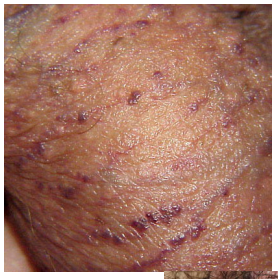

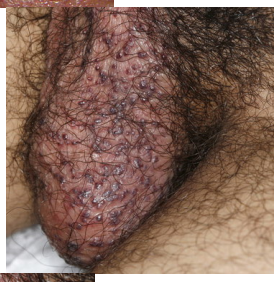

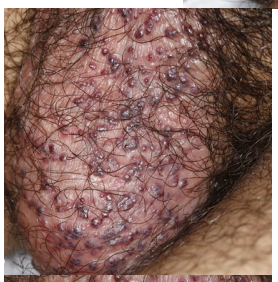

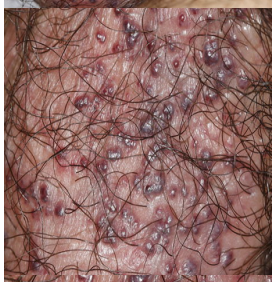

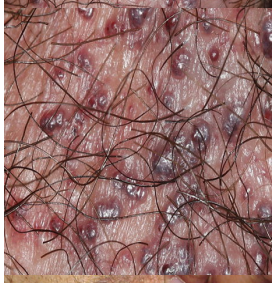

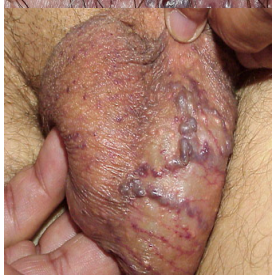

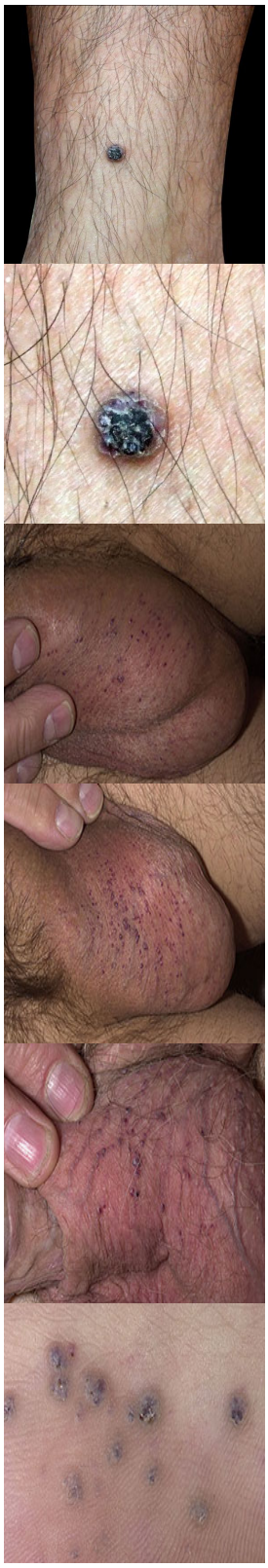

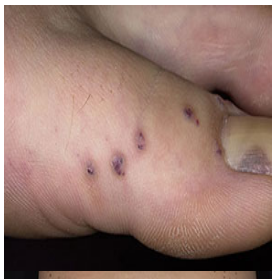

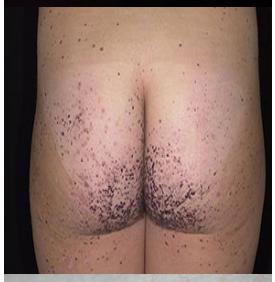

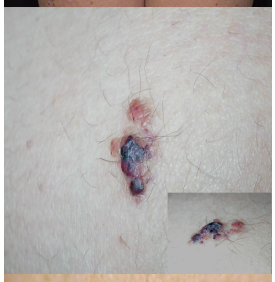

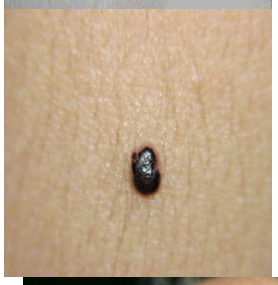

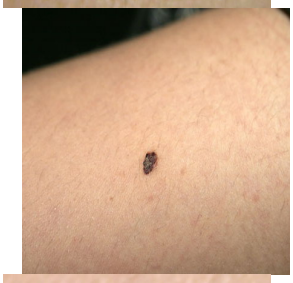

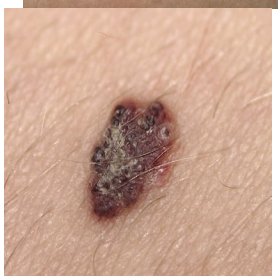

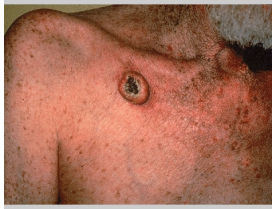

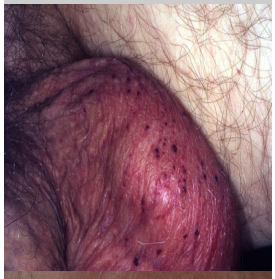

