Hereditary ATTR (hATTR) Amyloidosis: Polyneuropathy—An Overview
Identifying the link can lead to a crucial diagnosis
Hereditary ATTR (hATTR) Amyloidosis: Polyneuropathy

Information about mechanism of disease, signs and symptoms, diagnosis, and treatment
What is amyloidosis?

• The amyloidoses are a heterogeneous group of disorders characterized by deposition of insoluble misfolded protein aggregates, known as amyloid fibrils, in tissues\(^1\)\(^,\)\(^2\)
  — 36 unique amyloid fibril proteins have been identified in humans\(^2\)
  — Amyloidosis can be acquired or hereditary, and systemic or localized\(^3\)

References:
The most common types of systemic amyloidosis

Four types are seen most frequently:

<table>
<thead>
<tr>
<th>Type</th>
<th>Precursor Protein</th>
<th>Organs/Systems Targeted</th>
</tr>
</thead>
<tbody>
<tr>
<td>AL</td>
<td>Immunoglobulin light chain</td>
<td>All organs except central nervous system</td>
</tr>
<tr>
<td>AA</td>
<td>(Apo) serum amyloid A</td>
<td>All organs except central nervous system</td>
</tr>
<tr>
<td>Aβ₂M</td>
<td>β2-microglobulin, wild type</td>
<td>Musculoskeletal system</td>
</tr>
<tr>
<td></td>
<td>β2-microglobulin, variant</td>
<td>Autonomic nervous system</td>
</tr>
<tr>
<td>ATTR</td>
<td>Transthyretin, wild type</td>
<td>Heart mainly in men, tenosynovium</td>
</tr>
<tr>
<td></td>
<td>Transthyretin, variants</td>
<td>Nerves, heart, and GI tract</td>
</tr>
</tbody>
</table>

Nomenclature: The amyloidoses are named based on the disease-causing protein, with an “A” designating amyloid fibril. For example, when the type is “ATTR” the “A” designates amyloid fibril, and the “TTR” designates the transthyretin protein.

References:
### Types of ATTR amyloidosis

<table>
<thead>
<tr>
<th>Description</th>
<th>wtATTR</th>
<th>hATTR</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Description</strong></td>
<td>Wild-type ATTR (wtATTR) amyloidosis, formerly known as senile systemic amyloidosis (SSA), is a nonhereditary, progressive disease of undefined etiology.</td>
<td>Hereditary ATTR (hATTR) amyloidosis is an inherited, rapidly progressive, life-threatening disease.</td>
</tr>
<tr>
<td><strong>Etiology</strong></td>
<td>Misfolded transthyretin (TTR) proteins accumulate as amyloid fibrils in multiple organs, including the heart.</td>
<td>Caused by a mutation in the TTR gene that results in misfolded TTR proteins accumulating as amyloid fibrils in multiple tissues including the nerves, heart, and gastrointestinal tract.</td>
</tr>
<tr>
<td><strong>Symptoms</strong></td>
<td>Can cause cardiomyopathy and neuropathy, resulting in heart failure and mortality.</td>
<td>A multisystemic disease with a heterogeneous clinical presentation that includes sensory and motor, autonomic (e.g., diarrhea, erectile dysfunction, hypotension), and cardiac symptoms. Can lead to significant morbidity, disability, and mortality.</td>
</tr>
<tr>
<td><strong>Time to Mortality</strong></td>
<td>Within 2 to 6 years (median overall survival of 3.6 years).</td>
<td>Within 2 to 15 years.</td>
</tr>
</tbody>
</table>

**References:**
Formation of amyloid fibrils in hATTR amyloidosis\textsuperscript{1,2}

Liver \quad TTR \quad TTR \quad Misfolded Amyloid Fibrils \quad Amyloid Deposits

- TTR is primarily synthesized in the liver.
- Normally, TTR is a tetramer composed of four identical monomers.
- In hATTR amyloidosis, the tetramer becomes destabilized, resulting in protein misfolding and aggregation into amyloid fibrils.
- Amyloid fibrils are deposited at multiple sites in the body, including the nerves, heart, and the GI tract, causing damage that leads to clinical symptoms.

