Cystatin C and NT-proBNP as prognostic biomarkers in Fabry disease

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A B S T R A C T

Fabry disease (FD) is a lysosomal storage disorder caused by mutations in the α-galactosidase A gene. It is characterized by the deposition of the incompletely metabolized substrate globotriaosylceramide in several cell types and multisystem involvement. Major morbidity results from renal, cardiac and cerebrovascular pathology, mediated by endothelial dysfunction. We examined the potential utility of Cystatin C and natriuretic peptides as biomarkers in FD, and evaluated serum levels in 89 FD patients with varying degrees of disease severity. The results revealed that as a prognostic marker, Cystatin C is a good and cost effective indicator of early renal dysfunction and/or heart failure in FD. It is also more useful than serum creatinine in detecting mild renal damage and small decreases in glomerular filtration. In addition, the natriuretic peptide NT-proBNP, was elevated in patients with FD and cardiac involvement, and found to be an adequate detection marker, not only of cardiac involvement, but also of diastolic dysfunction.

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1. Introduction

Fabry disease (OMIM 301500) is an X-linked disorder caused by a deficiency in the lysosomal enzyme degradation of complex lipids and the resultant accumulation of globotriaosylceramide (Gb3) [1]. Lysosomal Gb3 storage on account of α-galactosidase A deficit (E.C.3.2.1.22), produces a range of clinical manifestations which could be regarded as a reflection of universal vascular endothelial dysfunction. Fabry disease (FD) lowers life expectancy due to cardiac, renal or cerebrovascular failure in the fourth or fifth decade of life [2] in men. It has traditionally been regarded as an X-linked recessive disorder affecting only males. However it is known, that females can experience manifestations of the disease which in some cases may be as severe as those seen in males [3].

Treatment of FD with enzyme replacement therapy (ERT) has proven to be efficient, not only in controlling pain, but also in controlling and reversing anatomopathological lesions in the cardiac and renal capillaries and skin [4]. Nevertheless, some issues must still be resolved. It is not clear which patient should be treated and at which time point, nor are there good biochemical markers of response to ERT.

Cystatin C (CsC) is a protein of approximately 13 kDa comprised of 122 amino acids and belongs to the family of cysteine protease inhibitors [5]. It is constantly produced by all nucleated cells, and due to its size and cationic nature, is freely filtered by the glomerulus. In normal conditions, the CsC is reabsorbed and catabolized by the tubular epithelial cells, thus preventing it from re-entering the bloodstream or the urine, and preventing measurement of clearance values. In the general population, CsC has proven to be highly useful as a marker for early renal and cardiac damage and endothelial dysfunction [6,7] suggesting a potential for application in FD.

Moreover, BNP (brain natriuretic peptide) and NT-proBNP (N-terminal brain natriuretic propeptide), are synthesized by the cardiac ventricle, by stimuli such as pressure overload, or ventricular wall distension. Comparatively, NT-proBNP has a longer half life (about 120 min) and the amount of time it remains in the blood is greater (about 12 h). NT-proBNP has a negative predictive value in the assessment of heart failure and may also provide valuable prognostic information about mortality and cardiovascular events [8].

In our study we hypothesize that CsC and NT-proBNP are potentially useful as biomarkers in FD and correlate our observations with MSSI.
2. Material and methods

An observational and multicenter study was performed involving the Neurogenetics Unit of the New York University Medical Center (New York, USA), the Department of Haematology of the Royal Free & University College Medical School (London, United Kingdom) and Departments of Internal Medicine and Biochemistry of the Lozano Blesa University Hospital (Zaragoza, Spain). Healthy control subjects came from the Blood Bank and tissue donor repository of Aragon (Aragon, Spain). None of the latter subjects were smokers, taking medication or had a significant medical history.

All FD patients were diagnosed through the identification of the mutation in the α-galactosidase A gene and/or showed reduced activity of α-galactosidase A enzyme in leukocytes and/or plasma.

A total of 178 samples obtained from 89 patients and a corresponding number of age- and gender-matched healthy controls were studied. Samples were obtained between the 1st May 2007 and 30th September 2008, after the study subjects provided informed consent.