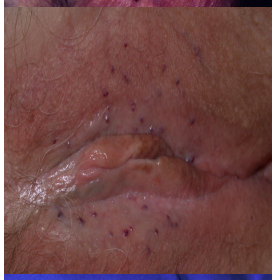

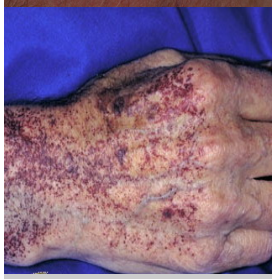

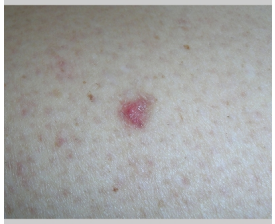

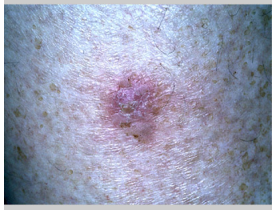

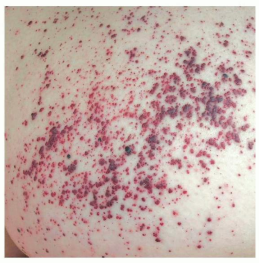

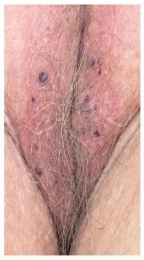

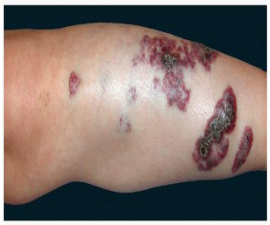

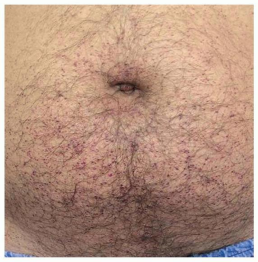

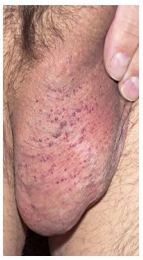

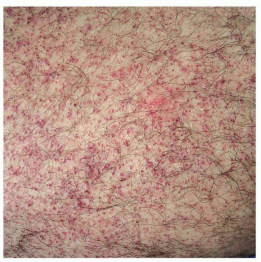

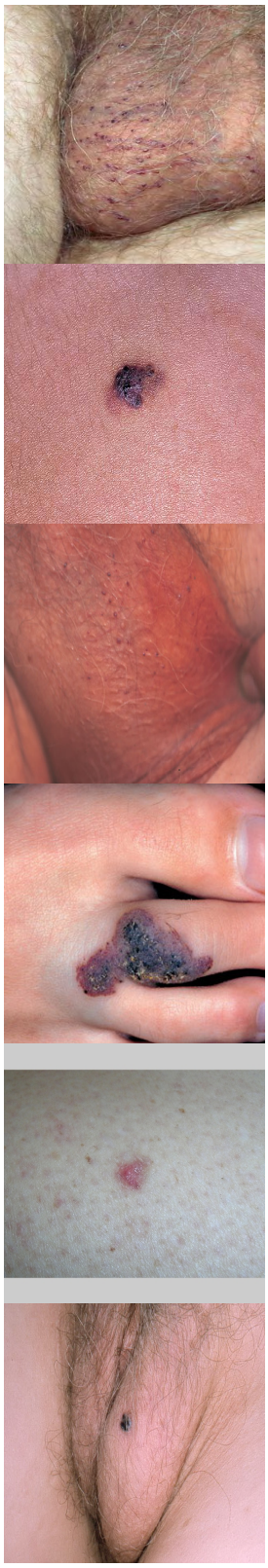

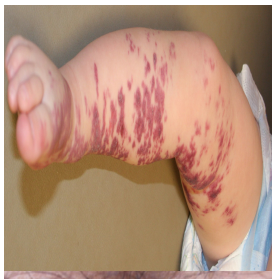

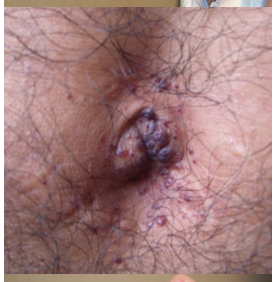

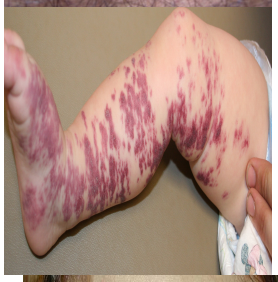

