


ORIGINAL ARTICLE

Pulmonary manifestations and the effectiveness of enzyme replacement therapy in Fabry Disease with the p. Arg227Ter (p.R227*) mutation

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Abstract

Background: Fabry disease (FD) is caused by a defect in α -galactosidase A gene (GLA) which leads to a progressive accumulation of neutral shingolipids, mainly globotriaosylceramide and its metabolites in several organs. Pulmonary manifestations of FD mimic chronic obstructive pulmonary disease and are disproportionate to smoking status. The effect of enzyme replacement therapy (ERT) on pulmonary function is inconclusive.

We studied the effect of ERT on pulmonary function in FD with a mutation p. Arg227Ter (p.R227*) which is one of the most common mutations causing classical FD in Finland and worldwide.

Methods: Patients were annually examined by multidisciplinary team. Based on the maximal pulmonary oxygen consumption at the baseline, either cardiopulmonary exercise test or combination of spirometry and 6-minute walking test were performed annually during 5-year follow-up.

Results: Four males and eight females met the criteria for ERT and were included in this study. Three of 12 patients had obstruction by GOLD criterion before ERT, and one had a borderline obstruction. In 5 years, five patients were classified as obstructive, although the real change in FEV1/FVC was unchanged in the whole cohort. Only one patient was an active smoker.

Conclusion: In nonsmokers, pulmonary manifestations in classical FD are mild and might be stabilized by ERT.

KEYWORDS

enzyme replacement therapy, Fabry disease, nonsmoker

1 | INTRODUCTION

Fabry disease (FD, OMIM # 301500) is a rare lysosomal disease caused by a mutation in α -galactosidase A (GLA,

OMIM * 300644) gene (the GenBank reference sequence NM_000169.3) in X-chromosome (Desnick et al., 2001). The catabolism of neutral sphingolipids, primarily globotriaosylceramide (Gb3) is disturbed and leads to

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progressive accumulation of Gb3 and its metabolically active degradation products, especially globotriaosylsphingosine (lysoGb3), in various organs (Aerts et al., 2008; Desnick et al., 2001).

Approximately, 1000 different mutations have been described (Stenson et al., 2017). The severity of the phenotype varies from attenuated late-onset to severe classical phenotype where the accumulation of Gb3 and lysoGb3 begins in the fetal period and leads slowly to organ failure, decreased quality of life, and premature death especially in males (MacDermot et al., 2001; Tsutsumi et al., 1984; Waldek et al., 2009).

In males, low alpha-Gal A enzyme (α -Gal A) activity confirms the diagnosis of FD. In contrast, in females, normal α -Gal A does not exclude FD. Skewed X-chromosome inactivation pattern can at least partly explain why some females are asymptomatic mutation carriers while the others can be as severely diseased as males (Balendran et al., 2020; Lenders et al., 2016).

The 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 (Fellgiebel et al., 2014).

Pulmonary symptoms of classical FD include mild expiratory wheezing, dyspnea, and dry cough (Desnick et al., 2001; Rosenberg et al., 1980). Lamellated inclusion bodies which are typical in FD 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 (Rosenberg et al., 1980; Smith et al., 1991).

Spirometry typically reveals a mild, irreversible obstruction (Franzen et al., 2018; Odler et al., 2017; Rosenberg et al., 1980).

To date, there are few studies that have investigated the effect on enzyme replacement therapy (ERT) on pulmonary symptoms and function (Franzen et al., 2017; Shafi, 2013). It is generally accepted that ERT should be started before the disease proceeds to an irreversible state (Biegstraaten et al., 2015; Wanner et al., 2018).

In this paper, we report pulmonary findings in a prospectively collected cohort of 12 patients with a classical FD caused by nonsense mutation p. Arg277Ter (p.R227*, c.679C > T) in Finland and the effect of ERT on these parameters. R227* is one of the most common mutations causing classical FD worldwide (Eng et al., 1993; Giugliani et al., 2019).

2 | MATERIALS AND METHODS

Our study FD in Ostrobothnia (FAST) was planned to describe the natural history of the classical mutation NM_000169.3(GLA):c.679C > T [p.Arg227Ter, (p. R227*)]

and the effect of ERT on disease progression. The natural history of this cohort of four males and 10 females, who were willing to participate in the follow-up, has previously been published (Pietilä-Effati et al., 2019).

