OASIS DERMATOLOGY GROUP

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# Fabry Disease

Fabry disease, first described by Johann Fabry and Anderson in 1898, is a rare X-linked genetic disorder with an estimated prevalence of approximately 1 in 40,000 live births. Also known as angiokeratoma corporis diffusum or alpha-galactosidase-A deficiency, Fabry disease is caused by mutations in the GLA gene, which leads to a deficiency of the enzyme alpha-galactosidase A. This enzyme plays a crucial role in the metabolism of lipids, specifically the breakdown of globotriaosylceramide (GL-3), a glycosphingolipid. When this enzyme is deficient or ineffective, GL-3 accumulates in various tissues, leading to progressive damage in multiple organs, including the skin, kidneys, heart, and central nervous system.

**Pathophysiology**

The deficiency of alpha-galactosidase A leads to the accumulation of globotriaosylceramide in cells, particularly in endothelial cells, fibroblasts, and renal podocytes. This lipid buildup contributes to vascular dysfunction and tissue damage across multiple organ systems. The condition predominantly affects males due to its X-linked inheritance pattern, though females can also manifest symptoms, often more mildly. The disease progression and severity are influenced by the extent of X-chromosome inactivation in females and the specific mutation in males.

**Clinical Manifestations**

The clinical features of Fabry disease are wide-ranging and include cutaneous, neurologic, renal, cardiac, and ophthalmologic involvement:

- ***Skin*:** One of the hallmark symptoms of Fabry disease is the development of angiokeratomas—small, red, punctate, telangiectatic lesions that typically appear on the lower abdomen, groin, buttocks, and upper thighs. These lesions may also occur in the conjunctiva and oral mucosa. Approximately two-thirds of male patients and one-third of female patients develop angiokeratomas, which may become more prominent with age. Additionally, hypohidrosis (reduced ability to sweat) and, in more severe cases, anhidrosis (complete inability to sweat), are common, leading to heat intolerance and discomfort.
- ***Pain*:** The most debilitating symptom of Fabry disease is neuropathic pain, especially in the hands and feet. This burning, episodic pain is often triggered by stress or changes in temperature and can be debilitating for patients. Abdominal pain, which may mimic other conditions like appendicitis or kidney stones, is also common. The pain tends to worsen with age, and some patients may experience chronic pain despite episodic fluctuations.
- ***Renal Involvement*:** Lipid accumulation in the kidneys can lead to proteinuria and progressive kidney dysfunction. Azotemia and renal failure are common complications, typically occurring in the 4th decade of life unless the patient receives hemodialysis or

undergoes renal transplantation. The characteristic "Maltese Cross" pattern of lipid globules can be identified in urine samples under polarized light microscopy, aiding in the diagnosis of Fabry disease.

- ***Cardiac Involvement:*** Fabry disease often leads to cardiovascular issues, including hypertension, ischemic heart disease, myocardial infarction, and heart failure. The accumulation of GL-3 in vascular smooth muscle cells and endothelial cells of coronary arteries can lead to coronary artery occlusion and the subsequent development of arrhythmias.
- ***Cerebrovascular Involvement*:** Stroke and cerebrovascular accidents are common due to lipid deposition in the vasculature of the brain. Affected individuals may also develop seizures, cerebral hemorrhages, and neurologic changes such as personality changes or psychotic behavior.
- ***Ophthalmologic Findings:*** Patients with Fabry disease often develop corneal opacities and whorl-like deposits in the corneal epithelium. Approximately half of individuals may also develop spoke-like cataracts, although these do not typically affect vision.

**Diagnosis**

The diagnosis of Fabry disease is based on a combination of clinical signs, family history, and biochemical testing. The gold standard for diagnosis is measuring alpha-galactosidase A activity in blood leukocytes or fibroblasts. Genetic testing to identify mutations in the GLA gene confirms the diagnosis, particularly in females who may have normal enzyme activity due to X-inactivation. Early diagnosis is critical to prevent or mitigate organ damage, particularly to the kidneys and heart.

**Management**

The treatment of Fabry disease has evolved with the advent of enzyme replacement therapy (ERT), which aims to restore deficient enzyme activity. The primary agents used are agalsidase beta and agalsidase alfa, which provide exogenous enzymes to help degrade globotriaosylceramide and reduce its accumulation. ERT has been shown to stabilize kidney function, alleviate neuropathic pain, and improve gastrointestinal symptoms. However, it does not appear to reverse the damage to the heart and coronary arteries, highlighting the need for further therapeutic advances.

In addition to ERT, pain management in Fabry disease can be challenging. Carbamazepine and diphenylhydantoin, anticonvulsants, have been reported to provide some relief for neuropathic pain. However, conventional analgesics such as opioids or nonsteroidal anti-inflammatory drugs often provide limited benefit.

Given the X-linked inheritance pattern, genetic counseling is essential for families affected by Fabry disease. Family members should be informed about the inheritance pattern, with 50% of male offspring inheriting the disease from their carrier mothers, and 50% of female offspring becoming carriers. Male patients will pass the X chromosome to all their daughters, making them carriers, but their sons will not inherit the condition.

## Conclusion

Fabry disease is a rare, progressive lysosomal storage disorder that affects multiple organ systems, including the skin, kidneys, heart, and CNS. Early diagnosis and treatment with enzyme replacement therapy can help manage symptoms and slow disease progression, although cardiac and vascular complications remain challenging to treat. Advances in understanding the genetic basis and pathophysiology of the disease continue to drive improvements in both diagnosis and treatment.

## References

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