Year: 2013

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Pulmonary involvement in Fabry disease: Overview and perspectives

Daniel Franzen, M.D. [a, b], Pierre A. Krayenbuehl, M.D. [a], Olivier Lidove, M.D. [c], Prof John-David Aubert, M.D. [d], Frederic Barbey, M.D. [e]

[a] Department of Internal Medicine, University Hospital Zurich, Zurich, Switzerland

[b] Division of Pneumology, University Hospital Zurich, Zurich, Switzerland

[c] Department of Internal Medicine and Rheumatology, Hôpital de la Croix Saint Simon, Paris, France·

[d] Division of Pneumology, Centre Hospitalier Universitaire Vaudois, University of Lausanne Lausanne, Switzerland

[e] Transplantation centre, Centre Hospitalier Universitaire Vaudois, University of Lausanne, Lausanne, Switzerland

Corresponding author:

Dr Daniel Franzen

Division of Pneumology

University Hospital Zurich

Raemistrasse 100

8091 Zurich

Switzerland

Phone: + 41 44 255 11 11

Fax: + 41 44 255 45 67

E-Mail: daniel.franzen@usz.ch

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Abstract

Fabry disease (FD) is an X-linked lysosomal storage disorder caused by deficiency of alpha-galactosidase A, which leads to storage of sphingolipids in virtually all human cells and consequently to organ dysfunction. Pulmonary involvement is still debated. But, obstructive lung disease is up to ten times more prevalent in patients with FD compared to general public. Also, an accelerated decline in forced expiratory volume in one second (FEV1) over time was observed in these patients. Lysosomal storage of glycosphingolipids is considered leading to small airway disease via hyperplasia of the bronchiolar smooth muscle cells. Larger airways may become involved with ongoing disease process. There is no evidence for involvement of the lung interstitium in FD. The effect of enzyme replacement therapy on respiratory involvement remains to be determined in large, prospective controlled trials.

Keywords:

Fabry disease – lung – pulmonary – respiratory – obstructive – bronchiolar

Word count: 3891

1.   Introduction

Fabry disease (FD) is an X-linked lysosomal storage disorder caused by deficiency of alpha-galactosidase A, which leads to storage of neutral glycosphingolipids, particularly globobtriaosylceramide and galactosylceramide in virtually all human tissues and cells. The progressive storage of these molecules may lead to dysfunction of the affected cell triggering inflammation and/or fibrosis. Essentially, the cells of the vascular endothelium are the main target of the disease, which in turn leads to impaired perfusion of kidneys, heart, nervous system, and skin. However, direct damage from deposits in other cell types may also contribute to organ dysfunction [1].

The original patient described by Johannes Fabry in 1898 was suffering from "asthma" and frequent respiratory tract infections, and died at age 43 of lung disease [2,3]. In 1966, pulmonary involvement was supposed to be the second most common cause of death in FD [4]. However, pulmonary involvement in FD was neglected or even questioned for the next decades. Albeit the pathologic evidence of pulmonary involvement has been provided in several studies [5–9], the functional impact of these changes has been debated until today [10,11]. The Fabry outcome survey revealed that respiratory involvement was related to one of 42 deaths in Fabry patients between 2001 and 2007 suggesting that it rather contributes to morbidity than to mortality [12]. Enzyme replacement therapy (ERT) is available in FD since 2001 and remains the treatment of choice until now. Although there are many publications about effects of ERT on heart, kidney and nervous system involvement, there are only a few reports concerning the effect of ERT when the lung is affected. ERT has been reported to stabilize or even alleviate the burden of pulmonary involvement in FD, mainly bronchial obstruction and/or sleep apnoea [8,13]. Of note, lung involvement has been described in other lysosomal storage disorders in adulthood, such as Gaucher's disease, acid sphingomyelinase deficiency (Niemann Pick type B), maltase acid deficiency (Pompe disease), and in mucopolysaccharidoses.

The present systematic review article summarizes the past and current literature, including case reports, case series and cohort studies concerning pulmonary involvement in FD, and gives the reader an overlook of future investigational issues on this topic.

