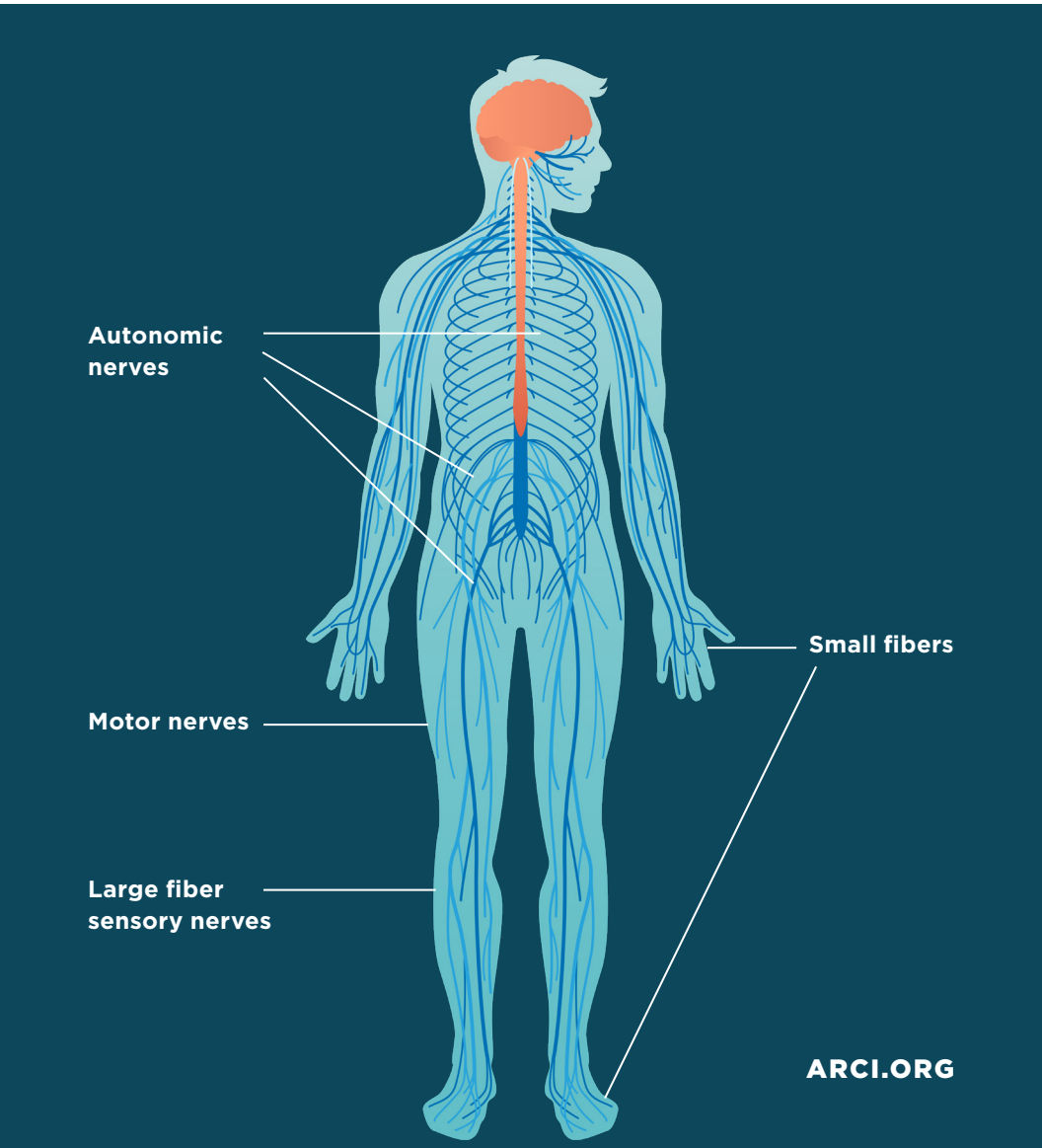
Amyloidosis Research Consortium

# NEUROPATHY IN AMYLOIDOSIS

## SYMPTOMS AND MANAGEMENT

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# KNOWLEDGE IS POWER

## ABOUT THE **AMYLOIDOSIS RESEARCH CONSORTIUM**

The Amyloidosis Research Consortium (ARC) is a nonprofit organization dedicated to driving advances in the awareness, science, and treatment of amyloid diseases. Its mission is to improve and extend the lives of those with amyloidosis. ARC is committed to collaborative efforts that accelerate the pace of discovery, expand patient access to the most effective care, and improve short- and long-term outcomes. Working with partners in industry, government, and academia, ARC seeks to spark innovation and to bring promising treatments from labs to clinics. Our outreach and educational efforts inform and empower patients, families, caregivers, physicians, and researchers.

