Joint Bone Spine 83 (2016) 421–426

Available online at ScienceDirect www.sciencedirect.com

Elsevier Masson France EM|consulte www.em-consulte.com/en

Original article

# Musculoskeletal manifestations of Fabry disease: A retrospective study☆

Olivier Lidove[a,b,c,*], Valérie Zeller[a,b], Valérie Chicheportiche[d], Vanina Meyssonnier[a,b], Thomas Sené[a,b], Sophie Godot[a,b], Jean-Marc Ziza[a,b]

[a] Service de Rhumatologie, Médecine Interne, Site Diaconesses Croix St.-Simon, 125, rue d'Avron, 75020 Paris, France
[b] Centre de Référence Maladies Lysosomales, Site Diaconesses Croix St.-Simon, 125, rue d'Avron, 75020 Paris, France
[c] Inserm-UMRS 974, UPMC-équipe muscle inflammatoire/thérapies innovantes ciblées, 75013 Paris, France
[d] Service de Radiologie, 125, rue d'Avron, 75020 Paris, France

ARTICLE INFO

*Article history:*
Accepted 17 July 2015
Available online 14 December 2015

*Keywords:*
Acroparesthesia
Pain
Fabry disease
Early-onset osteoporosis
Charcot foot

ABSTRACT

*Objectives:* Fabry disease is a rare X-linked metabolic disorder characterized by a deficiency in the enzyme alpha-galactosidase A. Both males and females can be affected. The main presenting symptom is pain in the extremities, whereas at a more advanced stage, the manifestations include hypertrophic cardiomyopathy, cardiac dysrhythmia, proteinuria, chronic kidney dysfunction, stroke, and hearing loss. When not diagnosed and treated, Fabry disease causes early death. No studies specifically designed to describe the musculoskeletal manifestations of Fabry disease are available.

*Methods:* We conducted a single-center retrospective study of patients receiving follow-up at a Fabry disease referral center. We described the musculoskeletal manifestations and analyzed the differential diagnoses.

*Results:* Our study included 40 patients belonging to 20 families, including 25 females with a mean age of 44.2 years (range, 20–76 years) and 15 males with a mean age of 40.1 years (range, 16–61 years). Mean age at the diagnosis of Fabry disease was 37.2 years (range, 7–71 years) in the females and 26.9 years (range, 9–51 years) in the males. Specific enzyme replacement therapy was given to 10 (40%) females and 12 (80%) males. Musculoskeletal manifestations were as follows: past or present pain in the extremities (13 females and 10 males), combined in some patients with vasomotor disorders in the extremities and telangiectasia; exercise intolerance (12 females and 12 males); osteoporotic fractures (2 brothers aged 45 and 44 years, respectively); osteoporosis (3 females, aged 57, 63, and 75 years, respectively), which contributed to death in the oldest patient; osteopenia (2 females aged 38 and 47 years, respectively; and 1 male aged 43 years); Charcot foot and lymphedema with serious infectious complications (4 males older than 40 years), with avascular osteonecrosis of the lower limbs in 2 cases; toe amputations (3 cases); bilateral lower-limb amputation (1 case); abnormally slender lower limbs (5 females and 8 males); acute gout (3 males with severe chronic kidney failure); and carpal tunnel syndrome (1 female and 1 male, both younger than 40 years). Mistaken diagnoses that were made at an early stage, contributing to delay the identification of Fabry disease, included rheumatic fever (2 females and 2 males), growing pains (2 males), pain with paralysis (1 female), chilblains of the lower limbs (1 female), and erythermalgia (1 female). In adulthood, the following mistaken diagnoses were made: Sjögren's syndrome and/or sicca syndrome (6 females), systemic sclerosis (1 male), dysautonomia (1 female), and familial Mediterranean fever (1 female).

*Conclusion:* The diagnosis of Fabry disease is usually delayed, due to confusion with more common disorders. Musculoskeletal manifestations may constitute the presenting symptoms. Past or present pain in the extremities is typical. Osteoporosis may develop early and become severe. Together with the family history, the presence of musculoskeletal manifestations can lead to the correct diagnosis by prompting alpha-galactosidase assays in males and genetic testing in females. Fabry disease is often responsible for musculoskeletal manifestations, of which the most common are pain in the extremities and osteoporosis. These manifestations can be inaugural and lead to diagnostic wanderings. They require specific treatment strategies.



☆ This work was presented as an oral communication at the 26th meeting of the French Society for Rheumatology (SFR) in December 2013 and at the 68th meeting of the French National Society for Internal Medicine (SNFMI) held in Saint-Malo in December 2013.

* Corresponding author. Service de Rhumatologie, Médecine Interne, Site Diaconesses Croix St.-Simon, 125, rue d'Avron, 75020 Paris, France.
*E-mail address:* olidove@hopital-dcss.org (O. Lidove).

http://dx.doi.org/10.1016/j.jbspin.2015.11.001
1297-319X/

## 1. Introduction

Fabry disease is an inherited X-linked metabolic disorder due to a mutation in the gene encoding the lysosomal enzyme alpha galactosidase A [1], which breaks down neutral glycosphingolipids, particularly globotriaosylceramide (Gb3 or GL-3). Accumulation of these neutral glycosphingolipids causes the gradual development of systemic manifestations. The incidence of Fabry disease in the general population is estimated at 1/117,000 to 1/40,000 [2,3]. The symptoms vary widely and change over time in both males and females [4,5]. In females, disease severity ranges from mild to severe [6,7].

