Cardiac Microvascular Pathology in Fabry Disease
Evaluation of Endomyocardial Biopsies Before and After Enzyme Replacement Therapy

Beth L. Thurberg, MD, PhD; John T. Fallon, MD, PhD*; Richard Mitchell, MD, PhD*; Thomas Aretz, MD*; Ronald E. Gordon, PhD; Michael W. O’Callaghan, DVM, PhD

Background—In classic Fabry patients, accelerated coronary atherosclerosis and left ventricular hypertrophy manifest in the fourth decade; however, signs of cardiovascular disease also are observed later in life in “cardiac variant” patients and symptomatic female heterozygotes. These disturbances are caused by globotriaosylceramide (GL-3) accumulation in the heart resulting from lysosomal α-galactosidase A deficiency.

Methods and Results—We analyzed pretreatment and posttreatment endomyocardial biopsies from 58 Fabry patients enrolled in a 5-month, phase 3, double-blind, placebo-controlled trial, followed by a 54-month open-label extension study of recombinant human α-galactosidase A. Baseline evaluations revealed GL-3 deposits in interstitial capillary endothelial cells and large, laminated inclusions within cardiomyocytes. In this study, we evaluated microvascular GL-3 clearance; no clearance of GL-3 was observed in the cardiomyocytes during this trial. Five months of recombinant human α-galactosidase A treatment in the phase 3 trial resulted in complete microvascular clearance of GL-3 from 72% of treated patients compared with only 3% of placebo patients (P<0.001). The placebo group achieved similar results after 6 months of treatment in the open-label trial. In addition, the capillary endothelium remained free of GL-3 for up to 60 months in 6 of 8 patients who consented to an end-of-study biopsy.

Conclusions—The findings suggest that long-term treatment with recombinant human α-galactosidase A may halt the progression of vascular pathology and prevent the clinical manifestations of atherosclerotic disease. This histopathological study should be a useful guide for clinicians and pathologists who diagnose and follow Fabry patients. (Circulation. 2009;119:2561-2567.)

Key Words: hypercholesterolemia ▪ hypertrophy ▪ ischemia ▪ microcirculation ▪ pathology

The genetic deficiency of α-galactosidase A in Fabry patients leads to the histopathological accumulation of globotriaosylceramide (GL-3) within the lysosomes of multiple cell types throughout the body, particularly in the kidney, skin, and heart. The involvement of these 3 organs is responsible for the most common presenting signs and symptoms of Fabry disease, including renal failure, acroparesthesias, and ischemic heart disease. We have previously reported the results of enzyme replacement therapy with recombinant human α-galactosidase A (r-hoGalA) on the histological clearance of GL-3 from both renal and dermatologic biopsies obtained during a phase 3 trial. Here, we report the histopathological findings from the pretreatment and posttreatment cardiac biopsies from this same cohort of Fabry patients.

Editorial see p 2539
Clinical Perspective on p 2567

The involvement of the heart by Fabry disease is associated with a number of cardiac signs and symptoms, including left ventricular hypertrophy, mitral insufficiency, conduction abnormalities, and ischemic heart disease. In addition, a high incidence of thrombotic events exists in Fabry patients in both men and women, which plays a role in acute events such as stroke and myocardial infarction. Light and electron microscopic examination of cardiac biopsies from Fabry patients reveals GL-3...
accumulation in the microvasculature, which has been associated with elevations in markers of endothelial injury and activation, leukocyte activation, and coagulation. Such proinflammatory and procoagulant alterations in normal endothelial homeostasis are well-characterized components of atherosclerotic disease in general and are likely responsible for similar clinical manifestations observed in Fabry patients. The successful clearance of microvascular GL-3 as a result of enzyme replacement therapy would therefore be expected to restore normal endothelial cell function and to prevent the downstream adverse events associated with endothelial dysfunction.

Survey studies indicate that cardiac involvement by Fabry disease can go undiagnosed when initially labeled hypertrophic cardiomyopathy. The female Fabry population, which until recently had been assigned the assumptive label of asymptomatic carrier, has commonly experienced a delay of 16 to 19 years between onset of symptoms and diagnosis. Such reports demonstrate that an increased awareness of disease prevalence is important for both patients and physicians. In particular, in those cases in which a diagnostic cardiac biopsy is sought, it is important that Fabry disease be considered in the differential diagnoses of both the ordering physician and the examining pathologist, so that the biopsy specimen can be optimally fixed and processed for light and electron microscopy to enable confirmation of all possible diagnoses. With the current availability of enzyme replacement therapy for Fabry disease, a correct diagnosis will ensure that patients are treated in a timely manner to alleviate symptoms and to prevent further disease progression.

