Early Recognition of Amyloid Neuropathy

with a focus on hereditary transthyretin amyloidosis (hATTR)

Violaine PLANTE-BORDENEUVE
Department of Neurology – Hopital Henri Mondor
East Paris University - France
Disclosures

• Scientific Advisor for the development of the THAOS database (Pfizer Inc.), without financial support
• Pfizer and Alnylam supported expenses with travel and attendance to several scientific meetings (2016–2019)
• Consultant for Pfizer, Alnylam and Ionis Pharmaceuticals
• Has spoken on behalf Prothena, Alnylam and Ionis/Akcea at scientific meetings and received financial compensation
Learning objectives

• Have an overview of the amyloid polyneuropathy with a focus on the phenotypic and genotypic picture of the familial transthyretin amyloidosis (hATTR-PN)

• Get awareness on the therapeutic approaches available in this condition with a need to treat as early as possible

• Recognize the early clinical features of the amyloid polyneuropathy

• Learn the role of the neurophysiological tools and the skin nerves biomarkers at an early stage of the neuropathy

• Learn when and how to organize a multidisciplinary approach of the asymptomatic gene carriers to reach early recognition of hATTR-PN
Hereditary Transthyretin Amyloid Polyneuropathy (hATTR-PN): a devastating disease

- Length-dependent **axonal sensory-motor and autonomic polyneuropathy**, associated with **systemic manifestations**
- Progressive amyloid deposition of TTR fibrils in organs

![Image of symptoms and systemic manifestations]

- Loss of feeling in feet and hands
- May not feel pain or temperature changes, except in the head and neck
- Difficulty in a wheelchair, with memory disturbances, weight loss, loss of appetite, and loss of ability to control bladder and bowel

Adams et al. *Nat Rev Neurol* 2019, 15: 387-404

Courtesy Pr G Said
- **Autosomal dominant transmission, Gene TTR > 140 pathogenic variants**

  - **Significant geographic variation**
  - **Variable age of onset (AO)**

  ![World map showing hATTR-PN geographic distribution]

  - **Portugal Latin America**
    - ATTR-Val30Met
    - AO 30 y-o
  - **Sweden**
    - ATTR-Val30Met
    - AO 56 y-o
  - **Japan**
    - ATTR-Val30Met + 30 ATTR variants
    - AO 33/60 y-o
  - **Western Europe / France**
    - ATTR-Val30Met + 40 ATTR variants
    - AO 58 y-o
  - **USA**
    - ATTR-Val122lle + 30 ATTR variants
    - AO 60 y-o
hATTR-PN: an overview of the diagnosis nowdays

Average diagnosis delay of 4 years (up to 15 years)

No family history (« sporadic ») in 60% of cases

Heterogeneity of the clinical presentation Misdiagnosis in 1/3 of cases

Wide range of age of onset from the 3rd to 8th decade

CNS manifestations
- Dementia, Seizures
- Headache, Stroke-like episodes
- Ataxia, Spastic paresis

Kidney
- Proteinuria
- Renal failure

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

Carpal tunnel syndrome

Peripheral sensory-motor neuropathy
Typically axonal, fiber length-dependent, symmetric, and relentlessly progressive in distal to proximal direction

Ocular
- Vitreous opacities
- Glaucoma
- Abnormal conjunctival vessels
- Papillary abnormalities

Cardiovascular
- Conduction blocks
- Cardiomyopathy
- Arrhythmia
- Mild regurgitation

Gastro Intestinal
- Nausea and vomiting
  - Early satiety
  - Diarrhea
  - Severe constipation
  - Alternating episodes of diarrhea and constipation
  - Unintentional weight loss

hATTR-PN: a disease now treatable

- Major therapeutic advances in the past decade
- Available treatments aim to prevent TTR amyloid deposition in organs and halt the progression of symptoms
hATTR – We should intervene much earlier in order to preserve the neurological function

The early recognition of hATTR is now a real challenge
Early recognition of the hATTR neuropathy: clinical aspects

- Neurological examination including assessment of all sensory modalities
  - Temperature, pain
  - Vibration, position sense
- Autonomic manifestations
  - Can be difficult to assess
  - Test blood pressure in recumbent/standing position
  - CADT questionnaire to review the main autonomic manifestations

![Table 1: Compound Autonomic Dysfunction Test (CADT)]

<table>
<thead>
<tr>
<th></th>
<th>4</th>
<th>3</th>
<th>2</th>
<th>1</th>
<th>0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Postural hypotension</td>
<td>No</td>
<td>No</td>
<td>Asymptomatic</td>
<td>Lipohyria</td>
<td>Postural syncope</td>
</tr>
<tr>
<td>Nausea preventing normal</td>
<td>No</td>
<td>No</td>
<td>Nausea/Slow</td>
<td>Vomiting: Less than once a week</td>
<td>Vomiting: More than once a week</td>
</tr>
<tr>
<td>feeding, vomiting</td>
<td></td>
<td></td>
<td>digestion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea/Constipation</td>
<td>No</td>
<td>No</td>
<td>Once a month</td>
<td>Once a week</td>
<td>More than twice a week</td>
</tr>
<tr>
<td>Sphincter disturbances</td>
<td>No</td>
<td>No</td>
<td>Dysuria</td>
<td>Dysuria + episode of incontinence</td>
<td>Intermittent bladder catheterization</td>
</tr>
<tr>
<td>Erectile dysfunction</td>
<td>No</td>
<td>No</td>
<td>Difficulties</td>
<td>Impotency</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Useful Scores:
- Neuropathy Impairment Score (NIS)
- Modified Peripheral Neuropathy Disability (mPND)
- Body Mass Index (BMI)
- Karnofsky Performance status Scale (KPS)

