II JORNADAS AMILOIDOSIS HEREDITARIA por TRANSTIRRETINA (AhTTR)

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EARLY DIAGNOSIS IN hATTR AMYLOIDOSIS: A MULTISYSTEMIC DISEASE

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Disclosures

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• Serves on the THAOS scientific advisory board, financial support from Pfizer
hTTR-Amyloidosis

- An autosomal-dominant, adult-onset disorder associated with over 130 different mutations in the transthyretin (TTR) gene

- TTR protein deposits as amyloid in peripheral and autonomic nerves, heart, gastrointestinal (GI) tract, kidneys, eyes, and connective tissue of the transversal carpal ligament

- This results in progressive organ dysfunction as a multisystemic disease leading to death within an average of 10 years

1-Ando et al., 2013; 2-Rowczenio et al., 2014; 3- Sekijima, 2015
hATTR Amyloidosis

- The low prevalence of hTTR Amyloidosis worldwide and the high variation in both genotype and phenotypic expression of the disease can lead to difficulty in identifying symptoms outside of a specialized diagnostic environment.

References: Adams et al. Current opinion in Neurology 2016;29(1); Rapezzi and al European Heart Journal 2013; 34, 520–528
A clear cut-off point for the diagnosis of active disease is usually difficult to achieved due to some confounding factors:

- Genotype/phenotype variability
- Phenotype variability within the same mutation

*R transthyretin Amyloidosis Outcomes Survey (THAOS) is financially supported by Pfizer

Wixner et al. Orphanet J Rare Dis 2014;9:61
hATTR-Amyloidosis: misdiagnosis

- In sporadic or scattered cases, the lack of awareness among physicians of variable clinical features and limited access to diagnostic tools can contribute to high rates of misdiagnosis.

- In general, early and late-onset variants of hATTR-Amyloidosis, found within endemic and nonendemic regions, present several additional diagnostic challenges.
Early and accurate diagnosis of TTR-FAP represents one of the major challenges faced by physicians when caring for patients with idiopathic progressive neuropathy.

Accurate diagnosis of TTR-FAP is often delayed for years\textsuperscript{1–4}.

\textsuperscript{1}Adams et al., 2014; 2-Dohrn et al., 2013; 3-Koike et al., 2011; 4-Planté-Bordeneuve et al., 2007; 5-Coelho et al., 2013; 6-Ericzon et al., 2015
hATTR-Amyloidosis

- An heterogeneous disease associated with a wide range of clinical manifestations, which leads to the phenotypic heterogeneity that characterizes the disease.

(Conceição et al., 2015; Sekijima, 2015)
“Red Flag” Symptom Cluster Recommended for hATTR Amyloidosis Presenting with Polyneuropathy


**Family history**

- Early autonomic dysfunction
- GI complaints
- Unexplained weight loss
- Cardiac hypertrophy, arrhythmias, ventricular blocks, or cardiomyopathy
- Renal abnormalities
- Vitreous opacities

+ ≥1 of

**Progressive symmetric sensory motor neuropathy**

**Additional alert signs:**

- Rapid disease progression
- Lack of response to prior therapies
**TTR-FAP THE NEUROPATHY...**

**“EARLY-ONSET (<50 Y) V30M**

- Length dependent progressive sensory-motor and autonomic neuropathy
  - First, small fiber involvement (decrease in pain and temperature sensation + neuropathic pain)
  - Larger fiber involvement occur later in disease (decrease in proprioception + motor weakness)
- **Autonomic neuropathy** can be the clinical presentation

**LATE ONSET DISEASE (>50 Y)**

- Male predominance and an apparently sporadic disease presentation.
- **NEUROPATHY** - characterized by relative preservation of unmyelinated nerve fibers
  - **Larger fibers** more rapidly affected than in early onset cases
  - Sensory and motor neuropathy symptoms of both upper and lower extremities may appear within a short period or even simultaneously
  - Impaired superficial and deep sensation
  - Severe neuropathic pain
  - Early distal motor involvement,
- **Mild autonomic symptoms**

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Violaine Planté-Bordeneuve, Gerard Said . Lancet Neurol 2011; 10: 1086–97; Andrade, 1952; Coutinho et al., 1980; Koike et al., 2004; Conceição and De Carvalho, 2007; Koike et al., 2011; Misu et al., 1999; Sobue et al., 2003
<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Neuropathic symptoms</th>
<th>Bilateral CTS</th>
<th>Autonomic</th>
<th>GI</th>
<th>Cardiac</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Positive</td>
<td>Negative</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Val30M early onset</td>
<td>+++</td>
<td>++</td>
<td>±</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Val30M late onset</td>
<td>+</td>
<td>++</td>
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<tr>
<td>Non V30M/Cardiac Phenotype</td>
<td>±</td>
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<td>±</td>
</tr>
<tr>
<td>Mixed phenotype</td>
<td>+</td>
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hTTR-Amyloidosis: diagnosis

- Diagnosis of symptomatic disease in TTR gene mutation carriers should occur upon manifestation of the earliest detectable disease sign/symptom\(^1\)

- Diagnosis in the early stages of disease is essential to allow for timely treatment to prevent or delay disease progression.
  - Pre-symptomatic treatment of gene mutation carriers is not an accepted indication at this time\(^2\)

- Due to the highly heterogeneous, multi-systemic nature, and nonspecific symptoms of TTR-FAP, to define a gene carrier as symptomatic can occasionally be a challenge\(^2\)

Active disease?