CsC was measured with a N latex Cystatin C test kit (BN Dade Behring) in a nephelometer (BNII Dade Behring, Siemens Healthcare Diagnostics). NT-proBNP was measured with an Elecsys immunoanalyzer using an ECLIA proBNP kit (Roche, Inc. Mannheim, Germany).

Statistical analysis was performed with SPSS software and data were expressed as means ± standard deviation (SD). To evaluate the association between CsC and NT-proBNP and the rest of the quantitative variables, Pearson”s r” test was applied if a normal distribution was followed, and if not, Spearman’s rho coefficient was applied. To evaluate the correlation between the quantitative variables and the dichotomic variables, biserial correlation coefficient was determined.

Hypothesis contrast was done for means comparison between qualitative and quantitative variables for gender, age, presence of renal disease, cardiac disease, and the need for ERT, using Student t-test for variables which followed a normal distribution and Mann–Whitney U-test for variables which did not. When any of the qualitative variables had more than 2 categories, an ANOVA test was used for variables with normal distribution, and a Kruskal–Wallis test was used for those without.

A multiple regression logistic and linear regression test was used to determine the association between the CsC and NT-proBNP parameters and disease parameters adjusted for age as a continuous variable, gender, body-mass index, the presence or absence of a history of hypertension, and the presence of other cardiovascular diseases.

ROC curves were developed to evaluate the discrimination capacity of CsC and NT-proBNP, with the other diagnostic tests. Next, we determined the confidence intervals of area under the curve, whereas values between 1 (perfect test) and 0.5 (useless test).

Finally we calculated the MSSI in all patients. To verify if the MSSI score correlated with CsC and NT-proBNP, we carried out a linear regression analysis, and also a bivariate correlation test (rho of Spearman) and dispersion diagrams, in global terms and by gender.

3. Results

3.1. Descriptive study

Forty-seven percent of the total samples were from females (N = 42) FD patients; 53% were from male patients (N = 47). The mean age was 45 years (SD 15), range from 16 to 79 years. Mean duration of patient monitoring was 12 ± 10.8 years (range 1–43 years, median 9 years). Seventy-five patients (84%) were receiving ERT, and of these, there were 29 females and 46 males. Mean duration of ERT was 4 years (SD 2.5), ranging from 1 to 9 years.

Altogether 26 different FD mutations were identified (Fig. 1), with the N215S mutation accounting for 33.7% of causal gene defects.

Fifty-four patients (61%) presented with cardiovascular involvement, 53 (60%) digestive involvement, 48 (54%) renal involvement, 42 (47%) peripheral nervous system (PNS) involvement, 31 (35%) cutaneous involvement, 26 (29%) ocular involvement with cornea verticillata, and 14 (16%) involvement of the central nervous system (CNS). Distribution by gender is reflected in Fig. 2.

The mean value of the left ventricular ejection fraction (LVEF) was 66% in both male and female patients. Eighteen percent (23% of the males; 12.5% of the females) presented with diastolic dysfunction (defined as impaired transmitral flow (reversal of E/A ratio) in asymptomatic patients or increase of the left atrial size or left ventricular mass in clinical or symptomatic diastolic dysfunction), which was mild or moderate in all cases. The mean measurement of the left ventricular wall was 47.44 mm (SD, range 10–68). It was similar in both the males and the females, although the range of

![Fig. 1. Mutation frequency and gender distribution.](image)
values was different. In the males, the range in left ventricular (LV) wall measurement was 10–68 mm; in the females, the range in LV wall measurement was 42–55 mm.

For renal evaluation, the mean serum creatinine level was 1.11 mg/dl—with higher values in the males (mean level 1.44 mg/dl) than in the females (mean level of 0.73). Seven patients (7.9%)—all males—were on a dialysis program, and 6 patients (6.7%)—also males—had undergone kidney transplantation prior to the study. Glomerular filtration rate (GFR) was calculated by MDRD formulae. Mean GFR was 90 ml/min (SD 29, range 7–150): in males, the mean GFR rate was 84.5 ml/min (SD 34, range 7–150), and in the females it was 96 (SD 22, range 49–141).