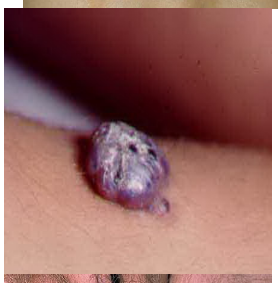

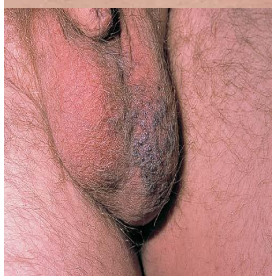

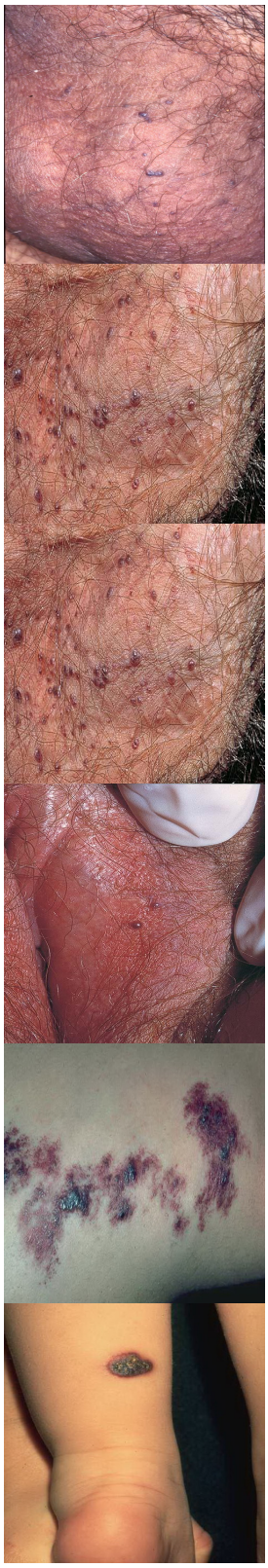

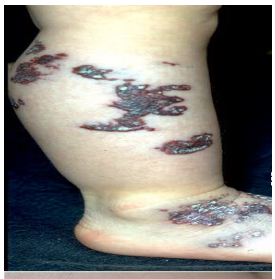

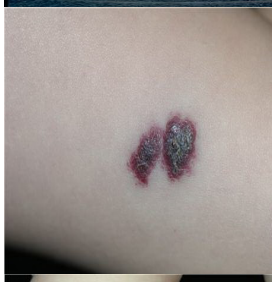

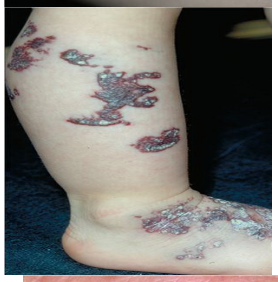

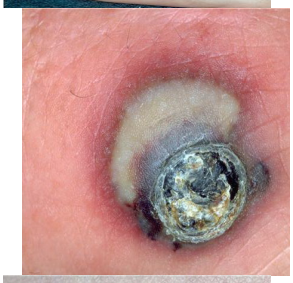

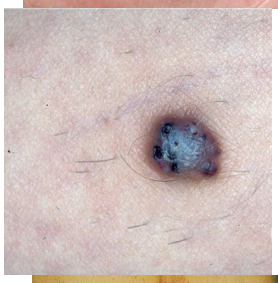

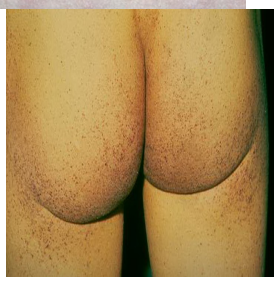

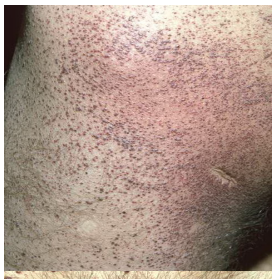
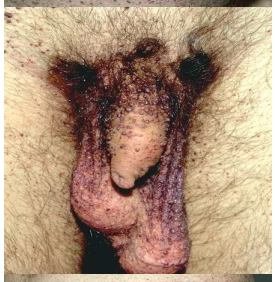
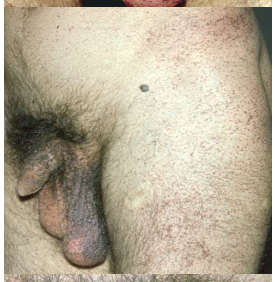
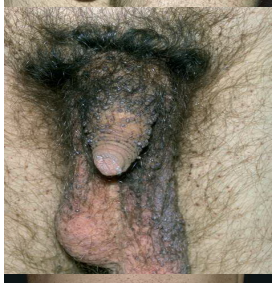
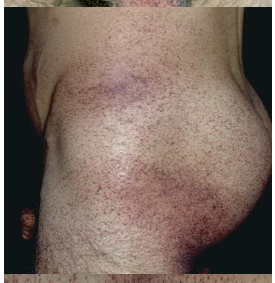
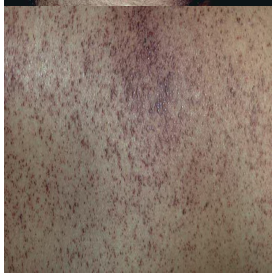

