,[7] and performed by trained staff to ensure consistency of the procedure. A standardised calibration was

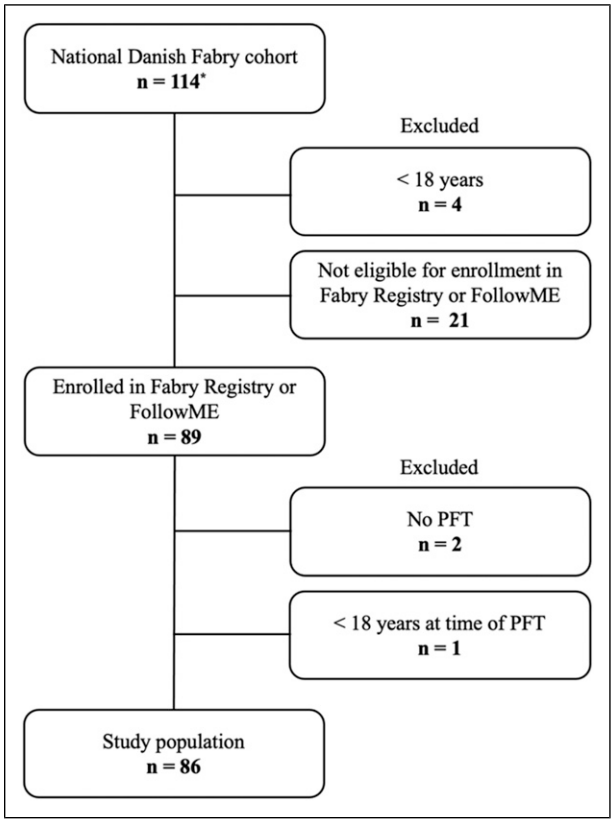

Figure 1. Patient flowchart of the National Danish Fabry cohort * includes 16 dead patients; PFT, pulmonary function test.

performed daily at both sites. The procedure was completed in sitting position, with a nose clip, and the patient was asked to take a maximal inspiration followed by a forceful expel of air for as long as possible. Forced expiratory volume in the first-second (FEV_1) and forced vital capacity (FVC) were determined. FEV_1/FVC ratio was calculated, identifying obstructive or restrictive ventilatory defects. FEV_1/FVC $\leq$70% indicated an obstructive defect, whereas FEV_1/FVC $\geq$90% indicated a restrictive defect.[8] FEV_1 and FVC values were calculated as percentages of predicted normal values, based on age, gender and height values used at both sites.[7]

Smoking status

Smoking status for Fabry patients enrolled in the Fabry Registry was extracted from the registry and categorized as follows: Current smoker: currently smoking; former smoker: smoked at least 100 cigarettes over lifetime; or never smoker: not smoked at least 100 cigarettes over lifetime. The smoking status for Fabry patients enrolled in FollowME were viewed in their medical file and categorized as in Fabry Registry.

Mainz Severity Score Index

The Mainz Severity Score Index (MSSI) is a clinical scoring system to determine the severity of the signs and symptoms of Fabry disease and to monitor disease course (Supplementary Table 1).[9] It is composed of four sections that assess the general, neurological, cardiovascular and renal signs and symptoms of Fabry disease. The maximum MSSI is 76 points (maximum score of 18, 20, 20, 18 points for the general, neurological, cardiovascular and renal section, respectively). The severity of Fabry disease can be classified, based on the MSSI, as mild (score <20), moderate (score 20-40) and severe (score >40).[9] For this study, the MSSI was adjusted to exclude "characteristic facial appearance" in the general section, because clinical facial photos of dead patients were not possible to obtain. The maximum score in the general section was therefore 17 and the MSSI was maximum 75 points. Furthermore, orthostatic hypotension was rated as "mild vertigo," cardiomyopathy $\geq$15 mm was rated as "severe cardiomyopathy (>15 mm)" and the rating "no" for the New York Heart Association (NYHA) classification was excluded. Cardiac involvement was rated positive if patients had at least one fulfilled cardiovascular variable in the MSSI.

Measurement of α-galactosidase A enzyme activity

Measurement of α-galactosidase A activity was determined in mixed leukocytes using a fluorimetric assay with 4-methylumbelliferyl-α-D-galactopyranoside as substrate.[10,11] The fluorescence intensity was measured in a Fluostar Optima plate reader (BMG Labtech) at excitation and emission wavelengths of 360 nm and 450 nm, respectively.