Mean CsC concentration in FD patients was 0.95 mg/l (SD 0.8 and range 0.50–6.20). By gender, mean concentration was 1.15 mg/l (SD 1.05 and range 0.60–6.20) in males and 0.74 mg/l (SD 0.15 and range 0.50–1.10) in females. In controls, CsC concentration was 0.69 mg/l (SD 0.11, range 0.03–0.9). In males CsC concentration was 0.71 (SD 0.11, range 0.3–0.9) whereas in females it was 0.68 mg/l (SD 0.11, range 0.5–0.9).

Mean NT-proBNP concentration in FD patients was 1012 pg/ml (SD 3469 and range 5–27,161)—greater in the males (mean 1511 pg/ml, SD 4700, and range 5–27,161) than in the females (mean 454 pg/ml, SD 667, range 5–2382). In controls, the mean NT-proBNP was 25 pg/ml (SD 27, range 5–180), with similar concentrations in men (mean 21 pg/ml SD 16, range 5–67.5), than in women (mean 30 pg/ml SD 34.5, range 5–180).

MSSI was calculated in all patients, with an average of 23 (SD ±14) and range between 2 and 69. Among males, average MSSI score was 28 (SD 15, and range 2–69), while in females it was 17 (SD ±9, range 2–47) (Table 1). A difference was observed between males and females in age-based scores. While 61% of males under 40 had a MSSI score lower than 20 points (mild disease), in females the corresponding percentage was 100%. In patients over 40, only 10% of males had mild disease, compared with 55% of females.

### Table 1

<table>
<thead>
<tr>
<th>Variable</th>
<th>FD males</th>
<th>Controls (males)</th>
<th>FD females</th>
<th>Controls (females)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CsC (mg/l)</td>
<td>1.15 (0.6–6.2)</td>
<td>0.71 (0.3–0.9)</td>
<td>0.74 (0.5–1.1)</td>
<td>0.68 (0.5–0.9)</td>
</tr>
<tr>
<td>NT-proBNP (pg/ml)</td>
<td>1511 (5–27,161)</td>
<td>21 (5–67.5)</td>
<td>454 (5–2382)</td>
<td>30 (5–180)</td>
</tr>
<tr>
<td>MSSI score</td>
<td>28 (2–69)</td>
<td>17 (2–47)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

3.2. Comparison of CsC and NT-proBNP with qualitative and quantitative variables

A positive correlation with CsC concentration and cardiovascular involvement was observed in FD patients, as was a weak positive correlation with the ocular, cutaneous and CNS involvement. A significant positive correlation was also noted between CsC concentration and renal involvement, dialysis and renal transplant. There was no correlation between the concentrations of CsC and PNS or gastrointestinal involvement.

A significant negative correlation between CsC concentration and plasmatic leukocytary α-galactosidase A activity was observed, as well as a significant positive correlation between CsC and NT-proBNP concentrations. There was also a strong positive correlation between CsC concentration and urea and creatinine levels, along with a strong negative correlation with eGFR. A significant correlation between CsC and age, the duration of ERT and the duration of the disease, was found.

CsC concentration displayed a weak positive correlation with diastolic dysfunction, while no correlation existed between the concentrations of CsC and the LV wall thickness. We found a significant correlation between NT-proBNP and cardiac, ocular and renal involvement, and strikingly, the need for dialysis or renal transplantation. However, we found no correlation between the concentration of NT-proBNP and gastrointestinal, cutaneous and PNS or CNS involvement.

For the rest of the variables, no correlation between the NT-proBNP and leukocyte or plasma α-galactosidase A activity was recorded but a significant positive correlation with the levels of urea and creatinine were shown with a strong significant negative correlation between the NT-proBNP and eGFR concentrations. Moreover, NT-proBNP did not reveal a significant correlation with the duration of the disease, but did correlate with the age of the patients and the duration of treatment.

