

LETTER TO THE EDITOR

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Screening for Fabry disease in unknown origin axonal polyneuropathy: to do or not to do, this is the question!

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Abstract

Fabry disease (FD) is a systemic X-linked lysosomal disorder. A 'peripheral nerve variant' of FD has been hypothesized in subjects with neuropathy, without the early manifestations of the classic phenotype. A cohort of undiagnosed neuropathy patients with chronic polyneuropathy of undetermined aetiology and demyelinating neuropathy, unresponsive to immunomodulating treatment, were screened for FD. A total of 103 patients (64% males), were enrolled. No typical pathogenetic mutations for FD were identified. We are aware that the study sample was very small, but only a large, unfeasible theoretical sample size could demonstrate a statistically significant increased prevalence of FD in neuropathy patients, as peripheral neuropathy of undetermined cause is uncommon and there is a low prevalence of FD in the general population. Therefore, we are of the opinion that including tailored FD screening in the neuropathy diagnostic work-up, particularly when there are additional clinical characteristics, should be considered.

Keywords: Fabry disease, Neuropathy, Axonal, Polyneuropathy, Lysosomal disorder, Screening

Main text

Fabry disease (FD) is a systemic X-linked lysosomal disorder, caused by decreased activity of the enzyme α -galactosidase A (α -GAL A). Early diagnosis is pivotal, as enzyme replacement therapy is currently available for these patients. FD has a wide clinical spectrum, encompassing impaired peripheral nerve function, mostly of the small fibres, leading to an early-onset, usually painful, polyneuropathy.

Late-onset cardiac and renal variants of FD, due to missense mutations, with residual α -GAL A activity, have been described in subjects without the early, classical phenotype [1, 2]. Pathogenetic mutations of the α -GAL A gene (*GLA*) and genetic variants of unknown clinical significance (VUS) have been reported also in patients

affected by small fibre neuropathy (SFN) of unknown aetiology, screened for FD, in a pilot study [3] and in a small case series [4]. Based on these data, a 'peripheral nerve variant' of FD has been hypothesized in subjects with neuropathy, without the early manifestations of the classic phenotype [4].

However, subsequent studies by other authors did not seem to support this hypothesis. Indeed, after FD screening, de Greef et al. [5] diagnosed no FD in 725 patients presenting with isolated SFN [5]. There was a reduced α -GAL A activity in 8 patients and a *GLA* gene variant was observed in 13, including one likely pathogenic variant in a female, although the diagnosis of FD could not be confirmed over time in this subject [5]. FD and Hereditary ATTR amyloidosis screening was done in another sample of 172 Nordic patients, affected by idiopathic small-fibre and mixed neuropathy [6]. A possible pathogenic variant, R118C, in the *GLA* gene

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was detected in a single patient, although clinical investigation identified no firm signs of FD [6]. Indeed, over the last few years, some *GLA* gene mutations previously classified as pathogenetic in screening studies (1995–2007) without confirmatory analyses, have recently been recognized as ‘benign/likely-benign’ variants [7].

On the other hand, newborn screening for lysosomal storage disorders (Pompe, Gaucher, Fabry disease, Mucopolysaccharidosis type I) by tandem mass spectrometry in North East Italy [8] revealed that the combined incidence of the 4 disorders was 1/4411 births and FD was the most frequent (1/8882). These data on FD prevalence in the general population raise the suspicion that the frequency of FD might have been underestimated in selected clinical samples.

Herein we report the results of an observational, cross-sectional, pilot study, carried out to investigate into the frequency of FD in a cohort of selected, undiagnosed neuropathy patients, with chronic polyneuropathy of undetermined aetiology [9] and with demyelinating neuropathy [10] unresponsive to immunomodulating treatment.

Patients (aged 18–80 years), referring to 5 Italian Neurology Units in 2 Northern Italian Regions (Piedmont: Torino, Casale Monferrato, Novi Ligure, Mondovì; Liguria: Genoa), with idiopathic axonal polyneuropathy (sensory or sensory-motor, painful or not, with or without comorbid SFN) were enrolled into the study, after obtaining written informed consent. Inclusion diagnostic criteria was chronic polyneuropathy of undetermined cause [9] or a previous diagnosis of chronic demyelinating neuropathy [10], unresponsive to immunomodulating treatment (at least three types of therapies). Exclusion criteria were: a positive family history of hereditary neuropathy, diabetes, alcohol abuse, dysthyroidism, monoclonal gammopathy, rheumatic and/or hemolymphoproliferative diseases, recent therapy with neurotoxic drugs.

All the patients were examined for α -GAL activity by Dried Blood Spot (DBS). Genetic analysis was carried out in all females and in males with a reduced α -GAL A activity (< 15.3 nmol/L/h) and/or in the low range, between 15.3 nmol/L/h and 20 nmol/L/h, of the normal limit interval (“pseudo-deficiency”). In line with the diagnostic protocol, whenever a mutation in the α -GAL A gene was identified, then the globotriaosylceramide (Gb3) levels were measured in urine and lyso-Gb3 in blood.