The clinical manifestations include pain in the extremities, exercise intolerance, hearing loss, angiokeratomas, ocular abnormalities, decreased sweating, and cardiac and renal involvement. Transient ischemic attacks and stroke can occur [1,4–6]. Fabry disease is not always the first diagnosis to be considered in patients with these manifestations. If the symptoms go unrecognized and the specialized investigations needed to diagnose Fabry disease are unavailable, irreversible organ damage may develop. Once diagnosed, Fabry disease can be treated with specific recombinant enzyme replacement therapy [8–10].

To date, the musculoskeletal manifestations of Fabry disease have been described in only a few small cohort studies. Among these manifestations, some are common, can occur as presenting symptoms, and can cause confusion with other diagnoses. The objective of this retrospective observational study was to describe the musculoskeletal manifestations of Fabry disease and to discuss mistaken diagnoses made before the diagnosis of Fabry disease.

## 2. Methods

We identified patients who received outpatient or inpatient care between July and September 2013 at our rheumatology and internal medicine department, which is a referral center for Fabry disease. Their medical charts were reviewed retrospectively. We recorded all musculoskeletal manifestations, defined as possible reasons for assessment by a rheumatologist, including pain in the extremities, acute gout, osteoporosis (defined as a fracture or T-score < 2.5 SD after 30 years of age), and osteoarticular infections. In addition, we recorded patient characteristics, systemic manifestations, age at disease onset, and the mistaken diagnoses established before the diagnosis of Fabry disease. The study was approved by the local ethics committee. We did not include patients with mutations classified as genetic polymorphisms affecting the alpha-galactosidase A gene.

## 3. Results

In all, 40 patients received follow-up for Fabry disease at our center during the study period. Table 1 reports the main patient characteristics. Mean age at the diagnosis of Fabry disease was 26.9 years (range, 9–51 years) in the 15 males and 37.2 years (range, 7–71 years) in the 25 females.

Of the 40 patients, 36 patients had at least one musculoskeletal manifestation. The remaining 4 patients were women younger than 30 years of age.

### 3.1. Pain

Past or present pain in the extremities was a symptom in 10/15 (67%) males and 13/25 (52%) females. These patients reported acute episodes of burning pain that was exacerbated in the event of a fever or heat exposure. A third of them also had less severe permanent pain. Exercise intolerance was present in 12/15 (80%) males and 11/24 (46%) females. Two-thirds of patients had both pain in the extremities and exercise intolerance. Joint pain was common during the attacks of pain in the extremities (Fabry crises) and predominated at the four extremities, involving the wrists and ankles. There was no joint swelling or synovitis, and the joint pain ran parallel with the pain in the extremities.

### 3.2. Gout

Gout was present in 3 males, all of whom had chronic kidney failure (creatinine clearance < 30 mL/min/1.73 $m^2$). They experienced recurrent attacks of acute gout involving the great toes and ankles.

### 3.3. Osteoporosis

Among the patients who underwent bone absorptiometry, 3 of 4 males and 5 of 10 females had abnormal results. Of the 3 males with osteoporosis, 2 had vertebral fractures diagnosed at 44 and 45 years of age, respectively, (Fig. 1) and 1 had a thoracolumbar junction syndrome with a height loss of 10 cm. Osteoporosis was diagnosed in 3 females at 57, 63, and 75 years of age, respectively; 2 females had osteopenia at 38 and 47 years of age, respectively. Risk factors for osteoporosis, including the use of specific drugs, were present in some patients:

- glucocorticoid therapy > 7.5 mg/day for longer than 3 months (5 males and 4 females);
- carbamazepine therapy for longer than 1 year (10 males and 5 females);
- immunosuppressants (2 males and 2 females);
- heparin therapy for longer than 6 months (1 male and 2 females);
- organ transplantation (2 males);
- chronic respiratory failure (3 males and 1 female);
- chronic obstructive pulmonary disease in nonsmokers (6 males and 2 females);
- asthma (1 male and 6 females);
- inhaled glucocorticoid therapy (4 males and 7 females);
- body mass index < 20 kg/$m^2$ (6 males and 2 females);
- very low serum vitamin D levels (5 males and 5 females);
- early menopause (2 females, at 40 and 45 years of age, respectively).

Of the 5 males given glucocorticoid therapy, 4 received this treatment as premedication before enzyme replacement therapy and 1 to treat central nervous system inflammation. One female received a first glucocorticoid therapy course to treat meningitis, which was thought to be due to tuberculosis, then a second course to treat intracranial hypertension complicating chronic meningeal inflammation. The reasons for immunosuppressant therapy were heart-kidney transplantation in the 2 males, rheumatoid arthritis in 1 female, and Crohn's disease in 1 female. Heparin therapy followed by oral vitamin K antagonist therapy was used to treat atrial fibrillation in 1 male and cardioembolic stroke in 1 female.

### 3.4. Other lower-limb manifestations (slender limbs, lymphedema, Charcot foot)

The lower limbs were unusually slender in 8 males and 5 females. Lymphedema was a feature in 6 males and 1 female; it affected the face in 1 of the males (Fig. 2). At least one episode of erysipela was noted in 3 patients, including 2 who had recurrent episodes of lower-limb erysipelas complicating lymphedema.

Charcot foot was present in 4 males, all of whom were older than 40 years and had multiorgan disease with chronic kidney failure and severe heart disease (Fig. S1; See the supplementary material associated with this article online). All 4 patients had pain in