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Impact of cardio-renal syndrome on adverse outcomes in patients with Fabry disease in a long-term follow-up

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ABSTRACT

Aims: Fabry disease (FD) is a rare X-linked lysosomal storage disease with a deficiency of α-galactosidase A leading to progressive sphingolipid accumulation in different organs, among them heart and kidney. We evaluated the impact of cardio-renal syndrome (CRS) on the incidence of major cardiovascular complications and death in a prospective FD cohort.

Methods and results: A total of 104 genetically proven FD patients were annually followed at the University Hospitals Zurich and Bern. The main outcome was a composite of incident renal replacement therapy (RRT), hospitalisation due to decompensated Heart Failure, new onset atrial fibrillation, pacemaker/ICD implantation, stroke/TIA and death. Estimated glomerular filtration rate (eGFR) and left ventricular myocardial mass index (LVMMI) where explored as the primary exposure variables. During the median follow-up of 103 [59–155] months, events occurred in 27 patients. In a Cox regression analysis, both higher LVMMI and lower eGFR were independently associated with a greater risk of developing adverse events after adjustment for multiple confounders (HR 1.67 [1.04–2.73] P = 0.03 per SD increase in LVMMI, HR 0.45 [0.25–0.83], P = 0.01 per SD decrease in eGFR). In patients with CRS, the risk to develop events was significantly increased if adjusted for demographics and RRT (HR 4.46 [1.07–18.62], P = 0.04), approaching significance if additionally adjusted for hypertension (HR 4.05 [0.95–17.29], P = 0.06). In Kaplan-Meier-Analysis, the poorest event-free survival was observed among patients with CRS.

Conclusions: CRS was associated with a high risk to develop cardiovascular complications and death, emphasizing the importance of its prevention and early recognition. A focus on cardio-reno-protective therapies is crucial.

1. Introduction

Fabry disease (FD) is an X-linked lysosomal storage disorder in which mutations of the *GLA* gene cause a decreased or absent activity of the enzyme alpha-galactosidase A (α-Gal A) and subsequent progressive intracellular accumulation of globotriaosylceramide (Gb_3) and other sphingolipids in various tissues [1,2]. The initial classic signs and symptoms include acroparesthesias, angiokeratoma, abdominal pain, hypohidrosis, corneal dystrophy and typically appear in childhood. With advancing age, vital organ dysfunction increasingly occurs resulting in cardiovascular disease, renal failure and premature strokes, on average more severely in males [3]. Combined renal and cardiac dysfunction is common in FD and associated with an increased mortality and morbidity risk [4,5].

Cardio-renal syndrome (CRS) is an increasingly recognized clinical entity which refers to the reciprocal association between cardiac and renal dysfunction, whereby injury to one organ directly promotes deterioration of the other [6]. This complex bilateral organ crosstalk can result from a variety of conditions where the primary failing organ may be the heart, the kidney or both. The latter is defined as CRS Type 5 and occurs secondarily to an underlying systemic process. FD is a typical example of the CRS Type 5, as described very recently [7]. CRS has been related to a particularly high morbidity and mortality in several settings [6,8,9], however, little is known about its impact on adverse long-term outcomes in FD patients.

In patients with FD, the indexed left ventricular myocardial mass (LVMMI) has repeatedly been shown to be a reliable parameter reflecting the onset and progression of Fabry disease-related cardiomyopathy [10,11]. The estimated glomerular filtration rate (eGFR) has

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been used to quantify the renal involvement and shown to be a major risk factor for cardiovascular complications in FD [5]. The aim of this study was to assess the impact of CRS, reflected by LVMMI and eGFR, on clinical outcomes in a large prospective multicentre cohort of genetically confirmed FD patients and a long-term follow-up. The recognition of CRS should lead to specific prevention strategies and therapeutic approaches in order to at least attenuate the organ failure in those patients.

2. Methods

This is a retrospective analysis of a prospective, multi-centre cohort in Switzerland. The study was conducted in accordance with the principles of the Helsinki Declaration. The patients who could be contacted gave written informed consent. The authors have read and approved the manuscript.

