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ORIGINAL ARTICLE

Distal Extremity Pain as a Presenting Feature of Fabry's Disease

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Objective. **Fabry's disease (FD) is an X-linked lysosomal storage disease. Distal extremity pain can be an early finding and renal, cardiac, and cerebrovascular complications may lead to complications and mortality. Treatment is now available for these patients, who may not be diagnosed correctly for years if the neuropathic nature of the pain is not recognized. The aim of our study was to describe early clinical features in a cohort of patients with FD and to emphasize the importance of distal extremity pain for early diagnosis.**

Methods. **The medical charts of 35 patients with FD followed in a single center were reviewed. When data were incomplete, a detailed pain questionnaire was sent to patients. Nonresponders were contacted by telephone.**

Results. **Distal extremity pain was present in the majority of cases (25 of 35). The mean age at diagnosis of FD was 43.5 years (range 5–77 years). Distal extremity pain was more prevalent in males than females and occurred mostly in childhood or adolescence. When present at onset, the disease progressed with subsequent organ system involvement. Misdiagnoses were frequent and included growing pains, juvenile idiopathic arthritis, connective tissue disease, and gout.**

Conclusion. **Clinical manifestations of FD, including episodes of severe pain in the feet and hands, often start in childhood. Distal extremity pain may be the only symptom for a considerable period of time. Patients may be wrongly labeled as having rheumatologic conditions, resulting in long diagnostic and therapeutic delays. Rheumatologists should be aware of the clinical aspects of FD and include it in the differential diagnosis of distal extremity pain in childhood and adolescence.**

INTRODUCTION

Fabry's disease (FD) is a lysosomal storage disease caused by mutations in the gene encoding the lysosomal enzyme α-galactosidase (α-gal) A. As a result of the enzyme deficiency, neutral glycosphingolipids accumulate in most tissues and organ systems, including the skin, nerves, eyes, kidney, heart, and brain, leading to a variety of progressive clinical signs and symptoms (1,2). FD is a relatively rare, panethnic condition with reported incidences ranging between 1:40,000 and 1:117,000 live births (3,4). The disorder is X-linked (chromosome Xq22.1) (5), but females may also be affected by largely unknown mechanisms (6,7).

Most males with FD usually have the classic phenotype, but in females, clinical presentation is more variable, generally with a later onset of symptoms and slower disease progression (7,8). Painful peripheral neuropathy due to progressive loss of small nerve fibers is a common complication (9–12). Related clinical manifestations include burning pain, particularly in the feet and hands, hypohidrosis, and gastrointestinal (GI) disturbances (postprandial abdominal pain, diarrhea, nausea). Attacks of sharp neuropathic pain may be accompanied by fever and arthralgia ("Fabry's crisis"). Other features frequently seen in young patients include angiokeratoma, cornea verticillata, and hearing abnormalities (e.g., hearing loss, tinnitus) (1,2). In adulthood, renal function may progressively deteriorate (13,14); microalbuminuria evolves into (overt) proteinuria and the glomerular filtration rate steadily declines. Males are more likely to progress to end-stage renal disease (15). Left ventricular hypertrophy develops in approximately half of the patients. Cardiovascular events (e.g., arrhythmia, heart failure, myocardial ischemia, or infarction) (14,16,17) and early stroke (18,19) may considerably reduce life expectancy.

Early diagnosis and treatment of FD are of crucial im-

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portance. Outcomes after enzyme replacement therapy (ERT) have generally been reported to improve in patients with less advanced stages of the disease (20–22). The diagnosis is based on an assay of α-gal A activity (using plasma or leukocytes) in males and genetic analysis of the α-gal A mutation in females (1,2). However, ordering these diagnostic tests relies on a clinical suspicion of FD. Given the reported diagnostic delay of more than a decade (7), early disease manifestations must be recognized. Even the most serious complications occurring in adult patients may be misdiagnosed (23).

Pediatric rheumatologists often encounter children or adolescents with distal extremity pain who may be undiagnosed and are often not evaluated for rare disorders such as FD, particularly if symptoms are intermittent or mild. The purpose of our study was to describe the early clinical features in a single-center cohort of male and female patients with FD, focusing on distal extremity pain and its importance for early disease diagnosis.