References:
hATTR amyloidosis—a hereditary condition

• hATTR amyloidosis is an autosomal dominant disease; thus, a person only needs to inherit one copy of the mutated TTR gene from one parent to develop the condition\(^1,2\)

• Penetrance is variable, and some individuals may remain asymptomatic despite having a TTR mutation\(^1,3\)

References:
TTR gene mutations

• More than 120 different TTR gene mutations have been discovered\(^1-3\)
  — The most common mutation is Val30Met. Individuals with this mutation often initially present with polyneuropathy
    • Prevalence is higher in Portugal, Sweden, Japan, Brazil, and Spain
  — The Val122Ile mutation is common in individuals who initially present with cardiomyopathy; found in 3 to 4% of the African American populations

• Symptoms can present differently, even among people in the same family and in the same mutation\(^3\)

References:
hATTR amyloidosis affects an estimated 50,000 patients worldwide\(^1\)

In the disease continuum of hATTR amyloidosis:

- Some patients present primarily with polyneuropathy symptoms, historically known as familial amyloidotic polyneuropathy (FAP)\(^1,2\)
- Other patients present primarily with cardiomyopathy symptoms, historically known as familial amyloidotic cardiomyopathy (FAC)\(^1,2\)
- A substantial proportion of patients with hATTR amyloidosis presents with a mixed phenotype\(^3,4\)

References:
hATTR amyloidosis: a life-threatening, multisystem disease

Because amyloid fibrils are deposited in tissues throughout the body, including the nerves, heart, and GI tract, patients with hATTR amyloidosis can present across a spectrum that includes sensory and motor, autonomic, and cardiac symptoms.

In addition to the varied symptom presentation, age of onset varies among patients—with a median age of 39 years, with some presenting as early as their 20s.

References:
Constellation of possible signs and symptoms of hATTR amyloidosis

- CNS manifestations
  - Progressive dementia
  - Headache
  - Ataxia
  - Seizures
  - Spastic paresis
  - Stroke-like episodes

- Nephropathy
  - Proteinuria
  - Renal failure

- Autonomic neuropathy
  - Orthostatic hypotension
  - Recurrent urinary tract infections (due to urinary retention)
  - Sexual dysfunction
  - Sweating abnormalities

- Ocular manifestations
  - Vitreous opacification
  - Glaucoma
  - Abnormal conjunctival vessels
  - Papillary abnormalities

- Cardiovascular manifestations
  - Conduction block
  - Cardiomyopathy
  - Arrhythmia

- GI manifestations
  - Nausea & vomiting
  - Early satiety
  - Diarrhea
  - Severe constipation
  - Alternating episodes of diarrhea & constipation
  - Unintentional weight loss

- Peripheral sensory-motor neuropathy
  - Neuropathic pain
  - Altered sensation (i.e., change in sensitivity to pain and temperature)
  - Numbness and tingling
  - Muscle weakness
  - Impaired balance
  - Difficulty walking

Reference:
Symptom presentation can vary among patients\(^1\)

In a multicenter study that included 186 individuals with hATTR amyloidosis, 58% (109/186) of hATTR amyloidosis patients presented with a mixed phenotype characterized by cardiac and neurologic involvement\(^2\)

- Baseline clinical characteristics of 186 individuals with hereditary ATTR amyloidosis in a multicenter study\(^2\)
- Echocardiographic abnormalities included increased LV wall thickness, granular sparkling of ventricular myocardium, increased thickness of atrioventricular valves or interatrial septum, or pericardial effusion\(^2\)
- Electrocardiographic abnormalities included advanced A-V block or intraventricular conduction disturbances\(^2\)

References:
Symptoms of hATTR amyloidosis can progress quickly, leading to life-threatening dysfunction\textsuperscript{1-3}

- As the disease progresses, symptoms increase in severity, leading to significant disability, decreased quality of life, and untimely death\textsuperscript{3,4}
- hATTR amyloidosis can lead to mortality within 2 to 15 years\textsuperscript{1,5}
- Due to the variability of the disease, progression of symptoms can also be considerably different from patient to patient\textsuperscript{6}