On the basis of the analysis of baseline and multiple posttreatment cardiac biopsies, we report here the characterization of baseline pathology and the rapid and sustained clearance of GL-3 from the cardiac microvasculature after r-hoGalA. As more Fabry patients receive treatment for their disease, the practicing pathologist may also face this new class of posttreatment specimens as clinicians seek to follow their patients’ progress with biopsies.

Methods

Patients and Study Design

Fifty-eight Fabry patients (56 male, 2 female) were enrolled in the 5-month phase 3 double-blind, randomized, placebo-controlled trial (29 patients in the placebo and treatment arms; mean±SD age, 28.4±11.0 and 32.0±9.4 years, respectively). A 1-month break occurred after the double-blind study, followed by a 54-month open-label extension study in which all 58 patients received enzyme replacement therapy. Patients were required to be ≥16 years of age with native plasma α-galactosidase A levels <1.5 nmol·h⁻¹·mL⁻¹ or leukocyte activity levels <4 nmol·h⁻¹·mg⁻¹ and baseline creatinine levels ≤2.2 mg/dL. Patients who had undergone kidney transplantation or who were undergoing dialysis were excluded. r-hoGalA (agalasidase β; Fabrazyme, Genzyme, Cambridge, Mass) was administered intravenously at 1 mg/kg body weight every 2 weeks. Endomyocardial biopsies from the right ventricle were taken from all 58 Fabry patients at baseline. Additional biopsies were obtained from the majority of patients at 5 and 12 months after study initiation. Eight patients consented to a final end-of-study biopsy at month 60. The institutional review boards at all sites approved the double-blind and open-label protocols, and all patients gave written informed consent.

Table 1. Scoring Criteria for GL-3 Load in Cardiac Biopsies

<table>
<thead>
<tr>
<th>Score</th>
<th>Scoring Criteria</th>
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<tbody>
<tr>
<td>None or trace (“normal”): score=0</td>
<td>No visible endothelial inclusions/trace amounts. A score of 0 is confined to vascular endothelium in which there is either no evidence of visible endothelial inclusions in the vessels examined or in which the majority of the vessels contain no visible inclusion and the remaining vessels contain only traces of visible inclusions. A trace is defined as vessels containing only single, isolated, small inclusions in the remaining minority of the vessels examined. Key features: the majority of vessels are clear of inclusions; a minority of vessels may contain single or isolated granules. Overall impression of minimal or trace involvement.</td>
</tr>
<tr>
<td>Mild: score=1</td>
<td>The majority of vessels in the fields examined contain evidence of inclusions in the cytoplasm of the endothelium. This grade ranges from single small granules in almost all vessels to occasional multiple loosely organized granules often distributed randomly in different areas of the cytoplasm. Occasional vessels may have small clusters of granules. There is rarely evidence of bulging into the capillary lumen. Key features: almost all clearly defined vessels contain at least a single inclusion; isolated, randomly distributed, or occasional small loose clusters; rarely protruding into the lumen.</td>
</tr>
<tr>
<td>Moderate: score=2</td>
<td>Multiple areas throughout the endothelial cytoplasm contain single or multiple granules often in small clusters. All or nearly all clearly defined capillaries contain multiple inclusions. In the juxtanuclear area, there may be occasional coalescing of inclusions with minor bulging into the vessel lumen. Coalescence is not a feature away from the nucleus. Key features: multiple visible granules in most capillaries; small clusters of individually identified inclusions; occasional lumen bulging.</td>
</tr>
<tr>
<td>Severe: score=3</td>
<td>Vascular endothelium contains large accumulations of inclusions, some of which coalesce into clusters both at the juxtanuclear region and around the free cytoplasmic borders and where many bulge into the vessel lumen. The majority of vessels are readily identified as containing large numerous granules often at several different sites around the periphery of the endothelium. Key features: coalescence of inclusions into small masses often bulging into lumen; several sites of inclusions around vessel periphery; majority of clearly identified vessels contain numerous inclusions.</td>
</tr>
</tbody>
</table>

