Amyloid Transthyretin (ATTR) Amyloidosis

AN OVERVIEW
AMYLOID TRANSTHYRETIN (ATTR) AMYLOIDOSIS

- ATTR amyloidosis is a rare, progressive, and fatal disease that manifests clinically with motor and sensory neuropathy, autonomic neuropathy, gastrointestinal disturbances, and cardiomyopathy.

- There are 2 main types of ATTR amyloidosis:
  - Hereditary ATTR amyloidosis—affects multiple organs and body systems (eg, heart, nervous system, gastrointestinal tract, and kidney)
  - Wild-type ATTR amyloidosis—primarily affects the heart

PATHOPHYSIOLOGY

- ATTR amyloidosis is caused by the buildup of amyloid fibrils in organs and tissues in the body.

- The amyloidogenic precursor in ATTR amyloidosis is transthyretin (TTR), a transport protein synthesized primarily by the liver.

- Normally, TTR comprises 4 single-chain monomers (ie, tetramer).

- TTR gene mutations are thought to induce changes that result in weaker interactions between monomer subunits.
  - Weakened interactions render the normal tetrameric assembly prone to dissociation into monomers that misfold and have a greater propensity for aggregation.
  - Misfolded protein accumulates, forming fibrils that deposit in tissues and organs.

MECHANISM OF AMYLOID FIBRIL FORMATION

*Amyloid fibrils can be caused by a variety of toxic intermediates, including small oligomers and amorphous aggregates.

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GENETICS

• TTR is encoded by a single-copy gene; however, more than 120 mutations have been identified.\(^{10,11}\)

• Hereditary ATTR amyloidosis is typically associated with a single amino acid substitution caused by a point mutation in the TTR gene.\(^{2,10,12,13}\)
  - For example, valine to methionine substitution at position 30 (V30M)

• Most TTR mutations are amyloidogenic and promote instability of TTR tetramers.\(^{2,11}\)

• Hereditary ATTR amyloidosis is transmitted in an autosomal dominant manner, with variable penetrance.\(^{1}\)

GENOTYPE-PHENOTYPY CORRELATION

• Specific genotypes are associated with predominant polyneuropathy or cardiomyopathy features; however, most mutations affect multiple organs and there is considerable heterogeneity in disease manifestations.\(^{1}\)

• V30M is the most common mutation worldwide associated with hereditary ATTR amyloidosis with polyneuropathy.\(^{1,4}\)
  - The highest occurrence of V30M is in northern Portugal (incidence, 1 in 538 individuals); however, this mutation is also common in other regions of the world.\(^{1,2,4}\)

• Although V30M is commonly associated with polyneuropathy, many patients with V30M have cardiomyopathy.\(^{1}\)

• V122I is the most common mutation worldwide associated with hereditary ATTR amyloidosis with cardiomyopathy.\(^{1,4}\)
  - In the United States, V122I is the most common mutation and primarily occurs in African American individuals.\(^{3,15}\)
  - 3%-4% of African American individuals are V122I carriers compared with 0.44% of white individuals and 0% of Hispanic individuals.\(^{2}\)

• Although V122I is commonly associated with cardiomyopathy, many patients with V122I have polyneuropathy.\(^{1}\)

CLINICAL PRESENTATION

• ATTR amyloidosis is characterized by substantial clinical heterogeneity.

• Nonspecific symptoms and manifestations overlap with more common disorders, hindering recognition of amyloidosis.

• Bilateral carpal tunnel syndrome (CTS) is a common presenting manifestation in patients with ATTR amyloidosis and can be diagnosed up to 10 years before confirmation of ATTR amyloidosis.\(^{16-19}\)
  - Patients often have a history of CTS release surgery; in a single report, 100% of patients with amyloidosis had bilateral CTS and 70% of patients had a history of CTS surgery.\(^{19}\)

• Spinal canal stenosis has been detected in patients with ATTR amyloidosis and is a common misdiagnosis in patients with hereditary ATTR amyloidosis.\(^{16,20}\)
  - TTR amyloid deposits have been detected in as many as ~50% of surgical specimens from patients with lumbar spinal canal stenosis.\(^{11}\)
DIAGNOSIS

Diagnostic challenges

- Low index of clinical suspicion coupled with lack of disease awareness impedes early and accurate diagnosis. Additional impediments to timely diagnosis include substantial clinical heterogeneity, nonspecific symptoms, and overlap with other medical conditions.
- Substantial delays between initial symptoms and diagnosis are common in patients with ATTR amyloidosis, and misdiagnosis is common.
- Patients visit multiple physicians, often 5 or more, across a broad range of clinical specialties before receiving a diagnosis.
- Clinical presentation of ATTR amyloidosis is often indistinguishable from acquired monoclonal immunoglobulin light chain amyloidosis.

