

## A Possible Link Between the Vascular Dysfunction and Skin Manifestation in Fabry Disease

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### What is Fabry Disease?

In 1898, William Anderson reported a 39-year old patient who had “angiokeratomas” on his trunk, genitals, and proximal limbs [1]. The patient developed varicose veins, rectal bleeding, and albuminuria. William Anderson suggested that the patient’s symptoms were caused by general changes in the vascular system in his paper. In the same year, Johannes Fabry reported a case of “purpura hemorrhagica nodularis” [2]. Further cases were subsequently recognized, and the term “angiokeratoma corporis naeviforme” was coined by Johannes Fabry in 1915. It is now referred to as “Anderson-Fabry disease” or “Fabry disease”. Later, a deficiency of the lysosomal enzyme  $\alpha$ -galactosidase A was identified as the cause and was found to induce progressive accumulation of glycosphingolipids, particularly globotriaosylceramide, in visceral tissues and the vascular endothelium throughout the body. The inability to catabolize globotriaosylceramide leads to progressive multisystemic damage to the kidneys, heart, and cerebrovascular system. As the disease progresses, these complications may become life-threatening. It has been suggested that Fabry disease is an X-linked recessive pan-ethnic disorder with an estimated frequency of 1 in about 100,000 male births. However, if later-onset variants are included, the incidence of  $\alpha$ -galactosidase A deficiency is 1 in 3,100 [3]. This is because some signs and symptoms suggestive of Fabry disease including painful episodes, angiokeratomas, and corneal changes are easily ignored, and most Fabry complications are non-specific (e.g., left ventricular hypertrophy, conduction abnormalities, vascular spasms, proteinuria, and renal insufficiency). According to Nakao et al. (1995) [4] left ventricular hypertrophy is a rather common cardiac disease: it was found in 14 % of 1603 patients who displayed cardiac symptoms, cardiac murmurs, arrhythmias, hypertension, abnormal electrocardiograms, or enlargement of the cardiac silhouette on chest radiography. Notably, 3% of the patients with left ventricular hypertrophy were found to have an underlying  $\alpha$ -galactosidase A deficiency.

### How to Diagnose Fabry Disease Without Angiokeratomas?

The hallmark cutaneous manifestation of Fabry disease is angiokeratomas, and it can be diagnosed by measuring leukocyte  $\alpha$ -galactosidase activity or verifying the presence of electron-dense granules in the endothelial cells of the angiokeratoma with electron microscopy. However, these examinations are not usually performed without a suspicion of Fabry disease. In addition, some patients do not display angiokeratomas, and the initial stages sometimes only involve painful fingers, heat intolerance, and telangiectasias in childhood [5]. In a study by Orteu et al., (2007) [6] hypohidrosis (53% males, 28% females), telangiectasia (23% males, 9% females), and lymphedema (16% males, 6% females) were reported in 714 Fabry patients (345 males, 369 females). In addition, patients may complain of fever, fatigue, or nausea during exercise in summer. This heat intolerance may be associated with hypohidrosis. On physical examination, angiokeratomas or telangiectasia are classically distributed in the bathing trunk area, including the genitals, buttocks, lower back, and inner thighs, but these lesions are occasionally detected in non-bathing

trunk areas such as the breasts, ears, chin, and hands. Lymphedema often presents as edema of the feet or stasis ulcers due to vascular permeability. Suspected Fabry disease patients should also be asked whether they have a history of episodic diarrhea or abdominal pain because these symptoms are relatively common. These symptoms often reduce quality of life in children but, because of their non-specific nature, usually do not lead to a correct diagnosis without the family history being known. In cases in which these manifestations are ignored, the correct diagnosis is generally made later when the clinician is faced with end-stage organ damage. Therefore, the recognition of Fabry disease among patients without a positive family history still remains a challenge to dermatologists and other physicians.