Light Microscopy

Cardiac biopsies were fixed in 3% glutaraldehyde in 0.2 mol/L sodium cacodylate buffer, pH 7.3, followed by postfixation in 1% osmium tetroxide in 0.2 mol/L sodium cacodylate (Electron Microscopy Sciences, Fort Washington, Pa). Tissue was infiltrated overnight and then embedded in a 1:1 mixture of Epon 811 A and B (Electron Microscopy Sciences) plus DMP-30/Propylene Oxide (Electron Microscopy Sciences). Sections (1 μm) were stained with a 1:1 mixture of methylbenzine blue in 1% sodium borate and 1% Azure II (Fisher Scientific, Fairlawn, NJ).
Scoring of Light Microscopy
Light microscopic examination of the cardiac biopsies was performed by 3 independent cardiac pathologists blinded to patient identity and pivotal treatment status. To establish consistent criteria for grading baseline GL-3 content and subsequent clearance from affected tissues, all pathologists underwent a preliminary training session during which criteria for scoring were reviewed (see Table 1). The majority score (the score common to at least 2 of the 3 evaluating pathologists) was derived from the individual scores of the 3 pathologists. When no common score could be determined, an adjudication meeting of all pathologists at a multipathed scope was held to reach a consensus score. Clearance of GL-3 from cardiac capillary endothelial cells, one of the secondary end points of the phase 3 trial, was based on changes in scores over time. Table 2 shows the distribution of scores of 0 at each time point and the mean values for all scores available at each time point. For statistical analysis, the \( \chi^2 \) test was used to compare the number of scores of 0 in the r-hoGalA–treated group and the placebo-treated group during the 5-month placebo-controlled period of the study. Two-sample, 2-tailed tests were used for all analyses. A value of \( P \leq 0.05 \) was considered to indicate statistical significance.

Electron Microscopy
Thin sections cut from the same tissue blocks were stained with 5% uranyl acetate (in a 1:1 methanol:water mixture) and modified Reynolds lead citrate. Photographs were taken at a range of \( \times 2000 \) to \( \times 6000 \) magnification with a JEM 100CX electron microscope (JEOL, Ltd, Tokyo, Japan). Electron micrographs were not used to score GL-3 content but were made available to confirm its presence or absence as observed in light microscopic sections.

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results

Baseline Biopsies
At baseline, GL-3 accumulation in cardiac interstitial capillary endothelial cells appears as small, dense, beaded cytoplasmic inclusions under light microscopy. These inclusions were present singly and in clusters. Figure 1A shows small inclusions present around the edges of capillaries (yellow arrows) with little to no protrusion into the lumen. Biopsies with a predominance of this feature were assigned a score of 1, as detailed in Table 1. In more severely affected cells, the accumulations appeared as larger grouped inclusions in the peripheral cytoplasm that clustered together and often protruded into the vascular lumen (see green arrows in Figure 1C); biopsies with this feature were assigned a grade of 2. On electron microscopy, many of these inclusions appear as dense and laminated myelin figures (Figure 2A and 2B, white arrow). Cardiomyocytes accumulated large clusters of GL-3 as myelin figures present in a perinuclear distribution localized between contractile elements (Figure 1, red asterisk; Figure 2C, white arrows).

Posttreatment Biopsies
Treatment with r-hoGalA resulted in effective clearance of lipid from interstitial capillary endothelial cells (Figures 1B, 1D, 2B, and 2D). In the patient group receiving r-hoGalA from baseline to 5 months, 72% of patients achieved a score of 0 after 5 months of treatment (baseline mean \( 0.9; 5\)-month posttreatment mean \( 0.3; \) Table 2). After an additional 6 months of open-label treatment, 86% of patients who remained in the study attained a score of 0 (month 12 mean = 0.1; Table 2).

In the placebo group, 3% of patients had a score of 0 at month 5 (baseline mean = 0.9; 5-month postplacebo mean = 1.2; Table 2). A statistically significant difference was found between r-hoGalA– and placebo-treated patients in the placebo-controlled (5-month) study (\( P < 0.001; \chi^2 \) test). After crossover to treatment for 6 months in the open-label trial, 72% of former placebo patients remaining in the study attained a score of 0 (month 12 mean = 0.3; Table 2).

Eight patients consented to a final biopsy at month 60. After 60 months of treatment for the r-hoGalA group and 54 months of treatment for the former placebo group, 6 of 8 patients maintained a score of 0 (3 of 3 patients in the r-hoGalA group and 3 of 5 patients in the placebo group). The remaining 2 patients had a score of 1.

Discussion
Cardiac microvascular function abnormalities in Fabry patients have been demonstrated by measurements of myocardial blood flow and coronary flow reserve, an index of microvascular function.14 In addition, a survey of female Fabry patients revealed that cardiac ischemia could be confirmed by ECG and serological markers in the absence of coronary artery stenosis, suggesting that the ischemia in these patients was of microvascular origin.11 However, widespread coronary artery disease also

Table 2. Mean GL-3 Scores and Percentage of Patients With Scores of 0 for Endothelial GL-3 at Baseline and Months 5, 12, and 60

<table>
<thead>
<tr>
<th>Study</th>
<th>Time</th>
<th>Variable</th>
<th>n</th>
<th>Mean (%)</th>
<th>SD</th>
<th>A-gal/A-gal</th>
<th>Placebo/A-gal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Double blind, placebo controlled</td>
<td>Baseline</td>
<td>Score</td>
<td>29</td>
<td>0.9</td>
<td>0.4</td>
<td>29</td>
<td>0.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Score=0</td>
<td>29</td>
<td>(17)</td>
<td></td>
<td>29 (17)</td>
<td>29</td>
</tr>
<tr>
<td></td>
<td>5 mo</td>
<td>Score</td>
<td>29</td>
<td>0.3</td>
<td>0.5</td>
<td>29</td>
<td>1.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Score=0</td>
<td>29</td>
<td>(72)</td>
<td></td>
<td>29 (3)</td>
<td></td>
</tr>
<tr>
<td>Open label</td>
<td>12 mo</td>
<td>Score</td>
<td>22</td>
<td>0.1</td>
<td>0.4</td>
<td>29</td>
<td>0.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Score=0</td>
<td>22</td>
<td>(86)</td>
<td></td>
<td>18 (72)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>60 mo</td>
<td>Score</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>5</td>
<td>0.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Score=0</td>
<td>3</td>
<td>(100)</td>
<td></td>
<td>5 (60)</td>
<td></td>
</tr>
</tbody>
</table>

A-gal/A-gal indicates the patient group treated with enzyme during the 5-month double-blind trial and subsequent 54-month open-label trial; Placebo/A-gal, patient group treated with placebo during the 5-month double-blind trial and with enzyme during the 54-month open-label trial. There was a 1-month break between the 5-month double-blind and the 54-month open-label studies. Note that the total number of biopsies at month 60 was 8.
has been documented in Fabry patients\textsuperscript{15} and noted at autopsy in a male patient who died of a massive myocardial infarction.\textsuperscript{16} In the present study, we characterized the baseline pathology of GL-3 accumulation in cardiac biopsies and demonstrated its successful clearance from the microvasculature after enzyme replacement therapy.

It has long been established that GL-3 is transported in low- and high-density lipoprotein particles\textsuperscript{17–19} and that vascular cells

Figure 1. Capillary GL-3 is cleared from the cardiac capillaries after enzyme replacement therapy. A patient biopsy from the r-huGalA (treatment) group was assigned a grade of 1 at baseline (A) and a grade of 0 at 12 months after treatment (B). A patient biopsy from the placebo group was assigned a score of 2 at baseline (C) because of the prominence of clustered inclusions that protruded into the vascular lumen (green arrows). The same patient attained complete clearance after crossover to treatment for 6 months with a score of 0 (D). Cardiomyocyte GL3 (red asterisk) was present at baseline and persisted after treatment in both the r-huGalA and placebo groups. (Epon, methylene blue–azure II stain; ×100 objective.)