2.   Search strategy and selection criteria

English, French and German language medical literature was reviewed to identify abstracts and articles relating to pulmonary involvement in FD. References for this review were identified through searches of PubMed for articles published from January, 1916, to August, 2012, by use of the terms 'Fabry', 'Anderson-Fabry', 'lysosomal storage disorder', 'alpha-galactosidase', 'agalsidase', 'sphingolipids', 'spirometry', 'pulmonary', 'respiratory, 'lung, and combinations thereof. Inclusion criteria for the systematic review were randomized controlled trials, cohort studies, case-control studies, review articles, case reports, case studies, letters to the editor and articles based on registry data (Fabry Outcome Survey or Fabry Registry).

2.1   Included studies

The literature search revealed thirteen publications addressing pulmonary involvement in FD containing a total of 299 patients (151 male) [6,8–19]. These publications involved seven prospective cohort studies [6,11,14–16,18,19], one retrospective outcome survey [17], one case series [10], and four case reports or letters to the editor [8,9,12,13].

3.   Historical background

In 1978, Kariman et al. described a case of severe pulmonary involvement in the form of airway obstruction and emphysema in absence of alpha1-antitrypsin deficiency in a 32-year-old patient with known FD in a letter to the editor [14]. However, the direct pulmonary parenchymal or vascular involvement in FD was put into question by Bartimmo et al., who based their statement on the observation of three brothers with FD, of whom one showed a restrictive, and another a mixed obstructive-restrictive pattern in the pulmonary function test. Although the authors accepted the pathologic evidence for pulmonary involvement of some

degree, they stated limited evidence indicating significant pulmonary functional involvement in Fabry patients. Hence, they concluded that pulmonary abnormalities in Fabry patients rather seemed to be related to prior illnesses or universal involvement of other organ systems, mainly the heart [10]. The first and until 2006 largest cohort study on pulmonary involvement in FD was published by Brown et al., who described 25 affected male patients [15]. Of these, nine (36%; including five smokers) were found to have significant airway obstruction on spirometry, which was considered to be the result from fixed narrowing of the airway by accumulated glycosphingolipids [15]. Later studies confirmed the evidence of pulmonary involvement in terms of obstructive lung disease in patients with FD [16–20].

4.   Overview of pulmonary involvement in Fabry's disease

4.1   Obstructive lung disease

Pulmonary function testing

Based on the current literature, the majority of the published data refers an increased prevalence of obstructive lung disease in patients with FD *(table 1)*. An obstructive airway disorder is a disproportionate reduction of maximal bronchial or bronchiolar airflow in relation to the maximal exhaled volume implying airway narrowing during exhalation [21]. The definition of an obstructive respiratory defect is not homogenous throughout the literature. According to the 1991 ATS (American Thoracic Society) statement interpretation [22] and the ATS/ERS (European Respiratory Society) task force on standardisation of lung function testing [23], the forced expiratory volume in one second (FEV1) is referred to the (slow inspiratory) vital capacity (VC), and the cut-off value of this ratio is set at the fifth percentile of the normal distribution (lower limit of normal). In contrast, the definitions of both the Global Initiative for Chronic Obstructive Lung Disease (GOLD) [24] and ATS/ERS guidelines on chronic obstructive lung disease (COPD) [25] suggest referring the FEV1 to the forced (expiratory) vital capacity (FVC) with a fixed cut-off value of below 0.70. The latter definition is considered to overestimate obstructive lung disease in older people with no history of exposure to noxious particles or fumes [26,27]. However, the cut-off value of 0.70 is straight

forward and easy to measure, with a greater prevalence of obstructive lung disease when using the fixed value of FEV1/FVC compared to the lower limit of normal [28]. Moreover, as the diagnosis of obstructive lung disease in patients with FD is usually made in younger aged persons (usually below 40 years) [18], we feel that the FEV1/FVC cut-off value of 0.70 is justified for diagnosing clinically significant bronchial obstruction in these patients.