Due to the rapid natural progression of the disease, patients with hATTR amyloidosis require an early and accurate diagnosis.\textsuperscript{4,7,8}

References:
Consider hATTR amyloidosis in your differential diagnosis

Because the symptoms of hATTR amyloidosis may overlap with those of other diseases, detailed diagnostic history may help to identify patients with hATTR amyloidosis.1-4

### Diseases with symptoms that overlap with those of hATTR amyloidosis1-4

<table>
<thead>
<tr>
<th>Diagnostic assessment5-9</th>
<th>Potential diagnoses5-9</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ataxia and foot numbness</td>
<td>CIDP</td>
</tr>
<tr>
<td>Motor involvement</td>
<td>ALS</td>
</tr>
<tr>
<td></td>
<td>Motor polyradiculoneuropathy</td>
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<tr>
<td>Upper limb neuropathy</td>
<td>Carpal tunnel syndrome</td>
</tr>
<tr>
<td></td>
<td>Idiopathic polyneuropathy</td>
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<tr>
<td></td>
<td>Paraneoplastic neuropathy</td>
</tr>
<tr>
<td></td>
<td>CIDP</td>
</tr>
<tr>
<td></td>
<td>Motor neuron diseases</td>
</tr>
<tr>
<td>Weakness in feet, ankles, legs</td>
<td>Charcot-Marie-Tooth disease</td>
</tr>
<tr>
<td>Pain and tingling with alcohol abuse</td>
<td>Alcoholic neuropathy</td>
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<tr>
<td>Polyneuropathy with diabetes</td>
<td>Diabetic neuropathy</td>
</tr>
<tr>
<td>Polyneuropathy with evidence of amyloid deposition</td>
<td>AL amyloidosis</td>
</tr>
<tr>
<td></td>
<td>AA amyloidosis</td>
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</tbody>
</table>

For patients with neuropathic symptoms, the most common misdiagnosis previously received is CIDP10

AA=amyloid A; AL=amyloid light chain; ALS=amyotrophic lateral sclerosis; CIPD=chronic inflammatory demyelinating polyneuropathy.

References:
Recognize the red-flag symptoms.
Suspect hATTR amyloidosis.

Red-flag symptom clusters associated with hATTR amyloidosis

<table>
<thead>
<tr>
<th>Bilateral carpal tunnel syndrome</th>
<th>Nephropathy (e.g., proteinuria or renal failure)</th>
<th>Early autonomic dysfunction (e.g., erectile dysfunction or postural hypotension)</th>
<th>Gastrointestinal complaints (e.g., chronic diarrhea, constipation, or diarrhea/constipation)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unexplained weight loss</td>
<td>Cardiovascular manifestations (e.g., conduction block, cardiomyopathy, or arrhythmia)</td>
<td>Vitreous opacities</td>
<td>Positive family history</td>
</tr>
</tbody>
</table>

Additional signs: Rapid disease progression and failure to respond to immunomodulatory treatment

Obtaining a family history is an important step in the diagnostic process

References:
Confirming an hATTR amyloidosis diagnosis

### Diagnostic tools for patients presenting with polyneuropathy

<table>
<thead>
<tr>
<th>Procedure</th>
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<tbody>
<tr>
<td>Complete neurologic examination</td>
</tr>
<tr>
<td>Electromyography</td>
</tr>
<tr>
<td>Sympathetic skin response (SSR)</td>
</tr>
<tr>
<td>Heart rate deep breathing</td>
</tr>
<tr>
<td>Sudoscan assessment of electrochemical skin conductance</td>
</tr>
<tr>
<td>Medical history</td>
</tr>
<tr>
<td>Laboratory tests to exclude mimicking polyneuropathies</td>
</tr>
<tr>
<td>Genetic analysis to determine pathologic mutation</td>
</tr>
<tr>
<td>Tissue biopsy + Congo red staining</td>
</tr>
<tr>
<td>Salivary gland</td>
</tr>
<tr>
<td>Abdominal subcutaneous adipose tissue</td>
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<tr>
<td>Rectal mucosa</td>
</tr>
<tr>
<td>Sural nerve</td>
</tr>
<tr>
<td>Skin</td>
</tr>
<tr>
<td>Gastric</td>
</tr>
<tr>
<td>Identification of amyloid protein</td>
</tr>
<tr>
<td>Immunohistochemistry</td>
</tr>
<tr>
<td>Mass spectrometry</td>
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</tbody>
</table>