Figure 2. Electron microscopy demonstrates clearance of GL-3 from cardiac capillaries. A and C, The substrate accumulates in the endothelial cells of the cardiac capillaries and protrudes into the capillary lumen. B and D, By 12 months after treatment, the substrate has been cleared from the endothelium. (Magnification ×2600.)
accumulate GL-3 from the circulation through the low-density lipoprotein receptor.\textsuperscript{3,20} The defect in GL-3 metabolism caused by the enzyme deficiency present in Fabry disease causes an excess of plasma GL-3, which is distributed among the major lipoprotein classes in the same proportion as normal individuals but at higher absolute levels.\textsuperscript{21} This in turn would deliver higher GL-3 levels to vascular cells through low-density lipoprotein particle uptake via the low-density lipoprotein receptor. Therefore, enzyme replacement therapy would be expected to correct this excess delivery of GL-3 to and its accumulation within endothelial cells.

To date, the literature on the lipoprotein profile of Fabry patients is limited, and observations vary. In 1 study of 23 Fabry patients, measurements of total, low-density lipoprotein, and high-density lipoprotein cholesterol did not indicate a typical atherosclerotic profile; indeed, 65% of patients were found to have elevated high-density lipoprotein levels, the cardioprotective species.\textsuperscript{22} Furthermore, enzyme replacement was found to have no effect on the lipid profile measured in this study.\textsuperscript{22} However, other investigators report patients with abnormally low levels of high-density lipoprotein in association with severe coronary artery disease and myocardial infarction.\textsuperscript{16} Laboratory studies have examined alternative mechanisms of disease that might link the common clinical findings in patients. Cell-based models of apolipoprotein A-I–mediated cholesterol efflux from cultured Fabry fibroblasts demonstrated an inhibition of cholesterol efflux in Fabry cells compared with controls.\textsuperscript{23} These findings point to an inherent cellular defect in cholesterol trafficking resulting from substrate accumulation, thereby suggesting that the vascular disease observed in Fabry patients is not due solely to a mechanophysical accumulation of substrate in the endothelial cells but also to an alteration in the lipid homeostasis of the endothelial cells. This endothelial cell alteration is further supported by studies that indicate an upregulation of the endothelial cells.

Recent studies have identified increased circulating levels of globotriaosylsphingosine, a water-soluble, deacylated metabolite of GL-3, in the plasma of Fabry patients.\textsuperscript{24} The metabolite stimulated the proliferation of smooth muscle cells in vitro,\textsuperscript{24} providing a potential mechanism for the increased intima-media thickness recorded in the carotid artery, brachial artery, and abdominal aorta of Fabry patients.\textsuperscript{25,26} Interestingly, the investigators also reported that long-term enzyme replacement treatment was associated with a reduction in plasma globotriaosylsphingosine within a year,\textsuperscript{24} thereby suggesting another, indirect, benefit of long-term enzyme replacement therapy.

The second major component of the cardiac pathology in Fabry disease is the massive accumulation of GL-3 in cardiomyocytes, which leads to hypertrophic cardiomyopathy, detectable as early as childhood and adolescence.\textsuperscript{27,28} These large accumulations can occupy >50% of the cell and cause a significant increase in individual cardiomyocyte cross-sectional area, thereby contributing to the cardiac hypertrophy routinely observed in Fabry patients.\textsuperscript{29} Although we did not observe histological changes in cardiomyocyte GL-3 in this histological study, the systematic evaluation of myocardial mass by magnetic resonance imaging and echocardiography has been shown by others to decline with treatment,\textsuperscript{30,31} which may reflect a gradual clearance of substrate.

Magnetic resonance imaging of the myocardium demonstrated statistically significant decreases in left ventricular posterior wall thickness and myocardial mass in a group of 16 patients treated with enzyme replacement therapy for 12 months.\textsuperscript{32} Left ventricular posterior wall thickness decreased by 27.6\%, and myocardial mass decreased by 10.4\%.\textsuperscript{32} A later study that used echocardiography to examine changes in 9 patients showed decreases in the left ventricular posterior wall thickness and interventricular septum thickness and a statistically significant decrease in left ventricular mass by 10% after 12 months of treatment.\textsuperscript{33} Similar changes in heart size also have been observed by magnetic resonance imaging and echocardiography after treatment with agalsidase α.\textsuperscript{30,31,34}

It is likely that the changes in these global cardiac measures are due to progressive clearance of GL-3 mass from cardiomyocytes. The changes reported in imaging studies, however, are in the range of 10% to 27% and are highly variable from patient to patient. These relatively modest macroscopic changes would be imperceptible by eye at the microscopic level and likely account for our difficulty in identifying GL-3 reductions in cardiomyocytes in these small endomyocardial biopsy samples. Others also have reported poor histological clearance of GL-3 from cardiomyocytes.\textsuperscript{35} Given that the load of GL-3 in terminally differentiated cardiomyocytes represents a lifetime of substrate accumulation, it will likely require longer periods of treatment for changes in cardiomyocyte GL-3 to be reflected in endomyocardial biopsy samples.