Measurement of plasma Gb_3, plasma lyso-Gb_3 and urine-Gb_3

Plasma-Gb_3, plasma lyso-Gb_3 and urine-Gb_3 serve as disease severity biomarkers as aid in the diagnosis and subclassification of Fabry disease as well as treatment monitoring markers during treatment with ERT or Migalastat. Gb_3 measurements were performed at Sahlgrenska University Hospital, Sweden up to 2006 by densitometric evaluation after high performance thin layer chromatography for plasma Gb_3 and orcinol detection in the case of urine-Gb_3[12] and afterwards in Genzyme's laboratories, using a rapid liquid chromatography with tandem mass spectrometry method for quantification of total plasma lyso-Gb_3 and urine-Gb_3.[13] Gb_3 units from Sahlgrenska were given in mg/L (reference: 1.6 – 3.3), while more recent measurements from Genzyme and LabCorp were given in µmol/L (reference: <7.0) and µg/mL (reference: 1.39 – 4.04), respectively. Urine-Gb_3 was given in µg/mmol creatinine (reference: <81) at Genzyme, µg/mmol creatinine (reference: <16) at LabCorp and µmol/mol creatinine (reference: <10) at Sahlgrenska. The calibration of methods has changed over time, but no attempts were made to correct values for unification. Therefore, each individual measurement was compared to the respective method and laboratory derived normal reference range. Plasma lyso-Gb_3 was only measured in Genzyme's and LabCorp's laboratory.

Statistical analysis

IBM SPSS Statistics 2017 version 25.0.0.0 was used for statistical analyses. Data are compared by conducting one-way Analysis of Variance (ANOVA). Changes in pulmonary function are examined with multivariate regression adjusted for variables of importance for developing airway illness: smoking status, cardiac involvement, respiratory medication, respiratory symptoms, MSSI and ERT. *p*-values less than or equal to 0.05 were considered statically significant.

Results

The patient characteristics of the 86 Fabry patients (32 males and 54 females) at the time of lung screening are listed in Table 1. Seventeen patients (20%, nine males) showed obstructive airflow limitation with an FEV_1/FVC ratio ≤70% and seven patients (8%, six females) showed restrictive airflow limitation with an FEV_1/FVC ratio ≥90%.

The mean (SD) MSSI for the 86 Fabry patients was 23.4 (9.9). Two patients with known asthma were receiving anti-asthma treatment at the time of the PFT. Forty-three patients (50%) received ERT at the time of their first PFT (10 agalsidase-alfa and 33 agalsidase-beta), and 43 (50%) were not treated with ERT nor migalastat. The median (range) time from the initiation of ERT to the first PFT was 5.4 [0.6–16.3] years.

The *GLA* gene pathogenic variants and α-galactosidase A enzyme activities are listed in Supplementary Table 2. Seventy-nine (92%) of the patients had *GLA* gene pathogenic variants classified as classic based on the International Fabry Disease Genotype-Phenotype Database (dbFGP) (https://dbfgp.org/dbFgp/fabry/), accessed November 16, 2021), 2 (2%) had *GLA* gene pathogenic variants classified as late-onset and 5 (6%) had previously unreported disease-

Table 1. Characteristics of the 86 Fabry patients at time of first pulmonary function test between 2007 and 2021.

Variable	*n* = 86
Demographic	
Female	54 (63)
Age (years)	39.5 ± 15.6
Height (cm)	171.3 ± 9.0
Weight (kg)	71.7 ± 16.7
BMI (kg/m^2)	24.4 ± 5.5
Pulmonary function measurement	
FEV_1 (L)	3.0 ± 1.0
FEV_1 (% predicted)	88.1 ± 14.8
FVC (L)	4.0 ± 1.1
FVC (% predicted)	98.6 ± 13.0
FEV_1/FVC ratio	0.76 ± 0.01
Smoking	
Current smoker	27 (31)
Former smoker	22 (26)
Never smoker	37 (43)
Respiratory symptom	
Breathlessness	7 (8)
Cough	14 (16)
Wheezing	2 (2)
Sputum	3 (3)
Feeling pressure in the chest	5 (6)
Nocturnal symptoms	2 (2)
Exercise-induced dyspnoea	31 (36)
MSSI	
Total score	23.4 ± 9.9
Mild score <20	35 (41)
Moderate score 20–40	48 (56)
Severe score >40	3 (3)
Cardiac involvement	75 (87)
Lung treatment	
SABA	10 (12)
ICS	8 (9)
ICH-LABA	11 (13)
Other type of lung medication	2 (2)
Fabry treatment	
ERT	43 (50)
Migalastat	0
Time from ERT initiation to first PFT (years)	5.4 [0.6–16.3]