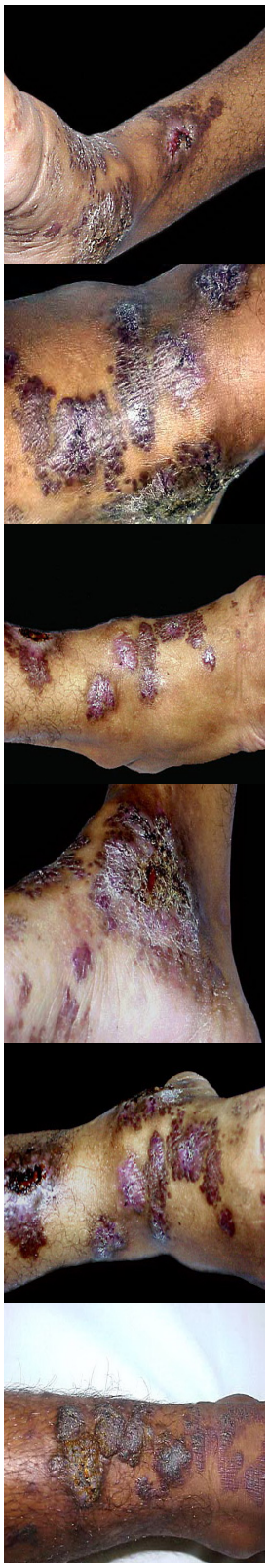

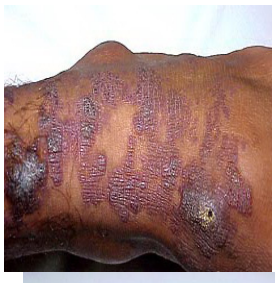

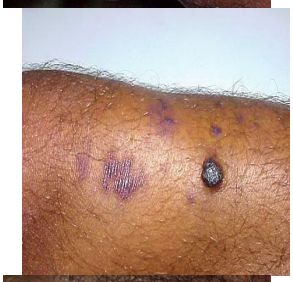

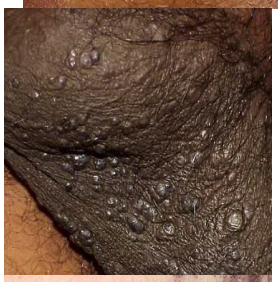

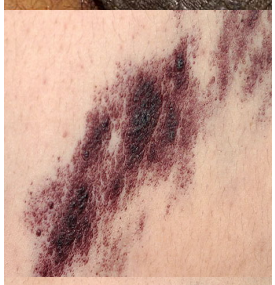

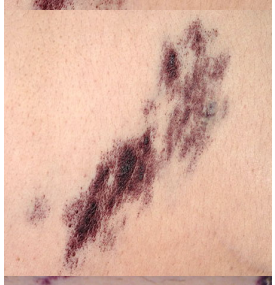

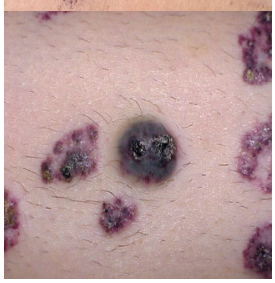

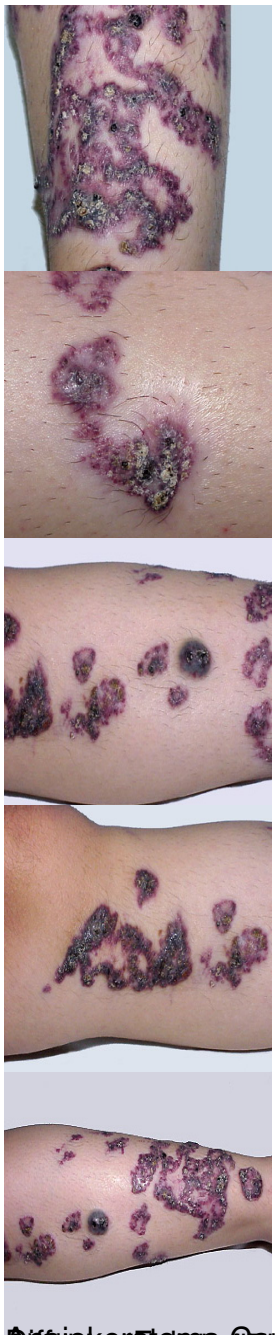

Angiokeratoma Corporis [illegible] by a

Pathophysiology

A defect in the activity of alpha-galactosidase, a lysosomal enzyme, results in the insidious storage of 2 neutral glycosphingolipids: trihexosylceramide (galactosylgalactosylglucosylceramide) and digalactosylceramide (galabiosylceramide). These glycosphingolipids accumulate in many different types of cells. The most affected are the vascular endothelium and smooth muscle cells. Deposition of glycosphingolipids can be attributed to both endogenous production and diffusion of material from the circulation. As a result of the lack of this lysosomal enzyme that breaks down the glycolipid, persons with Fabry disease have 3-10 times the normal amount in their serum.

