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Article

Erysipelas in Patients with Classic Fabry Disease

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Abstract: Background: Fabry disease is a rare, X-linked, lysosomal disorder caused by pathogenic variants in *GLA* and consequent deficient activity of alpha-galactosidase A, resulting in glycosphingolipid storage. Although many systemic manifestations of the disease have been documented, the association between Fabry disease and erysipelas has not previously been reported. Objective: To describe a case series of thirteen patients with Fabry disease and erysipelas and identify potential predisposing factors in this population. Patients and Methods: We retrospectively studied a cohort of 223 French patients with a confirmed molecular and enzymatic diagnosis of Fabry disease. Results: Twelve of the 223 patients with Fabry disease had experienced one or more episodes of erysipelas for a total of 70. All 12 patients had classic Fabry disease. There were ten males and two females, one of whom had highly skewed X chromosome inactivation silencing the wild type *GLA* allele. Lymphedema of the lower legs (10/11), male gender (10/12), and clinically advanced classic Fabry disease (11/12) were the characteristics identified in patients who experienced erysipelas. No patient with the later-onset form of Fabry disease had any episode of erysipelas. Conclusion: Our findings suggest that clinicians should be aware of the risk of erysipelas in patients with Fabry disease and promptly prevent or treat any skin wound or infection in those with lower limbs lymphedema.

Keywords: Fabry disease; erysipelas; lymphedema; expanded phenotype; dermatological manifestations

Introduction

Fabry disease (FD, OMIM #301500) is an X-linked genetic disorder of glycosphingolipid metabolism caused by a functional deficiency in the lysosomal enzyme alpha-galactosidase A (α-Gal A, EC 3.2.1.22) (Germain, 2010; Tuttolomondo et al. 2013; Wanner et al. 2023). The α-Gal A deficiency leads to the widespread deposition of neutral glycosphingolipids (primarily globotriaosylceramide (Gb3) and its deacylated derivative lyso-Gb3) in lysosomes and fluids throughout the body. The FD phenotype can be classified as classic or non-classic (also known as later-onset) (Cubellis et al. 2015). Patients with classic FD have little or no residual α-Gal A activity and generally start to experience the signs and symptoms of the disease such as neuropathic pain (Politei et al. 2016a), gastrointestinal problems, hypohidrosis and angiokeratoma in early childhood (Germain et al., 2019). The long-term manifestations of FD include proteinuric chronic kidney disease (CKD) (Ortiz et al., 2020), hypertrophic cardiomyopathy with cardiac arrhythmia (Linhart et al., 2020), hearing loss (Germain et al., 2002), and stroke (Rost et al., 2016). In some patients with FD, the Gb_3 deposits disrupt the microlymphatic network and ultimately produce lymphedema (Amann-Vasti et al. 2006, Alkhatib et al., 2023). According to data from the Fabry Registry (comprising patients with classic FD and patients with non-classic FD), the estimated prevalence of lymphedema in FD was 16.5% overall, 21.7% in males, and 12.7% in women, with no report of erysipelas (Alkhatib et al., 2023). Dermatological manifestations in Fabry disease were also reported using data from the Fabry Outcome Survery (FOS). Seventy-eight percent of males and fifty percent of females had at least one skin abnormality, the most frequent being angiokeratoma (in 67% males and 36% females, respectively), hypohidrosis

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(53% males, 28% females), telangiectasia (23% males, 9% females) and lymphedema (16% males, 6% females). No mention was made of erysipelas (Orteu et al. 2007).

Patients with later-onset FD have some residual α-Gal A activity and thus less severe sign and symptoms. The heart is often the only organ affected, although cardiac involvement may nevertheless be severe (Germain et al., 2018). FD phenotypes are well characterized in males but less so in heterozygous females, in whom X chromosome inactivation leads to greater variability in disease severity (Echevarria et al., 2016).