### Vascular Dysfunction in Fabry Disease Patients’ Skin

Among the skin manifestations of Fabry disease, telangiectasia and lymphedema in particular may be caused by vascular dysfunction. Fabry disease is to a large extent a systemic vascular disorder causing cardiovascular complications and renal dysfunctions. Blood components, blood flow, and vessel wall abnormalities are involved in the vasculopathy of Fabry disease. The levels of soluble intercellular adhesion molecule-1, soluble vascular cell adhesion molecule-1, P-selectin, and plasminogen activator inhibitor are increased, and that of thrombomodulin is decreased [7], suggesting that a prothrombotic state exists in Fabry disease. Circulation dysregulation has also been demonstrated in a number of studies [8]. Since vascular smooth muscle hypertrophy due to deacylated lipids has been observed in Fabry disease, the vascular smooth muscle cell may be primarily involved in the vasculopathy of Fabry disease [9]. Recent studies have implied that the vascular dysfunction observed in Fabry disease is due to the increased release of reactive oxygen species (ROS), resulting in persistent vasodilation [10]. The reason for the excessive ROS production in Fabry disease may be related to glycolipid accumulation altering endothelial caveolar function [11]. Caveolae are cell membrane lipid rafts that contain endothelial nitric oxide synthase (eNOS). It is possible that glycolipid accumulation interferes with caveolae and subsequently causes the uncoupling of eNOS from ROS generation such as superoxide generation. Excess superoxide reacts with nitric oxide to form peroxynitrite. Nitric oxide, superoxide, and peroxynitrite are all known to cause continuous vasodilation and vascular dysfunction. Moreover, Fabry disease patients with deranged eNOS

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activity and polymorphisms of the eNOS gene were found to have thicker left ventricular posterior walls [12]. Electron-dense granules in the cutaneous vascular endothelial cells of Fabry disease patients may also suggest altered endothelial caveolar function and deranged eNOS activity in the skin. It is reasonable to consider that continuous vasodilation combined with vascular dysfunction is associated with telangiectasias and lymphedema in the skin of Fabry disease patients.

### What Treatments are Available?

Enzyme replacement therapy for Fabry disease is already available in many countries throughout the world. There are two different forms of  $\alpha$ -galactosidase A replacement, one produced in a Chinese hamster ovary cell line (agalsidase  $\beta$ ; Fabrazyme<sup>™</sup>, Genzyme Inc., Cambridge, USA) and the other produced in a genetically engineered human cell line (agalsidase  $\alpha$ ; Replagal<sup>™</sup>, Transkaryotic Therapies Inc., Cambridge, USA). Both enzyme therapies are well tolerated and seem to be effective at catabolizing lipid deposits [13,14]. However, they are not perfect therapies: 1) Further time is necessary to assess whether this strategy really prolongs life. 2) Curiously, enzyme replacement therapy does not ameliorate cutaneous angiokeratoma. 3) Some patients do not respond to enzyme replacement therapy at all. 4) The role of neutralizing antibodies against  $\alpha$ -galactosidase A needs further assessment. 5) Patients have to bear the high cost of this lifelong treatment. 6) Needless to say, the effects of enzyme replacement therapy on cutaneous vascular dysfunction are unknown. Therefore, physicians must consider other non-specific therapies. Anti-platelet agents such as clopidogrel and aspirin/long acting dipyridamole should be used to prevent stroke in all patients with Fabry disease because strokes can even occur during enzyme replacement therapy. Angiotensin converting enzyme inhibitors and angiotensin receptor blockers are necessary for the treatment of kidney dysfunction in Fabry disease. Anti-epileptic medications such as carbamazepine, Neurontin, and lamotrigine should be considered to treat neuropathic pain when non-steroidal anti-inflammatory drugs are not effective. Interestingly, low blood levels of ascorbic acid have been suggested to cause cerebral hyperfusion in Fabry patients, and ascorbic acid infusion decreases cerebral hyperfusion [15]. As cutaneous vasculopathy is also caused by cutaneous hyperfusion combined with ROS production due to caveolae/eNOS dysfunction, ascorbic acid and other antioxidant drugs will hopefully prove to be effective adjuvant treatments for angiokeratoma, telangiectasia, and lymphedema.

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