Larralde et al[3] have extensively explained the mechanism behind Fabry disease. The enzymatic defect in Fabry disease results in the accumulation of uncleaved glycosphingolipids in many human cell types. Particular types consist of endothelial cells, blood vessel cells, pericytes, vascular smooth muscle cells, renal epithelial cells, myocardial cells, skin structure cells, neuronal cells, and corneal cells.

Persons with Fabry disease who have type AB or B blood also accumulate blood group B glycosphingolipids (those with alpha-galactosyl-terminated residues) and can have more severe Fabry disease (related to greater body substrate mass) than patients with blood group A. This is because these blood groups have 2 additional terminal alpha-galactosyl moieties.

Specifically, deposits in lysosomes of endothelial, perithelial, and smooth muscle cells of blood vessels cause swelling into the hollow bore of the blood vessel. In so doing, the vessels are narrowed and reactively expand, which leads to ischemia and infarction. This occurs, to a greater or lesser extent, in all affected cells, underlying the protean manifestations of Fabry disease.

In 2004, Larralde et al[3] report that most families have "private" mutations (ie, mutations found only in that particular family). Fabry disease is transmitted in an X-linked recessive pattern. The gene is located at band Xq22. Similar to other entities with this inheritance pattern, hemizygous males are most severely affected. The female carrier of this disease has diminished levels of alpha-galactosidase, which is enough to cause some symptoms but also to be spared the full clinical manifestations. Deficient alpha-galactosidase A activity can be present in the plasma in persons who do not have the full manifestations of Fabry disease. The deficiency must be extensive for full effects to manifest.

Molho-Pessach et al,[4] in 2007, reported a 36-year-old Arab woman with beta-mannosidosis who presented with mental retardation and multiple angiokeratomas with a novel null mutation involving a G → A transition in exon 6 at nucleotide position c.693, resulting in the formation of a stop codon (W231X).

Frequency

United States

Angiokeratoma corporis diffusum (Fabry disease) is rare; the estimated incidence is 1 case per 40,000 population. Others believe this prevalence is an overestimation. According to Larralde et al,[3] inheritance of the abnormal gene among whites (resulting in a hemizygous boy or a heterozygous girl) has been estimated to occur once in every 117,000 live births.

International

Most occurrences of angiokeratoma corporis diffusum (Fabry disease) are in whites; however, Fabry disease has been reported to occur in black persons, Latin Americans, Native Americans, Egyptians, and Asians.

Mortality/Morbidity

Before the advent of enzyme replacement therapy, renal failure secondary to uremia and hypertension was the major cause of death for men with angiokeratoma corporis diffusum (Fabry disease) aged 30-39 years, followed by congestive heart failure and cerebrovascular accidents. Currently, mortality due to renal pathology seems to be decreasing, leaving cardiac issues as an increasing cause of morbidity and mortality among patients with Fabry disease.[5]

Heterozygous females develop angiokeratomas and cataracts and experience a milder clinical course. Some patients may have more serious involvement; however, lifespan is longer for women than for men diagnosed with this disease.

Hormonal function and fertility rates are normal in both male and female Anderson-Fabry patients compared with controls.

A variety of clinical findings occur in female carriers. The scope is vast and ranges from asymptomatic carriers to carriers with fully expressed Fabry disease. Asymptomatic corneal dystrophy occurs in approximately 70% of carriers. This is an indication of the carrier state. Approximately 30% of female carries have angiokeratomas, with less than 10% having paresthesias. A 2004 study by Larralde et al[3] of obligate female carriers found significant disease manifestations in 20 of 60 women. Another study performed on 20 carriers of Fabry disease showed that each woman had some symptom of Fabry disease, with a wide scope of manifestations. Larralde et al [3] concluded that Fabry disease might be designated a storage disease transmitted as an X-linked–dominant, not X-linked–recessive, disease.

Clinical

History

Angiokeratoma corporis diffusum (Fabry disease) is variable in its clinical symptoms and, as a result, can be a challenge to define if it does not manifest in classic fashion or in a person whose family is not known to have Fabry disease. The classic presentation of Fabry disease is a male with initial manifestations occurring in childhood or adolescence. The initial findings are intermittent or chronic paresthesias and episodes of severe acral and/or GI distress (Fabry crisis), heat intolerance, hypohidrosis or anhidrosis, and generalized angiokeratomas.

If the diagnosis is missed, it will, in almost all cases, be made when a patient presents with (1) end-stage kidney failure or (2) cardiac or cerebrovascular pathology with early mortality. If the disease is milder (intermediate forms), it may not be diagnosed until late adulthood.