Erysipelas is a bacterial infection affecting the superficial layer of the skin, including the lymphatic vessels in the upper dermis. The disease is generally considered to be a subtype of cellulitis, although some authors consider that the latter is restricted to deeper skin layers. In Europe, the estimated incidence of erysipelas is 190–240 per 100,000 inhabitants per year (Goettsch et al., 2006; Bartholomeeusen et al., 2007). Breaks in the skin serve as entry points for bacterial invasion. The causative agent is usually a group A β-hemolytic *Streptococcus*, occasionally a group B, C, or G *Streptococcus,* and very occasionally *Staphylococcus aureus*. The diagnosis of erysipelas is essentially clinical; the disease typically manifests itself as a raised, well-demarcated, erythematous, tender, warm plaque. Erysipelas has to be differenciated from autoinflammatory diseases (Spierings et al., 2017) Along with the dermal signs and symptoms, patients may also experience systemic signs and symptoms like as fever, chills, malaise, and regional lymphadenopathy. If the erysipelas is not treated promptly, the potential complications include necrotizing fasciitis, thrombophlebitis, gangrene, and metastatic infection. A number of risk factors for incidence or recurrence of erysipelas have been identified : these may be local (e.g. lymphedema, venous insufficiency …) (Quéré et al. 2018) or general (Sapula et al. 2020, Bystritsky 2021, Li et al. 2021; Ren and Silverberg 2021, Burian et al. 2024)

To the best of our knowledge, there are no literature data on erysipelas in patients with FD (Kelmann 2023). Given the elevated incidence of lymphedema (a risk factor for erysipelas) in patients with FD, the objectives of the present study were to report on a case series of eleven patients with Fabry disease having experienced at least one episode of erysipelas and to delineate demographics, biological and clinical data extracted from those patients' medical records.

Patients and Methods

Subjects

In a retrospective, descriptive, observational case series, we analyzed the medical records of all individuals who experienced at least one episode of erysipelas among a cohort of 223 consecutive patients with FD followed at the French Referral Center for Fabry disease from January 1st, 2007, to March 31st, 2024. All patients with a confirmed pathogenic variant in the *GLA* gene (classic form : n=176, later-onset form : n=47) and one or more documented episodes of physician-diagnosed erysipelas were included.

Data Collection and Analysis

The data were collected from the patients' hospital records and, when necessary, during additional phone interviews with patients. Data on demographic variables (including sex, age at first erysipelas episode and, when applicable, age at death), Fabry disease (patient's phenotype, main signs and symptoms, *GLA* variant, and alpha-galactosidase activity), the characteristics of the erysipelas (the date of the first episode, number of episodes, and associated complications), and potential contributory or triggering factors (including the known risk factors for erysipelas, and comorbidities) were collected.

Results

Our retrospective analysis showed that 12 (all unrelated) of the 223 patients with FD followed at our referral center for Fabry disease and lysosomal storage disorders (www.centre-geneo.com)

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had experienced at least one episode of erysipelas (total number n=70) during the study period (Table 1).

Patient (P) #1: A male patient (currently aged 43) was diagnosed with FD at the age of 23, during family screening. He developed a first episode of left leg erysipelas at the age of 27. There were no known contributory or triggering factors. A standard 21-day course of oral antibiotic led to complete resolution of the infection. In the following 2 years, the patient experienced three additional episodes of erysipelas – all recurring on the left leg. The patient was given advice on hygiene. At the patient's last follow-up (at the age of 43), the erysipelas had not recurred. In the meantime, the patient had been diagnosed with stage G2A3 CKD (according to the Kidney Disease Improving Global Outcomes (KDIGO) classification), an aortic sinus of Valsalva aneurysm, frequent supraventricular extrasystoles (SVES), lymphedema, and hypohidrosis.