Initial disease process

Degree of symptoms

Onset of early symptoms

Onset of early symptoms

The amyloid ‘process’

Neuropathic Phenotype

Cardiac Phenotype

Assessments to support diagnosis of hATTR amyloidosis\textsuperscript{1,2}

- Clinical Assessment (Onset of symptoms and/or signs)
- Family history
- TTR genotyping
- Changes in neurophysiologic tests vs baseline
- Biopsy evidence of amyloid

Confirmation of diagnosis is by TTR genotyping\textsuperscript{3} alone or with tissue biopsy\textsuperscript{4}

Clinical Tools for Diagnosis and Monitoring of hATTR Amyloidosis: Invasive Tests

Sensitivity of biopsy can vary significantly by biopsy site and center

<table>
<thead>
<tr>
<th>Biopsy site</th>
<th>Sensitivity</th>
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</thead>
<tbody>
<tr>
<td>Abdominal fat pad biopsy</td>
<td>20–83%&lt;sup&gt;1–4&lt;/sup&gt;</td>
</tr>
<tr>
<td>Salivary gland biopsy</td>
<td>75–91%&lt;sup&gt;5,6&lt;/sup&gt;</td>
</tr>
<tr>
<td>Nerve biopsy</td>
<td>55–92%&lt;sup&gt;1,2,7,8&lt;/sup&gt;</td>
</tr>
<tr>
<td>Cardiac biopsy</td>
<td>~100%&lt;sup&gt;9&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

Amyloid deposition can be missing in biopsy sample, due to patchy deposition<sup>3,10</sup>

- A positive biopsy confirms the presence of systemic amyloidosis
- A negative finding should not exclude the diagnosis

Clinical Tools for Diagnosis and Monitoring of hATTR Amyloidosis: Non-invasive Tests

<table>
<thead>
<tr>
<th>Genetic Molecular Test</th>
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<tbody>
<tr>
<td>• Full sequence of TTR gene</td>
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<table>
<thead>
<tr>
<th>Neuropathy assessment</th>
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<tbody>
<tr>
<td>• Compass31; Norfolk QOL</td>
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<tr>
<td>• NIS assessment</td>
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<tr>
<td>• Electromyography with Nerve Conduction Studies</td>
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<td>• Sudomotor tests (Sudoscan; Sympathetic Skin Response; QSART)</td>
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<tr>
<td>• Quantitative Sensory Tests (QST)</td>
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<tr>
<td>• Postural blood pressure, HRdB</td>
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<th>Cardiac assessment</th>
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<tbody>
<tr>
<td>• ECG and echocardiography</td>
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<tr>
<td>• CMRI</td>
</tr>
<tr>
<td>• Nuclear scintigraphic imaging</td>
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<tr>
<td>• Serum cardiac biomarkers</td>
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</tbody>
</table>

HRdb, heart rate during deep breathing.
### Clinical Tools for Diagnosis of hATTR Amyloidosis

<table>
<thead>
<tr>
<th>Clinical Tools</th>
<th>Clinical Evaluation</th>
<th>Neurophysiology</th>
<th>Biomarkers</th>
<th>Cardiac Evaluation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NIS</td>
<td>BP supine vs orthostatic</td>
<td>BMI</td>
<td>NCS</td>
</tr>
<tr>
<td>Val30M early onset</td>
<td>+</td>
<td>+</td>
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99mTc-DPD, technetium-99m-3,3-diphosphono-1,2 propanodicarboxylic acid; MRI, magnetic resonance imaging; NIS, Neuropathy Impairment Score; NT-proBNP, N-terminal pro-brain natriuretic peptide.
The practical approach: asymptomatic carrier

**TTR asymptomatic carrier**

- **CARDIOLOGY**
  - Patient history
  - EKG
  - ECHO
  - HOLTER
  - ABPM
  - MIBG

- **NEUROLOGY**
  - LABORATORY DATA
    - Blood
    - Urianalysis
  - NEUROPHYSIOLOGY
    - NCS
    - SSR
    - SUDOSCAN
  - Patient history
  - Neurological examination (NIS)

- **LABORATORY DATA**
  - Blood
  - Urianalysis

- **SELF ASSESSMENT**
  - Norfolk, EQ5D
  - Compass

- **VITAL SIGNS**
  - Orthostatic BP
  - Weight

**EVERY YEAR**

Lisbon TTR-FAP Reference Center
Proposed Diagnosis Criteria

At least one quantified/objective sign or symptom definitely related to onset of ATTR amyloidosis disease

- sensorimotor neuropathy (change from baseline)
- Autonomic neuropathy
- Cardiac involvement
- Renal or ocular involvement

OR

Any symptom possibly related to ATTR amyloidosis disease in the absence of objective signs

+ at least 1 abnormal test finding

OR

Absence of symptoms possibly related to ATTR disease

+ at least 2 abnormal test findings
hATTR Amyloidosis: the early diagnosis

• Diagnosis of symptomatic hATTR amyloidosis and treatment initiation in gene mutation carriers should occur upon manifestation of the earliest detectable disease sign/symptom.

• Decision of first disease manifestation should be done based on a set of clinical symptoms and signs.

• Objective evidence of neuropathy, such as a change from baseline, can be considered sufficient to reach a diagnosis of hATTR amyloidosis in gene carriers.

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AMILOIDOSIS HEREDITARIA
por TRANSTIRRETINA (AhTTR)

THANK YOU