Some variants of Fabry disease only have renal and/or cardiac pathology and no angiokeratomas. A physician can establish that a patient has Fabry disease by searching for low activity of alpha-galactosyl A in plasma, leukocytes, cultured skin fibroblasts, or dried blood spots on filter paper.[3] Because of the Lyon effect, enzymatic detection of carriers can be misleading; thus, specific genetic analysis can be helpful in making the diagnosis.

In its typical form, Fabry disease starts in early childhood and manifests with constant acral paresthesia (acroparesthesia, ie, chronic burning, neuropathic tingling, or unmitigated acral discomfort). Intermittent Fabry crisis is the term for incapacitating sharp pain lasting minutes to days. This can occur in children, but it often stops occurring in adulthood. Crises can be triggered by any kind of stress, including disease, extremes in temperature, exercise, or emotional trauma. In addition to pain, a crisis can also manifest with fatigue, low-grade fever, and joint pain.[3]

The Fabry Registry[7] published the baseline demographic and clinical characteristics of the first 1765 patients enrolled in the Fabry Registry. Of these patients, 54% are males (16% aged <20 y) and 46% are females (13% aged <20 y). The median ages at symptom onset and at diagnosis are 9 and 23 years, respectively, for males and 13 and 32 years, respectively, for females. Frequent presenting symptoms in males include neurological discomfort and pathology (62%), skin signs (31%), gastroenterological signs (19%), unspecified renal pathology (17%), and ophthalmological pathology (11%). Frequent presenting symptoms in females include neurological pain (41%), gastroenterological symptoms (13%), ophthalmological symptoms (12%), and skin eruptions (12%).

In men and women with Fabry disease reporting renal progression, the median age at occurrence was 38 years for both men and women. In men and women with Fabry disease reporting an onset of cerebrovascular and cardiovascular events, the median age at occurrence was 43 and 47 years, respectively, for females, and 38 and 41 years, respectively, for males.

Recurrent fevers and vague pain in the hands and feet, resulting in periodically incapacitating pain in the fingers, toes, and occasionally the entire extremity, usually precede physical signs of Fabry disease. Typically, fever, heat, cold, and exertion trigger pain. Paroxysmal vertigo has occurred as an initial manifestation of Fabry disease, which may initially help to establish the diagnosis.

In 2007, Moeller and Jensen[8] noted that females with Fabry disease who present with pain and neurological symptoms are often not appropriately assessed and are misdiagnosed. This is likely because many physicians assume that Fabry disease's X-linked pattern of inheritance

means it cannot occur in women.

As stated, the second type of pain is a nagging, chronic, constant discomfort in the hands and feet, characterized by burning tingling paresthesias.

Some patients with Fabry disease manifest with chronic exercise-induced pain, fasciculations, and cramps of the feet and legs. This can affect other members of their families.[9]

Subsequently, angiokeratomas develop, which are the typical skin lesions for which the disease is named. Angiokeratomas usually manifest after puberty and increase in number with age; they can become generalized and involve the mucosa. Angiokeratomas occur as a result of lysosomal storage of Gb3 in cutaneous endothelial cells. This results in impairment of capillary wall integrity and the development of secondary ectasias.

Atypical presentations can occur. In 2005, Choudhury et al[10] reported an 11-year-old boy with Fabry disease who had a 6-year history of widespread petechia, rare papules with an overlying crust, and acral paresthesias of the hands and feet.

Not every case of angiokeratoma corporis diffusum is due to Fabry disease. An idiopathic or cutaneous variant of angiokeratoma corporis diffusum has been described as a discrete clinical category of disease occurring only in the skin in persons with no metabolic disease or lysosomal defect.

Ocular changes may be detected during the disease course. Although ocular involvement may be extensive (affecting the lens, cornea, conjunctiva, and retina), visual impairment is unusual. The fact that Fabry disease does not compromise ocular acuity is notable. It is sometimes a useful finding that helps diagnose Fabry disease. Fabry disease is commonly associated with a corneal opacity that can only be noted with slitlamp biomicroscopy. This corneal opacity shows a whorled pattern. Persons with Fabry disease sometimes manifest anterior capsular deposits in the lens or granular spokelike deposits on the posterior lens, termed Fabry cataract.[3]

Patients may develop chronic edema of the feet before true renal or cardiac dysfunction.

A history of heat intolerance secondary to hypohidrosis is often noted.

With the relentless progression of the disease, cardiac infiltration can result in angina, myocardial infarction, mitral valve prolapse, congestive heart failure, hypertension, mitral insufficiency, and left ventricular hypertrophy. Other cardiac findings may include angina pectoris, aortic outflow abnormalities, arrhythmia, coronary artery disease, myocardial infarction, myocardial ischemia, ECG abnormalities, valvular lesions, varicose veins, and altered vasomotion.

Similarly, glycolipid deposits in the CNS result in paresis, seizures, hemiplegia, labyrinthine disorders, aphasia, tremor, sensory disturbances, and loss of consciousness.

