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COULD YOUR PATIENTS HAVE AA AMYLOIDOSIS?

Amyloidoses are a group of diseases characterized by the extracellular deposition of proteins in amyloid fibrils. These fibrils can accumulate locally, affecting one organ (e.g., pancreas or brain), or systemically, affecting several vital organs (e.g., kidneys, liver, spleen, and heart). The result is organ dysfunction and failure. The clinical manifestation of the disease depends on the type of protein involved—more than 20 human proteins have been identified as amyloid fibril proteins so far (*1*,*2*).

AA Amyloidosis is a progressive and fatal condition that occurs in some patients with chronic inflammatory and infectious disorders, including rheumatoid arthritis (RA), ankylosing spondylitis, juvenile RA, Crohn's disease and tuberculosis. "AA Amyloidosis involves systemic deposition of AA amyloid fibrils," says Martha Skinner, MD, Director, Amyloid Treatment and Research Program, Boston University School of Medicine. "Amyloid can be found in different tissues in patients with this disease, and the kidneys are affected in most patients." Median survival after diagnosis is 4-8 years (*3*).

"AA Amyloidosis should be considered in any patient who presents with long-standing inflammatory disease, especially if this disease has been poorly controlled,"

-Martha Skinner MD

Development of AA Amyloidosis

The tissues of patients with chronic inflammatory diseases are subjected to inflammatory stimuli that can cause an increase in the concentration of the acute-phase protein serum amyloid A (SAA). When SAA levels remain elevated for prolonged periods, SAA aggregates form and are cleaved, resulting in SAA fragments that are deposited in the tissues as AA amyloid fibrils.

Amyloid deposits in AA Amyloidosis are composed of AA amyloid fibril proteins intertwined with many other proteins, including basement membrane components, serum amyloid P component (SAP), complement components, ApoE, and heparan sulfate proteoglycan (HSPG) (*4*,*5*,*6*). HSPGs are found in amyloid deposits in all known types of amyloidosis and appear to play an active role in the initiation of fibril formation and deposition through binding of the highly sulfated glycosaminoglycan (GAG) moiety to amyloid proteins.

Once formed, amyloid fibrils deposit around cells in affected organs and disrupt overall organ function. For example, the formation and deposition of fibrils in the kidney contribute to the progression from renal impairment to end-stage renal disease (ESRD).

Diagnosis of AA Amyloidosis

AA Amyloidosis is a challenge to diagnose and treat, in part because symptoms tend to present only in the later stages of the disease, by which time, tissues and organs have suffered substantial damage.

"AA Amyloidosis should be considered in any patient who presents with long-standing inflammatory disease, especially if this disease has been poorly controlled," says Dr. Skinner. "Renal involvement is the most

common presentation of this condition, so tests should be conducted to look for signs of renal impairment, such as persistent proteinuria or an elevated serum creatinine level. We also look for chronically elevated C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR)." Patients might also present with unexplained weight loss, enlarged liver, or orthostatic hypotension, says Dr. Skinner.

Methods for identifying AA Amyloidosis

The first step in identifying this disease is to detect the presence of amyloid in a biopsy of the patient's tissues. "Aspiration of subcutaneous abdominal fat is the least invasive way to obtain tissue for testing," says Dr. Skinner. "We can diagnose about two-thirds of patients with AA Amyloidosis using that simple test. If amyloid fibrils are not detected in a fat biopsy and AA Amyloidosis is still suspected, we'll do a more invasive biopsy—on the organ we think is affected, such as the kidney."

Amyloid deposits stain with Congo red and produce characteristic green birefringence under specific polarized light. Immunohistochemical methods using specific monoclonal antibodies to AA protein can confirm the presence of AA-type proteins.

A useful test for diagnosis and monitoring the progression of AA Amyloidosis involves injecting radiolabelled serum amyloid P component (123I-SAP) and performing a whole-body scan of the patient. This test is non-invasive and quantitative, but it is expensive and is currently available only in a few specialized centers in Europe.

Treatment of AA Amyloidosis: A vital unmet medical need

No specific therapy for AA Amyloidosis currently exits—treatment is limited to managing the underlying inflammatory disease and supporting declining organ function. Agents that suppress the inflammatory response and the production of SAA may help slow progression of the disease: when SAA levels are maintained below 10 mg/L, amyloid deposits can regress and organ function can stabilize or improve. (*3*) "Cytotoxic drugs such as chlorambucil or cyclophosphamide are used to treat the underlying disease for patients with RA," says Dr. Skinner, "But these drugs don't treat AA Amyloidosis." Anti-TNF agents can decrease SAA production, but might also lower the patient's ability to fight infections and destroy malignancies (*2*,*7*).

Therapies in development for AA Amyloidosis

Researchers in academic and industrial settings are working to elucidate the pathophysiology of AA Amyloidosis and develop effective therapies. A promising line of research involves agents designed to mimic the anionic properties of GAGs in order to interfere with the formation and deposition of amyloid aggregates. One such compound in development by Neurochem, Inc. (Laval, Quebec, Canada) is nearing completion of phase II/III clinical studies. "Physicians may soon have a treatment to offer patients" says Dr. Skinner, "and I hope that we'll see an increase in the diagnosis and treatment of this disease."

For more information concerning Neurochem Inc, call 1-877-680-4500, or visit the company's Web site at www.neurochem.com.

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