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To learn more about ARC, visit **www.arci.org** or call **(617) 467-5170**.

Amyloidosis Research Consortium

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*ARC gratefully acknowledges Kelsey Barrell, MD, Assistant Professor in the Division of Neuromuscular Medicine within the Department of Neurology at the University of Utah for her contributions to the development of this booklet.*

# INTRODUCTION

Many types of amyloidosis can affect patients' nerves, causing painful, annoying, or even debilitating symptoms. It is common for patients with amyloidosis to experience neuropathy and in fact, some patients may have nerve-related symptoms as their most predominant sign or chief complaint.

This booklet discusses the various impacts that amyloidosis may have on a patient's nerves, the symptoms associated with the disease process, and potential management techniques. We encourage you to contact your health care provider if you have specific questions about your diagnosis of amyloidosis and the nerve symptoms you may be experiencing.

A well-informed patient is better able to be an active partner with their health care team in making decisions about treatment, managing their care, and advocating for their needs.

**This booklet is here to serve as a comprehensive resource and a guide for making informed treatment decisions.**

# WHAT IS AMYLOIDOSIS?

Amyloidosis is a disease of misfolded proteins that build up in the body's organs and tissues, making them unable to work the way they should. Over 30 different proteins cause amyloidosis. Each is referred to by an "A" for amyloid followed by an abbreviation for the misfolded protein (for example ATTR is amyloidosis caused by the misfolded TTR protein). Treatment is determined by the type of amyloidosis and which organs and tissues are affected.

**Amyloid is a starch-like substance caused by the misfolding of proteins. Amyloid binds together into rigid fibrils that accumulate in tissues and organs.**

### WHY ARE PROTEINS SO IMPORTANT?

Many thousands of proteins do essential work inside our cells. Each has a specific function to keep us healthy. Normal proteins fold in a specific way, complete their tasks, and are then recycled or removed from the body. Misfolding of certain proteins leads to amyloid deposits that build up in tissues, organs, and nerves, causing problems. As amyloid deposits accumulate over time, symptoms intensify, telling us something is wrong.

## WHAT ARE THE SYMPTOMS OF AMYLOID NEUROPATHY?

There are a wide range of symptoms that vary depending on which type of nerve fibers are affected. Amyloid-related neuropathy symptoms typically start in the limbs, so in the hands or feet. When symptoms begin in the toes, over time, they will typically progress to the upper limbs in a distribution classically described as a “stocking-glove” pattern. The smallest nerve fibers lack protective insulation (called a myelin sheath) and therefore tend to be involved early on in the course of the disease. These small fibers convey pain and temperature sensations, and patients will experience burning, tingling, “pins-and-needles” or “electric shock” sensations, and even increased sensitivity to touch.

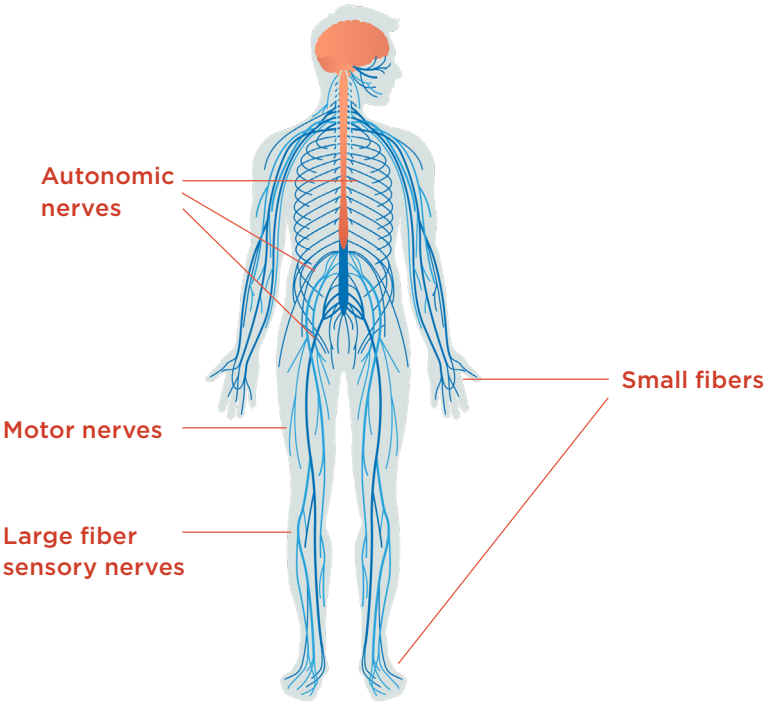
The smallest fibers are also the most common type of nerve affected in amyloidosis. Medium and large fibers are responsible for vibratory sensations and sensing joint positioning. When these fibers are affected, it may result in numbness and trouble with balance. The largest fibers carry signals to the muscles and can result in weakness or muscle loss which is usually more pronounced in the feet or hands and tends to affect people