P#2: A male patient (currently aged 42 and diagnosed with FD at the age of 32 years, due to the presence of angiokeratomas) developed an initial episode of lower limb erysipelas at the age of 39. There were no known precipitating factors. Antibiotic treatment (oral amoxicillin, 1 g 3 times per day for 7 days) resolved the condition, and there were no complications. No erysipelas had not recurred at last follow-up. P#2 currently has stage G2A2 CKD, early signs of hypertrophic cardiomyopathy (HCM), persistent sinus bradycardia, left hearing loss and tinnitus, *cornea verticillata*, and vascular retinal tortuosity.

P#3: A male patient (currently aged 59) had been diagnosed with FD in childhood, during family screening. At the age of 40, he experienced a first episode of left leg erysipelas. There were no known precipitating factors. The condition recurred on the left forearm at the age of 49. In both instances, the infections resolved with oral antibiotic treatment without complications. The patient was given advice on hygiene, and erysipelas had not recurred at last follow-up. P#3 had suffered a stroke at the age of 34 and four separate transient ischemic attacks (TIAs) between the ages of 34 and 45. He received a kidney transplant at the age of 43, and currently presents with lymphedema, hypohidrosis, HCM with aortic root dilation, bilateral hearing loss, vertigo, tinnitus, intermittent diarrhea, myalgia, cold intolerance, and carpel tunnel syndrome.

P#4: This male patient had been diagnosed with FD at the age of 63, in a context of end-stage renal disease (ESRD). The patient presented a chronic lower limb venous disorder, hypohidrosis, heat intolerance, hearing loss, chronic diarrhea, and HCM when he experienced his first episode of erysipelas (in the lower limb) at the age of 61. The infection resolved with antibiotic treatment, and there were no complications. The patient's ESRD prompted the initiation of hemodialysis. The development of atrial fibrillation (AF) led to the implantation of a cardioverter-defibrillator. P#4 died from a stroke at the age of 68.

P#5: A male patient (currently aged 44) was diagnosed with FD at 18 years of age, after the observation of multiple angiokeratomas. He subsequently developed lymphedema, hypohidrosis, HCM and CKD. At 38 years of age, the patient developed erysipelas of the right hand that required surgical drainage and antibiotic treatment. There were no sequalae. No recurrence of erysipelas was observed at last follow-up. He currently has CKD stage G3bA2, HCM, first-degree atrioventricular block, tinnitus, heat intolerance, intermittent abdominal pain, and chronic diarrhea.

P#6: This male patient was diagnosed with FD at 42 years of age, in the context of ESRD. He had already experienced a first episode of erysipelas of the lower limb 3 years before diagnosis of FD, and three recurrences were observed after the diagnosis of FD. P#6 had severe lymphedema of the lower limbs and feet, hypohidrosis, and toe web intertrigo. All the episodes resolved with antibiotic treatment, and there were no complications. The fourth episode of erysipelas was the last observed. The patient also suffered from HCM, atrial fibrillation, diffuse cerebral subcortical atrophy, heat intolerance, and osteopenia. P#6 received a kidney transplant at the age of 51 and died at the age of 68.

P#7: A female patient was diagnosed with FD at the age of 64, following the discovery of left ventricular hypertrophy. A pacemaker had already been implanted for AF, and brain MRI showed white matter lesions. The patient had undergone a series of surgical operation: removal of a craniopharyngioma with sequelae (hypopituitarism, diabetes, and partial blindness), repair of a

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ruptured abdominal aortic aneurysm, bilateral knee replacement, carpal tunnel release, and multiple vein stripping operations. P#7 was subsequently diagnosed with stage G3bA3 CKD, lymphedema, hypohidrosis, and diarrhea and complained of abdominal pain. At the age of 65, she experienced an acute exacerbation of congestive heart failure following a severe, disseminated *Staphylococcus aureus* infection that had seeded from an episode of erysipelas. No previous episodes of erysipelas had been reported. The patient died 8 months later before X chromosome inactivation studies could be performed.

