FAST*facts*

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HEREDITARY TRANSTHYRETIN AMYLOIDOSIS WITH POLYNEUROPATHY

Amyloidosis is a serious disease characterized by abnormal protein deposits in the body's tissues and organs. Transthyretin amyloidosis, sometimes called ATTR amyloidosis, is caused by abnormal deposits of a specific protein – transthyretin.

The disease is difficult to recognize and diagnose, particularly in the United States, where patients have many different genetic variants. Additionally, no U.S. treatment guidelines are available for hereditary transthyretin amyloidosis, known as ATTRv amyloidosis, with polyneuropathy. To help address these gaps, a group of neurologists with expertise in ATTRv amyloidosis published expert recommendations on diagnosis and treatment.

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Q: What causes hereditary transthyretin amyloidosis?

Hereditary transthyretin amyloidosis is caused by certain variations in the transthyretin gene that make the protein more likely to form abnormal deposits. For this reason, it is often referred to as ATTRv amyloidosis, with the "v" referring to "variant."

Q: What are the symptoms of ATTRv amyloidosis?

Hereditary transthyretin amyloidosis can trigger different signs and symptoms, depending on where the protein deposits are located. But it often involves nerves (polyneuropathy) and the heart (cardiopathy).

Patients who have ATTRv amyloidosis with polyneuropathy can experience a variety of symptoms. No specific signs or symptoms of polyneuropathy are unique to ATTRv amyloidosis.

Neurologic manifestations may include sensory, motor, and autonomic signs and symptoms.

Sensory: pain, altered sensation, tingling/prickling, imbalance

Motor: weakness and atrophy of arms, legs, hands and feet, leading to tripping, foot drop, difficulty walking, difficulty opening jars, loss of dexterity, difficulty climbing stairs or getting up from a chair

Autonomic: lightheadedness/ orthostatic hypotension/syncope, genitourinary problems such as incontinence, erectile dysfunction, gastrointestinal manifestations, loss of hair, sweating abnormalities, heat intolerance, blurred vision or dry eyes, dry mouth

ATTRv amyloidosis often affects other organs and systems besides the nervous system, leading to problems with the heart, muscles, and eyes.

Q: What red flags can point to an ATTRv amyloidosis diagnosis?

Given that ATTRv amyloidosis is not associated with specific signs or symptoms, red flags are important in making the diagnosis. For patients with neurologic signs or symptoms, the most important red flags are:

- Rapid progression of polyneuropathy
- Early autonomic dysfunction
- Bilateral carpal tunnel syndrome
- Symptoms and signs in other systems (cardiac, musculoskeletal, ophthalmologic, renal, gastrointestinal)
- Motor weakness (predominant or early in the course of neuropathy)
- Family history of ATTRv amyloidosis
- Lack of response to treatment for other neuropathies
- Family history of unexplained rapidly progressing neuropathy, heart failure, sudden cardiac death, cardiac arrythmia

COMMON MISDIAGNOSES OF ATTRv AMYLOIDOSIS WITH POLYNEUROPATHY

Neuropathy Manifestation	Common Misdiagnoses
Peripheral neuropathy *(length dependent)*	• Diabetic neuropathy • Idiopathic neuropathy • Alcohol neuropathy
Demyelinating neuropathy	• Chronic inflammatory demyelinating polyneuropathy, or CIDP
Motor neuropathy	• Motor neuron disease / amyotrophic lateral sclerosis, or ALS • CIDP
Small-fiber neuropathy	• Fibromyalgia • Idiopathic small-fiber neuropathy
Bilateral carpal tunnel syndrome	• Occupational carpal tunnel syndrome
Unexpected weight loss	• Malignancy or autoimmune disease

Q: What is the recommended pathway for diagnosis?

Assess

In patients with sensory or sensorimotor peripheral neuropathy, clinicians assess:

a. Relevant family history

b. Comorbidities

c. Bilateral carpal tunnel syndrome (current or previous)

d. History of any progressive neuropathy with an unknown cause that does not respond to treatment

Test

a. Patients who show any of the above plus polyneuropathy may benefit from genetic testing for TTR variants. Negative TTR genetic variant testing confirms that it is not ATTRv amyloidosis.

b. Positive TTR genetic variant testing in patients ≥40 years of age in the presence of multiple risk factors indicates likely ATTRv amyloidosis.

Confirm

Clinicians can confirm TTR amyloid with tissue biopsy (skin, fat pad, nerve, cardiac tissue) OR cardiac scintigraphy.

a. If TTR amyloid test is ***negative*** for amyloid, clinicians monitor patient closely for neuropathy progression or additional symptoms.

b. If TTR amyloid test is ***positive***, the diagnosis of ATTRv amyloidosis is confirmed.

Q: What challenges do providers face when diagnosing a patient?