Renal pathology is one of the hallmarks of Fabry disease and is the most frequent cause of death, usually when patients are aged 30-50 years. Note the following renal findings:

- Polyuria due to concentration defects can be among the first manifestations of kidney malfunction but, in many cases, does not prompt testing that leads to a diagnosis. [3] As persons with Fabry disease approach age 20 years, proteinuria increases as the patient ages.

- Polarization microscopy of the sediment of urine demonstrates birefringent lipid globules (ie, renal tubular epithelial cells or cell fragments with lipid inclusions) with the characteristic Maltese cross configuration.
- Birefringent inclusions in the urinary sediment (ie, fat-laden epithelial cells or mulberry cells) may be noted.
- While protein, red blood cells, casts, desquamated urinary tract cells, and the characteristic Maltese crosses of lipid globules can be seen in childhood, the kidneys do not exhibit signs of deterioration until the patient is older. By middle age, azotemia and progressive proteinuria reflect deteriorating renal function. Uremia usually ensues and heralds end-stage renal disease.

When the GI system is affected, a patient with Fabry disease has a history of intermittent nonbloody diarrhea and proctocolitis.

Rheumatologically, patients may have arthritis of the distal interphalangeal joints with some loss of motion and limitation of movement of the temporomandibular joints.

Angiokeratoma corporis diffusum is linked to beta-mannosidosis. Mental retardation, hearing loss, and renal failure are also linked to angiokeratoma corporis diffusum. In one case, the activity level of beta-mannosidase in the patient's plasma was 2% of the normal range, while the level in the patient's mother was 40%.[2]

Persons with Fabry disease have a high rate of subclinical hypothyroidism.

Other nervous system findings of Fabry disease include headache, hearing loss, psychologic/psychiatric disease, tinnitus, tremors, vertigo, and aphasia.

Depression is common in adults with Fabry disease and is an underdiagnosed problem.[11]

Dominguez et al,[12] in 2007, found that restless legs syndrome is common in Fabry disease patients and is associated with neuropathic pain.

Physical

Physical findings involve the skin, heart, lungs, extremities, eyes, and neurologic system.

Skin findings are as follows:

- The hallmark of the disease, angiokeratoma, is a lightly verrucous, deep-red to blue-black papule varying in size from punctate to 0.5 cm.
- Early, small lesions may not be hyperkeratotic; however, as lesions age and enlarge, their surfaces become somewhat crusty. Discrete verrucous overgrowth can occur.
- Great variation in lesion size is evident, making patients appear as if they are "peppered with buckshot."
- The papules of Fabry disease are symmetric and do not blanch with pressure (diascopy negative).

- Angiokeratomas can appear almost anywhere; however, typically they spare the face, scalp, and ears. Lesions tend to concentrate between the umbilicus and the knees, with a predilection for the scrotum, penis, lower back, thighs, hips, buttocks, and lips. Some authors have stated that the angiokeratomas occur in the "bathing trunk" area.
- Patients with Fabry disease can have scant body hair.
- Other skin findings include varicose veins, stasis-related edema, lymphedema of the arms and legs, and edematous upper eyelids.

Cardiac findings are as follows:

- Fabry disease is associated with a high prevalence of cardiac morbidity. In 2007, Linhart et al [13] noted that while Fabry disease has well-described associations with microvascular disease, deficiency of GLA is associated with premature macrovascular events such as stroke and, likely, heart attack.
- Sadick and Thomas[14] studied the heart pathology in 12 patients and reported that 5 had cardiovascular symptoms, 9 had left ventricular hypertrophy on ECG tracings, 1 had a short PR interval, 3 had epicardial coronary disease, 4 had a rat-tail appearance on left-sided ventriculogram images, and 6 were assessment by myocardial biopsy, which demonstrated extensive vacuolation of the myocytes on light microscopy and concentric, myelinoid lamellar cytoplasmic inclusion bodies on electron microscopy.
- Alterations in parameters as reported by Sadick and Thomas[14] were (1) traditional parameters of diastolic function, including peak E velocity, peak A velocity, and deceleration time, were no different between Fabry disease patients and normal controls; (2) isovolumic relaxation time was significantly prolonged in Fabry disease patients; (3) pulmonary venous atrial reversal duration exceeded that of mitral A wave duration in patients with Fabry disease; and (4) septal E' velocity with Doppler tissue imaging was much lower in Fabry disease patients compared with normal controls.

- Murmurs associated with mitral regurgitation and stenosis may be heard.
- Left ventricular hypertrophy is apparent in patients with more advanced disease.
- Signs of congestive heart failure and hypertension are noted.