A significant positive correlation between NT-proBNP concentration and diastolic dysfunction was observed, but not with LVEF or LV wall thickness (Table 2).
3.3. Comparison of arithmetic means

On studying biological markers CsC and NT-proBNP, we observed significant differences in CsC concentration for all the variables with which it was correlated: gender, presence or absence of renal involvement, cardiovascular involvement (p<0.01), need (or not) for ERT (p<0.01), dialysis (p<0.001) and renal transplantation (p<0.001).

Similar results were observed with NT-proBNP concentration with significant differences in relation to renal involvement, cardiovascular involvement (p<0.01), ERT (p<0.05), dialysis (p<0.05) and renal transplantation (p<0.05).

3.4. Multiple regression analysis

The multiple regression analyses ANOVA and Kruskal–Wallis test showed that the mean values for urea concentration were different (p<0.01) in relation to age quartiles, but the same in relation to the duration of the disease and treatment. In creatinine concentrations, there were no differences between mean values in patient age, duration of the disease or duration of the treatment. There were, however, significant eGFR differences depending on patient age (p<0.001), but no differences regarding duration of the disease and duration of the treatment.

For CsC and NT-proBNP as biological markers, we observed significant differences for CsC concentration in relation to patient age (p=0.001) and duration of the disease (p<0.01), but not in relation to duration of the treatment (p<0.05). With NT-proBNP the mean values were different depending on patient age (p<0.05), but not on duration of the disease.

In the case of the controls, we performed the same tests for the comparison of the CsC and NT-proBNP variables with gender and age quartiles. In both cases (gender and age quartiles), there were no differences in the average values of either biological marker.

3.5. Multiple regression logistic and linear regression test

After the use of the multivariate multiple regression analysis as a method of control for confounding factors (age, gender, and body mass index), we found that CsC concentration has a statistically significant correlation with the thickness of the LV wall, the possible need for dialysis, and the eGFR (p<0.001). We also confirmed a statistically significant correlation (p<0.001) between NT-proBNP concentration and thickness of the LV wall and eGFR.

3.6. ROC curves and area under the curve

We observed a good correlation between CsC and NT-proBNP concentration and cardiovascular involvement, as well as kidney damage. In the case of cardiovascular involvement, the area under the curve was greater for CsC and NT-proBNP concentration in relation to creatinine, with a diagnostic accuracy of 72.4%, and 74% respectively (Figs. 3 and 4). However, the confidence interval for determination of creatinine suggests a neutral value.

For renal disease, the global diagnostic capacity of CsC concentration was 81.3% (reaching 90.2% like the confidence interval), and 71.7% for NT-proBNP concentration, which in both cases is higher than for creatinine (confidence interval contains the value 0.5).

3.7. Evaluation of the Mainz Severity Score Index and the correlation with CsC and NT-proBNP

The linear regression analysis with a significance level p<0.01, found that CsC levels are predictive of MSSI score.

Moreover, the bivariate correlation test (rho of Spearman) showed a strong and positive correlation involving the rate of MSSI score and CsC concentration (correlation coefficient 0.653, p<0.01). However, it was moderate in the case of NT-proBNP concentration (correlation coefficient 0.515, p<0.01). According to gender, for CsC concentration
we found a higher correlation in females (correlation coefficient 0.611, p<0.01) than in males (correlation coefficient 0.548, p<0.01). For NT-proBNP concentration, the same pattern was observed in the correlation coefficient: 0.618 (p<0.01) in the females and 0.547 (p<0.01) in the males.

The dispersion diagrams show the relationship of previous numerical variables (Figs. 5 and 6).

Table 2 Summary of correlation coefficients.