### References:

Genetic screening

If patient symptoms and a family history lead to a suspicion of hATTR amyloidosis, genetic counseling can help patients understand the potential diagnosis, the genetic screening process, and the implications of the disease.
hATTR amyloidosis: linking pathophysiology to potential therapeutic approaches\textsuperscript{1,2}

**Pathophysiology**

Liver TTR TTR

Liver

TTR

Misfolded TTR

Amyloid Fibrils

Suppression of amyloidogenic TTR

Liver transplantation

Antisense oligonucleotides (ASO)

RNAi therapeutics

Tetramer Stabilizers

Inhibition of amyloid deposits

Monoclonal antibody

Fibril disruptors

**THERAPEUTIC APPROACHES**\textsuperscript{*}

\textsuperscript{*}This visual represents approved and investigational approaches.

Current investigational approaches: TTR tetramer stabilizers, RNAi therapeutics, ASOs, monoclonal antibodies, and fibril disruptors\textsuperscript{1-3}

References:
Current treatment options: liver transplant

• Orthotopic liver transplant removes approximately 95% of the production of TTR. It has improved survival rates but does not permanently halt disease progression and requires lifelong use of immunosuppressants\textsuperscript{1,2}
  — Transplant may be less effective for patients who present primarily with cardiomyopathy
  — The limited availability of organs, as well as the exclusion of older patients and patients with advanced disease or with comorbidities, warrants the development of other treatment options

References:
Investigational therapies in development

There are multiple investigational therapies in development that target different points in the disease pathway\textsuperscript{1-4}

Therapies that may help to reduce fibril accumulation:

• Monoclonal antibodies may suppress ATTR amyloid deposition by binding to amyloid fibrils and targeting them for immune system destruction\textsuperscript{1,2,4}
• Fibril disrupters bind to amyloid fibrils and disrupt their association\textsuperscript{1,2}

Therapies that may address the underlying cause of amyloidosis:

• Antisense oligonucleotides (ASOs) are short chemically modified oligonucleotides that bind to TTR mRNA and prevent production of TTR protein via ASO-RNAse H mediated cleavage\textsuperscript{1-3}
• RNAi therapeutics are double stranded small interfering RNAs that bind to transthyretin (TTR) messenger RNA (mRNA) and prevent production of TTR protein via the RNA interference (RNAi) pathway\textsuperscript{1-3}

References:
Treatments that stabilize TTR protein

TTR tetramer stabilizers bind to the thyroxine binding site on the TTR protein, stabilizing circulating TTR tetramers and preventing the dissociation into monomers, but do not inhibit the synthesis of disease-causing protein\textsuperscript{1,2}

References:
Recognize the signs. Suspect hATTR amyloidosis.

- Hereditary ATTR (hATTR) amyloidosis is an autosomal dominant disease\textsuperscript{1-3}
- hATTR amyloidosis is caused by a mutation in the transthyretin (TTR) gene that results in misfolded TTR proteins accumulating as amyloid fibrils in multiple sites including the nerves, heart, and GI tract\textsuperscript{1,2,4}
- Affects multiple organs, resulting in varying symptoms\textsuperscript{5-7}
- hATTR amyloidosis can lead to mortality within 2 to 15 years\textsuperscript{1,8}
- Obtaining a family history is an important step in the diagnostic process\textsuperscript{5,9,10}
- There are multiple investigational therapies in development that target different points in the disease pathway\textsuperscript{3,11-13}

Access this information and these updates, and learn about genetic screening made available at no charge in the US, by visiting: https://hATTRamyloidosis.com

References: