Amyloidosis
General Overview

Amyloidosis was first discovered 150 years ago by the well know German pathologist, Dr. Rudolf Virchow. Although the disease has been recognized for many years, treatments have only been widely available for the past 25 years. Amyloidosis is a very complicated disease that is often difficult for doctors to diagnose. This, in part, accounts for why it has taken so long to develop effective treatments.

This booklet is provided to offer information and understanding of the amyloid diseases in a general manner.

This pamphlet is dedicated to the patients who have participated and are currently participating in clinical trials for amyloidosis. Their involvement is absolutely essential as we test new treatment strategies and advance towards our goal of a cure.

What is Amyloidosis?

The amyloidoses (the plural word for amyloidosis) are rare diseases first described over 150 years ago. There are different types of amyloidosis that are all unified by a common pathological process. Amyloid diseases all cause deposits of amyloid proteins in the body's organs and tissue, and the amyloidoses are classified by the protein that deposits as amyloid. This accumulation may happen systemically (throughout the body) or locally (in one tissue or organ).

Each year approximately 3000-5000 new cases of light chain (AL) amyloidosis are diagnosed in the United States, with many more cases of age-related and inherited transthyretin amyloidosis (ATTR) also diagnosed. Amyloidosis is generally a disease of middle-aged people and older, although the disease has been seen in individuals in their thirties. Other diseases can increase the risk of amyloidosis, and family history of the disease may indicate a hereditary version. 10 to 15% of people with multiple myeloma develop amyloidosis. Long-term kidney dialysis may increase the risk of dialysis-associated amyloidosis.

Symptoms of the disease are non-specific and could include the following; fatigue, weight loss, a feeling of fullness, tingling and numbness in the lower extremities, shortness of breath, irregular heart rhythm, foaming urine, and possibly an enlarged tongue. Amyloid protein deposition is also the cause of Alzheimer's dementia, but the proteins that cause Alzheimer's dementia are not the same as those that cause systemic amyloid diseases, and thus the two are not thought to be directly related.

Systemic Amyloidosis

Systemic amyloidosis involves the deposition of amyloid throughout various tissues; including muscles, connective tissues, organs and peripheral nerves. There are a number of types of systemic amyloidosis. The most common include AL (light chain) amyloidosis, hereditary amyloidosis (usually related to the protein transthyretin or TTR) and AA amyloidosis.

Localized Amyloidosis

Localized amyloidosis involves tumor-like nodules that can be found on the lung, larynx, skin, bladder, bowel and tongue. Localized amyloidosis may affect people with type II diabetes, people with certain cancers of the thyroid or endocrine system, and many people over the age of 80.

The ratio of systemic to localized amyloidosis is 9:1.

AL Amyloidosis – Light Chain

AL amyloidosis was previously thought to be the most common form of the disease, but recent advances in diagnostic techniques have changed that perception. AL amyloidosis is a bone marrow plasma cell disorder, the cause of which is unknown, related to multiple myeloma. In fact, treatments for AL amyloidosis that target and destroy the pathological plasma cells mirror those for multiple myeloma. The bone marrow produces many cells: red and white blood cells, platelets and antibodies (which are proteins). In the case of AL amyloidosis, the bone marrow plasma cells produce misfolded antibody protein fragments (parts of antibodies called "light chains") that travel through the body and self-

assemble and deposit in various organs, ultimately causing organ failure if the deposition if not stopped.

AL amyloidosis can affect a single organ or multiple organs. Common combinations of organ involvement include; heart/kidney, heart/GI tract and kidney/peripheral nerves, but almost any combination may present. About one third of people with AL have a high level of protein in the urine with few symptoms of organ involvement. Another third have symptoms of protein accumulation in the heart and in one quarter of AL patients the protein builds up in the liver and gastrointestinal tract. Kidney and heart involvement are the most common organ manifestations.

AA Amyloidosis

AA amyloidosis may occur in the course of a chronic inflammatory disease or chronic infection such as rheumatoid arthritis, familial Mediterranean fever (FMF), osteomyelitis, tuberculosis or inflammatory bowel disease. In the United States, this form of amyloidosis is rarely seen. This is because the medical treatment available for inflammatory diseases and chronic infection keeps them in check thus not triggering the development of AA. AA is much more prevalent in third world countries. The kidneys are the most common organ affected by AA amyloidosis.