Mean ± SD, n (%) or median [range]. *n*, number of patients; BMI: body mass index; FEV_1: one-second forced expiratory volume in the first-second; FVC: forced vital capacity; FEV_1/FVC ratio: forced expiratory volume in the first second divided by forced vital capacity; MSSI: Mainz Severity Score Index; SABA: short-acting β_2-agonist; ICS: inhaled corticosteroids; ICS-LABA: inhaled corticosteroids combined with long-acting β_2-agonist; ERT: enzyme replacement therapy; PFT: pulmonary function test.

causing variants in the *GLA* gene. All males and 35 (65%) females had an α-galactosidase A activity below normal (normal range: 20–65 nmol/h/mg protein) with a median [range] of 1.7 [0.3–11] nmol/h/mg protein and 11 [1.6–19] nmol/h/mg protein, respectively. Sixteen females had normal α-galactosidase A activity, and three females did not have available α-galactosidase A activity measurements.

Gb_3 in plasma and urine was available in 73 (29 males and 49 females) and 42 (14 males and 28 females) patients, respectively. Lyso-Gb_3 in plasma was available in 24 patients (11 males and 13 females). Nevertheless, males and females had plasma Gb_3 concentrations, respectively, lower than the normal upper limit (high vs normal plasma Gb_3: 8 (28%) versus 21 (72%); 4 (8%) versus 45 (92%)), while plasma lyso-Gb_3 was, respectively, higher than the normal upper limit in males compared to females (high vs normal plasma lyso-Gb_3: 9 (82%) versus 2 (18%); 2 (15%) versus 11 (85%)). Urine-Gb_3 was higher than the normal upper limit in females (high vs normal urine-Gb_3: 7 (50%) versus 7 (50%); 16 (57%) versus 12 (43%)).

One-way ANOVA revealed that FEV_1/FVC ratio was dependent on smoking status, being never (78.4 ± 8.6), former (73.5 ± 9.2) and current (74.0 ± 8.6), with a significant difference in smoking status and FEV_1/FVC ratio being low value ($F(1,84) = [6.002]$, $p = .016$). The analysis also revealed that FEV_1/FVC ratio was dependent on MSSI being mild (80.7 ± 7.5), moderate (72.1 ± 8.3) and severe (68.6 ± 4.9), respectively, with a significant difference ($F(2,83) = [13.439]$, $p < .001$) (Figure 2), as FEV_1/FVC ratio was lower in MSSI being severe and higher in MSSI being mild. The relationship between FEV_1/FVC ratio and MSSI in former and never smokers revealed that never ($p < .001$, Figure 3) and former ($p = .031$, Figure 3) smokers were significantly associated with MSSI and FEV_1/FVC ratio was low in both groups, whereas this was not found among smokers.

In the multivariate analysis of the relation between FEV_1/FVC ratio and the variables of importance for developing airway illness, only high MSSI had a significantly and independently inverse association with impaired FEV_1/FVC ratio ($p < .001$) (Figure 4) with a correlation coefficient of −0.29, and FEV_1 (% predicted) (Figure 5) with a correlation coefficient of −0.21.

Examining airflow limitation, using FEV_1 (% predicted) as the dependent variable and variables of importance for developing airway limitations revealed, that current use of inhaled corticosteroids ($p < .001$, Figure 6), other types of lung medications ($p < .001$), and moderate MSSI ($p < .001$), respectively, had a significant association with FEV_1 (% predicted). Furthermore, chest tightness tended towards a negative association with FEV_1 (% predicted) ($p = .057$).

Fabry patients showed nocturnal symptoms ($p = .001$) and tendency to breathlessness ($p = .067$). Both nocturnal symptoms ($p = .003$) and breathlessness ($p = .044$) were due to cardiac illness, and not reduced pulmonary function.

