

## The Current State of Amyloidosis

by

*Natalee Sheppe*

College of Medicine Class of 2007  
Medical University of South Carolina  
Molecular Basis of Medicine Treatise

*My loving grandfather's recent diagnosis of Amyloidosis, a disease with an unknown cause, few experimental treatment options, and no cure, inspired this article. I hope that this discussion affords awareness for clinicians and researchers and that it provides some answers for family and friends of those diagnosed.*

### Abstract

Amyloidosis is a disease associated with the build up of amyloid protein in organs and tissues, which ultimately leads to organ failure. The heart, liver, kidneys, and gastrointestinal tract are commonly targeted. Historically, clinicians have classified three types of amyloidosis: primary, secondary, and hereditary. However, today amyloidosis is categorized biochemically by its fibril protein. This disease is rare with an incidence rate of approximately 8 per 1,000,000 and reportedly affects males more often than females (2:1). Amyloidosis is potentially difficult to diagnose because patients present either with no symptoms or an array of symptoms including swelling of extremities, irregular heart rhythm, voice changes, diarrhea, weight loss, or an enlarged tongue. Currently there is no cure for amyloidosis, but treatment aims to stop amyloid protein production in the bone marrow cells of the affected patient.

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### Author's Addresses:

sheppe@musc.edu

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### Definition

Amyloidosis is classified biochemically as a secondary protein structure disorder; amyloid protein is composed of linear nonbranching fibrils organized as pleated sheets that resemble starch and make it relatively inert and insoluble resulting in its extracellular aggregation.<sup>(1)</sup> Clinically, it is known as a disease in which bone marrow cells

produce antibodies resistant to proteolysis.<sup>(2) (3)</sup> The antibodies buildup in the bloodstream and eventually deposit in bodily tissues as amyloid.<sup>(2)</sup> The amassing of the atypical protein in target organs results in organ malfunction and may be localized, general, or systemic.<sup>(13)</sup> The liver, spleen, heart, kidneys, gastrointestinal

tract, and nervous system are common sites of amyloid accumulation.<sup>(4)</sup>

### Types

Historically, physicians have classified three major types of amyloidosis: primary, secondary, and hereditary, which may all become systemic with disease progression. Primary amyloidosis, also referred to as immunoglobulin light chain amyloidosis (AL), is not associated with a concurrent illness and typically affects organs such as the tongue, skin, heart, lung, nerves, and intestines.<sup>(4) (8)</sup> AL is described as the most aggressive and lethal form of systemic amyloidosis.<sup>(9)</sup> Secondary amyloidosis follows chronic infections and inflammatory disorders such as osteomyelitis, rheumatoid arthritis, and tuberculosis. Common target organs are the liver, spleen, kidneys, and intestines.<sup>(4)</sup> Secondary amyloidosis is the most common type of systemic amyloidosis with an occurrence around 0.5 to 0.86% as reported from multiple autopsy studies.<sup>(10)</sup> Currently there is little available research in the United States on secondary amyloidosis, but a study of 287 secondary amyloidosis cases in Turkey determined familial Mediterranean fever (FMF) as the main cause of this malady, accounting for 64% of the cases, and the second leading cause was tuberculosis (10%). The Turkish study also concluded that edema in conjunction with proteinuria was present in 88% of the cases.<sup>(11)</sup> Finally, hereditary amyloidosis is an inherited form of this malady, passed on as an autosomal dominant trait, which classically affects the skin, heart, and kidney.<sup>(4)(12)</sup>

More recently, biochemical classifications have been assigned to

amyloid. Dr. Daniel Jacobson of New York University School of Medicine claims that the descriptive terms are not based on etiology, do not provide much useful information, and are no longer suggested. Instead, the most widely used categorization of amyloidosis is designated by the abbreviation for the associated fibril protein preceded by a capital A (for amyloid). For example, since primary amyloidosis is usually associated with an immunoglobulin light chain fibril protein (abbreviated L), primary amyloidosis is commonly termed AL. Currently, there are 20 different fibril proteins known in human amyloidosis; thus, there are at least twenty types of amyloidosis.<sup>(2)(12)</sup>

However, even though there are 20 types of fibril proteins associated with amyloidosis, these proteins share some physical and pathologic properties that are helpful in diagnosis. For instance, each has a regular fibrillar structure that can be viewed by electron microscopy and a beta pleated sheet structure that is observable via x-ray diffraction. Also, after hematoxylin and eosin staining, the proteins yield an amorphous eosinophilic manifestation on light microscopy. Additionally, the fibril proteins share similar solubility in water and low ionic strength buffers. Finally, after Congo red staining of the fibrils, a bright green fluorescence is apparent under polarized light.<sup>(3)</sup>

### Epidemiology

Amyloidosis is an uncommon and potentially fatal disease with an annual incidence rate of 8 per 1,000,000 in America.<sup>(2) (3)</sup> However, Jacobson determines the annual incidence rate of AL specifically as 1-5 per 100,000 in the United States with a similar international

prevalence among all populations. AL is reported to affect persons of all racial and ethnic groups, although there are no current data available for incidence comparison.<sup>(6)</sup> A study from the Mayo Clinic states that approximately 60% of persons diagnosed with amyloidosis are male, and Jacobson's study on Immunoglobulin-Related Amyloidosis finds that AL has a 2:1 male-to-female incidence ratio.<sup>(4)(6)</sup> In addition, typical amyloidosis onset occurs after the age of 40, and the Mayo Clinic reports the median age at diagnosis is 64 years.<sup>(4)(6)</sup> Cardiovascular amyloidosis ultimately occurs in the majority of patients with systemic AL and is the most frequent cause of death.<sup>(6)</sup> Systemic AL is accompanied by fatality within one to three years.<sup>(5)</sup>

