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Original article

Screening for Fabry disease in male patients with end-stage renal disease in western France

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Abstract

Context

Fabry disease is a rare X-linked genetic disease due to pathogenic variants in the *GLA* gene. Classic Fabry disease is characterized by glycosphingolipids accumulation in all organs including the kidney, resulting in end-stage renal disease in a subset of male patients. Fabry disease should therefore be considered in the differential diagnosis of patients with unexplained end-stage renal disease.

Objective

We performed a prospective screening study in Western France to determine the prevalence of Fabry disease in a large population of dialyzed and transplanted patients.

Patients and methods

Patients meeting the inclusion criteria (males, 18-70 years with end-stage renal disease of unknown or vascular origin) were selected from the REIN® registry and the CRISTAL® database. Screening on filter papers was performed after patient consent was obtained during either a dialysis session or a transplantation follow-up visit.

Results

One thousand five hundred and sixty-one end-stage renal disease male patients were screened and 819 consented (dialysis: *n*=242; transplant: *n*=577). One single patient was found with decreased alpha-galactosidase levels <25%. *GLA* sequencing identified the p.Phe113Leu variant in favor of an unknown superimposed kidney disease responsible for end-stage renal disease since this *GLA* pathogenic variant is associated with a later-onset cardiac form of Fabry disease with minimal kidney involvement. Family cascade genotyping revealed a previously undiagnosed affected brother.

Conclusion

The prevalence of Fabry disease in end-stage renal disease patients was 0.12%, questioning the efficacy of this screening strategy with respect to the low prevalence. However, beside the benefit for the patient and his family, the increased awareness of Fabry disease among participating nephrologists may be of interest for future patients.

Introduction

Fabry disease (FD; OMIM #301500) is a rare X-linked genetic disease due to pathogenic variants in the *GLA* gene coding for the lysosomal α-galactosidase A [1], [2], [3]. FD is characterized by glycosphingolipids accumulation [4] in renal glomerular, tubular and vascular cells, leading to end-stage renal disease (ESRD) in a subset of male and, more rarely, female patients. There is a cardiac and central nervous system component with hypertrophic cardiomyopathy, malignant arrhythmia, and strokes [5], [6], [7].

Prevalence of the classic form of the disease has been estimated to be 1 in 50,000 in the general population but screening studies in newborns and high-risk populations have revealed unexpected high frequencies [8], [9]. Prevalence in cohorts of ESRD patients were historically found from 0 to 1.1% in dialyzed patients and from 0.2 to 0.4% in transplanted patients [10], [11] but a recent review compiling all 63 studies available to date was more in favor of a rate of 0.15% [12].

In Western France, the prevalence of Fabry disease is unknown, especially in ESRD patients. The objective of the study was to screen for FD, using an enzymatic assay on dried blood spot (DBS) in a large population of dialyzed or transplanted male subjects [13].

Section snippets

Patients and methods

The *Société de Néphrologie de l'OUest maladie de FabrY* (SNOUFY) study was a cross-sectional study that involved most of the nephrology centers of the four regions of Western France: Bretagne, Centre Val de Loire, Pays de la Loire and Poitou-Charentes, accounting for over 11 millions inhabitants (Fig. 1)….

Methods

An enzymatic assay on dried blood spots (DBS) collected on filter paper was used for screening [13]. It was sampled during a dialysis session or an outpatient transplantation follow-up visit. Nurses were trained before the procedure started. The DBS was sent (with the patient number) to the French national referral center for Fabry disease (https://centre-geneo.com ↗) for analysis. When a patient was tested positive for FD, his nephrologist was notified by the principal investigator and…

Results

The extraction of the REIN® and CRISTAL® registries led to the identification of 1561 eligible patients, 711 on dialysis (46%) and 850 with a kidney transplant (54%). Between September 2016 and July 2018, 819 out of these 1561 patients (52%) were screened with DBS: 242 on dialysis (34% of the selected dialyzed cohort) and 577 transplanted (68% of the selected cohort). Seven hundred and forty-two patients were not screened for various reasons: some centers refused participation to the study…

Discussion

This screening of a large cohort of 819 male patients with ESRD in Western France led to the diagnosis of FD in one single patient, resulting in a prevalence of 0.12%. This percentage is in agreement with most previous screening studies performed in ESRD patients in various countries [12]. However, these figures are half of the prevalence recently reported by a large

group of Argentinian nephrologists who identified 22 cases of Fabry disease out of 9604 dialysis patients screened, all confirmed …

Conclusion

A large screening using enzymatic assay on dried blood spots in 819 male patients with ESRD in Western France identified one single patient with FD, corresponding to an estimated prevalence of 0.12%. Subsequent cascade genotyping identified an affected brother leading to initiation of disease specific therapy in those two male patients. Whether it is worth to screen over 800 patients to identify 2 cases is debatable. In view of the complexity of such a large study, this strategy does not appear …

Disclosure of interest

Dominique P. Germain has received honoraria and consulting fees from Amicus Therapeutics, Sanofi Genzyme and Takeda.…

CRediT author statement

Cecile Vigneau: Conceptualization, funding resource, investigation, methodology, project administration, supervision and writing the first draft.

Dominique P. Germain: Investigation, writing the first draft, reviewing and editing.

David Larmet: Data curation, investigation and methodology.

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All authors read and approved the…

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The list of investigators is available at: https://docs.google.com/spreadsheets/d/1hE_dzDgpxlXzVPtjHVkkSRssC6laRljCgK5mLYdZx-4/edit?usp=sharing ↗

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