P#8: A male patient (currently aged 54) was diagnosed with FD at the age of 50, following the sudden onset of bilateral deafness. He also suffered from HCM, stage G3aA2 CKD, atrial fibrillation, New York Heart Association (NYHA) class 2 heart failure, chronic asthenia, severe lymphedema with positive Stemmer's sign, and hypohidrosis. The patient reported multiple (n=42) episodes of lower limb erysipelas (starting at the age of 33) and previous bilateral vein stripping. All infectious episodes resolved with antibiotic treatment, and there were no complications. Despite the initiation of enzyme replacement therapy (ERT), P#8 has experienced a further five episodes in the last four years for a total of seventeen erysipelas in his life. Prophylaxis with oral phenoxymethylpenicillin (1,000,000 IU, two times a day) was initiated in 2024 for the prevention of recurrent erysipelas (Vignes et al., 2021). Temporary interruption of oral phenoxymethylpenicillin recently resulted in the occurrence of another episode of erysipelas upon 48 hours of prophylaxis discontinuation by the patient.

P#9: A male patient (currently aged 50) was diagnosed with FD at the age of 43, in the context of family screening. He had CKD stage G2A2, HCM, a short PR interval, abdominal pain, frequent diarrhea, lymphedema, and hypohidrosis. Around the time of diagnosis, the patient experienced 3 episodes of erysipelas of the right leg; toe web intertrigo was the likely starting point. Erysipelas in the right leg recurred when the patient was 47. The infection resolved with oral antibiotic treatment, in the absence of complications. No other recurrence was noted at last follow-up. At the age of 43, the patient experienced a (sequela-free) TIA and a sudden but transient episode of hearing loss.

P#10: A male patient was diagnosed with FD at the age of 48, in the context of family screening. He experienced two episodes of erysipelas at the age of 35. The infections resolved with oral antibiotic treatment without complications. No other recurrence of erysipelas was documented at last follow-up. The patient experienced two TIAs and a sub-tentorial hemorrhage and also presented HCM, ischemic cardiomyopathy, chronic asthenia, lymphedema, and hypohidrosis. Chronic kidney disease progressed to ESRD, and the patient received a kidney transplant (followed by a cytomegalovirus infection) at the age of 51. He died at the age of 56.

P#11: A female patient was diagnosed with FD at the age of 29, during family screening. Her X-chromosome inactivation profile was highly skewed (0%/100%) with the wild-type *GLA* allele fully silenced. She had CKD, non-sustained supraventricular tachycardia, *cornea verticillata,* hearing loss, vertigo, osteopenia, lymphedema of the lower limbs, hypohidrosis, and asthma. At the age of 41, she developed lower limb erysipelas; the likely origin was toe web intertrigo and mycosis. The infections resolved with antibiotic and antifungal treatment and did not recur or result in any complications. No recurrences of erysipelas were documented at last follow-up. The patient (currently aged 48) has developed left HCM with right bundle branch block and end stage renal disease (ESRD) requiring hemodialysis.

P#12: A 55-year-old male patient was diagnosed with FD at the age of 44 by next generation sequencing (genes panel) for hypertrophic cardiomyopathy. He had two strokes at age 45 and 47 while on enzyme replacement therapy (agalsidase beta) with neutralizing antibodies. He was switched to pharmacological chaperone therapy due to the theoretical amenability of its *GLA* variant (p.N34H) (Benjamin et al. 2017). However progressive kidney deterioration reaching CKD stage on migalastat therapy prompted reverse switch to enzyme replacement (agalsidase alfa). The patient condition has been stable on agalsidase alfa with the exception of two episodes of erysipelas of the right lower limb on which he has moderate lymphedema. He was successfully treated with amoxicillin.