Discussion

In this unselected nationwide study of the largest cohort in the Nordic area of patients suffering from Fabry disease we showed a significant manifestation of obstructive airflow limitation among Fabry patients, not entirely explained by tobacco consumption, but importantly with relationship to severity of the Fabry disease thus without relationship with respiratory symptoms.

Severity of disease measured by MSSI was correlated to a significant decline of both FEV_1 (% predicted) and FEV_1/FVC ratio. Cigarette smoking strengthened this association, whereas no association between respiratory symptoms and lung function was found among Fabry patients. These findings contributed to the notion that Fabry patients frequently develop an obstructive airflow limitation, not only in smokers, but also in never smokers, possibly due to Fabry disease mechanism. Furthermore, Fabry patients with obstructive airflow limitation were also found to have the classic Fabry phenotypes, with high concentrations of plasma lyso-Gb_3 in males, urine-Gb_3 in females and low α-galactosidase A activity (much lower in males compared to females). Hypothetically, this finding is most likely due to increased tissue destruction possibly at the alveolar level or bronchial mucosa or smooth muscles accumulation of Gb_3, although other mechanisms may play a role. We would expect development of fibrosis due to its development in other organs by Gb_3 accumulation, and we did find, that patients with obstructive defects had high levels of Gb_3. We demonstrated, that pulmonary involvement seemed more prominent in patients with classic rather than late-onset gene variants as α-galactosidase A activity in late-onset phenotypes is very likely sufficient to clear the bronchial smooth-muscle cells from Gb_3 accumulation.[4] Only 2% patients had late-onset phenotypes in our study and none of them had pulmonary involvement, versus patients with classic gene variants, where pulmonary involvement was seen in 28%.

Furthermore, the study showed that higher MSSI, were associated with a lower lung function, revealing that the increased disease burden and progression of Fabry disease can be explained by development of airway obstruction as well. It was not possible to verify if increasing MSSI leads to airway obstruction or if airway obstruction leads to increasing MSSI. The adjustments made in the MSSI questionnaire were minor, and not sufficient to change the MSSI substantially and the relation with FEV_1/FVC ratio and FEV_1 (% predicted) remained significant. Additionally, the

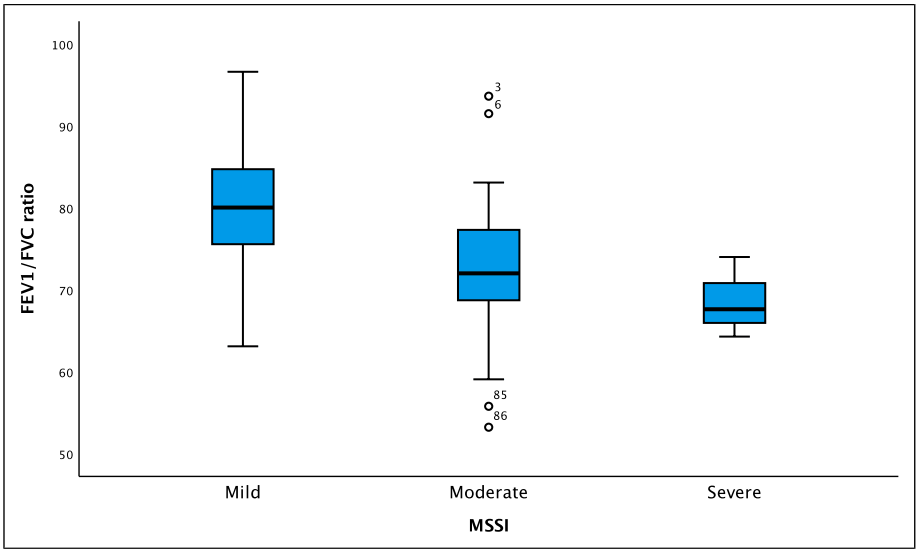

Figure 2. Box plot of the association between MSSI mild, moderate, and severe and FEV_1/FVC ratio in the National Danish Fabry cohort. FEV_1/FVC ratio: forced expiratory volume in the first-second divided by forced vital capacity; MSSI: Mainz Severity Score Index. ANOVA analysis $p < .001$.

