Research Article

iMedPub Journals
www.imedpub.com

Journal of Rare Disorders: Diagnosis & Therapy
ISSN 2380-7245

2021
Vol.7 No.9:39

Pulmonary Manifestations and the Effectiveness of Enzyme replacement in Fabry Disease with the p.R227X Mutation

Päivi Pietilä-Effati[1]*, Johan Söderström[2], Jukka T. Saarinen[3], Eliisa Löyttyniemi[4] and Ilkka Kantola[5]

1 Department of Cardiology, Vaasa Central Hospital, Hietalahdenkatu 2-4, 65130 Vaasa, Finland
2 Department of Pulmonology, Vaasa Central Hospital, Hietalahdenkatu 2-4, 65130 Vaasa, Finland
3 Department of Neurology, Vaasa Central Hospital, Hietalahdenkatu 2-4, 65130 Vaasa, Finland
4 Department of Biostatistics, University of Turku, Kiinamyllynkatu 10, Medisiina A, 20520 Turku, Finland
5 Division of Medicine, Turku University Hospital, University of Turku, Kiinamyllynkatu 4-8, PL 52, 20520 Turku, Finland

***Corresponding author:** Päivi Pietilä-Effati

paivi.pietila-effati@vshp.fi

Department of Cardiology, Vaasa Central Hospital, Hietalahdenkatu 2-4, 65130 Vaasa, Finland.

Citation: Pietilä-Effati P, Söderström J, Saarinen JT, Löyttyniemi E, Kantola I (2021) Pulmonary Manifestations and the Effectiveness of Enzyme replacement in Fabry Disease with the p.R227X Mutation. J Rare Disord Diagn Ther Vol.7 No.9:39

Abstract

Introduction: Fabry disease is a rare X-linked multiorgan disease caused by a defect in α-galactosidase A gene which leads to a progressive accumulation of globotriaosylceramide (Gb3) and its metabolites in several organs. Pulmonary manifestations of Fabry disease mimic chronic obstructive pulmonary disease and are disproportionate to smoking status. The effect of enzyme replacement therapy on pulmonary function is inconclusive.

Objectives: We studied the effect of enzyme replacement therapy on pulmonary function in Fabry disease with a classical mutation p.R227X in Finland to minimize confounding factors caused by genetic and environmental variation. R227X is one of the most common mutations causing classical Fabry disease worldwide.

Methods: 12 of 14 patients with R227X met the criteria for enzyme replacement therapy and were included in this study. Based on the maximal pulmonary oxygen consumption at the baseline, either cardiopulmonary exercise test or combination of spirometry and six-minute walking test were performed annually during five-year follow-up.

Results: Three of 12 patients had obstruction by the Global Initiative for Obstructive Lung Disease (GOLD) criterion before enzyme replacement therapy, and one had borderline obstruction. In five years, five patients were classified obstructive, although the real change in FEV1/FVC was unchanged in the whole cohort. Only one patient was active smoker.

Conclusion: The findings of our study suggest that pulmonary manifestations in classical Fabry disease are mild in a predominantly non-smoking cohort. Enzyme replacement therapy might stabilize natural history of the lung disease in this condition.

Keywords: Enzyme replacement therapy; Fabry disease; Mutation; Pulmonary; Respiratory; Spirometry

Received: September 12, 2021; **Accepted:** September 29, 2021; **Published:** October 07, 2021

Introduction

Fabry disease (FD, OMIM # 301500) is a rare lysosomal disease caused by a mutation in α-galactosidase A (GLA) gene (the GenBank reference sequence NM_000169.2) in X-chromosome [1]. The catabolism of sphingolipid globotriaosylceramide (Gb3) is disturbed and leads to progressive accumulation of Gb3 and its degradation products, mainly globotriaosylshingosine (lysoGb3), in various organs [1]. Approximately 1000 different mutations have been described [2]. The severity of the phenotype varies from asymptomatic benign polymorphism to severe classical phenotype where the accumulation of Gb3 and lysoGb3 begins in fetal period and leads slowly to organ failure, decreased quality of life and premature death especially in males [3-5]. Prevalence of smoking in patients with FD is not known. In a German cohort of 41 FD patients except for one patient, all were smokers [6].