All of the 12 patients (10 males and 2 females) were French. The age on inclusion ranged from 42-59 years (mean ± standard deviation (SD): 50 ± 6.4). Four patients died; the age at death ranged

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from 56 to 68 years (mean ± SD: 63 ± 5.7); none of the deaths was related to erysipelas. All patients had a confirmed molecular diagnosis of FD (7 missense, 2 nonsense, 1 frameshift, 1 indel and 1 splice-site *GLA* variant). All male patients had classic FD and extremely low (<1.5%) residual levels of α-galactosidase activity. The two female patients show various manifestations of FD: P#7 had residual level of α-galactosidase activity (1.5 µmol/h/mg, when the norm is >2.0), a variety of signs and symptoms of classic FD, but late initiation of ERT. P#11 has classic FD with a highly skewed X-inactivation profile with complete silencing of the wild-type allele in four tissues (Echevarria et al. 2016), no residual α-galactosidase activity and multisystem clinical involvement.

The most frequently observed manifestations of Fabry disease before the onset of erysipelas were lymphedema (in 10 of the 11 patients with data), hypohidrosis/anhidrosis (10 out of 12), proteinuria (in all 12), CKD (10 out of 12), rhythm disorder (11 out of 12), hypertrophic cardiomyopathy (9 out of 12) and angiokeratoma (8 out of 12). The mean ± SD age at the time of the first episode of erysipelas was 46 ± 10.6 (range: 27-65), and most of the episodes affected the lower limbs (11 out of 12). There were no complications of erysipelas except for P#7 (disseminated infection during the second episode of erysipelas). When considering potential additional risk factors for erysipelas, ten patients had lymphedema, three patients were overweight, three had varicose veins, two had mycosis, and two had toe web intertrigo. The two youngest patients at the time of the first episode of erysipelas (P#1 and P#2) had no known risk factors.

Data sharing with an Italian expert center in the context of the MetabERN European reference network (ERN) led to the identification of a 37-year-old Italian male patient (P#13) who had been diagnosed with FD in 2001 through family screening. A pathogenic variant (c.860G>A, p.Trp287*) was disclosed in *GLA* in association with the classic phenotype of the disease. The patient had suffered of episodes of fever *sine materia*, hyperidrosis, and acroparesthesia from the age of 7 years. Physical examination revealed angiokeratoma, *cornea verticillata*, and lymphedema of the lower limbs. The patient experienced a stroke at age 47 with left hemiparetic syndrome. A first episode of erysipelas of the left leg (the paretic leg) occurred at age 49, and was treated with oral antibiotics, with complete *restitutio ad integrum.* At the age of 50, the patient had a second episode of erysipelas at the left leg, preceded by fever. He was treated with antibiotics and below-knee gradient compression stockings with full recovery. At the age of 52 years, a third episode of erysipelas of the left leg was diagnosed and treated with antibiotics, with no sequelae. At age 56, he was admitted for a second stroke while chronic kidney disease stage 3A and hypertrophic cardiomyopathy had developed despite enzyme replacement therapy (with poor adherence from the patient). He died of pulmonary embolism following deep venous thrombosis at age 57.

Table 1. Summary of the characteristics of the 13 patients, with a focus on the existing signs and symptoms prior to the first episode of erysipelas.

Patients	P#1	P#2	P#3	P#4	P#5	P#6	P#7	P#8	P#9	P#10	P#11	P#12	P#13
Demographic variables													
Age	43	42	59	NA	44	NA	NA	54	49	NA	48	55	NA
Age at death	NA	NA	NA	68	NA	68	65	NA	NA	56	NA	NA	57
Sex	M	M	M	M	M	M	F	M	M	M	F	M	M
Characteristics of FD													
Age at diagnosis of Fabry disease	23	32	50	63	30	47	65	50	45	49	30		37
GLA variant cDNA	c.118C>T	c.678G>A	c.979C>A	c.1185dupG	c.778G>A	c.916C>T	c.823_825del	c.798T>A	c.1145G>A	c.1000-1G>A	c.154T>C	c.100A>C	c.860G>A
a-Gal amino-acid change	p.P40S	p.W226*	p.Q327K	p.F396Vfs*3	p.G260R	p.Q306*	p.L275del	p.D266E	p.C382Y	NA	p.C52R	p.N34H	p.W287*
Phenotype	Classic	Classic	Classic	Classic	Classic	Classic	Classic	Classic	Classic	Classic	Classic	Classic	Classic
α-Galactosidase activity (%)	1.5	0.0	1.3	0.1	0	0.25	15	0.0	0.1	0.9	0.0	NA	NA