### **Signs and Symptoms**

Diagnosis is complicated because a patient may present with no symptoms or an extensive range of indicators. Signs and symptoms may consist of swollen extremities, weakness, joint pain, weight loss, shortness of breath, dysphagia, an enlarged tongue, hoarseness, or changing of the voice. Symptoms may also include diarrhea, clay colored stools, decreased urine output as well as dizziness and tingling in the hands and feet.<sup>(4)(5)</sup> Initially, the most typical physical signs comprise peripheral edema and orthostatic hypotension due to congestive heart failure and nephrotic syndrome. In addition, the patient may exhibit purpura generated by amyloid buildup in the subendothelium of small blood vessels, and carpal tunnel syndrome is observed in 20% of patients with AL.<sup>(6)</sup> Circumstances that determine the site of amyloid accumulation are currently unknown.<sup>(3)</sup> However, Amyloidosis

symptoms do reflect the organ affected by the amyloid protein buildup, and patients portray similar symptoms for common amyloid target organs such as the kidney, heart, gastrointestinal tract, and the peripheral nervous system.<sup>(6)</sup>

### **Kidney**

The kidney is the most frequently affected organ in primary amyloidosis, and patients develop proteinuria or nephrotic syndrome in 75% of cases.<sup>(7)</sup> Thus, nephrotic syndrome, peripheral edema, and renal failure are common signs of renal involvement in amyloidosis. Also, patients with kidney involvement often experience a change in appetite, with aversion for foods high in protein.<sup>(4)</sup>

### **Heart**

Amyloid deposition in the heart results in diastolic dysfunction, arrhythmias, congestive heart failure, and postural hypotension. Patient complaints include lightheadedness, weakness, dyspnea, palpitations, and peripheral edema.<sup>(6)</sup> The most frequent symptom of heart damage via amyloidosis is shortness of breath with minimal exertion.<sup>(4)</sup> In addition, amyloid accumulation in coronary arteries may produce angina.

### **Gastrointestinal Tract**

Typical gastrointestinal symptoms are constipation and irregularity. Specifically, gastric involvement may produce hematemesis, nausea, and vomiting. While, intestinal participation causes immobility in the patient and may result in hemorrhage, obstruction, constipation, and diarrhea. Despite these findings, gastrointestinal amyloidosis is not symptomatic in the majority of cases.<sup>(4)</sup>

### **Nervous System**

In 20% of patients with AL the peripheral nervous system is affected. Nerve deposition results in dysesthesia and decreased sensation and strength, which typically impacts lower extremities more than the upper ones.<sup>(6)</sup> In addition, nerves that control blood pressure may be targeted resulting in dizziness or fainting upon standing too hastily.<sup>(4)</sup>

### **Diagnosis**

Amyloidosis screening is conducted through blood and urine tests for the presence of abnormal protein. The diagnosis is confirmed via tissue needle biopsy, typically taken from abdominal fat, rectal mucosa, or bone marrow in an outpatient setting with local anesthetic. The presence of amyloid protein positively identifies amyloidosis.<sup>(4)</sup> In addition, an electrocardiogram and an echocardiogram are used to detect heart abnormalities and cardiomyopathy, respectively. Similarly, kidney function is evaluated by urinalysis testing for protein levels, by a blood urea nitrogen (BUN) test, and by an increased level of serum creatinine. Abdominal ultrasounds may reveal an enlarged liver or spleen, and evaluation of carpal tunnel syndrome may confirm nerve involvement.<sup>(6)</sup> Additionally, heart, kidney, liver, and nerve biopsies can also help identify the particular organs affected, but these procedures may necessitate hospitalization.<sup>(4)</sup>

### **Causes and Contributing Factors**

The cause of amyloidosis is unknown: stress level, employment type, and diet, including the amount of protein intake, show no correlation with the onset of this disease. However, other medical disorders are associated with

amyloidosis. For example, 10% of patients with multiple myeloma develop the disease.<sup>(2)</sup> Also, secondary amyloidosis (AA) is associated with leprosy, osteomyelitis, tuberculosis, rheumatoid arthritis, familial Mediterranean fever, Hodgkin's disease, and renal cell carcinoma. Likewise, Beta<sub>2</sub>-microglobulin amyloidosis (A $\beta$ <sub>2</sub>M) is common among patients on dialysis. In addition, transthyretin amyloidosis (TTR) is associated with inheritable point mutations. The most common TTR mutations are TTR Val30Met (prevalent in Japan, Portugal, and Sweden) and TTR Val122Ile (3.9% of African Americans are carriers) and are passed on as an autosomal dominant disease.<sup>(3)</sup> Some studies have also suggested amyloidosis may be associated with human herpesvirus 8 (HHV8).<sup>(6)</sup> However, some patients with amyloidosis neither have associated conditions nor family history of the disease.<sup>(4)</sup>

### **Treatment**

There is no known cure for amyloidosis. Thus, medication is employed to limit additional creation of amyloid protein, and diet is altered to treat specific symptoms and associated conditions such as a low-sodium diet when the heart or kidney is affected.<sup>(2)</sup> Additional treatment is used to target specific conditions associated with an affected organ or the primary disease or infection associated with secondary amyloidosis. Liver transplantation has been an effective way of managing hereditary amyloidosis, and Colchicine prevents renal failure in secondary amyloidosis associated with FMF.<sup>(3)</sup> Mayo Clinic research has shown peripheral stem cell transplantation, melphalan (Alkeran), and prednisone due to its anti-

inflammatory effects to be effective treatments.<sup>(4)</sup> Further, Iododoxorubicin is under clinical trial because of its ability to bind to and solubilize amyloid fibrils.<sup>(3)</sup>

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