ATTRv amyloidosis is difficult to diagnose because symptoms vary, and the disease progresses at different rates in different people. It is not associated with a distinct set of signs and symptoms in the U.S. as it is in some other countries. Additionally, not everyone with the relevant gene variants will develop the disease.

Q: What happens if ATTRv amyloidosis isn't treated?

In the absence of treatment, ATTRv amyloidosis with polyneuropathy leads to progressive disability.

- **Stage 1** is characterized by sensory polyneuropathy.
- **Stage 2** involves progressive walking disability.
- **Stage 3** is characterized by confinement to a wheelchair or bed.

Problems with other organs also worsen over the disease course.

Q: What are the recommended treatments?

ATTRv amyloidosis with polyneuropathy is a progressive disease that can lead to irreversible nerve damage if left untreated. Two general classes of treatment are available: symptomatic (those that address symptoms but not the underlying cause of disease) and disease-modifying (those that directly target and alter the underlying cause of disease).

Both symptomatic and disease-modifying treatments are suggested for ATTRv amyloidosis.

Research has shown that early intervention with patisiran improves patient outcomes. Consequently, patients should receive disease-modifying treatment as soon as possible after they are diagnosed with ATTRv amyloidosis with polyneuropathy.

> Early treatment leads to better outcomes for patients.

TTR gene silencers are recommended as a first-line treatment in the U.S. for patients with ATTRv amyloidosis with neuropathy.[1]

This recommendation is based on benefits in both early and advanced stage disease.

SUGGESTED TREATMENTS FOR ATTRv AMYLOIDOSIS

Symptomatic: Numerous medications can help manage the symptoms of ATTRv amyloidosis with polyneuropathy, including neuropathic pain, gastrointestinal symptoms and orthostatic hypotension. Physical therapy and supportive devices such as orthoses may improve walking ability.

Disease-modifying: Disease-modifying medications include:

- TTR gene silencers. These medications work by preventing expression of the TTR gene.[2] Two classes of TTR gene silencers are available.
  - Antisense oligonucleotide medications include eplontersen.
  - Small interfering RNA medications include vutrisiran.
- TTR stabilizers. These medications work by stabilizing TTR and preventing it from forming aggregates.[2] Tafamidis is a TTR stabilizer that is approved in the U.S. for treating cardiomyopathy of ATTRv amyloidosis, but not specifically for polyneuropathy.[3] Diflunisal is nonsteroidal anti-inflammatory drug that also stabilizes TTR and is used off-label to treat ATTRv amyloidosis.[2]

Q: What are some considerations in choosing a disease-modifying treatment?

When choosing a disease-modifying treatment, physicians should consider the safety and efficacy of the individual medication given the patient's other health conditions, including whether the patient has had a liver transplantation. The medications have different injection requirements and schedules that may lead patients to prefer one over the others.

The authors make several other notes on treatment choice:

- Although the medications may act by different mechanisms, there is insufficient evidence for combining them.
- None of the currently available therapies has been investigated in patients with central nervous system or ocular manifestations of disease.
- The efficacy of disease-modifying treatments has not been well studied in patients with advanced disease. However, patients currently taking these medications should not discontinue them if their disease progresses.

Q: How should ATTRv amyloidosis be monitored?

Patients should undergo a neurological assessment every six-12 months that encompasses gait, weakness, risk of falls, lightheadedness, gastrointestinal issues, weight loss, questions about how the patient is feeling and a detailed neurological exam. Patient-reported questionnaires may also help monitor disease progression.

After treatment begins, patients should undergo a neurological assessment and exam at least every six months. A focused history should be taken to identify disease progression and other disease-related complications, including cardiac manifestations.

Treatment benefits may not be evident for a year or more, particularly in patients with advanced disease. Nerve damage may be irreversible and the main goal of treatment is to slow down the progression of disease.

CONCLUSIONS

In diagnosing ATTRv amyloidosis with polyneuropathy, physicians should be aware of the sensory, motor and autonomic signs and symptoms of the disease. Certain red flags can assist with diagnosis. Genetic testing for TTR variants combined with a test for transthyretin amyloid confirms the diagnosis.

Both symptomatic and disease-modifying treatments are suggested for ATTRv amyloidosis. Patients should receive disease-modifying therapy as soon as possible after they are diagnosed with ATTRv amyloidosis with polyneuropathy. TTR gene silencing medications are recommended as the first-line treatment.

Patients should be monitored regularly for disease progression and disease-related complications. A neurological assessment and exam are recommended at least every 6 months after initiating treatment.

Diagnosing and treating ATTRv amyloidosis with polyneuropathy can be a challenge, but new expert guidance stands to offer clarity and improve patient outcomes.

RESOURCES

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3. Pfizer Labs. Vyndaqel® (tafamidis meglumine) and Vyndamax™ (tafamadis) Prescribing Information. 2019. Available at: https://labeling.pfizer.com/ShowLabeling.aspx?id=11685. Accessed November 8, 2024.

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