<table>
<thead>
<tr>
<th></th>
<th>Cystatin C</th>
<th>NT-proBNP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Digestive</td>
<td>0.088</td>
<td>0.078</td>
</tr>
<tr>
<td>Cutaneous</td>
<td>0.242</td>
<td>0.104</td>
</tr>
<tr>
<td>Ocular</td>
<td>0.230</td>
<td>0.296</td>
</tr>
<tr>
<td>Heart</td>
<td>0.377</td>
<td>0.407</td>
</tr>
<tr>
<td>PNS</td>
<td>−0.020</td>
<td>−0.093</td>
</tr>
<tr>
<td>CNS</td>
<td>0.186</td>
<td>−0.008</td>
</tr>
<tr>
<td>Kidney</td>
<td>0.552</td>
<td>0.375</td>
</tr>
<tr>
<td>Dialysis</td>
<td>0.475</td>
<td>0.315</td>
</tr>
<tr>
<td>Rennal transplantation</td>
<td>0.432</td>
<td>0.260</td>
</tr>
<tr>
<td>Diastolic dysfunction</td>
<td>0.245</td>
<td>0.362</td>
</tr>
<tr>
<td>FEVI</td>
<td>−0.120</td>
<td>0.025</td>
</tr>
<tr>
<td>LV thickness</td>
<td>0.173</td>
<td>0.068</td>
</tr>
<tr>
<td>Urea</td>
<td>0.504</td>
<td>0.403</td>
</tr>
<tr>
<td>Creatinine</td>
<td>0.753</td>
<td>0.347</td>
</tr>
<tr>
<td>FGR (Cockcroft–Gault)</td>
<td>−0.543</td>
<td>−0.588</td>
</tr>
<tr>
<td>FGR (MDRD)</td>
<td>−0.678</td>
<td>−0.557</td>
</tr>
<tr>
<td>Plasmatic α-galactosidase</td>
<td>−0.363</td>
<td>−0.068</td>
</tr>
<tr>
<td>Leukocyte α-galactosidase</td>
<td>−0.389</td>
<td>−0.179</td>
</tr>
<tr>
<td>Age</td>
<td>0.451</td>
<td>0.568</td>
</tr>
<tr>
<td>Treatment years (SET)</td>
<td>0.290</td>
<td>0.293</td>
</tr>
<tr>
<td>Years since diagnosis</td>
<td>0.331</td>
<td>0.031</td>
</tr>
<tr>
<td>Cystatin C</td>
<td>1</td>
<td>0.488</td>
</tr>
<tr>
<td>NT-proBNP</td>
<td>0.488</td>
<td>1</td>
</tr>
</tbody>
</table>

Fig. 4. Areas under the curve for creatinine, CsC and NT-proBNP in relation to renal damage.

4. Discussion

The results of our study suggest that CsC concentration is a superior and more sensitive marker than serum creatinine in detecting visceral involvement in FD patients, specifically renal and cardiovascular involvement. Similarly, NT-proBNP is a superior and more sensitive marker in detecting early changes in cardiac involvement, such as diastolic dysfunction.

CsC and NT-proBNP concentration are easy to quantify in readily accessible clinical material. Concentrations or activity of both are not subject to wide variation in the general population and reflect the total burden of the disease wherever the disease is manifest, except involvement of the digestive and peripheral nervous system. Additionally there appears to be no overlap between the biomarker levels in untreated patients and control subjects. However, due to the cross-sectional study design, we could not evaluate changes in NT-proBNP or CsC concentration in relation to initiation of ERT. Future studies should clarify changes in biomarker levels, if any, in patients on ERT.

Diagnosis of FD is based on clinical suspicion and must be confirmed biochemically (decrease in α-galactosidase A) and genetically (presence of mutation in the gene encoding the cognate enzyme) [1]. Once the diagnosis is made, according to published guidelines, ERT may be recommended. However, there are unresolved issues regarding treatment. For example, the full scope of response to ERT, dose and duration in different patient groups at different stages of the disease are issues which must be approached. Thus, it is necessary in clinical practice to have a measure of the extent of target-organ involvement in FD. In this respect, it is highly useful to have a biological marker capable of alerting clinicians to the need for treatment or a modification of enzyme dosage, as in cases where dosage adjustments may be considered with changes in biomarker concentrations indicating disease progression prior to overt organ failure. Future studies should clarify whether serial monitoring of CsC and NT-proBNP concentration does have predictive or prognostic value.
Fig. 5. MSSI score and correlation with CsC and NT-proBNP.

Fig. 6. MSSI score and correlation with NT-proBNP and CsC by gender.