2.1. Study population and treatment

The prospective FD cohort consisted of 104 patients, who were genetically tested (for further information see the Supplementary Table 1). The cohort was established in 2001 when enzyme replacement therapy (ERT) was newly developed and offered to all FD patients. Consecutive FD patients were registered and received routine annual multidisciplinary examinations at two tertiary care hospitals – University Hospitals Zürich (93 patients) and Bern (11 patients). Here, we report on the clinical course and adverse outcomes of 64 females and 40 males.

The baseline clinical evaluation was performed at the time the patients were included in the cohort. For the present analysis, the clinical data and information on hospitalisation were extracted from medical records.

FD patients in Switzerland are personally followed-up and examined at the Fabry Centres, the adverse events were evaluated during annual examinations. All patients had a comprehensive workup, including medical history, cardiac evaluation with echocardiography, renal, and neurological evaluations. A 24- or 48-hours ECG was performed annually and additionally if patients complained of palpitations or chest pain. Hospitalisation was defined as a hospital stay for at least 24 h. Standard transthoracic 2D-echocardiography was routinely performed in all patients.

For the evaluation of diastolic dysfunction, the left atrial volume index (LAVI), the mitral inflow (E/A ratio) and the mitral annular movement with tissue Doppler (e′ septal and lateral as well as an average of E/e′ ratio) was measured according to the current practice guidelines [12,13]. These measurements were performed using continuous recordings of mitral inflow, analysing the pulsed-wave during 10 s: the peak E-wave velocity (cm/s) in early diastole, the A-wave (cm/s) in late diastole at the leading edge of the spectral waveform and the pulsed wave tissue Doppler e′ velocity (cm/s) in early diastole. These measurements were available in the Zurich subgroup (N = 82) of patients. Diastolic dysfunction has been graded according to the recent algorithm from the ASE/EACVI recommendations for the evaluation of the left ventricular diastolic function [13] by reviewing and repeating all measurements of the archived echocardiographic studies.

Enzyme replacement therapy was initiated according to the written local guidelines and prescribed at the licensed dose of either 0.2 mg/kg body weight of recombinant α-agalsidase (Replagal) or 1 mg/kg body weight β-agalsidase (Fabrazyme) and given intravenously every 14 days. According to the guidelines, ERT was indicated in all males. In females, ERT was indicated if they had proteinuria of >300 mg per day, Fabry-typical kidney biopsy findings, signs of Fabry cardiomyopathy such as left ventricular hypertrophy or arrhythmia, stroke or transient ischemic attack (TIA), acroparesthesias despite conventional analgesic therapy, and/or gastrointestinal symptoms.

2.2. Endpoint definition and evaluation

As a primary endpoint, we defined the composite of requiring renal replacement therapy (RRT) (kidney transplantation or chronic dialysis), newly diagnosed atrial fibrillation (AF) of any type (paroxysmal/persistent), pacemaker and/or ICD implantation, hospitalisation due to decompensated heart hailure (HF), cerebrovascular events (stroke or TIA), and death, whichever occurred first. The follow-up was censored at the date of the first event to calculate Hazard Ratios. The follow-up time for patients without events was censored at the 1st of July 2015. If the patients died outside of the Fabry Centre, the date of death was evaluated by asking the responsible General Practitioner, the family or the nurse administering ERT in the home care setting.

2.3. Primary exposure variables: cardiac and renal involvement

LVMMI at baseline was used as the primary exposure variable to express cardiac involvement. For this, standard transthoracic 2D echocardiography was routinely performed in all patients. Left ventricular end-diastolic dimension and end-diastolic thickness of the posterior wall and the septum were measured using standard M-mode echocardiographic methods in parasternal long-axis images. LVMMI was calculated using the Devereux formula [14].

Estimated glomerular filtration rate (eGFR) at baseline was used as the primary exposure variable to express renal involvement. The eGFR was derived from serum creatinine and age using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) [15]. The CKD-EPI equation is known to have a similarly good statistical performance as previously used equations when the estimated GFR is below 60 ml/min/1.73 m^2, but with better performance in those with higher eGFR levels [16].