PATIENTS AND METHODS

We conducted a medical chart review and collected retrospective demographic and clinical data from a cohort of patients with FD. All of the patients had been followed by a multidisciplinary team of specialists (cardiologists, neurologists, dermatologists, nephrologists, pediatricians) at the Careggi University Hospital Fabry Regional Referral Center between 1997 and 2009. If medical chart data related to distal extremity pain were considered to be incomplete, patients were invited to complete a distal extremity pain questionnaire. The mailed questionnaire was designed to gather data on the presence or absence of distal extremity pain, age at onset, and intensity, frequency, and onset of other signs and symptoms. Nonresponders were subsequently contacted by telephone to collect the data. All relevant data were entered into a customized database. These included: date of birth, sex, mutation type, α-gal A levels, ERT, age at diagnosis, initial misdiagnoses, age at last followup visit, and signs and symptoms related to the skin (angiokeratoma, hypo- or anhidrosis), nervous system (painful neuropathy, stroke, transient ischemic attacks), heart (arrhythmias, left ventricular hypertrophy, vascular insufficiency, myocardial infarction, electrocardiogram [EKG] abnormalities, valvular disease), kidney (proteinuria, impaired concentration ability, glomerular filtration rate reduction, end-stage renal disease), GI tract (nausea, vomiting, diarrhea, postprandial bloating, abdominal pain), and the ear, nose, throat system (hypoacusia, tinnitus, vertigo). In all patients, the diagnosis of FD had been confirmed by a demonstration of low (<5%) or absent α-gal A activity in leukocytes (males) and genetic mutations in the α-gal A gene (males and females).

RESULTS

Patients with FD usually report 2 kinds of pain: chronic/burning/tingling pain and superimposed pain crises that are relatively infrequent, environmentally induced on occasions, and persist from minutes to several weeks. From a cohort of patients with FD followed at the Careggi University Hospital Fabry Regional Referral Center, we obtained reliable information on the presence or absence of distal extremity pain from 35 patients (15 females) through clinical chart review (n = 16), questionnaire (n = 15), or telephone interview (n = 4). Occurrence of distal extremity pain was reported by 25 patients (71%; 7 females). The pain was generally described as chronic, nagging, tingling, burning pain in the hands and feet. The median age at onset of pain for males and females was 10 and 14 years, respectively. Two patients could not recall the exact age at the first manifestation of pain, but it first presented during childhood or adolescence (i.e., age <18 years) in 15 (65%) of 23 patients, in early adulthood in 4 patients (17%), and later in adulthood in 4 (17%) patients. The frequency of painful episodes was variable: >1 per month in 8 patients, 1 per month in 2 patients, 1 per 6 months in 10 patients, and <1 per year in 5 patients. Males reported more frequent episodes (usually ≥1 per month) than females (usually 1 per 6 months). The intensity of pain was mild in 9 patients (36%), moderate in 7 patients (28%), severe in 6 patients (24%), and very severe (requiring analgesic treatment) in 3 patients (12%). Again, the pain was generally more intense in males (usually moderate/severe) than in females (mild/moderate).

At the time of data collection, distal extremity pain was still present in 16 patients (64%) and had disappeared in 9 patients (36%); the intensity was rated as mild in 5 of the cases, moderate in 8, severe in 2, and very severe (needing analgesics) in 1 patient. The frequency of pain episodes at data collection was variable: <1 per year in 2, 1 per 6 months in 5, 1 per month in 4, and >1 per month in 5. In most patients who were pain free, the pain had resolved 5 to 10 years after its onset.

Most of the 15 patients with distal extremity pain as the first symptom reported other signs and symptoms of FD during their clinical course. These other manifestations presented between 1 and 5 years after onset of pain in 2 patients, between 5 and 10 years after onset in 3, and more than 10 years after onset in 6 patients. Of note, distal extremity pain remained the only disease clinical manifestation up to the most recent visit in 4 patients (16%).