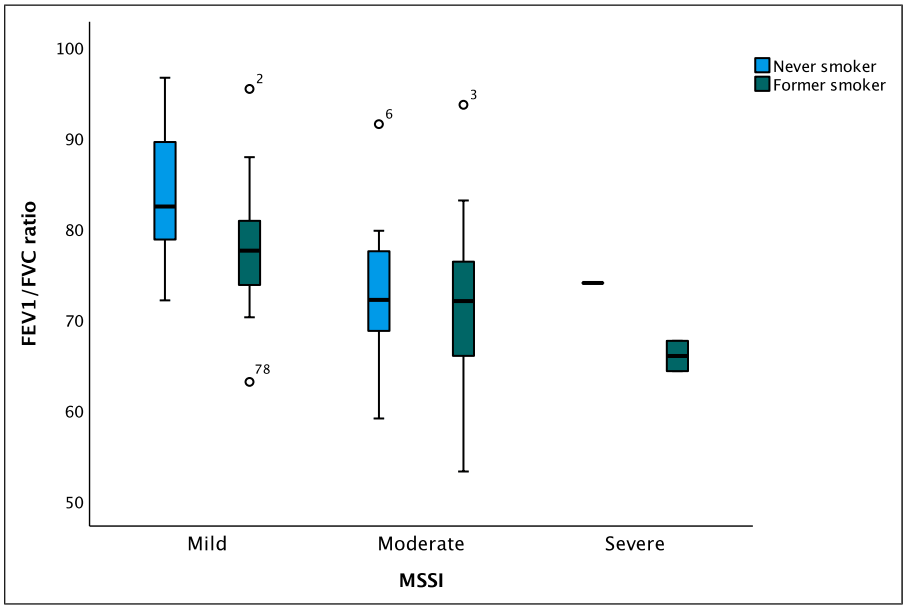

Figure 3. Box plot of the association between MSSI mild, moderate, and severe and FEV_1/FVC ratio in never and former smoking patients in the National Danish Fabry cohort. FEV_1/FVC ratio: forced expiratory volume in the first-second divided by forced vital capacity; MSSI: Mainz Severity Score Index. ANOVA analysis $p < .001$ (never smokers) and ANOVA analysis $p = .031$ (former smokers).

study showed that there was no difference between patients receiving ERT and not receiving ERT as both groups developed airway obstruction.

Age, smoking status, and gender have previously been described as significant predictors for FEV_1 (% predicted) decline and these factors were also among the main influencers in development of airflow limitation in Fabry patients.[14] Smokers developing airflow limitation, could be a general finding across different patient diagnoses, but an association between MSSI is specific for Fabry and different from the general findings. Also, a study by Rosenberg et al.[15] revealed that the obstructive impairment was much worse in Fabry patients who smoked, implying that even mild cigarette smoking was hazardous to Fabry patients.

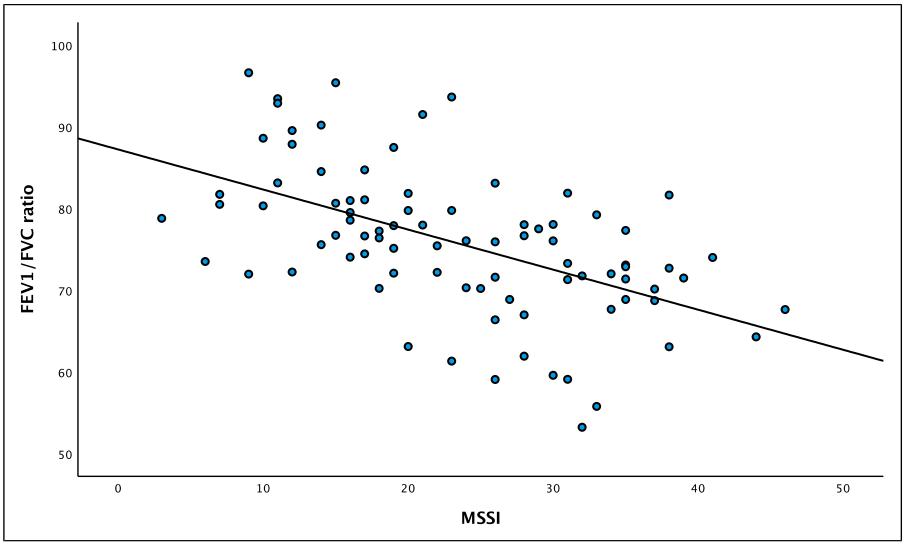

Figure 4. Scatter plot of the association between MSSI and FEV_1/FVC ratio in the National Danish Fabry. FEV_1/FVC ratio: forced expiratory volume in the first-second divided by forced vital capacity; MSSI: Mainz Severity Score Index. Correlation coefficient of −0.29.