<table>
<thead>
<tr>
<th></th>
<th>General Score</th>
<th>Neurological Score</th>
<th>Cardiovascular Score</th>
<th>Renal Score</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FEMALES MSSI</strong></td>
<td>0.384</td>
<td>0.123</td>
<td>0.418</td>
<td>0.001</td>
</tr>
<tr>
<td><strong>NT-proBNP</strong></td>
<td>0.251</td>
<td>0.097</td>
<td>0.747</td>
<td>0.188</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>General Score</th>
<th>Neurological Score</th>
<th>Cardiovascular Score</th>
<th>Renal Score</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MALES MSSI</strong></td>
<td>0.084</td>
<td>0.491</td>
<td>0.371</td>
<td>0.642</td>
</tr>
<tr>
<td><strong>NT-proBNP</strong></td>
<td>0.209</td>
<td>0.434</td>
<td>0.457</td>
<td>0.531</td>
</tr>
</tbody>
</table>
We are currently lacking an easy-to-use prognosis measure or disease severity index correlated with reproducible biological markers as an indicator of disease stage or course. In 2005, Young et al. reported that the plasma and urine levels of the substrate Gb3 could not be used to monitor the response to treatment [10]—an observation subsequently confirmed by the Dutch Fabry cohort study [11]. Recently, Aerts et al. found that the plasma deacylated globotriaosylsphingosine (LysoGb3) levels are increased only in male patients with the usual symptoms of FD, as compared with control subjects [12]. Furthermore, Rombach et al. showed that plasma LysoGb3 is a risk factor in FD, but only for development of cerebrovascular white matter lesions in male patients and LV hypertrophy in females [13]. Also, Tatagawa et al. reported that plasma LysoGb3 was higher in male (N = 10) patients with the common symptoms, but in FD females (N = 6) it was only moderately higher in both symptomatic and asymptomatic cases [14]. At this time, it is uncertain whether LysoGb3 in urine can serve as a biomarker, although it appears particularly useful in screening for Fabry disease in suspected cases (because it is consistently absent in the urine of healthy controls). However, it has not been proven useful in children, and LysoGb3 values have not been shown to correlate with the degree of renal involvement [15].

Other proteins that are proposed generally as markers of tubular damage or renal interstitial injury, such as Uromodulin [16] and KIM-1 (Kidney Injury Molecule) have not been used in FD and possess several limitations such as difficulty with performing the test, interpreting the findings and associated costs [17].

Although costlier to use routinely than creatinine, CsC and NT-proBNP monitoring may provide useful information regarding treatment efficacy, the appropriate starting-time, and adjustments in enzyme dosage to optimize outcome.

Due to the origins of our samples and challenges related to sample handling and transportation, we have not studied other markers of early renal dysfunction, such as microalbuminuria, which could be examined comparatively with CsC.

Additionally, in our study we found that Mainz Severity Score Index is a good indicator of visceral involvement in patients with FD and demonstrated that CsC and NT-proBNP concentration allow us to predict the score, given the good correlation we found between both markers and MSSI score. We have also shown that both are useful in interpreting the results of renal biopsy.

From a critical point of view, it would be advisable to test our findings in other FD patient populations. However, there must be an exhaustive follow-up of the different groups of FD patients to show any existing correlation between the activities of the peptides studied, particularly CsC, and phenotype.

In this study we were able to demonstrate the potential utility of CsC and NT-proBNP concentration as biological markers in FD. Serial measurements of CsC and NT-proBNP concentration in treated and non-treated FD patients may provide an indication of disease course, and changes in response to ERT.

5. Conclusions

Given the absence of inexpensive and easy-to-measure alternative biological markers, CsC concentration proved to be an excellent marker for FD, in both males and female patients. It cost-effectively detected the existence of early renal and/or heart failure and we found it superior to serum creatinine in the detection of mild renal damage or slight decreases in glomerular filtration. Moreover, the natriuretic peptide NT-proBNP is elevated in patients with FD and cardiac involvement and is a good marker for the detection of such involvement, especially diastolic dysfunction. Additionally, CsC and NT-proBNP concentration showed an excellent correlation with the clinical parameters evaluated by the Mainz Severity Score Index.

Conflict of interest

The authors declare no other conflict of interest.

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