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Amyloid is a term that is used to describe disorders characterized by protein misfolding in the extracellular deposition of these previously soluble proteins, which become insoluble and form amyloid fibril complexes. These deposits can disrupt tissue architecture and the function of various organs. The diagnostic standard is considered Congo red staining of tissues, with a classic finding of what is called the apple-green birefringence under a cross-polarized light. Amyloid can be classified in several ways. When it is not just localized to one organ, it is called systemic amyloidosis. Amyloid is commonly classified into immunoglobulin light chain (AL). This is an acquired type amyloidosis. It can be systemic or localized. Usually, the type of amyloid involving immunoglobulins is light chain. Rarely It can be a heavy chain. Reactive amyloidosis is known as AA amyloid, with the precursor protein being a serum amyloid A protein. This is also acquired and is usually systemic. It is becoming less frequently found due to better treatment of chronic inflammatory diseases. It is seen as a complication of chronic inflammation or infection. One could actually measure the serum amyloid protein (SAA) in blood testing. These deposits usually occur in the spleen and kidneys and cause protein leakage in the kidneys and can increase the risk of end-stage renal disease. Another type of amyloid is known as senile systemic amyloidosis, which is also known as wild-type (tATTR), with the precursor protein being a transthyretin wild-type protein. This is an acquired disorder, and is usually systemic and usually found in patients over the age of 75. In fact, up to 25 percent of people above the age of 80 may have it. It usually presents with cardiac involvement and rarely with a peripheral sensorineural neuropathy. It has been called senile amyloidosis in the past, but is now termed wild amyloidosis. It is abbreviated wtATTR. Another type of transthyretin amyloidosis is known as ATTR, and this type is hereditary. It is also known as transthyretin variant due to mutations in various genes. It can be found in more than 100 gene mutations. This usually presents as systemic amyloidosis also. There are rarer types of amyloidosis, which are hereditary and usually present with systemic amyloidosis. These include fibrinogen amyloid, apolipoprotein A1 amyloid, apolipoprotein A2, amyloid lysozyme amyloid, gelsolin amyloid, cystatin amyloid, and A-leukocyte amyloid.

With autonomic dysfunction, we often search for a cause of amyloidosis as being responsible, especially in patients who present with orthostatic hypotension. We predominantly test for AL amyloid and for hereditary transthyretin (hTTHR) amyloidosis.

Gene testing is often done to assess for hereditary TTR amyloidosis and to assess the prevalence of TTR mutations with genotyping. TTR mutations are high in Portugal, Sweden, and Japan, for example, a valine substitution, which causes this, may be found in 1 out of 500 people in northern Portugal. It is much lower in the United States, perhaps 1 in one million. The Japanese also have a higher incidence. Patients with this familial type, or hereditary amyloidosis, usually have a family history, which is easily identified. They can experience different types of neuropathies, from focal neuropathies, sensorimotor polyneuropathy, autonomic neuropathy, or a combination of the three. The median nerve at the wrist is commonly involved, and bilateral carpal tunnel syndrome can be noted. This can give paresthesias in the thumb and digits two and three, pain in the wrist, which may extend to the elbow, and weakness of the grip can occur. In familial amyloidosis, carpal tunnel syndromes are usually more common than those found in the general population when they acquire it. It is often bilateral. Patients with familial amyloidosis may also present with vocal cord paralysis and lower extremity pain on onset. It can affect the peripheral motor and sensory nerves in a length-dependent manner, leading to sensorimotor polyneuropathy. The fibers that tend to be affected are the small myelinated and unmyelinated fibers, and patients can have a pins and needles sensation, numbness in the extremities, often worse at night. There may be a decreased pin-prick sensation. When larger fibers are affected, there is loss of these fibers, and muscle weakness and more severe sensory loss may occur. Reflexes may be absent, and diminished vibration sense is often seen. Dysfunction of the autonomic nervous system is commonly seen in many of the early-onset familial, or hereditary amyloidosis, and is less common in those with delayed onset familial amyloidosis peripheral neuropathies. Patients can experience orthostatic hypotension and orthostatic intolerance when standing, with blurry vision. GI symptoms can include postprandial diarrhea alternating with constipation. Gastroparesis with postprandial vomiting may occur and lead to progressive weight loss and dehydration, and worsening postural hypotension. Urinary retention, or incontinence, can occur. If an individual has significant weight loss, oftentimes with diarrhea and orthostatic hypotension, amyloidosis should be at the top of the differential. Erectile dysfunction may