Pulmonary findings include wheezing respirations and dyspnea, which are frequent. Lymphedema and varicose veins are also common. Additionally, hearing loss can be a familial part of Fabry disease.[15] Vestibular and auditory deficits in Fabry disease patients are often responsive to enzyme replacement therapy. [16]

Ocular findings are as follows:

- Ocular changes may be specific, and the diagnosis may be made on the basis of ophthalmologic examination findings.
- Corneal changes vary from diffuse haziness to corneal opacities characterized by whorled streaks extending from a central point to the periphery of the cornea. This change is identical to chloroquine or amiodarone toxicity.
- Posterior capsular cataracts with whitish spokelike deposits of granular material may be seen. This type of cataract may be the first sign of ocular involvement and is so characteristic that it has been dubbed the Fabry cataract.
- Occasionally, aneurysmal dilatation of thin-walled venules is seen on the bulbar conjunctiva.
- Mild-to-marked tortuosity and angulation of the retinal vessels occur. Conjunctival vascular tortuosity may be the most common eye finding associated with Fabry disease.
- In a study of 25 patients with Fabry disease, Wasik et al found more bushy capillaries and clusters of vessels in persons with Fabry disease (72%) versus those without disease (10%). Seventeen of the patients were males who had not used enzyme replacement treatment. [17]

Neurologic findings include multifocal small vessel involvement, which may result in hemiplegia, hemianesthesia, balance disorders, and personality changes. Chiari type I malformation has been reported in some patients with Fabry disease and should be sought if apposite MRI screening is performed. The role of general screening for Chiari type I malformation is not clear. Chronic meningitis and thalamic involvement has been described in a woman with Fabry disease.[18]

Osteopenia and osteoporosis have been linked to Fabry disease.[19] Bilateral femoral head and distal tibial osteonecrosis have also been linked to Fabry disease. Osteopenia is common in Fabry disease patients. [20]

Gastrointestinal symptoms were found to be common patients with Fabry disease, as reported by Hoffmann et al in 2008. Symptoms were similar to inflammatory bowl disease; these symptoms improved with enzyme replacement therapy.[21]

Causes

A defect in the activity of alpha-galactosidase, a lysosomal enzyme, results in the insidious

storage of 2 neutral glycosphingolipids: trihexosylceramide (galactosylgalactosylglucosylceramide) and digalactosylceramide (galabiosylceramide). Angiokeratoma corporis diffusum is inherited in an X-linked recessive pattern.

Treatment
Medical Care

As a multisystemic disease, angiokeratoma corporis diffusum requires treatment by a number of specialists. Treatment is intended to extend the lifespan of affected patients and make their lives more comfortable, especially in light of the often excruciating pain they experience. Significant clinical improvement and enhancement of quality of life have been achieved with enzyme replacement therapy (ERT), in particular at the early stages of Fabry disease, with positive benefits for the cardiac and renal systems and a decrease in pain.

Early detection of Fabry disease has made extending the lifespan and improving the quality of life possible for these patients. The administration of recombinant human alpha-galactosidase or agalsidase beta replacement therapy can reverse and delay cardiac, renal, and neural damage to patients with Fabry disease. It is not clear which enzyme therapy is superior and both therapies are helpful at enhancing health.

Future treatments of Fabry disease that seem promising include (1) substrate deprivation based on the inhibition of an earlier step in the synthesis of the accumulating glycosphingolipid and (2) gene therapy.

Note the following treatments broken down by specialty:

- Dermatology: Carbon dioxide laser treatment can improve cosmetic appearance by removing angiokeratomas from the skin. Variable pulse width 532-nm Nd:YAG laser therapy, 578-nm copper vapor laser therapy, and flashlamp-pumped dye laser therapy can also be used to treat angiokeratomas. Hyperhidrosis can be treated with topical and systemic antiperspirant agents. Hypohidrosis or anhidrosis can be treated with moisturizers and topical applications of artificial lacrimal fluid and saliva.
- Nephrology: Renal insufficiency, the most common cause of mortality, can be treated with hemodialysis or kidney transplantation. Renal transplantation may benefit patients because it supplies a source of the missing enzyme alpha-galactosidase A.
- Neurology: Two antiseizure medications, diphenylhydantoin and carbamazepine, are the most helpful in alleviating the debilitating pain of neurologic involvement.
- Pulmonology: Obstructive lung disease is a problem late in the disease process. Discourage patients from smoking.

- Gene therapy: In recent years, nucleoside sequencing of the entire alpha-galactosidase A gene has enabled theoretical treatment using recombinant technology.
- Replacement therapy: Occasionally, infusions of plasma or partially purified enzyme from healthy donors have produced promising results.
- Politei suggested that statins might be helpful in the treatment of Fabry disease to help prevent stroke, owing to neuroprotective properties or pleiotropic effects. [26]
- Cardiology: Imbriaco et al reported that twice-monthly continuous treatment with agalsidase beta at 1 mg/kg every 2 weeks significantly reduced left ventricular hypertrophy, improving overall heart performance and decreasing clinical symptoms in Fabry disease. [27]

Surgical Care

Kidney transplantation often is beneficial. Kidney transplantation improves survival. In addition to restoring renal reserve, the transplanted kidney produces a portion of the lacking enzyme alpha-galactosidase.