Distal extremity pain was the first sign of FD in 15 (60%; 8 males, 7 females), while in 10 (40%) there were other signs or symptoms at disease onset, i.e., angiokeratoma (n = 5), hypohidrosis (n = 5), renal involvement (n = 3), heart involvement (n = 2), and ocular and ear, nose, throat involvement (n = 1 each). In the 35 patients with complete pain data, hypo- or anhidrosis, angiokeratoma, and GI symptoms were the most frequently reported associated findings, more so by males than by females (Table 1). The definite diagnosis of FD in the 25 patients with distal extremity pain was established at the mean age of 37.5 years for males (range 15–60 years) and 35.8 years (range 5–73 years) for females (Table 2). Initial misdiagnoses were frequent and included growing pains (n = 8 patients), juvenile idiopathic arthritis (n = 2 patients), and connective tissue disease, pain related to fever, gout, and anxiety disorder (n = 1 patient each).

The variability in genetic mutations did not allow analysis of genotype–phenotype correlations. ERT had been

Table 1. Signs and symptoms of Fabry's disease reported for the overall population of patients with complete data, for patients with distal extremity pain as the first symptom, and for patients who had distal extremity pain but not as the first symptom*

	Overall (patients with complete data with or without distal extremity pain)		Distal extremity pain as the first symptom (other signs/symptoms during the disease course)		Distal extremity pain reported but not as the first symptom (other signs/symptoms present at the onset of pain)	
	Males (n = 20)	Females (n = 15)	Males (n = 8)	Females (n = 7)	Males (n = 10)	Females (n = 0)
Age, median (range) years	46.8 (24–67)	47.1 (5–77)	40.8 (15–60)	46.5 (5–77)	37.5 (15–60)	35.8 (5–73)
Distal extremity pain	18 (90)	7 (47)	8 (100)	7 (100)	10 (100)	0 (0)
Hypo- or anhidrosis	20 (100)	10 (67)	6 (75)	0 (0)	4 (40)	0 (0)
Angiokeratoma	18 (90)	8 (53)	6 (75)	1 (14)	6 (60)	0 (0)
GI symptoms	10 (50)	1 (7)	7 (87)	0 (0)	2 (20)	0 (0)
Ocular signs (cornea verticillata)	3 (15)	0 (0)	3 (37)	0 (0)	1 (10)	0 (0)
ENT						
Hypoacusis, tinnitus, or vertigo	2 (10)	1 (7)	2 (25)	1 (14)	4 (40)	0 (0)
Kidney						
(Micro)albuminuria or proteinuria <1 gm/day	7 (35)	4 (27)	2 (25)	1 (14)	1 (10)	0 (0)
Impaired concentration ability and GFR decline	9 (45)	0 (0)	0 (0)	0 (0)	3 (30)	0 (0)
End-stage renal disease	8 (40)	0 (0)	3 (37)	0 (0)	3 (30)	0 (0)
Proteinuria >1 gm/day	0 (0)	1 (7)	0 (0)	1 (14)	1 (10)	0 (0)
Heart						
Left ventricular hypertrophy	19 (95)	6 (40)	5 (62)	3 (43)	6 (60)	0 (0)
EKG abnormalities or arrhythmias	11 (55)	9 (60)	5 (62)	0 (0)	3 (30)	0 (0)
Valvular disease, vascular insufficiency	14 (70)	6 (40)	4 (50)	1 (14)	4 (40)	0 (0)
Myocardial infarction	4 (20)	1 (7)	2 (25)	2 (28)	1 (10)	0 (0)
CNS						
Stroke	4 (20)	1 (7)	2 (25)	0 (0)	0 (0)	0 (0)
Transient ischemic attacks	2 (10)	2 (14)	2 (25)	2 (28)	4 (40)	0 (0)

* Values are the number (percentage) unless otherwise indicated. GI = gastrointestinal; ENT = ear, nose, throat; GFR = glomerular filtration rate; EKG = electrocardiogram; CNS = central nervous system.

started in 73% (22 of 30) of the males and 22% (7 of 32) of the females followed at our center. In the remaining patients (8 males, 25 females), ERT was either not clinically indicated based on the mild clinical manifestations or was neither tolerated nor accepted by patients.