Pulmonary symptoms of classical Fabry disease include mild

expiratory wheezing and dyspnoea and dry cough [1,7]. Lamellated inclusion bodies which are typical in Fabry disease have been detected in histological specimens in airway epithelial cells, bronchial smooth muscle cells, smooth muscle cells of pulmonary arteries and veins, endothelial cells and alveolar interstitial cells [7,8]. Spirometry typically reveals a mild, irreversible obstruction [7,9,10]. To date, there are few studies that have investigated the effect on enzyme replacement therapy (ERT) on pulmonary symptoms and function [11,12]. It is generally accepted that ERT should be started before the disease proceeds to irreversible state [13,14].

In this paper, we report pulmonary findings in a prospectively collected cohort of 12 patients with a classical Fabry Disease caused by mutation R227X in Finland and the effect of ERT on these parameters. R227X is one of the most common mutations causing classical Fabry disease worldwide [15,16].

Materials and Methods

Our study Fabry Disease in Ostrobothnia (FAST) was planned to describe the natural history of the classical mutation R227X and the effect of ERT on disease progression. The study was approved by the Ethics Committee of the Hospital District of Southwest Finland (ETMK: 41/1801/2017) and was conducted in accordance with the Declaration of Helsinki. All patients gave their informed consent to the study. The natural history of this cohort has previously been published [17]. 12 of 14 patients met the criteria for ERT [14] and were included in the follow-up study. ERT was initially not started for elderly female over 80 years of age with relatively mild symptoms. After having had an ischemic stroke, she was no longer considered to benefit from ERT. Another female without ERT had mild symptoms and no major organ manifestation.

Agalsidase-α at dose 0,2 mg/kg was prescribed for three patients and agalsidase-β at dose 1 mg/kg every other week for nine patients. Patient were annually examined by multi-disciplanary team including cardiologist (P.P-E), internist (I.K) and neurologist (J.T.S), and the other specialties, inclusive pulmonologist (J.S), were consulted if needed. The relevant clinical laboratory parameters, electrocardiogram (ECG), 24-hour continuous ECG, transthoracic ultrasound (TTE) and spirometry were prospectively collected in every visit. Audiogram was performed annually. Ophthalmologist examined patients every two years. Brain MRI or CT was performed approximately every three years and cardiac MRI every two years unless there was a clinical need to perform the studies earlier [18]. Mainz severity score index (MSSI), which is a validated multiorgan scoring system for Fabry disease, was used to monitor disease severity and progression during ERT. Scores from general, neurological, cardiovascular and renal categories give the maximal score of 76. Score more than 40 indicates severe disease, 20-39 moderate disease and less than 20 mild disease [19].

Performance ability was defined by cardiopulmonary exercise test (spiroergometry) before ERT if possible. The maximal pulmonary oxygen consumption (VO_2 ml/kg/min) was measured and related to age. VO_2 was considered normal when the measured VO_2 was over 70% of predicted value [20]. Combination of spirometry and 6-minute walking test (6MWT) was used in follow-up if performance ability was normal in spiroergometry before ERT or if spiroergometry was missing.

The presence of obstruction was determined according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criterion [21,22] where obstruction was diagnosed by a ratio of forced expiratory volume in one second and forced vital capacity (FEV1/FVC) less than 0.7. The severity of obstruction was defined by FEV1 % from predicted value. Values 80% or more were considered normal (GOLD 1), values between 50-79% moderately reduced (GOLD 2), 30-49% severely reduced (GOLD 3), and values less than 30% very severely reduced (GOLD 4). The reference values for Kainu et al. represent healthy non-smoking adults from all over Finland from the age of 16 to 84 [23]. 6MWT was performed indoor along a straight, plane 30-meter corridor following American Thoracic Society statement [24,25].

No pulmonary imaging studies were programmed in follow-up. However, the pulmonologist (J.S) retrospectively re-evaluated all the CT-studies from the thoracic region that had been taken for some reason during the 5 years follow-up of ERT.

Statistics

The results are presented as mean and Standard Deviation (SD) or range when the variable followed normal distribution. The mean changes during ERT were analyzed using linear mixed models for repeated measures. Kenward-Roger corrections was used for degrees of freedom. Only time effect was tested with this model, also time differences between every two time points were estimated. P-values less than 0.05 (two-tailed) were considered as statistically significant. The data analysis for this paper was generated using SAS software, Version 9.4 of the SAS System for Windows (SAS Institute Inc., Cary, NC, USA).

Results

The mean age at ERT start was 45 years (range 15-66) in the whole group, in males 30 years (15-39) and in females 52 years (25-66). One patient suffered from previously diagnosed asthma which was suspected to be occupational in the 1980s. After changing her occupation, she had not used inhaled steroids or β-agonists regularly. One patient in the cohort was a current smoker. She had also been suspected to have bronchial asthma, but the diagnostic criteria for asthma were not fulfilled.