A total of 103 patients, 66 males (64%), average age 59 years, were enrolled (Table 1). Five of them also had SFN, confirmed by skin biopsy. The α -GAL A activity was normal in all males (average: 26.4 nmol/L/h). No typical pathogenetic mutations for FD were identified in the *GLA* gene in the study sample. Interestingly, a single genetic polymorphism was detected in a 67-year-old

Table 1 Main clinical features

Total patients	103
Male (%)	66 (64%)
Age (years), mean (\pm SD)	60.3 (\pm 13.1)
Axonal sensory-motor polyneuropathy (%)	48 (46.6%)
Axonal sensory polyneuropathy (%)	45 (43.7%)
Demyelinating neuropathy (%)	10 (9.7%)
Sensory symptoms (%)	85 (82.5%)
Motor symptoms (%)	51 (49.5%)
Small fiber neuropathy (%)	5 (4.8%)
α -GAL A activity in males (mean (\pm SD))	26.4 nmol/L/h (\pm 12.6)
Patients with systemic symptoms or signs of FD (%)	9 (8.7%)

female patient with a SFN and diffuse neuropathic pain: c.937G > T (p.Asp313Tyr), previously classified as a VUS, more recently as a benign/likely benign exonic variant, according to [Ncbi.Nlm.Nih.Gov](https://www.ncbi.nlm.nih.gov/) database.

Systemic signs or symptoms suggestive of FD were detected in 9 patients, 4 with previous myocardial infarction, 1 with slightly abnormal renal function (mild, i.e. not severe enough to be considered an exclusion criterion), 2 had cardiac arrhythmias, 2 had a history of cerebrovascular episodes.

Although the results of this pilot study apparently do not support the hypothesis of the late onset, ‘peripheral nerve variant’ of FD, these findings, though negative, cannot rule out such a novel hypothesis, due to the shortcomings of the study, mainly the small size of the sample, the high proportion of females enrolled and the diagnostic protocol.

Although DBS is a quite reliable and user-friendly tool to examine patients for α -GAL activity and to select male candidates for genetic analysis, we can not exclude that an alternative diagnostic flowchart, starting with the blood Gb3 level dosage before DBS and/or genetic evaluation, could have yielded different results. Indeed, according to recent studies [11], Gb3 levels are detectable in blood in all the male late-onset FD patients with residual α -GAL activity. Therefore, they seem to be a reliable biomarker to diagnose such cases with atypical presentations.

The main limitation of the study is the small sample size, similar to some previous ones. Indeed, if the frequency of FD in the general population is considered, then a much larger sample size than those previously reported on SFN and/or mixed neuropathy studies [3–6] would have to be enrolled to demonstrate a higher FD prevalence in idiopathic neuropathy.

Indeed, if we were to predict the same frequency of FD as that in patients with cryptogenic stroke (0.13%) in patients with undetermined neuropathy, then a theoretical

sample size of: 31,853, 56,388 and 126,845 subjects respectively, for a relative inaccuracy accepted by 20, 15, 10%, would be necessary to demonstrate this prevalence (0.13%). Moreover, there would be an unacceptable level of confidence, i.e. with a probability equal that of to 20% of a chance result.

Therefore, it is not conceivable to carry out a study, although collaborative, multi-center, reaching such a large sample size on neuropathy patients, considering that peripheral neuropathy of undetermined cause is quite uncommon, i.e. much rarer than stroke or renal failure. Consequently, it seems unlikely to find an Evidence-Based Medicine answer to the question: does the frequency of FD in patients suffering from neuropathy of unknown aetiology suffice to justify a screening in this clinical setting? Nevertheless, we believe that an individualized approach to each neuropathy patient may provide better clinical guidance. Indeed, we are of the opinion whether to test for FD or not should be carefully considered in the neuropathy diagnostic work-up, on an individual basis, mainly in the presence of additional clinical characteristics, indicative of FD. A new score for clinical suspicion of FD could include: 1) childhood and/or young adult onset; 2) comorbid personal and/or family history of cardio-cerebro-vascular disease; 3) renal failure; 4) typical skin lesions. All of which could be useful in the diagnostic assessment of patients with neuropathy of unknown aetiology to prompt FD screening.

Clinical experience may help the neurologist more than literature evidence in the decision-making process as to screening for FD undiagnosed neuropathy patients.

Abbreviations

FD: Fabry disease; α -GAL A: α -galactosidase A; GLA: α -GAL gene; VUS: genetic variants of unknown clinical significance; SFN: small fibre neuropathy; Gb3: globotriaosylceramide

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Authors' contributions

ER: research conception, manuscript preparation; MG: data collection, manuscript review; ADS: data collection, manuscript review; PF: data collection; EG: data collection; AR: data collection; CG: data collection; CG: data collection; NM: manuscript review; AS: manuscript review; DC: research conception, manuscript review. All the authors read and approved the final manuscript.

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Availability of data and materials

The datasets used for the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

Were obtained; all patients signed written informed consent for the genetic study.

Consent for publication

Not applicable.

Competing interests

The authors declare they have no competing interests.

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