In order to highlight the devastating implications of late diagnosis, we report one patient in more detail. At the age of 3 years, this boy started to experience episodes of burning pain in the hands and feet. Feverish periods and physical exercise exacerbated the distal extremity pain. Over

Table 2. Age at onset of distal extremity pain or other first Fabry's symptom and delays in diagnosis*

	Overall (patients with complete data with or without distal extremity pain)		Distal extremity pain as the first symptom (other signs/ symptoms during the disease course)		Distal extremity pain reported but not as the first symptom (other signs/symptoms present at onset of pain)	
	Males (n = 20)	Females (n = 15)	Males (n = 8)	Females (n = 7)	Males (n = 10)	Females (n = 0)
Age at onset of first Fabry's symptom, median years	16	10	NA	NA	12	NA
Age at pain onset, median years	NA	NA	10	14	NA	NA
Age at Fabry's diagnosis, median years	41	46	37	36	27	NA
Delayed onset to diagnosis, median years	25	36	27	22	15	NA

* NA = not applicable.

the next years, the pain progressively interfered with his daily activities and treatment with nonsteroidal anti-inflammatory drugs was started. Nevertheless, he developed nonspecific arthralgia, diarrhea, and recurrent episodes of fever, usually after exercise, which prevented him from any physical activity. They were treated with several courses of antibiotics; he underwent a tonsillectomy at age 12 years. At age 18 years, peripheral swelling was noted and a laboratory evaluation revealed proteinuria and renal impairment. Subsequently, he presented angiokeratoma and had a transient ischemic attack. The diagnosis of FD (absence of α-gal A activity) was finally made at age 28 years. By then, he had developed advanced-stage FD; ERT was started a few months later. Nevertheless, his renal function further declined and dialysis had to be started at age 30 years. Three years later he underwent renal transplantation. After having experienced major strokes, the patient died at age 41 years.

DISCUSSION

In this cohort of patients, distal extremity pain had frequently presented during childhood or adolescence (median age 10 years for males and 14 years for females). It often was the first symptom of FD to appear. In several cases, pain had remained the only clinical manifestation reported over a considerable period of time. Our data, i.e., 90% of males and 47% of females reporting distal extremity pain, are in line with previously reported observations. Analyses of data from two Fabry's registries have shown that large proportions of children and adolescents (boys: 60–80%, girls: 40–60%) report neuropathic pain; boys often a few years earlier than girls (24,25).

In many individuals, the pain had not been recognized as an early symptom of FD and correct diagnosis was delayed until well into adulthood. Reducing such diagnostic delays to a minimum is critical because clinical benefits of ERT in FD are generally greater if treatment is started when organs (e.g., kidneys, heart) are relatively preserved (20–22,26). Pediatric and general rheumatologists may encounter unrecognized FD patients with distal extremity pain referred with a preliminary diagnosis of, for example, an inflammatory muscle or articular disorder. They are well positioned to clinically suspect FD as the underlying cause; however, this requires knowledge about the clinical aspects of the peripheral Fabry's neuropathy and FD in general.

The painful Fabry's neuropathy results from an early and progressive loss of small thinly myelinated Aδ fibers and unmyelinated C fibers (9,10,12,27). Persistent and/or episodic burning pain, with or without painless tingling sensations (acroparaesthesia), develops especially in the palms of the hands and the soles of the feet. The intensity of the pain is variable from case to case and, over time, even in individual patients. Severe attacks of sharp neuropathic pain ("Fabry's crises") can last from a few minutes to several weeks, and may be accompanied by fever and arthralgia. Such attacks are usually triggered by an increase in body temperature (fever, physical exercise) or variations in outside temperature. Ineffective thermoregulation due to hypo- or anhidrosis (reported for all of our male patients and two-thirds of the females) presumably is an important factor causing the attacks (11,12). In adults, stress and alcohol intake can also trigger painful crises. The pain is often not responsive to common analgesic treatment, and over time may disappear as a result of progressive loss of nerve fibers; however, it may also increase in intensity (10,28). Quality of life is usually reported as "poor." Moreover, the frequent or chronic use of nonsteroidal antiinflammatory drugs can be linked even in children to GI and renal side effects.