Spiroergometry was performed in six patients before ERT, five of them females. Mean VO_2 was 26 ml/kg/min (range 17-31). VO_2 was normal in all except a 15-year-old male, whose VO_2 was 31 ml/kg/min (67% of predicted value). His FEV1/FVC did not fulfill the GOLD criterion for obstruction. However, his FEV1 was only 2.4 l (69% of reference value). Pulmonary function results were available from nine out of 12 patients before ERT as a part of spiroergometry or as a separate test. Three patients met the GOLD criterion for obstruction. Two of them had an irreversible pulmonary obstruction. The third patient was not tested with β-agonist. Moreover, the female with untreated asthma did not meet the GOLD criterion and she had a negative response for β-agonist. The average FEV1/FVC before ERT was 73% (SD 10).

During the follow-up [mean 5.1 years (range 3.7-5.8)], FEV1 and FEV1/FVC remained unchanged in the whole cohort (detailed data of the whole cohort is presented in **Table 1** and data patient by patient in **Table 2**. The GOLD criterion was fulfilled in additional two patients in five years. Obstruction was not reversed in any patient. Four out of five patients had mild obstruction GOLD 2 in the end of the follow-up. The fifth patient had normal FEV1, which grades as GOLD 1. She had untreated asthma, and FEV1/FVC decreased clearly in five years. Even though her pulmonary function deteriorated, she did not have subjective pulmonary symptoms, and she was not willing to use inhaled medication. Moreover, her MSSI decreased from 21 to 8. A significant contributing factor for this improvement was her early retirement.

Mean MSSI was 17 (3-32), in males 21 (10-26) and in females 15 (3-32), and the scores did not change in the follow-up (mean score in the whole cohort decreased 0.38 from the baseline, p=0.93). In the end of the follow-up, 6MWT was in reference limit in all except the oldest patient, 66 -year-old female with a severe Fabry disease (MSSI 32, an irreversible obstruction in spirometry but a normal VO_2 before ERT). Her disease progressed despite ERT, and after three years of ERT, her MSSI was 44 and 6MWT was 288 meters, which was below reference limit 322 meters. Her spirometry was unchanged. The progression of diastolic heart failure was the main reason for the reduced performance ability.

In 15-year-old male, MSSI decreased from 10 to 7 in five years. His sweating normalized and was able to play soccer again. VO_2 and FEV1/FCV remained stable. His FEV1 increased from 2.4 to 3.5 l (from 69% to 74% of reference value) which may partly be explained by his adolescence. However, the shape of the exhalation curve was slightly obstructive and FEV1 increased by 11%. He noticed subjective relief after β-agonist. Bronchial asthma was diagnosed by the pulmonologist and an inhaled steroid and a long-acting β-agonist were started. Thorax region imaging studies after ERT initiation were available in six patients (four patients with coronary CT and two patients with CT because of trauma). No pulmonary parenchymal changes, emphysema or lymphadenopathy could be detected. The main bronchi were open and of normal caliber. Coronary arteries were normal in all four coronary CT.

Discussion

In our study Fabry Disease in Ostrobothnia (FAST), we followed the effect of ERT for five years in a cohort of patients with the classical Fabry mutation R227X. FEV1 and/or FEV1/FVC were decreased in one third of the patients before ERT and remained stable during ERT. MSSI, which reflects the disease severity, did not change during the follow-up.

Rosenberg DM, et al. [7] demonstrated that pulmonary symptoms in FD can be independent of cardiac disease and the airway obstruction is disproportionate to smoking status [7]. Pulmonary

Table 1 Change in pulmonary function in five years of enzyme replacement therapy.

Variables	Before initiation of ERT† (n = 9)	After 5 years of ERT (n = 12)	Change from initiation of ERT to 5 years of ERT	
FEV1‡ (liters) (SD§)	2.64 (0.92)	2.68 (0.64)	0.04	p = 0.49
FEV1 % from predicted value (%) (SD)	85 (17)	83 (14)	-	-
FEV1 / FVC ¶ (SD)	0.73 (0.10)	0.72 (0.09)	-1.16	p = 0.35
FEV1/ FVC (%) from predicted value (%) (SD)	88 (10)	92 (10)	-	-

†ERT = Enzyme Replacement Therapy,‡FEV1 = Forced Expiratory Volume in the First Second, §SD = Standard Deviation, ¶FVC = Forced Expiratory Vital Capacity.