Epidemiology

Overviewing all available studies reporting lung function measurement in a total of 272 patients (50.5% male, mean age 38.5 years) with FD, 32.2% fulfilled the GOLD criteria (FEV1/FVC ratio < 0.70) for an obstructive lung disorder *(table 1).*Compared to a healthy control population matched for gender, age, and smoking status, this prevalence is significantly higher. In an epidemiological study with 6126 subjects participating in the Swiss Cohort Study on Air Pollution and Lung Diseases in (healthy) Adults (SAPALDIA), the prevalence of airflow obstruction of any cause (FEV1/FVC < 0.70) in the nearly same age group (between 30 and 39 years) was 0.9% in women and 3.4% in men [27]. Also, the proportion of obstructive lung defect in patients with FD is comparably higher than the prevalence of COPD in the general population ranging from 5.1% to 16.7% in women, and from 8.5% to 22.2% in men [29]. However, prevalence estimates of COPD show considerable variability across investigated populations [30]. Considering the gender of the investigated Fabry patients, the pooling of published data demonstrates that bronchial obstruction is more prevalent in males (41.8 vs. 22.2%), although the mean age, which is an independent risk factor for bronchial obstruction as defined by the GOLD initiative, was ten years higher in the female cohort *(table 2 and 3)*. However, those female Fabry patients with proven bronchial obstruction seem to be as severely affected as their male counterparts, which is in line with other organ's involvement in female patients [31].

Severity and symptoms

In 48.1% of all Fabry patients reported in the literature, the FEV1 was below 80% of the predicted value pointing to bronchial obstruction of at least moderate degree in most of the cases according to the GOLD classification for severity of COPD *(table 1)* [24]. The calculated mean FEV1 in all patients was 75.1% of the predicted value, whereas the mean FVC was 94.6% *(table 1)*. According to *table 2* and *3*, FEV1 and FVC are lower in male Fabry patients compared to females (76.9% and 89.3%, 89.4% and 103.5%, respectively). One third to more than half of the 272 patients with FD reported respiratory symptoms (cough, dyspnoea or wheezing) attributable to bronchial obstruction. However, these symptoms are not specific for obstructive lung disorders and could also be explained by cardiac involvement in FD [11]. Another important clinical aspect is that Fabry patients generally do not present with excessive sputum production compared to COPD.

Smoking

Data concerning an objective association with cigarette smoking are conflicting. Brown et al. reported a weak association of tobacco abuse to early bronchial obstruction in their cohort [15]. In contrast, two other publications were not able to detect a significant impact of smoking on lung function or pulmonary symptoms. However, the reported subjects were young Fabry patients [17,18]. Anyway, the presence of obstructive impairment seems to be strongly age-dependent [15,17]. In two recent studies, the significant age-related reduction of predicted lung volumes could be stated in hemizygous males only, while the impact of age could not be affirmed in heterozygous women [18,20]. The same authors suspected a nonlinear progression of the obstructive lung defect in terms of accelerated decline in FEV1 of about 40 ml per year in male Fabry patients. An association with smoking in this regard was not investigated. This impairment is clearly pathological when compared to the findings of a recent, detailed systematic review of 47 studies in healthy individuals or patients with respiratory disease performed by Lee et al. These authors measured a FEV1 decline in active smokers of over 40 ml per year compared to less than 30 ml year in never smokers [32]. Notably, the FEV1 decline in Fabry patients, irrespective of their smoking status,

appears to be of the same order of magnitude of active smokers not affected with FD. Accordingly, Xu et al. found age- and height-adjusted rates of decline in active smokers of 45.4 ml per year compared to 33.4 ml per year in never smokers [33]. In a large COPD population, the mean rate of FEV1 decline in GOLD stages II and III was found to be between 47 and 79 ml per year and 56 and 59 ml per year, respectively [34].

Pathology

Obstructive lung disease in FD results most likely from progressive narrowing of the airways by accumulated glycosphingolipids in the bronchial cells [7,15]. Rosenberg et al. were the first authors who observed airway cells containing glycosphingolipid inclusion bodies in bronchoalveolar brushings and lavage fluid [6]. Even in induced sputum samples, these lamellar inclusion bodies typical for FD could be identified on electron microscopy within all ciliated bronchial epithelial cells [9]. Moreover, airway wall cells hyperplasia and/or fibrosis are other potential causes [18]. In one 51-year-old Fabry patient undergoing open lung biopsy, peribronchiolar fibrosis and smooth-muscle cells hyperplasia with prominent inclusion bodies in the bronchial, bronchiolar and arteriolar smooth muscle and endothelial cells could be demonstrated. Again, on electron microscopy, these dense granular inclusion bodies were lamellated zebra bodies consistent with globotriaosylceramide storage [8]. According to these findings, it is likely that the pulmonary lysosomal storage of glycosphingolipids may lead to small-medium airway disease via hyperplasia of the bronchial/bronchiolar smooth muscle cells and via insufficient smooth-muscle relaxation [8]. This mechanism may parallels with the mechanism of endothelial dysfunction in cardiomyocytes and arterial smooth-muscle cells observed in Fabry patients *(figure 1)* [35–37].