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Pre-treatment plasma lyso-Gb3 (ng/mL)	NA	74.4	NA	151.9	NA	NA	8.4	54.2	NA	101	20.3	NA	NA
FD specific treatment	ERT	ERT	ERT	ERT	ERT	ERT	ERT	ERT	ERT	ERT	ERT	ERT switch to chaperon, switched back to ERT	ERT
Age at treatment initiation	23	33	36	64	29	47	65	50	43	49	34	30	37
Cardiac symptoms	RD	RD	HCM, RD	HCM, RD	HCM, RD	HCM, RD	HCM, RD	HCM, RD	HCM, RD	HCM	HCM, RD	RD	HCM
Chronic kidney disease stage	G1 A3	G1 A2	G4 A3	G5 A3	G3 A3	G3 A3	G3 A2	G3 A2	G2 A2	G4 A3	G4 A2	G4 A2	G3 A2
Acroparesthesia	Yes	Yes	Yes	No	Yes	Yes	No	No	Yes	No	Yes	NA	Yes
CNS involvement	No	TIA	Stroke	No	No	No	Stroke	No	TIA	No	No	Stroke	Stroke
Angiokeratomas	Yes	Yes	Yes	Yes	Yes	No	No	Yes	No	Yes	Yes	NA	Yes
Hypohidrosis	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	NA	Yes
Lymphedema	NA	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	NA	Yes
Characteristics of erysipelas													
Number of episodes	4	1	2	1	1	4	1	42	4	2	1	2	1
Age at 1st episode	27	37	40	61	38	39	65	33	43	35	41	55	49
Body part affected by 1st episode	Lower limb	Lower limb	Lower limb	Lower limb	Upper limb	Lower limb	Lower limb	Lower limb	Lower limb	Lower limb	Lower limb	Lower limb	Lower limb
Metastatic infection	No	NA	No	NA	NA	NA	Yes	No	NA	Yes	No	No	No
Contributing factors													
Neutropenia	No	No	No	No	No	No	No	No	No	No	No	No	No
Integrity of the skin barrier	NA	NA	NA	NA	NA	Plantar hyperkeratosis	Pruritus	Severe lymphedema	Intertrigo	Mycosis	Mycosis	NA	No
Venous disease	No	No	No	Previous vein stripping	Varicose veins	Chronic dermohypodermitis	No	Bilateral saphenectomy	No	No	No	No	No
Obesity	No	No	Yes	No	Yes	No	Yes	No	No	No	No	No	No
Diabetes mellitus	No	No	No	No	No	No	No	No	No	No	No	No	No

P: patient; M: male; F: female; FD: Fabry disease; NA: not available; lyso-Gb3: globotriaosylsphingosine; ERT: enzyme replacement therapy; RD: rhythm disorder; TIA; transient ischemic attack.

Discussion

Our results constitute the first report of a case series of erysipelas in patients with classic Fabry disease. Among a cohort of 223 patients with confirmed Fabry disease followed at our national referral center for Fabry disease (http://www.centre-geneo.com), 12 patients were diagnosed with at least one erysipelas (for a total of 70 episodes of erysipelas in total). The association of erysipelas with Fabry disease had not been previously described in the literature. Sharing our data with Italian colleagues in the setting of the MetabERN European Reference Network led to the identification of a thirteenth patient who presented with four confirmed episodes of recurrent erysipelas. Our observations suggest that erysipelas is a previously unrecognized complication of Fabry disease-related lower limbs lymphedema.