**To learn more about specific types of amyloidosis, view ARC’s companion brochures at www.arci.org, or contact an ARC patient support specialist at (617) 467-5170.**

much later in the disease course. The autonomic nerves are also small fiber nerves, but these are unique in that they carry information which regulates the autonomic nervous system.

The autonomic nervous system helps control all bodily functions, such as the heart rate, blood pressure, and cardiovascular system, the digestive processes and gastrointestinal system, and urinary and sexual function.

### NERVES THAT MAY BE AFFECTED BY AMYLOID




Additionally, amyloid deposits can cause compression neuropathy such as carpal tunnel syndrome, where the median nerve is compressed at the wrist. This can result in hand numbness, wrist pain or grip weakness and dropping items. Early on, this may be episodic and occur with certain activities or wake you up from sleep, but over time the numbness, pain, and weakness may become persistent. It is important to discuss these symptoms with your provider because there are effective treatment options for carpal tunnel syndrome.

| COMMON SYMPTOMS OF NERVE INVOLVEMENT IN AMYLOIDOSIS BY NERVE TYPE | |
|---|---|
| **Small Fibers** | • Pain or increased sensitivity to touch<br>• Burning<br>• Tingling<br>• "Pins-and-needles"<br>• "Electric-shocks" |
| **Autonomic Nerves** | • Feeling faint/light-headed upon standing (orthostatic hypotension)<br>• Diarrhea, poor appetite, constipation, and other gastrointestinal issues<br>• Sexual dysfunction<br>• Incontinence, reduced sensation, urinary infections, and other urinary issues |
| **Large fiber sensory nerves** | • Numbness<br>• Imbalance |
| **Motor nerves** | • Weakness<br>• Muscle loss (atrophy) |

**Different types of amyloidosis may be more likely to present with nerve involvement, and even different variants within hereditary ATTR may be more likely to cause neurological issues rather than cardiac ones.**

Amyloid deposits can also affect other types of nerves, resulting in different symptoms. See the table on the following page for a more complete list.

## WHY AND HOW ARE THE NERVES INVOLVED?

There are several different reasons that amyloidosis may cause nerve-related symptoms.

Amyloid deposits can be:

- In and along the nerves themselves
- In blood vessels that supply the nerves
- In nearby tissues causing compression of the nerves
- Causing direct toxic effects to the nerves

| EFFECTS OF NERVE INVOLVEMENT IN AMYLOIDOSIS | | |
|---|---|---|
|  **Neuropathic** |  **Musculoskeletal** |  **Autonomic** |
| • Painful neuropathy in hands and feet<br>• Muscle weakness<br>• Difficulty walking<br>• Falls | • Carpal tunnel syndrome<br>• Back pain/ lumbar stenosis<br>• Shoulder, knee, and hip pain<br>• "Trigger finger," joint stiffness, locking or popping | • Orthostatic hypotension<br>• Chronic diarrhea/ contstipation/ weight loss<br>• Erectile dysfunction and/or urinary incontinence |

# DIAGNOSING AMYLOID NEUROPATHY

Although many patients self-report their neuropathy symptoms, there are also diagnostic tests that can evaluate the level of nerve and muscle impairment. Some examples include:

**Neurologic exam:** in a neurologic exam, a medical provider checks the patient's reflexes, coordination, balance, strength, and ability to feel various sensations such as temperature, pinprick and vibration.

**Nerve conduction study (NCS):** in a NCS, small electrodes are placed on the patient's skin over various nerves and muscles of the body. A pulse of electricity (which feels like a brief static carpet shock) is sent to the electrode and a tool measures the size of the response, as well as how quickly the nerve is carrying the electrical signal. Both motor and sensory nerves can be studied in this way and can reveal the distribution and severity of nerve involvement.