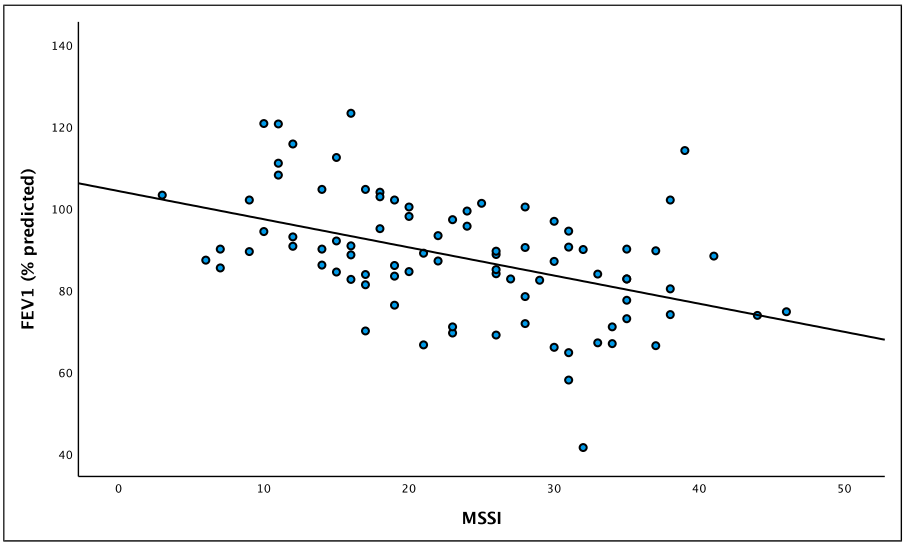

Figure 5. Scatterplot of the association between MSSI on FEV_1 (% predicted) in the National Danish Fabry cohort. FEV_1: forced expiratory volume in the first-second; MSSI: Mainz Severity Score Index. Correlation coefficient of −0.21.

On the other hand, in our study, former smokers had a more pronounced decline in the FEV_1/FVC ratio compared to never smoker, but Fabry patients who were never smokers also had signs of airflow limitation and were therefore also likely to develop obstructive airway limitation. Age was not found to be associated with either FEV_1 (% predicted) nor FEV_1/FVC ratio, even though it could be expected as age is a risk factor for bronchial obstruction, and FEV_1 generally declines approximately 1%–2% per year after the age of 25 in healthy people.[14] In the current study, no gender differences were found possibly due to too small numbers and power, however the number of females was substantially higher than in most studies, since all Fabry genotype positive family members found by cascade screening were offered inclusion in the study.[16]

Sixteen cohort studies from 1972 to 2018 focused on the pulmonary involvement in Fabry disease, and a summary of the studies is listed in chronical order in Supplementary Table 3.[3–5,15,17–28] Furthermore, 12 longitudinal case