Pulmonary involvement in Fabry disease – A matter of bronchiolar dysfunction?
The histological and pathophysiological mechanism of airway obstruction seems to be completely different in FD than in COPD or asthma. Underlining the latter statement, the proportion of an at least partially positive reversibility testing after bronchodilator inhalation

(changes in FEV1 and/or FVC values greater than 12% and 200 ml compared with baseline during a single testing session are considered a significant reversibility [23]) in Fabry patients is only 15.9%. Moreover, in the study of Brown et al., none out of ten Fabry patients, who underwent bronchial challenge testing with methacholine chloride, had a positive result [15]. The potential mechanisms of airflow obstruction in FD compared to COPD and asthma is summarized in *table 4*. In fact, the evidence is growing that the above mentioned glycosphingolipid accumulation in the bronchiolar smooth muscle cells in FD initially leads to small airway disease [16,20]. This hypothesis is supported by the observation that 44.3% of the Fabry patients show spirometric evidence of small airway obstruction, whereas female Fabry patients have a higher prevalence than males (50.0% vs. 39.4%, *table 2 and 3*).Those patients present a decreased mean forced expiratory flow rates between 25% and 75% of FVC (FEF25-75) below 70% of the predicted value *(table 1)*. However, abnormalities in these mid-range flow measurements during the FVC manoeuvres are not specific for small airway disease, as FEF25-75 measurements can be misleading and can cause an unacceptably large number of false-negative or false-positive results [23, 38]. Thus, the role of FEF25-75 for diagnosis of small airway disease is still debated. In healthy (non-Fabry) individuals, the functional characteristics of small airway obstruction may have no predictive value for development of chronic airways obstruction [39]. However, the earliest change associated with airflow obstruction in small airways is thought to be a slowing in the terminal portion of the spirogram, even when the initial part of the expiratory curve is barely affected [23]. Hence, in patients with FD, mainly small and medium sized bronchi, and potentially other pulmonary structures may become involved with ongoing disease process [20]. Additionally, the typical radiological feature of small airway disease have been shown in the case report by Kim et al. demonstrating bilaterally severe mosaic attenuation pattern, which is due to a combination of ground-glass opacities and air trapping [13]. A pattern of mosaic attenuation on thoracic high resolution computed tomography (HRCT), especially when seen on expiratory images, is consistent with air-trapping characteristic of bronchiolitis obliterans or constrictive bronchiolitis [40]. Accordingly, in the study of Brown et al., air-trapping measured

by increased residual volume (RV) was present in the majority of the investigated Fabry patients (mean RV 141.7% predicted) without morphological evidence of pulmonary emphysema [15]. Perhaps, this finding reflects occult or early airway obstruction – or small airway obstruction, which may not be detected by spirometry alone.

4.2 Interstitial lung disease

Though the pulmonary involvement of FD primarily features obstructive airway disease, the lung interstitium may be concerned in later stages of the disease process [20]. Accordingly, Koskenvuo et al. described two out of seventeen Fabry patients with morphological changes in thoracic HRCT showing mild to marked pulmonary fibrosis. However, these CT findings were not associated with pulmonary function abnormalities; especially the single-breath carbon monoxide diffusing capacity (DLCO) was within normal limits [11]. Moreover, there are no systematic reports of chest CT findings in patients with FD.