Patients belonged to two extended families. The mean age at diagnosis was 46 years (range 15–80 years). Even if R227* is known to cause a classical FD, some of the patients had a disease course mimicking attenuated cardiac variant.

Patients were annually examined by multidisciplinary 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, imaging studies, and spirometry were prospectively collected in every visit. Brain magnetic resonance imaging (MRI) or computed tomography (CT) was performed approximately every 3 years and cardiac MRI every 2 years. Mainz severity score index (MSSI), which is a validated multiorgan scoring system for FD, was used to monitor disease severity and progression during ERT (Whybra et al., 2004).

Performance ability was defined by cardiopulmonary exercise test (spirometry) before ERT if possible. The maximal pulmonary oxygen consumption (VO₂ ml/kg/min) was measured and related to age. VO₂ was considered normal when the measured VO₂ was over 70% of the predicted value (Rietjens et al., 2001). Combination of spirometry and 6-minute walking test (6MWT) was used in follow-up if performance ability was normal in spirometry before ERT or if spirometry was missing.

The presence of obstruction was determined according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criterion (Güder et al., 2012; Rabe et al., 2007), where obstruction was diagnosed by a ratio of forced expiratory volume in 1 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. (2018) represent healthy nonsmoking adults from all over Finland from the age of 16 to 84.

6MWT was performed indoor along a straight, plane 30-meter corridor following the American Thoracic Society statement (ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories, 2002; Enright & Sherrill, 1998).

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

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.

2.1 | Statistics

The results are presented as mean and standard deviation (SD) or range when the variable followed a 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).

3 | RESULTS

Four males and eight females met the criteria for ERT (Biegstraaten et al., 2015) 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.

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). Originally, 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. During the follow-up, two patients were switched from agalsidase- α to agalsidase- β and one patient from agalsidase- β to agalsidase- α .

One patient suffered from previously diagnosed asthma, but she had not used inhaled steroids or β -agonists regularly. One patient in the cohort was a current smoker.

Spiroergometry was performed in six patients before ERT, five of them females. Mean VO₂ was 26 ml/kg/min (range 17–31). VO₂ was normal in all except a 15-year-old male, whose VO₂ was 31 ml/kg/min (67% of predicted value). His FEV₁ was only 2.4 L (69% of reference value), but his FEV₁/FVC did not fulfill the GOLD criterion for obstruction.

Pulmonary function values 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 with an irreversible pulmonary obstruction. The third patient was not tested with 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 5 years. 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. Obstruction was not reversed in any patient.

The mean MSSSI was 17 (3–32), in males 21 (10–26) and in females 15 (3–32). The scores did not change in the

TABLE 1 Change in pulmonary function in 5 years of enzyme replacement therapy

	Before initiation of ERT (n = 9)	After 5 years of ERT (n = 12)	Change from initiation of ERT to 5 years of ERT	
FEV ₁ (liters) (SD)	2.64 (0.92)	2.68 (0.64)	0.04	p = 0.49
FEV ₁ % from predicted value (%) (SD)	85 (17)	83 (14)		
FEV ₁ /FVC (SD)	0.73 (0.10)	0.72 (0.09)	−1.16	p = 0.35
FEV ₁ /FVC (%) from predicted value (%) (SD)	88 (10)	92 (10)		

Abbreviations: ERT, enzyme replacement therapy; FEV₁, forced expiratory volume in the first second; FVC, forced expiratory vital capacity; SD, standard deviation.

ID	FEV1 before ERT (liters)	FEV1 in 5 years of ERT (liters)	FEV1/FVC before ERT (%)	FEV1/FVC in 5 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

TABLE 2 Pulmonary parameters of every patient before enzyme replacement therapy and in 5 years follow-up

Abbreviations: ERT, enzyme replacement therapy; FEV1, forced expiratory volume in the first second; FVC, forced expiratory vital capacity; ID, patient identification number.

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 FD (MSSI 32, an irreversible obstruction in spirometry but a normal VO₂ before ERT). Diastolic heart failure was the main reason for her reduced performance ability.

None had chronotropic incompetence before ERT. However, beta-blocker therapy was not tolerated in any patient without pacemaker because it revealed the latent chronotropic incompetence. Pacemakers had been implanted before the diagnosis of FD in two patients because of sick sinus syndrome and paroxysmal atrial fibrillation.

Coronary angiography or coronary CT was performed in seven patients with angina pectoris or positive cardiac troponin T. None had significant coronary artery disease.

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.