Table 2 Pulmonary parameters of every patient before enzyme replacement therapy and in five years follow-up.

ID†	FEV1‡ before ERT§ (liters)	FEV1 in five Years of ERT (liters)	FEV1/FVC¶ Before ERT (%)	FEV1/FVC In five years of ERT (%)
1	2,39	3,5	73	75
2	-	3,58	-	72
3	2,82	2,75	63	62
4	-	3,41	-	72
5	2,95	2,76	90	90
6	2,33	2,18	65	64
7	3,35	3,11	78	78
8	2,75	2,43	71	64
9	2,71	2,56	85	84
10	2,51	2,51	72	73
11	-	1,56	-	67
12	1,99	1,84	63	62

symptoms and signs were present in about one third of Fabry male patients irrespective of smoking status [22] which equals results seen in our study. Franzen et al. reported in a retrospective study that a clinical or subclinical airway obstruction deteriorates without ERT in both genders referred to matched controls [23]. In our study, it was not ethically possible to follow patients without ERT when the criteria for ERT were fulfilled [14].

In our study, nine patients had spirometry available before ERT. All 12 patients had two or three spirometries during five years of follow-up. Two females and one male had obstruction before ERT, and another male borderline obstruction. In five years, five patients were classified obstructive by the GOLD criterion, although the real change in FEV1/FVC was unchanged in the whole cohort. The obstruction did not reverse in any patient.

The effect of ERT on pulmonary parameters have been inconclusive in previous trials. Shafi N [11], reported stabilization of pulmonary function parameters on 37 patients at 12 months follow-up. In the retrospective cohort of 95 patients, the overall decline in FEV1 was 29 ml per year and was not improved by ERT Franzen DP, et al. [12]. In our study (12 newly diagnosed patients with classical R227X mutation), FEV1/FVC values during five-year ERT were stable in both genders. In another study by Franzen DP, et al. [12] in males with the classical phenotype, smoking and late ERT initiation predicted faster FEV1 decline. In that study, 30 of 40 patients received agalsidase-α throughout the whole follow-up. In our study, majority of patients were treated with agalsidase-β which might explain different results between the studies.

Pulmonary high-resolution computed tomography in 17 patients with Fabry disease demonstrated only mild changes in lung parenchyma, and the findings did not correlate with pulmonary functional parameters [26]. In our study, no signs of interstitial lung involvement could be demonstrated. One limitation of our study is the lack of serial spiroergometry during follow-up. Patients felt spiroergometry uncomfortable and were unwilling to repeat test at regular intervals. The small sample size in this cohort limited the potential for statistical analysis between sexes. Another limitation is the lack of validated international criterion for spirometry in non-smoking population with diseases resembling chronic obstructive lung disease. GOLD criterion can underestimate obstruction in adults less than 45 years [21]. Although we have a validated Finnish criterion for spirometry, we decided to use GOLD criterion for diagnosis of obstruction because GOLD is widely used and makes comparison with other international studies more objective.

Further, incompleteness of data before ERT limited the power of analyses. The first patient in our hospital was diagnosed in 2013 after an ischemic stroke and ERT was started shortly after Fabry disease was confirmed. The other patients were diagnosed between 2014 and 2015 through family tracing and through another index patient with hypertrophic cardiomyopathy. After diagnosing several patients with the same mutation R227X in our district we decided to perform this study. Some patients had started ERT before our study with fixed protocol for follow-up had started.

Lastly, a genetically and environmentally homogenous cohort with only one mutation minimizes the confounding factors which allow studying the real effect of ERT on disease progression. On the other hand, it might limit the generalizability of results in other mutations and populations worldwide.

Conclusions

The purpose of the current study was to determine the long-standing effect of ERT on pulmonary function in a predominantly non-smoking cohort of patients with classical Fabry disease causing mutation R227X. Despite its limitations, the findings of our study suggest that ERT might stabilize pulmonary function. Further results should be carried out to establish the role of ERT used and the generalizability of results in other environments and different genetical back grounds.

References

1 Desnick RJ, Ioannou YA, Eng CM (2001) A-galactosidase a deficiency: Fabry disease. In: The metabolic and molecular bases of inherited disease. New York: McGraw-Hill.p.3733-3774.

2 Stenson PD, Mort M, Ball EV (2017) The human gene mutation database: Towards a comprehensive repository of inherited mutation data for medical research, genetic diagnosis and next-generation sequencing studies. Hum Genet 136:665-677.