TTR Amyloidosis

This form of amyloidosis can be inherited from affected parents or develop spontaneously. Recent advances in diagnosis have suggested that TTR amyloidosis is probably the most prevalent form of the disease. In the inherited form, also

called ATTRv (varient), presence of the disease is due to inheritance of an abnormal gene (a mutation) present since birth that leads to abnormal folding of the TTR protein and then deposition of the unfolded protein as amyloid in affected organs and tissues. Symptoms of this disease normally do not present themselves until middle age or later and typically involve heart and nerve problems leading to heart failure or peripheral neuropathy. Certain mutations can be found in different ethnic or racial groups. Examples include the T60A mutation, found in persons of Irish ancestry, or the V122I mutation, seen in persons of African ancestry. If a particular person has the mutated gene, each of their children has a 50% chance of inheriting the mutation (we call this autosomal dominant) but not all people with a mutated gene will necessarily get sick (we call this incomplete penetrance). Some individuals only develop a small amount of amyloid in their body and some people may not accumulate any amyloid at all. The non-inherited form of TTR amyloidosis is called ATTRwt (for wild type or genetically normal protein). It was previously known as age-related or senile cardiac/systemic amyloidosis. This is a disease seen mainly in Caucasian males, and in those over the age of 60 years, although cases in women, non-Caucasians, and those in their 50's have been identified.

How Amyloidosis is Diagnosed

The diagnosis starts with a thorough physical examination and establishment of the patient's medical history. The symptoms presented will help to determine tests that may be performed.

For AL amyloidosis, monoclonal light chains found in the blood serum or urine by immunofixation electrophoreses (IEF) or free light chain (FLC) assay indicate the precursor protein that causes AL amyloid may be present. Free light chain assays are only 80-90% sensitive and many facilities do not have them or use them as an initial screening test. Additional testing including a bone marrow biopsy may be required to confirm the presence and nature of the underlying plasma cell disease.

There are presently no good blood tests for ATTR either wild-type or mutant forms. Identification typically involves recognition of particular patterns in imaging testing of the heart (such as nuclear imaging, echocardiography, and magnetic resonance imaging) or physical manifestations of heart or nervous disease in the right clinical scenario. In all forms of amyloidosis, a high index of suspicion is necessary to perform the appropriate testing to identify the disease.

BNP (or nT-pro-BNP), a hormone produced when the heart is stressed, is measured via a blood test. If elevated, it may indicate heart involvement with amyloid. An echocardiogram may show the thickening of the heart walls, and abnormal heart relaxation, which could also indicate cardiac involvement. If urinary protein levels are markedly elevated, it may indicate kidney involvement with amyloid. Elevated alkaline phosphatase is an indicator of possible liver involvement with amyloid. As some of these tests are indicators of several forms of the disease it is important that the results be reviewed in conjunction with all the other test results to assure a proper diagnosis and not be looked at alone.

For AL amyloidosis, diagnosis must be confirmed with a positive biopsy. Common tissue samples for the biopsy can be taken from abdominal fat, suspected organ involved, or the rectum. Biopsy of the suspected organ is not always necessary but can be useful. Tissue specimens can be analyzed in the pathology laboratory for identification of amyloidosis and the specific protein involved, or the specimen can be sent for confirmatory analysis using a specialized technique called mass spectrometry. For ATTRwt, recent advances in nuclear cardiac imaging permit this diagnosis to be made with a high degree of confidence with an abnormal imaging test and normal blood testing to rule out AL amyloidosis.

If a hereditary form of amyloidosis is suspected, genetic testing is required to confirm the type. This is a simple blood test where the genes are analyzed to determine which mutation is present.

It is essential that the correct diagnosis of protein type be made, as treatment follows from this identification. This typically requires a biopsy and proof of amyloid and responsible protein on the tissue specimen. It is also important to exclude inherited or sporadic TTR amyloidosis in the right clinical context, even when AL is suspected.

Treatment of Amyloidosis

The treatments for each type of amyloidosis differ. Extension of life, reversal of organ damage and improved quality of life are the major outcomes that are sought.

AL Amyloidosis – The treatment target for AL therapies is to eliminate the precursor protein of the amyloid that is depositing in the body. The amount of light chain in the blood indicates the activity of disease, with lowering light chain values indicating response to treatment. The first thing that needs to be done for patients once the diagnosis is made is to assess the extent of organ involvement. This will steer the proper treatment option. The majority of patients can be treated with new combinations of drugs no matter how many organs are damaged. Patients with severe heart damage, however, may need to be considered for a heart transplant as first treatment. Younger patients with minimal organ damage can often be treated with an autologous stem cell transplant.

Autologous stem cell transplant involves utilizing the patient's own stem cells. The process begins with mobilizing the stem cells from the bone marrow into the blood stream so that they can be collected. The next step is to administer a pre-determined dose of IV melphalan (chemotherapy) to kill off all of the cells in the bone marrow. At this point the collected stem cells are re-infused into the blood stream to allow for them to migrate back into the bone marrow where they generate the red and white blood cells and platelets needed for normal blood counts. Recovery from the acute side effects of stem cell transplant, particularly on the gastrointestinal tract, takes 2 to 3 months. Some patients with AL amyloidosis treated with successful stem cell transplantation are alive 20 years after treatment.