Although endomyocardial biopsies confine the assessment of histological disease to cells of the more superficial cell layers of the right ventricular endocardium, other advanced radiological studies have suggested the additional presence of myocardial fibrosis in other regions of the heart\textsuperscript{36–38} that are less accessible to biopsy, particularly in the apex and in basal inferolateral segments of the left ventricle. Fibrosis was not observed in right ventricular endomyocardial biopsies; indeed, these radiological studies suggest that the myocardial fibrosis in Fabry disease is usually observed in the left ventricle. A case study of a 43-year-old Fabry patient by Hasegawa et al\textsuperscript{36} used single-photon emission computed tomography and positron emission tomography imaging to identify marked decreases in left ventricular apical and lateral wall thickness associated with dyskinesis. The areas of dyskinesis did not correlate with segments of the coronary arteries; in fact, angiography ruled out the presence of obstructing lesions in this patient.\textsuperscript{36} This led investigators to conclude that the areas of dyskinesis represented areas of myocardial fibrosis secondary to impaired microvascular circulation caused by Fabry disease.\textsuperscript{36} Such a conclusion suggests the potential evolution of a vicious cycle in cardiac Fabry disease. As the microvascular disease continues to contribute to regional fibrosis and impaired ventricular wall motion, an associated impairment of the cardiac circulation can be observed with potential impairment of enzyme delivery to these regions of the heart. This cascade of events might be averted with early enzyme therapy, before the onset of
secondary changes such as fibrosis, ventricular wall thinning, and motion abnormalities and the associated clinical symptoms of disturbed exercise tolerance, angina, myocardial infarction, heart failure, and sudden death.

The monitoring of cardiac pathology in Fabry patients will become more important as the treated population expands from male to female patients and from older, previously diagnosed symptomatic patients to younger, newly diagnosed and relatively asymptomatic patients. It is anticipated that such efforts will halt the progression of this disease at an earlier stage. This study should serve as a useful guide for clinicians and pathologists in the diagnosis and tracking of the cardiovascular manifestations of Fabry disease and the long-term response to therapy.

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Disclosures
Drs. Thurberg and O’Callaghan are full-time employees of Genzyme Corp. Drs. Mitchell, Fallon, Aretz, and Gordon are outside collaborators and paid consultants for Genzyme.

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20. Utsumi K, Yamamoto N, Kase R, Takata T, Okumiya T, Saito H, Suzuki M, Desnick RJ, O’Callaghan M. Monitoring the three year efficacy of enzyme replacement therapy in Fabry disease by repeated skin biopsies.
CLINICAL PERSPECTIVE

Among the many differential diagnoses for ischemic heart disease is one on the lower end of the list: cardiac involvement by Fabry disease, a rare lysosomal disorder resulting from a genetic deficiency of α-galactosidase A. This deficiency leads to accumulation of globotriaosylceramide within vascular endothelial cells and cardiomyocytes, resulting in angina, myocardial infarction, and left ventricular hypertrophy, thus mimicking more common diagnoses such as hyperlipidemia and hypertrophic cardiomyopathy. The present study uses endomyocardial biopsies to examine the effectiveness of a new enzyme replacement therapy for Fabry disease on its ability to clear globotriaosylceramide from the cardiac microcirculation. In clinical cases in which a diagnostic cardiac biopsy is sought, it is important that Fabry disease be considered in the differential diagnoses of both the ordering physician and the examining pathologist, so that the biopsy specimen can be optimally fixed and processed for light and electron microscopy to enable confirmation of all possible diagnoses. With the current availability of enzyme replacement therapy for Fabry disease, a correct diagnosis will ensure that patients are treated in a timely manner to alleviate symptoms and to prevent further disease progression.
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