Diagnostic procedures

- Tissue biopsy is necessary for confirmation.
- Congo red staining of amyloid is the gold standard for diagnosis.
  - Congo red staining of tissue with resultant green birefringence when viewed under polarized light is pathognomonic for amyloid.
- Amyloid typing can be achieved using a variety of techniques.
  - Laser microdissection followed by mass spectrometry is the gold standard for amyloid typing.
- Genetic testing is recommended for confirmation and detection of specific TTR gene mutations.
- A diagnostic algorithm proposed by Gillmore, et al. based on myocardial radiotracer uptake on bone scanning has been developed for use in patients with cardiac ATTR amyloidosis.
  - In addition to diagnosis, 99mTc-technetium-pyrophosphate (99mTc-PYP) scanning can differentiate cardiac manifestations of ATTR amyloidosis from acquired monoclonal immunoglobulin light chain amyloidosis.
  - Use of myocardial radiotracer uptake on bone scanning may also eliminate the need for biopsy in patients with cardiac ATTR amyloidosis.
**BURDEN OF DISEASE**

- ATTR amyloidosis is a devastating, progressive disease that results in a rapid decline in quality of life.
- Symptoms of hereditary ATTR amyloidosis impact multiple aspects of daily life, and disease burden increases with illness progression.
- Patients report difficulty with fine motor skills, bathroom/self-care, movement/mobility, activities of daily living, an inability to stand for hours, run, and work.
- Resource use is high among patients with hereditary ATTR amyloidosis, and hospitalization rates range from 14% to 30%, with a 14% to 24% rate for emergency visits.
- Functional health and well-being are severely compromised in patients with ATTR amyloidosis.
- More than half (55%) of the patients with hereditary ATTR amyloidosis report that their mental health/outlook on life is impacted by amyloidosis and they have anxiety (71%), stress (62%), and depression (43%).

**CURRENT TREATMENT AND LIMITATIONS**

- Treatment options are limited for patients with ATTR amyloidosis.
  - In the United States, no therapies for ATTR amyloidosis are approved by the US Food and Drug Administration (FDA).
  - In Europe, tafamidis is approved for use in adults with stage 1 (stage 1 on a scale from 1 [lowest disease burden] to 3 [greatest disease burden]) symptomatic polyneuropathy to delay peripheral neurologic impairment.
- Current treatments, used off label, have limited effectiveness and are only used in specific patient populations.
- There is an urgent unmet need for treatments specifically designed for ATTR amyloidosis.

**UNMET NEEDS**

**DIAGNOSIS**
- Increasing clinical suspicion and disease awareness are high unmet needs.
- Increased efforts are needed to keep amyloidosis “front of mind” among clinicians.

**PATIENT ACCESS TO COORDINATED CARE**
- Access to and coordination of care between amyloidosis centers of excellence and academic specialists is greatly needed.

**APPROVED THERAPIES TO TREAT ATTR AMYLOIDOSIS**
- Safe and effective disease-modifying therapies are needed that optimize patient quality of life, which is severely compromised by the disease, and improve clinical outcomes.

**RESOURCES**
- **Amyloidosis Support Group**
  www.amyloidossupport.org
- **Amyloidosis Foundation**
  www.amyloidosisfoundation.org
- **Amyloidosis Research Consortium**
  www.arci.org
- **My Amyloidosis Pathfinder**
  Discover treatment centers and clinical trials that match your amyloidosis
  www.myamyloidosispathfinder.org
REFERENCES

30. Adams D, Amitay O, Coelho T. Orphanet J Rare Dis. 2015;10(suppl 1):PS8
34. Lane T, et al. Orphanet J Rare Dis. 2015;10 (suppl 1):026.