For patients who are not candidates for stem cell transplant, or choose to not undergo that form of treatment, there are a

number of highly effective chemotherapy treatments. They include combinations of dexamethasone, oral melphalan, oral cyclophosphamide and the proteasome-inhibitor Bortezomib (Velcade®). Another commonly used agent is lenolidamine (Revlimid). Many new agents are being investigated in recently developed clinical trials that will prove useful in the future. One exciting new approach is the use of antibodies that cause the body to resorb the amyloid that has been deposited. This is a new approach to treatment because chemotherapy works to kill the abnormal plasma cells and thereby stop ongoing amyloid damage. While critically important to prolonging survival, chemotherapy itself does not resolve in significant removal of amyloid in tissues.

In January 2021 Darzalex Faspro in combination with bortezomib, cyclophosphamide and dexamethasone (D-VCd) was approved by the FDA for newly diagnosed AL patients. Other drugs are various chemotherapy agents that have shown to have a positive effect on reducing the cells that make the light chains. Sometimes it may be necessary to use a number of the different protocols in succession. Throughout treatment, the serum free light chains and other blood counts are monitored to determine the effectiveness of the treatment.

TTR Amyloidosis – In ATTRv amyloidosis, the inherited form, the amyloid forming protein is produced in the liver, but the liver function itself is usually normal. With this in mind, liver transplants are sometimes performed in patients with the intention of preventing further amyloid deposition, though the number of transplants performed is falling rapidly. This is because recently the FDA approved two agents, Onpattro (patisiran) and Tegsedi (intersen) for the treatment of ATTRv

with polyneuropathy. AMVUTTRA is another drug approved by the FDA for ATTRv polyneuropathy.

The agents Vyndamax, Vyndeqel (tafamadis) and Attruby (acoramidis) have also been approved by the FDA for use with cardiac involved ATTR, both hereditary and wild-type.

AA Amyloidosis – Since AA amyloidosis is caused by an underlying inflammatory or infectious disease treatment involves eliminating the source of the inflammation and/or infection.

Clinical Trials

Clinical trials are an important aspect in developing new treatments for amyloidosis. Patients may be asked to be part of a clinical trial and will be provided with extensive information on the treatment plan, its purpose, eligibility criteria and potential side effects. Some clinical trials carry the possibility of being randomly assigned a placebo or inactive drug. This is unfortunately necessary to determine if a drug is effective of not. The decision to enroll in a clinical trial is strictly up to the patient. Patients can inquire at the various specialty centers to see if they are eligible to enroll in a clinical trial.

The purpose of clinical trials is to determine the effectiveness and safety of new treatment protocols. Not all patients will benefit from participation in a clinical trial, but the information generated during the trial is very important in the development of treatments for future amyloidosis patients.

Supportive Care

Supportive care is important to address specific problems and symptoms that are caused by the amyloid deposits in the body. In the case of cardiac or kidney involvement, edema (fluid buildup) may be a problem and a diuretic can be prescribed to help minimize the problem. In some cases, compression stockings can be of benefit and elevating the legs can help lessen the swelling. Patients with congestive heart failure due to amyloid in their heart need special diets and medication under the care of a cardiologist who understands the needs related to amyloid heart disease. If the gastrointestinal tract is involved, diet modifications and some medications can help with diarrhea and the feeling of fullness. Some patients with macroglossia (enlarged tongue) have difficulty swallowing and sometimes aspirate fluids into their lungs. Thickeners can be obtained to mix into everyday fluids that will help to minimize aspiration into the lungs.

Prognosis for an Amyloidosis Patient

With early diagnosis, the outlook for patients with amyloidosis has shifted to hopeful in the last decade. The early diagnosis allows treatment to begin before the amyloid protein burden in the body becomes too great to overcome. Without treatment, the outlook for patients with amyloidosis is not good, therefore, early diagnosis is the key to managing the disease.

In familial TTR amyloidosis, the outlook varies depending on the type of gene mutation, symptoms and manifestations of disease, and when the condition is diagnosed. ATTRwt is generally the slowest disease to progress, but many patients

have other medical problems that complicate treatment due to an older age at diagnosis.

Localized amyloid tumors can be surgically removed and generally do not recur.

Conclusion

Although a cure for amyloidosis and a cause for some of the forms of the disease still have not been found, the outlook for amyloid patients has improved greatly in the last decade especially if diagnosed early on. The information contained in this pamphlet is intended to provide a general overview of the disease and its treatment.

It is important to note that although advances in treatment options have progressed there is still much to be discovered. It is not known how certain proteins and immunoglobulin light chains form amyloid. How to stop the light chains from sticking together and forming amyloid, and the exact way that this makes patients sick is also unknown. The answers to these and many other questions are important for the continued development of treatments and will lead to our goal of a cure.

NOTES:

To Locate an Amyloidosis Clinic, please visit the Resources page on our website:

www.amyloidosis.org

amyloidosis foundation

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