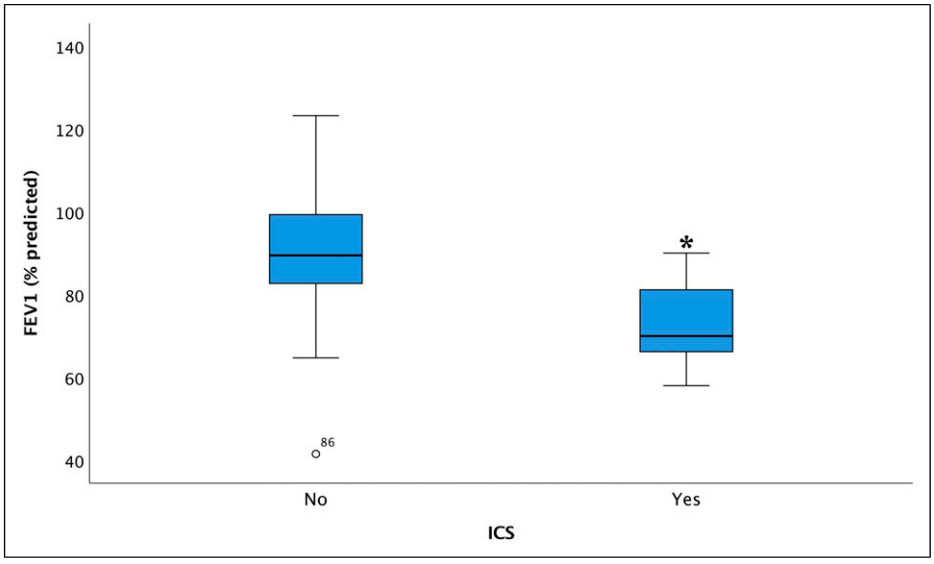

Figure 6. Box plot of the association between ICS and FEV_1 (% predicted) in Fabry patients with or without use of ICS. FEV_1: forced expiratory volume in the first second; ICS: inhalation corticosteroid. $p < .001$.

reports have been published,[29–40] using similar methods for pulmonary function examinations as those used in the cohort studies. The longitudinal case report outcomes were that restrictive and obstructive patterns were a general finding with reduced diffusion capacity and mild-moderate chronic airway limitation. However, none of these studies related to smoking nor to MSSI status.

There was no relationship between level of lung function and respiratory symptoms among patients suffering of chronic obstructive pulmonary disease,[41] leading to a large group of underdiagnosed airflow limitations, which is in agreement with findings in Fabry patients examined in this study. These findings are important for the clinicians which might be attempted to measure FEV_1 in patients with respiratory symptoms, whereas a screening approach might be suggested based on our findings.

There are limitations to our study, first, the retrospective study design is a possible source of bias, although the main University hospital is the single Nationwide centre for Fabry. Second, plasma lyso-Gb_3 concentrations usually decrease rapidly upon commencement of ERT, which 50% of the patients received, suggesting that the plasma lyso-Gb_3 concentration in the patients would be higher if they were measured pre-ERT. Similarly, FEV_1 (%predicted) would be lower in patients receiving inhaled corticosteroids and other type of lung medication if they were measured pre-medication. Third, the number of late-onset phenotypes was low, and the findings should therefore be confirmed in a larger cohort with more late-onset patients. Also, the low number of asthma patients might indicate that patients with Fabry disease suffer of non-Type-2 illness, although this study is too small to demonstrate any associations. Furthermore, this study has been initiated before lower limit of normal was introduced, which will account for some of the development of airway obstruction (REF: Howraman Meteran), on the other hand the level of FEV_1 also was found to be reduced, which seems to suggest that the level of obstruction is due to pathologic process, rather than a decrease due to age. Also, 28% of the patients exhibited pulmonary involvement by PFT, and it is possible that specific pathogenic variants may be more frequently associated with pulmonary defect and that these pathogenic variants were not present in our cohort. Other limitations included the cross-sectional nature of the study, why causality could not be documented. In general, subgrouping was not possible due to too low numbers in each subgroup. Finally, our measurements do not allow assessment of diffusion capacity to investigate if the reduced lung capacity might be due to a diffusion defect.

Conclusion

The prevalence of affected lung function variables among the National Danish Fabry cohort, with 86 patients included in this study, was 28% and only Fabry patients with classic phenotypes developed a pulmonary defect. This is the first study to show that patients with Fabry disease frequently develop an obstructive lung function defect regardless of their smoking status being current, former, or never smoker, and it is worse in patients with high MSSI. Furthermore, the MSSI was associated with a reduction in both FEV_1/FVC ratio and FEV_1 (% predicted). Further studies with more

late-onset patients, are needed to confirm a broader disease spectrum of these findings. However, this study suggests that care-takers of patients with Fabry disease, should be aware of the development of respiratory illness as part of the disease.

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Author contributions

H.A.: Methodology, Formal analysis, Writing – Original Draft, Visualization. V.B.: Conceptualization, Methodology, Formal analysis, Writing – Review and Editing, Visualization, Supervision. G.E.: Methodology, Formal analysis, Writing – Review and Editing, Visualization. Å.K.R.: Writing – Review and Editing, Visualization. C.M.K.: Writing – Review and Editing, Visualization. U.F.-R.: Conceptualization, Methodology, Investigation, Resources, Writing – Review and Editing, Visualization, Supervision, Funding acquisition.

Declaration of conflicting interests

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Data availability statement

The original anonymised data can be provided upon reasonable request to the corresponding author.

Supplemental Material

Supplemental material for this article is available online.

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