**Needle electromyography (EMG)**: in an EMG, a very thin needle with a small recording electrode is inserted through the skin and into a muscle. The muscle is then activated in a specific way, allowing the electrode to record the electrical activity of the muscle.

**Nerve biopsy:** during a nerve biopsy, a minor incision is made and a small piece of nerve tissue is removed and examined to look for the presence of amyloid.

# DOES TREATMENT FOR MY DISEASE ALSO IMPROVE NERUROPATHY SYMPTOMS?

Treatment for amyloidosis can be broken down into two main approaches:

1. Targeting the underlying disease

2. Treating the symptoms themselves

The goal of treatments is to slow or stop the production of amyloid. As the disease process slows, the body attempts to breakdown the amyloid deposits that have already infiltrated various tissues and organs. This can allow for some nerve regeneration, or improvement of symptoms, although it can be a slow process.

For AL amyloidosis, treatment regimens are comprised of chemotherapy, steroid drugs, and in some cases a stem cell transplant. Available treatments for different types of ATTR amyloidosis are classified as either TTR stabilizers or gene silencers. For more information on treatment options, visit ARC's Patient Hub at: www.arci.org

Symptom management may include topical agents, prescription medications, and alternative therapies.

**For one type of amyloidosis, AL, the backbone of treatments is based on chemotherapy, which can lead to additional nerve-related symptoms. Be sure to talk to your doctor about any new or worsening symptoms that you are experiencing.**

# MANAGEMENT OF NEUROPATHY SYMPTOMS

There are many different therapeutic options that neurologists and other clinicians can prescribe to help you manage your symptoms. These tend to be most helpful for painful or uncomfortable symptoms rather than numbness or weakness. Aside from prescription medications, this section will also cover over-the-counter medications and homeopathic remedies.

## PRESCRIPTION MEDICATIONS

**Oral prescriptions:** There are many options for oral nerve pain

medications that your physician may prescribe to help manage your neuropathy symptoms.

- **Neurontin® (Gabapentin)** is generally a starting point for prescription neuropathy control, as it is available at a low cost, and has minimal side effects, although some people report experiencing "head fog," mild sedation feeling, or edema (leg swelling).
- **Elavil® (Amitriptyline)** is another option because it can also help with insomnia and depression, both of which can affect amyloidosis patients. Some potential side effects are dry mouth, constipation, and sedative effects.
- **Lyrica® (Pregabalin)** is viewed as the "next generation" of gabapentin, as the benefits are similar, but patients typically experience less of the "head fog" side effect. Pregabalin typically is a higher cost option.
- **Cymbalta® (Duloxetine)** can also help with depression and muscle pain, in addition to nerve pain, and is another option for amyloidosis patients.
- **Oxycodone, Tramadol, or other opioids** may be used if other treatment options were not effective at relieving symptoms. Some clinicians may exercise caution or advise against this route due to the lack of efficacy for nerve symptoms, as well as potential of addiction.

**Be sure to talk to your doctor before starting or stopping any medications, and always keep your care team informed of any new or worsening symptoms or side effects.**

**Topical treatments (ointments/creams):** compounded pain ointment or cream administers high concentrations of pain medication directly to specific sites for targeted relief. The cream formulation is customizable and typically has few side effects, as it targets the area of application and isn't circulated through the body in the same way as oral medications. Some active ingredients in the creams or ointments may include ketamine, gabapentin, baclofen, and other anesthetics or relaxants.

## OVER-THE-COUNTER (OTC) MEDICATIONS

Over-the-counter medications are medications that are widely available from local pharmacies or drug stores without a prescription. It is still recommended that you check with your physician before you start taking them.

- **Lidocaine ointment/lidocaine patch** can be available over the counter, and a stronger version is available with a prescription. These topical treatments contain an anesthetic medication that numbs the area where the ointment or patch is applied to reduce the sensation of pain.
- **Capsaicin (active ingredient in chili peppers)** is used in many creams, ointments, and patches to relieve pain.
- **CBD/THC products** can be an option if they are legally available in your state. These products are typically available in topical and oral forms. Although they can be expensive, these products are thought to be effective as anti-inflammatories, antioxidants, and analgesics, and may also relieve mild anxiety.

## COMPLEMENTARY/ALTERNATIVE THERAPIES

**Complementary/alternative therapies** may be used by patients to help manage neuropathy symptoms. Some physicians may not be as open to recommending various complementary therapies since there is limited research available to support their use in amyloidosis symptom management, while others are open to patients trying them, as the risk of side effects is generally low. Some patients have found relief in complementary/alternative therapies such as:

- Supplements
- Meditation
- Massage
- Acupuncture
- Electrotherapy
- Physical therapy

Other remedies that patients have anecdotally found to be helpful include consuming foods and beverages that may already be available at home such as: pickle juice, tonic water with quinine,

or yellow mustard for leg cramps. As always, it is a good idea to discuss further with your health care provider.