3 MacDermot KD, Holmes A, Miners AH (2001) Anderson-Fabry disease: Clinical manifestations and impact of disease in a cohort of 98 hemizygous males. J Med Genet 38:750-760.

4 Waldek S, Patel MR, Banikazemi M (2009) Life expectancy and cause of death in males and females with Fabry disease: Findings from the Fabry Registry. Genet Med 11:790-796.

5 Tsutsumi A, Uchida Y, Kanai T (1984) Corneal findings in a foetus with Fabry's disease. Acta Ophthalmol (Copenh).62:923-931.

6 Fellgiebel A, Gartenschlager M, Wildberger K (2014) Enzyme replacement therapy stabilized white matter lesion progression in Fabry disease. Cerebrovasc Dis 38:448-456.

7 Rosenberg DM, Ferrans VJ, Fulmer JD (1980) Chronic airflow obstruction in Fabry's disease. Am J Med 68:898-905.

8 Smith P, Heath D, Rpdgers B (1991) Pulmonary vasculature in Fabry's disease. Histopathology 19:567-569.

9 Odler B, Cseh Á, Constantin T (2017) Long time enzyme replacement therapy stabilizes obstructive lung disease and alters peripheral immune cell subsets in Fabry patients. Clin Respir J 11:942-950.

10 Franzen D, Haile SR, Kasper DC (2018) Pulmonary involvement in Fabry disease: Effect of plasma globotriaosylsphingosine and time to initiation of enzyme replacement therapy. BMJ Open Respir Res 5:e000277.

11 Shafi N (2013) Pulmonary involvement in Anderson-Fabry disease. Doctoral thesis.

12 Franzen DP, Nowak A, Haile SR (2017) Long-term follow-up of pulmonary function in Fabry disease: A bi-center observational study. PLoS One.12:e0180437.

13 Wanner C, Arad M, Baron R (2018) European expert consensus statement on therapeutic goals in Fabry disease. Mol Genet Metab 124:189-203.

14 Biegstraaten M, Arngrimsson R, Barbey F (2015) Recommendations for initiation and cessation of enzyme replacement therapy in patients with Fabry disease: The European Fabry Working Group consensus document. Orphanet J Rare Dis 10:36-6.

15 Eng CM, Resnick-Silverman LA, Niehaus DJ (1993) Nature and frequency of mutations in the alpha-galactosidase-A gene that cause Fabry disease. Am J Hum Genet 53:1186-1197.

16 Giugliani R, Beck M, Hughes D (2019) Classification of genetic variant in patients with Fabry disease enrolled in the Fabry Outcome Survey (FOS).

17 Pietilä-Effati P, Saarinen JT, Löyttyniemi E (2019) Natural course of Fabry disease with the p. Arg227Ter (p.R227) mutation in Finland: FAST study. Mol Genet Genomic Med 7:e00930-n/a.

18 Kolodny E, Fellgiebel A, Hilz MJ (2015) Cerebrovascular involvement in Fabry disease: Current status of knowledge. Stroke. 46:302-313.

19 Whybra C, Kampmann C, Krummenauer F (2004) The Mainz Severity Score Index: A new instrument for quantifying the Anderson-Fabry disease phenotype, and the response of patients to enzyme replacement therapy. Clin Genet 65:299-307.

20 Seliger V, Bartunek Z (1976) Mean values of various indices of physical fitness in the investigation of Czechoslovak population aged 12–55 years. Prague: ČSTV.

21 Güder G, Brenner S, Angermann CE (2012) "GOLD or lower limit of normal definition? A comparison with expert-based diagnosis of chronic obstructive pulmonary disease in a prospective cohort-study". Respir Res 13:13.

22 Rabe KF, Hurd S, Anzueto A (2007) Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. Am J Respir Crit Care Med 176 :532-555.

23 Kainu A, Timonen KL, Vanninen E (2018) Reference values of inspiratory spirometry for Finnish adults. Scand J Clin Lab Invest 78:245-252.

24 ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories (2002) ATS statement: Guidelines for the six-minute walk test. Am J Respir Crit Care Med 166:111-117.

25 Enright PL, Sherrill DL (1998) Reference equations for the six-minute walk in healthy adults. Am J Respir Crit Care Med 158:1384-1387.

26 Koskenvuo JW, Hartiala JJ, Nuutila P (2008) Twenty-four-month alpha-galactosidase-A replacement therapy in Fabry disease has only minimal effects on symptoms and cardiovascular parameters. J Inherit Metab Dis 31:432-441.