Considering all available data concerning DLCO measurements in Fabry patients, 15.7% (11/70) showed a significant impairment *(table 1)*, defined as DLCO < 80% of the predicted value [41]. An impaired DLCO is one of the earliest, although nonspecific, manifestations of interstitial lung diseases [42]. In two case reports of two female Fabry patients, an impaired gas exchange and patchy ground-glass opacities on the chest CT were reported [8,13]. In one case, the pathologic findings were reversible after introduction of enzyme replacement therapy (ERT) with agalsidase beta [13], whereas the other showed no response to treatment in terms of radiologic findings, although dynamic lung volumes (FEV1, FVC, and FEF25-75) and DLCO improved or stabilized, respectively [8]. The authors of the latter report concluded that the process of pulmonary interstitial fibrosis is progressive and does not respond to ERT, if a certain "point of no return" has been exceeded [8]. Anyway, based on the current literature, there is no clear-cut evidence for involvement of the lung interstitium in FD. Some of the reported changes are rather due to small airway disease as chest CT

abnormalities and an impaired DLCO are best compatible with bronchiolar dysfunction [40].

However, the filling of endothelial cells in the lung interstitium with sphingolipids may also

impair DLCO. This hypothesis is supported by the improvement of DLCO after ERT with

clearing of these deposits. On the other hand, improvement of DLCO could – at least in part

– be explained by improvement of cardiac function after ERT.

4.3   Sleep-related breathing disorder and muscular involvement

Chronic fatigue is a frequent and early reported symptom in patients with FD, which has a

major impact on their quality of life. In a cohort of 49 patients (27 males; mean age 43 years)

with genetically proven FD, the prevalence of excessive daytime sleepiness was 68%

exceeding the one of other symptoms related to FD [43].The underlying mechanism of

tiredness in FD is not well understood. On one hand, chronic renal or cardiac dysfunction

irrespective of the underlying cause is frequently leading to chronic fatigue. But more

recently, it has been shown that chronic fatigue also appeared in Fabry patients without renal

or cardiac dysfunction [44]. In one case report, a 56-year-old female Fabry patient with a

pathological Epworth Sleepiness Scale (ESS) of 20 (normal < 11) underwent an overnight

polysomnography and cerebral MRI revealing a severe Cheyne-Stokes breathing pattern

with a reported apnoea/hypopnea index (AHI) of 64 per hour (pathologic > five per hour) and

repeated oxygen desaturations, and confluent cerebral white matter lesions including the

brain stem [43]. As an earlier study demonstrated an association between cerebral white

matter lesions and sleep-disordered breathing [45], the authors accordingly suspected an

association between the radiologic findings in their patient and the Cheyne-Stokes breathing

disorder [43]. Their conclusion is supported by the fact that severe progressive cerebral white

matter lesions are common findings in FD and occur early in the disease process [46] and

worsen with time [47].

In summary, excessive daytime sleepiness in FD might be caused by sleep-related breathing

disorders, which could be due to an affection of brain regions associated with respiratory

control. Alternatively, the Cheyne-Stokes respiration may be a consequence of heart failure in the context of FD as this was shown in non-Fabry patients [48] or due to cerebral ischemic lesions. In a very recent study performed by Chimenti et al. who investigated endomyocardial and striated muscle biopsies in twelve Fabry patients, direct muscle involvement with glycosphingolipid accumulation occurred in older FD patients above 35 years of age, while there was no evidence of any affection in the myocytes of Fabry patients below 35 years [49]. Hypothetically, the muscular involvement in FD and a subsequent loss of function could possibly contribute to sleep-related breathing disorders, although myopathies would rather lead to obstructive sleep apnoea (if mainly the upper airway muscles are involved) or alveolar hypoventilation syndrome, and not to central sleep apnoea like a Cheyne-Stokes breathing disorder.

5.   Management of Fabry disease with lung involvement

Since introduction of the enzyme replacement therapy (ERT) with recombinant alpha-galactosidase in 2001 [50,51], its safety and efficacy has been shown in multiple trials [52-54]. In a multicentre, randomized, placebo-controlled, double-blind study involving 58 patients, a dose of one milligram of recombinant alpha-galactosidase per kilogram every other week for six to twelve months effectively reversed the accumulation of microvascular endothelial deposits of globotriaosylceramide in the kidneys, heart, and skin [51]. But despite these promising advances in the treatment of FD, the impact of ERT on pulmonary involvement has not been sufficiently evaluated in clinical trials. In one small retrospective, cross-sectional case series of 15 Fabry patients no significant lung function changes were observed in serial spirometries and DLCO measurements during a period of 15 months after ERT [17]. In contrast, two recent case reports showed the efficacy of ERT on lung involvement [8,13]. One patient demonstrated marked improvement of respiratory symptoms, dynamic lung volumes (FEV1, FVC, and FEF25-75), DLCO, and CT findings after ERT [13], whereas stabilization of lung function deterioration (mainly FEV1, FEF25-75, and DLCO) was observed in the other patient [8]. Moreover, a randomized controlled trial by Bierer et al.