Clinical signs of FD may be subtle and therefore missed if a physical examination is not thoroughly performed. For example, careful examination of the skin in the bathing trunk area may reveal clusters of reddish purple angiokeratomas. Such vascular skin lesions developed in almost all of the males and half of our female patients. Other skin color changes are usually absent. Slit-lamp examination can easily reveal a bilateral, whorl-like pattern of cream-colored lines in the cornea (cornea verticillata). The Fabry's small fiber neuropathy, however, is difficult to detect by conventional methods. The sensitive disturbances that are generally present can be demonstrated by measuring sensory (pain, thermal stimuli) thresholds. Skin reflex testing may be of interest for clinical studies but does not have diagnostic value (29,30). Large nerve fibers (Aα, Aβ) are generally spared in less advanced stages of FD and, therefore, deep tendon reflexes are usually conserved and nerve conduction studies as well as electromyography may not reveal abnormalities. For selected cases or for research purposes, cutaneous biopsies with intradermal innervation studies can be performed (30,31).

The majority of the patients for whom complete clinical data were available developed one or more of the serious disease complications that are generally seen in adulthood. As it could be expected, signs of progressive chronic kidney disease were more common in male patients; 40% had progressed to end-stage renal disease. Left ventricular hypertrophy, EKG abnormalities/arrhythmias, and valvular abnormalities were particularly prevalent in both sexes, whereas stroke and transient ischemic attacks occurred less frequently. Rheumatologists frequently see children and adolescents with transient or persistent distal extremity pain and the differential diagnosis includes a variety of disorders. In routine rheumatology practice, careful medical history taking, including the family history, physical examination, and laboratory tests, will provide important clues to the diagnosis of Fabry's neuropathy. In addition, it may eliminate other causes such as diabetes mellitus, vasculitis, infections (varicella zoster virus, *Borrelia*, human immunodeficiency virus), hereditary amyloidosis, acute intermittent porphyria, metabolic disorders such as Refsum and Tangier disease, erythromelalgia, and mercury intoxication.

The availability of ERT for FD has greatly changed the prognosis. It usually has a strong positive impact on pain (32). Early diagnosis is of utmost importance in order to prevent irreversible organ damage. This is demonstrated by the example of the patient we described, who had a very poor quality of life and started ERT only at age 28 years, since diagnosis was not suspected before. However,

he died 13 years later. The same concept applies to other inherited lysosomal storage diseases such as type I mucopolysaccharidosis (MPS I), for which a specific therapy is also available. We have previously shown that children with MPS I who present with joint contractures may be undiagnosed for decades, and have underlined the important role of the rheumatologist in diagnosing these patients (33). Neonatal screening for metabolic disorders (e.g., phenylketonuria) exists in many countries, but both of these lysosomal storage diseases are not included in such programs. A number of different specialists may be involved in diagnosing late-stage patients, but the rheumatologist is in a unique position to pick up the early hallmark of FD, the painful peripheral small fiber neuropathy, and accelerate the diagnostic process.

Descriptive data from the patients with FD monitored at our center were collected retrospectively and the questionnaire response rate was suboptimal. Therefore, we cannot precisely infer prevalence data; nevertheless, it is important to note that a proportion of FD patients presented at a young age with pain in the extremities either as the only symptom or coinciding with other early symptoms. Since pain is most intense in the hands and feet and is frequently associated with fever, misdiagnosis of juvenile idiopathic arthritis or connective tissue disorder is common. It has also been shown by a survey that awareness of FD among adult and pediatric rheumatologists is low (34).

In conclusion, pediatric rheumatologists should be aware of the clinical characteristics of FD and include this disorder in the differential diagnosis of distal extremity pain. Increased awareness should lead to earlier diagnosis and treatment by ERT, which is likely to improve the clinical outcome.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. Cimaz had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Pagnini, Borsini, Cecchi, Frullini, Cimaz.

Acquisition of data. Pagnini, Borsini, Cecchi, Frullini, Cimaz.

Analysis and interpretation of data. Pagnini, Borsini, Cecchi, Sgalambro, Olivotto, Frullini, Cimaz.

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