These are not “one-size-fits-all” solutions, and they may not work for everyone.

## EXERCISE AND PHYSICAL THERAPY

When patients are diagnosed with amyloidosis, they often have experienced worsening symptoms for many months or even years. Shortness of breath, nerve pain, muscle weakness, and unintentional weight loss often leads patients to be less physically active. Your care team may have discussed physical therapy if you’re feeling weak or less active than you once were. Many experts agree that exercise and/or physical therapy is a great way to increase muscle mass, mobility, and strength. Some studies have even demonstrated that an exercise program can increase the amount of nerve fibers in certain parts of the body, regenerating damaged nerves and improving symptoms. Exercise also reduces blood sugar and cholesterol, increases blood flow in the body, and reduces stress, all of which are factors that help to reduce discomfort and pain, and keep nerves healthy. Be sure to talk to your doctor about which exercises are safe for you to do.

## CARPAL TUNNEL SYNDROME MANAGEMENT

In mild cases, a wrist splint worn nightly for about a month can reduce or resolve symptoms. Physical therapy exercises and steroid injections in the wrist can also be effective strategies. If symptoms persist, a minor surgery called a carpal tunnel release may be an option.

## AUTONOMIC NERVE MANAGEMENT

Since amyloidosis can affect any type of nerve, there are often some autonomic nervous system functions that may be impacted, such as blood pressure and digestion. There are also some simple solutions to help patients manage these symptoms.

For **orthostatic hypotension**, or low blood pressure upon standing, patients can try compression stockings or abdominal binders, which prevent fluid from pooling in the legs and

abdomen. Patients can also work to optimize their hydration and salt intake, although it is important to speak with your physician before making any dietary changes. There are also medications that your doctor can prescribe to help regulate your blood pressure.

For **gastrointestinal issues**, such as diarrhea, constipation, vomiting, or bloating for example, there are some modifications that patients can make to their diet to minimize these issues. For some, eating smaller, more frequent meals, or decreasing fat and fiber intake may help. Some experts recommend liquid nutrition, such as nutritional shakes and smoothies and avoiding carbonated beverages, alcohol, and tobacco. There are also some over the counter and prescription medications that can ease symptoms. Be sure to read our companion booklet, **Amyloidosis and Gastrointestinal Involvement**, for more specific recommendations, and always keep your doctor informed of your symptoms and concerns.

For **urinary frequency**, urgency, or incontinence, there are a few medications that may help patients with this symptom. Terazosin and Oxybutynin are two such products, both of which require a prescription. Talk to your doctor to see if medication for urinary incontinence might be right for you.

Some patients may experience **erectile dysfunction** from their amyloidosis. Talk to your doctor about options, such as Viagra or Cialis.

**ARC can help you find clinicians that specialize in the diagnosis and treatment of amyloidosis with nerve involvement.**

**Visit www.arci.org or call us at (617) 467-5170.**

## TOOLS AND MODIFICATIONS

Aside from medications and treatments, there are also some lifestyle and home modifications that may help with various neurological symptoms. This next section will cover many of these recommendations, as well as where you can turn to next for additional support and resources.

**Orthostatic hypotension** may be reduced by some simple physical "counter-maneuvers," or movements that assist with blood flow and blood pressure. For example, when you wake up in the morning, sit for a few minutes before standing up, and try about 30 seconds of toe-raises and/or thigh muscle contractions. This helps to get your blood moving before standing and may help prevent lightheadedness, dizziness, or fainting. Another suggestion is to raise the head of your bed about 10-20 degrees (about 4-6 inches). A neurological-focused physical or occupational therapist can advise on more specific movements for you, as well as provide some recommendations for modifications to your home to make it safer.

Modifications referred to as **assistive technology**, are defined as any item, piece of equipment, software program, or product system that is used to increase, maintain, or improve functional capabilities. Assistive technology can be a high-tech item or something low-tech like a simple shoe slide to help you get ready for your day. Below is a list of some examples of more common aids that can assist with daily activities, but many more are available. Be sure to ask your care team if there are additional tools that may be helpful.