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Clinical Implications

The occurrence of erysipelas in a patient with FD has significant clinical implications. Firstly, patients may be vulnerable to the infectious sequelae of erysipelas: antibiotic therapy and wound care treatments must therefore be implemented judiciously while taking account of FD-associated comorbidities and potential drug interactions. Secondly, the recurrent nature of erysipelas described in the literature and observed in 8 of the 13 patients of this case series, underscores the need for preventive measures and close monitoring, particularly if lymphedema is present (Brouillard et al. 2021). Proactive measures (including prompt recognition of intertrigo or skin wound, early initiation of oral antibiotic therapy, skin hygiene education, and diligent wound care) are paramount in optimizing clinical outcomes and minimizing the impact of erysipelas on FD progression.

Underlying Mechanisms

The mechanisms underlying the link between FD and erysipelas have yet to be identified. One can nevertheless speculate that several factors including lower limb lymphedema, a known risk factor of erysipelas (Cannon et al. 2018, Quéré et al. 2018, Brouillard et al. 2021) but also microvascular dysfunction, an impaired immune response, chronic inflammation, hypohidrosis may all contribute. In our series, lymphedema preceded erysipelas in 11 of the 13 patients with available data and appeared as a key predisposing factor. Apart from lymphedema, microvascular dysfunction is a prominent feature of FD and manifests itself through endothelial cell damage, impaired vasomotor regulation, and aberrant angiogenesis (Altarescu et al. 2002; Demuth and Germain 2002). These microvascular perturbations may compromise tissue perfusion and predispose patients with FD to skin damage, bacterial invasion, and thus greater susceptibility to erysipelas. The dysregulation of the immune system in FD (as characterized by aberrant cytokine profiles, impaired leukocyte function, and altered inflammatory responses) compromise the host's defenses against bacterial pathogens. Furthermore, the chronic inflammatory state in FD (Rozenfeld and Feriozzi 2017) might exacerbate susceptibility to cutaneous bacterial infections like erysipelas. Hypohidrosis (Orteu et al. 2007) also compromises the skin barrier and facilitates bacterial invasion. Lastly, the deposition of glycosphingolipids within the vascular endothelium – a hallmark feature of FD (Nowak et al. 2022) – might exacerbate endothelial dysfunction (Choi et al. 2023) and exacerbate a pro-inflammatory milieu conducive to the development of erysipelas.

Anecdotally, patients with hereditary fibrosing poikiloderma with tendon contractures, myopathy, and pulmonary fibrosis (POIKTMP), another genetic disorder present with lymphedema and hypohidrosis as seen in many patients with FD, (Arowolo et al., 2022). The fact that erysipelas has been documented in approximately 8% of POIKTMP patients suggests that the pathogenic mechanisms underlying erysipelas may be, at least in part, similar in these two genetic disorders and further highlights the role of lymphedema as a risk factor for occurrence of erysipelas (Cannon et al. 2018, Quéré et al. 2018, Brouillard et al. 2021, Vignes et al. 2021).

In contrast, a literature search for an increased prevalence of erysipelas in other genetics diseases of the skin (including epidermolysis bullosa, ichthyosis, palmoplantar keratoderma or pseudoxanthoma elasticum, …) failed to retrieve an increased prevalence of erysipelas in genodermatosis with the exception of primary lymphedema (Vignes et al. 2021). Similarly, a literature search for erysipelas as a complication of other lysosomal storage diseases did not evidence any report.

Impact on Disease Progression

The recurrent erysipelas might exacerbate the disease burden, including fatigue and worse overall quality of life (Smith et al. 2018, Li et al. 2021) – particularly in individuals with concomitant renal, cardiac or neurological manifestations prompting for prophylaxis or early intervention aiming at reducing the recurrence of erysipelas in patients with Fabry disease.

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Conclusions

Our case series highlights that patients with Fabry disease are at risk for erysipelas, shedding light on a previously unrecognized complication of the disease. Lower limb lymphedema appears to be a frequent predisposing factor. Awareness of the risk calls for greater vigilance and proactive management strategies for preventing the occurence and mitigating both acute symptoms and long-term sequelae of erysipelas (International Society of Lymphology 2013, Bystritsky 2021, Burian et al., 2024) in patients with Fabry disease.

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