2.4. Statistical analysis

We used descriptive statistics for the baseline characteristics and laboratory parameters. Categorical variables were expressed as proportions, continuous variables as means with standard deviations and medians with interquartile ranges (IQR). Normal distribution was assessed by the Kolmogorov-Smirnov-Test.

The cut-off values for LVMMI and eGFR were calculated by maximizing the product of sensitivity and specificity by using receiver operating curve characteristics (ROCs).

Kaplan-Meier analysis was performed for event-free survival and log-rank values to assess statistical significance.

Cox regression analysis was used to examine the risk of adverse events associated with baseline LVMMI and eGFR on a continuous scale and for cardiac, renal and cardio-renal involvement as categorical variables. For the categorization, cardiac involvement was defined as LVMMI above the best calculated cut-off value of 107 (g/m^2), we used this value for both genders because males have a higher LVMMI and a higher risk to develop adverse outcomes due to the hemizygosity; renal involvement was defined as eGFR below the best calculated cut-off value of 90 ml/min/1.73 m^2; CRS was defined as LVMMI >107 (g/m^2) and eGFR <90 ml/min/1.73 m^2.

Multivariable models were applied to adjust for potential confounders using prior knowledge of variables that have been associated with risk in FD patients in previous studies. We hierarchically adjusted for demographics (age, gender) in model 1, RRT (kidney transplant or dialysis at baseline) in model 2 and presence of arterial hypertension (systolic RR > 140 or diastolic RR > 90 mm Hg or intake of antihypertensive drugs) in model 3. These models were used for all multivariable Cox regression analyses.

To evaluate the effect of ERT on the primary endpoint, Cox regression analysis was used, where ERT was expressed as a categorical covariate. In a multivariate Cox regression analysis, an adjustment for age and gender and for cardio-renal involvement was applied to evaluate if the ERT effect remained independent.

The statistical analyses were performed using the SPSS/PC (version 22.0; SPSS Inc., Chicago, IL, USA) software package. All statistical tests were two-sided, and P values <0.05 were considered significant.

3. Results

The baseline characteristics of all patients according to gender and to the presence of CRS are shown in Table 1. In total, 104 patients (40 males and 64 females) with a mean age of 45 ± 16 years were included into the analysis. A baseline echocardiography was available in 91, results on diastolic dysfunction in 82 patients. The left ventricular ejection fraction (LVEF) was normal in all patients. The patients with cardio-renal involvement at baseline were older, had more frequently a Classic disease phenotype, arterial hypertension, echocardiographic signs of diastolic dysfunction, had higher serum NT-proBNP levels and elevated urine protein/creatinine ratios.

Angiotensin converting enzyme inhibitor (ACE-i) or angiotensin receptor blocker (ARB) were used in 17 (16%) of the 104 patients at baseline. During the follow-up time, ACE-i or ARB were started in a further 17 patients.

The NYHA classes at baseline are summarized in Table 1. At the end of the follow-up time, NYHA I/II was present in 23 (22%) patients: 7 (18%) males, 16 (25%) females and 10 (23%) in patients with CRS at baseline; NYHA III/IV was present in 9 (8.6%) patients: 5 (13%) males, 4 (6.3%) females and 5 (12%) patients with CRS at baseline. NYHA class increased in 24 (23%) patients: 11 (28%) males, 13 (20%) females and 9 (21%) CRS patients.

48 patients were treated with α-agalsidase and nine with β-agalsidase throughout the follow-up time. Eight patients were switched from β-agalsidase to α-agalsidase (seven due to shortage of β-agalsidase, one at the discretion of the treating physician), one from α-agalsidase to β-agalsidase (due to patient's priority) an one from β-agalsidase to α-agalsidase (due to shortage) and back to β-agalsidase (due to patient's priority).

3.1. Events

During the median follow-up time of 105 [45–139] months, the first event occurred in 27 (26%) of the patient population: in 11 patients, the first event was stroke or TIA, in 2 kidney transplantation, in 4 chronic

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