### Assistive Devices

- **Auto assist grab bar:** a removable handle that is inserted in a car's door frame latch upon entering and exiting a vehicle to give individuals something to hold on to
- **Foam grip tubing:** foam covering for various utensils and tools such as pens and toothbrushes, so that the item has a wider circumference, making it easier for individuals to hold on to
- **Dycem®:** one brand of nonstick mats and wrapping to increase the grip on various items

- **Rocker knife:** a rounded knife that can cut food using more arm strength rather than hand/wrist/finger strength
- **Key turner:** a tool that attaches to keys so that your entire hand can grip and maneuver a key rather than relying on the strength of just 2 fingers
- **Button hook:** a tool that can assist with buttoning a shirt or pants

**Home Safety Equipment**

- **Bed rail**: a handle that can help you roll over in bed or help you get in and out of bed
- **Lift-chair:** recliner chairs that also have a lifting mechanism so that the individual does not need to use as much effort to stand up from the chair
- **Grab bars:** bars attached to a wall or in the shower to help stabilize the individual during movements (getting in and out of the shower, for example)
- **Toilet safety frame:** handles on either side of a toilet to help a person lower themselves onto a toilet or stand up from a seated position

**Home Modifications**

- **Stair lift:** motorized units that carry an individual on a seat up the stairs
- **Offset hinges:** special hinges installed in doorways that allow the door to move completely out of the frame, allowing an extra inch or two, which could make the difference between a walker or wheelchair fitting through the door
- **Ramp:** allows walkers and wheelchairs to climb what would normally be a few stairs. Ramps are also available in a removable travel version, so that individuals can climb stairs if visiting a family members house, for example
- **Roll-in shower:** a zero-threshold, flush flooring between your shower and the rest of your bathroom. Even a low-profile threshold can be dangerous for those that have lost feeling in their feet and toes, so having a completely level entryway to a shower can be a much safer modification

The above tools and modifications are not an exhaustive list. If you are struggling with your mobility or daily activities, we encourage you to speak with your health care team for recommendations on these options and more.

# ADDITIONAL RESOURCES

At ARC, we are here to help you navigate your medical journey and to support you in receiving the information and care that you need.

## MAP | My Amyloidosis Pathfinder

New trials are always in development to help expand treatment options and improve quality of life. Join MAP to receive notifications as new clinical trials and treatment centers are posted.

Treatment Center Selector

Clinical Trial Finder

**www.myamyloidosispathfinder.org**

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***Peripheral Neuropathy: What It Is and What You Can Do to Feel Better***
By Janice F. Wiesman, MD

Dr. Janice Wiesman, MD was a neurologist who was very active in the amyloidosis community. She cared for many amyloidosis patients and led formative research programs. Her book outlines peripheral neuropathy in an easy-to-understand way, as well as some options for symptom management. Dr. Wiesman's book can be purchased online. Contact ARC for a direct link.

# GLOSSARY

**Amyloidosis.** A disease caused by the accumulation of abnormally shaped proteins (amyloid proteins) in tissues and organs.

**Autonomic nerves.** Nerves that control functions of internal organs, such as heart (blood pressure) and intestines (digestion).

**Carpal tunnel syndrome.** A common condition that causes pain, numbness, and tingling in the hand and arm; caused when one of the major nerves to the hand—the median nerve—is squeezed or compressed as it travels through the wrist.

**Compression neuropathy.** Neuropathy that is caused by direct pressure on a nerve. In amyloidosis, it is usually caused by amyloid deposition in or near a nerve, as in the case with carpal tunnel syndrome.

**Fibril.** Long strands of normally soluble proteins that clump together to form insoluble fibers resistant to degradation.

**Hereditary ATTR (hATTR).** A rare, progressive form of systemic amyloidosis caused by an inherited genetic mutation that causes a buildup of amyloid in multiple organs and tissues.

**Light chain (AL) amyloidosis.** A progressive form of systemic amyloidosis caused by abnormal plasma cells that produce light chain proteins; these misfold into amyloid and circulate in the blood, building up deposits in multiple organs and tissues.

**Myelin sheath.** A layer of insulation that forms around nerves to transmit electrical impulses through the body.

**Neuropathy.** Numbness, tingling, pain and weakness caused by nerve damage or dysfunction, most commonly occurring in the hands and feet.

**Orthostatic hypotension.** Low blood pressure upon standing due to damage of autonomic nerves.

**Wild-type transthyretin amyloidosis (ATTRwt).** A progressive, systemic disease caused by factors related to aging, rather than a genetic mutation.

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Learn more at **ARCI.ORG**

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