4 | DISCUSSION

In our study FD in Ostrobothnia (FAST), we followed the effect of ERT for 5 years in a cohort of patients with the classical Fabry mutation R227*. 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 et al. (1980) demonstrated that pulmonary symptoms in FD can be independent of cardiac disease and the airway obstruction is disproportionate to smoking status.

In the study of Brown et al. (1997), pulmonary symptoms and signs were present in about one-third of FD male patients irrespective of smoking status which equals results seen in our study.

Franzen et al. (2017) reported in a retrospective study that a clinical or subclinical airway obstruction deteriorates without ERT in both genders referred to matched controls. In our study, it was not ethically possible to follow patients without ERT when the criteria for ERT were fulfilled (Biegstraaten et al., 2015).

In our study, nine patients had spirometry available before ERT. All 12 patients had two or three spirometries during 5 years of follow-up. Two females and one male had obstruction before ERT, and another male borderline obstruction. In 5 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 has been inconclusive in previous trials. Shafi (2013) reported stabilization of pulmonary function parameters on 37 patients at 12 months follow-up. In the retrospective cohort of 95 patients (Franzen et al., 2017), the overall decline in FEV1 was 29 ml per year and was not improved by ERT. In our study (12 newly diagnosed patients with classical R227* mutation), FEV1/FVC values were stable in both genders during 5 years of ERT.

In another study by Franzen et al. (2018) 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, the majority of patients were treated with agalsidase- β which might explain different results between the studies.

Pulmonary high-resolution CT in 17 patients with FD demonstrated only mild changes in lung parenchyma, and the findings did not correlate with pulmonary functional parameters (Koskenvuo et al., 2008). In our study, no signs of interstitial lung involvement could be demonstrated. A note of caution is due here since CT studies from the thoracic region were available only in half of the patients.

One limitation of our study is the lack of serial spirometries during follow-up. Patients felt spirometry uncomfortable and were unwilling to repeat test at regular intervals. Further, the small sample size in this cohort limited the potential for statistical analysis between the sexes.

Another limitation is the lack of validated international criterion for spirometry in nonsmoking population with diseases resembling chronic obstructive lung disease. GOLD criterion can underestimate obstruction in adults less than 45 years (Güder et al., 2012). Although there is 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.

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 FD 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 R227* in our district we decided to perform this study. Some patients had started ERT before our study with a fixed protocol for follow-up had started.

Lastly, a genetically and environmentally homogenous cohort with only one mutation minimizes the confounding factors which allow to study 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.

5 | CONCLUSIONS

We here determined the time course of pulmonary function change and effect of ERT on pulmonary function in predominantly nonsmoking patients with classical FD caused by mutation R227*. Data suggests that ERT stabilizes pulmonary function. Further study may determine the pulmonary function course and the role of ERT in

patients in other environments or with different genetical backgrounds.

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AUTHOR CONTRIBUTION

Päivi Pietilä-Effati was involved in the study design, data collection, data analysis, and manuscript drafting.

Jukka T. Saarinen was involved in the study design, data interpretation, and drafting and revising the manuscript for intellectual content.

Eliisa Löyttyniemi was involved in the statistical analysis and revising the manuscript for intellectual content.

Johan Söderström was involved in the analysis and interpretation of the data and revising the manuscript for intellectual content.

Ilkka Kantola was involved in data analysis and drafting and revising the manuscript.

All authors have read, edited, and approved the final manuscript.

DISCLOSURE STATEMENT

Dr. Pietilä-Effati has served on advisory committees for Amicus, Chiesi, Sanofi-Genzyme, Takeda. She has participated in a clinical study sponsored by Sanofi-Genzyme, has received research support from Sanofi-Genzyme, has received speaker fees from Sanofi-Genzyme and Takeda and has received travel support from Sanofi-Genzyme and Takeda.

Dr. Saarinen has received speaker honoraria from Sanofi-Genzyme and Takeda, funding for travel from Sanofi-Genzyme and Takeda, and research support from Sanofi-Genzyme and has participated in the scientific advisory board of Amicus, Chiesi, and Sanofi-Genzyme.

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Dr. Kantola has received speaker honoraria from Amicus, Sanofi-Genzyme, and Takeda; funding for travel from Amicus, Sanofi-Genzyme, and Takeda; research support from Sanofi-Genzyme and Takeda; and has participated in the scientific advisory board of Amicus, Chiesi, and Sanofi-Genzyme.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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