demonstrated improvement of exercise tolerance in patients receiving agalsidase-beta [19]. However, the improvement of both maximum oxygen uptake measured at peak exercise (VO2max) and cardiac stroke volume was rather due to removal of microvascular endothelial and myocardial glycosphingolipid deposits demonstrated by Eng et al. [52]. Future prospective studies should include pulmonary function tests as a pre-defined endpoint, and stratify the analysis according to potential confounding factors (e.g. smoking).

To date, the impact of cigarette smoking on the pathogenesis of early obstructive lung disease in FD has not been proved nor ruled out in the published studies. Only Brown et al. could show a weak association to cigarette use [15], whereas this was not confirmed by others [17,18]. Despite these uncertainties, with respect to the endothelial involvement in FD, patients should strongly be advised to quit or rather avoid smoking. Moreover, in case of a detectable bronchial obstruction we commonly prescribe a long-acting inhalational bronchodilator (e.g. formoterol). But, the use of bronchodilators or inhalational corticosteroids (e.g. budenoside) has not yet been prospectively studied in Fabry-related airflow limitation.

6.   Future perspectives

To better understand and prove the histopathological, pathophysiological and functional consequences of FD on the lung, more studies in animal models and human subjects are required. For this reason, the natural course of disease concerning pulmonary involvement in FD should be investigated in large cohorts. Secondly, it seems to be of paramount importance to prospectively perform serial lung function measurements including DLCO measurement before and after starting ERT. Serial thoracic low dose CT images may be undertaken before and after starting ERT in subjects with any signs of small airway disease and/or impaired DLCO. Furthermore, it would be interesting in the context of a prospective study to analyse broncho-alveolar lavage fluid samples before and after institution with ERT. Of course, it would be informative to perform post mortem examinations in Fabry patients with and without ERT in combination with a retrospective study. Regarding the suspected mechanism of sleep-related breathing disorders in Fabry patients, we acknowledge that

dedicated investigations should address this topic. For this reason, an epidemiological study on the prevalence of sleep-related breathing disorders in FD should be undertaken. In addition, the potential impact of ERT on sleep-related breathing disorders should be tested in a trial with an adequate design. Finally, we would like to emphasize the need for a pulmonary severity score index in order to quantify the respiratory function and/or impairment over the time according to the Mainz severity score index or the Fabry disease severity scoring system (DS3) [55,56].

7.   Learning Points

- The prevalence of obstructive lung defect in patients with FD (32.2%) is comparably higher than the one in general population. Male Fabry patients show a higher prevalence of obstructive lung disease and an accelerated decline in forced expiratory volume in one second (FEV1) than the female counterparts. One important issue of this work is that bronchial obstruction has the same prevalence in males and ten years older females suggesting that female patients are not only carriers.

- The obstructive lung disease in FD results from pulmonary lysosomal storage of glycosphingolipids primarily leading to small airway disease via hyperplasia of the bronchiolar smooth muscle cells.

- Excessive daytime sleepiness is a frequently underdiagnosed feature of FD, which could be caused by a sleep-related breathing disorder.

- The impact of ERT on these features of FD has not been studied adequately so far. Further systematic investigation on pulmonary involvement in FD to enlighten the pathophysiological mechanism and potential therapeutic approaches is urgently needed.

8.   Acknowledgment

9.   Conflicts of interests

None of the authors has any conflict of interest to declare.

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Figure 1. Open lung biopsy in a patient with hemizygote Fabry disease. Bronchial wall, stained with haematoxylin and eosin (HE). Pronounced hypertrophy/hyperplasia of the bronchial smooth-muscle cells (arrow) compared to an age-matched control.