be an early feature that precedes sensory symptoms of neuropathy in men. The diagnosis usually involves identifying the family history and doing DNA testing. Of course, one must exclude other causes of peripheral neuropathy, including metabolic causes, liver causes, diabetes, B12 causes, and thyroid abnormalities. Also, urine and serum immunofixation should be obtained, as monoclonal protein is found in approximately 90 percent of patients with light chain or AL amyloidosis. Also, one should exclude Sjögren's syndrome and test for SSA-A and SSB antibodies. If indicated, HIV testing, Lyme testing, hepatitis C testing, or heavy metal screening may be needed. In addition, one may consider testing for angiotensin-converting enzyme levels, anti-GM-1, and antineutrophil cytoplasmic antibodies (ANCA antibodies). Cryoglobulins, copper levels, anti-myelin-associated antibodies, screening for celiac disease, paraneoplastic antibody screening, and other genetic testing, such as mutations associated with Charcot-Marie-Tooth, may be needed. EMG may be useful if large fibers are involved. Pseudomotor testing if autonomic nervous system is involved. Pseudomotor testing will identify if there is small fiber involvement, which is typically involved early in the course of this disease. Cardiac amyloidosis may be found in some patients with hereditary amyloidosis, and technetium and pyrophosphate scans are helpful in identifying this and the senile type of amyloid, whereas AL amyloid will not be image-positive with nuclear testing. Drugs used to treat hereditary amyloidosis include diflunisal and tafamidis. Other genetic agents have been developed. Liver transplantation is a first line in the treatment for a valine type of genetic hereditary amyloid, and can even be curative. Apoprotein A1-related familial amyloid polyneuropathy has been found in some families, as has genetic-related familial amyloidosis. The latter is known as the familial amyloidosis of Finland.

Regarding acquired forms of amyloid neuropathy, primary systemic AL amyloidosis is the most common and is caused by a plasma cell abnormality and B-cell abnormality. Peripheral neuropathy occurs in 17 percent of patients with AL amyloidosis, making it the most common type of acquired amyloid. Two-thirds of these patients who have peripheral neuropathy, will also have autonomic system abnormalities. They will often have sensorimotor axonal polyneuropathy and carpal tunnel syndromes. Usually, symptoms begin with painful sensations in the feet, signifying small fiber involvement. As the disease progresses, the larger nerves may be affected. GI symptoms, such as nausea, vomiting, constipation, diarrhea, erectile dysfunction, and postural lightheadedness may occur.

Diagnosis is made by Congo red staining of tissue and by the presence of lambda or kappa light chains in the blood or urine. Treatment can include various types of chemotherapy agents, although others are available, such as peripheral blood stem cell transplantation.

AA amyloidosis is becoming more rare and rarely affects the nervous system, but autonomic neuropathy has been identified in some cases.

Senile amyloidosis (SSA) or age-related senile amyloidosis, also known as the wild-type (TTR), is found in up to 25 percent of people over the age of 80. Most of it occurs in the heart, leading to a cardiomyopathy and atrial fibrillation. It can also be found in the liver, kidneys, GI tract, aorta and connective tissue. Carpal tunnel syndrome is commonly found and can be bilateral, as it can be with the AL amyloid and with the hereditary amyloidosis. Rarely, one sees SSA amyloid causing a sensorimotor polyneuropathy, but this is not common, and rarely does it cause autonomic dysfunction.

It should be noted that the senile wild-type amyloid and the wild-type TTR amyloid, the TTR familial hereditary amyloid syndrome (these are usually autosomal dominant), and the primary AL amyloid are the most common types that can cause a cardiac amyloidosis syndrome with heart failure. These are usually infiltrative cardiomyopathies. The first two can be identified by technetium nuclear testing of the heart for imaging.

Cardiac amyloidosis is one of the leading causes of what is known as a restrictive cardiomyopathy. It presents with rapidly progressive diastolic dysfunction in which the heart is not enlarged but is stiff. It is very underdiagnosed, but there is treatment for this. Cardiac amyloidosis is the most common type of the so-called restrictive cardiomyopathies. The other two more common types are cardiac sarcoid and cardiac hemochromatosis. An echocardiogram can often give clues to a restrictive cardiomyopathy, and a cardiac MRI gives more additional data.

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As noted, the primary etiologies of cardiac amyloid include primary amyloidosis, also known as amyloid light chain amyloidosis or AL amyloidosis, and this is often found in patients with plasma cell dyscrasia and multiple myeloma. Rarely, secondary amyloidosis, or AA amyloid, due to infection and inflammation, is found as a cause of cardiac amyloid. More commonly, we see as acquired forms of cardiac amyloid, senile systemic amyloid, also called wild-type transthyretin amyloid, or ATTRW, causing cardiac involvement. This is the most common type of cardiac amyloidosis. A familial amyloidosis involving the ATTR protein, which is abbreviated ATTRm (the little m stands for mutated), may cause cardiac amyloid. Occasionally, a rare and isolated amyloidosis of the atrium, or the top chambers of the heart, is found. This is caused by deposition of amyloid from atrial natriuretic peptide, which is a protein found in the blood. The most common presentation of patients with amyloid, which affects the heart, is usually congestive heart failure. However, periorbital purpura or bruising around the eyes, and an enlarged tongue (macroglossia) are often seen with cardiac amyloid. Often, one will see swelling of the feet and elevated neck veins. Fluid in the belly can be appreciated on physical exam, and if a physician auscultates the lungs, crackles are noted. Neuropathy often accompanies cardiac amyloid, except if it is senile amyloid. There is treatment for all types of amyloid, so proper identification of the type is important.