<table>
<thead>
<tr>
<th>NIS (244 points)</th>
<th>mPND</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Normal</td>
</tr>
<tr>
<td>I</td>
<td>Sensory disturbances in the lower limbs, preserved walking capacity</td>
</tr>
<tr>
<td>II</td>
<td>Impaired walking, no need of aid or stick</td>
</tr>
<tr>
<td>IIIa</td>
<td>Walking with 1 stick</td>
</tr>
<tr>
<td>IIIb</td>
<td>Walking with 2 sticks</td>
</tr>
<tr>
<td>IV</td>
<td>Wheelchair or confined to bed</td>
</tr>
</tbody>
</table>

Early recognition of the hATTR neuropathy: neurophysiological tests

- **Large nerve fibres**
  - Motor and sensory nerve conduction in all 4 limbs
  - Normal at an early stage
  - A progressive decline of SNAP in the lower limbs may be a red flag!

- **Small nerve fibre tests may be helpful at an early stage**

  - **Heart rate variability**
  - **Laser Evoked Potential**
  - **Electrochemical skin conductance (ESC)**

  - **Quantitative Sensory Testing**
    - Cold, warm, pressure, heat-pain detection, pain, tolerance
    - Threshold measurement
    - Method of limits, levels, …
    - Investigates Aδ (cold) or C fibres (warm)

---

Neurophysiological markers of small fibre neuropathy in TTR-FAP mutation carriers

Jean-Pascal Lefaucheur · Sophie Ng Wing Tin · Philippe Kerschen · Thibaud Damy · Violaine Plante-Bordeneuve

<table>
<thead>
<tr>
<th>RRIV</th>
<th>SSR</th>
<th>QST</th>
<th>LEP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case 5</td>
<td>A</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Case 6</td>
<td>N</td>
<td>N</td>
<td>A</td>
</tr>
<tr>
<td>Case 9</td>
<td>N</td>
<td>N</td>
<td>A</td>
</tr>
<tr>
<td>Case 10</td>
<td>A</td>
<td>N</td>
<td>A</td>
</tr>
<tr>
<td>Case 11</td>
<td>N</td>
<td>N</td>
<td>A</td>
</tr>
<tr>
<td>Case 13</td>
<td>N</td>
<td>A</td>
<td>N</td>
</tr>
<tr>
<td>Case 14</td>
<td>A</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Case 15</td>
<td>N</td>
<td>A</td>
<td>N</td>
</tr>
<tr>
<td>Case 18</td>
<td>N</td>
<td>N</td>
<td>A</td>
</tr>
<tr>
<td>Case 19</td>
<td>A</td>
<td>N</td>
<td>A</td>
</tr>
<tr>
<td>Case 20</td>
<td>N</td>
<td>A</td>
<td>A</td>
</tr>
</tbody>
</table>

**Fig. 1** The various combinations of small-fibre neurophysiological test results in the 11 patients presenting at least one abnormality of these tests. A abnormal result, N normal result. RRIV RR interval variation, SSR sympathetic skin response, QST quantitative sensory testing, LEP laser-evoked potentials. Only SSR, QST, and LEP data of the lower limbs are presented.

**Table 1** Summary of neurophysiological results in 11 carriers of TTR mutations. Different combinations of small-fibre tests provided different results suggesting that a comprehensive battery of small-fibre tests is useful in the diagnosis of small-fibre polyneuropathy in these patients.
Early recognition of the hATTR neuropathy: skin biomarkers

- To measure intraepidermal nerve fiber density (IENFD)
  - In the frame of expert teams
- To detect amyloid deposits

### Table: Demographics and Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>TTR FAP</th>
<th>TTR noFAP</th>
<th>Healthy</th>
<th>Disease</th>
<th>AL</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td>20</td>
<td>10</td>
<td>20</td>
<td>20</td>
<td>2</td>
</tr>
<tr>
<td>Skin biopsy + amyloid, No.</td>
<td>14/20</td>
<td>2/10</td>
<td>0/20</td>
<td>0/20</td>
<td>2/2</td>
</tr>
<tr>
<td>Age, yr, median, range</td>
<td>65, 27–76</td>
<td>47.5, 17–83</td>
<td>58, 30–72</td>
<td>59, 30–73</td>
<td>70</td>
</tr>
<tr>
<td>Female, No. (%)</td>
<td>7 (35)</td>
<td>8 (40)</td>
<td>7 (35)</td>
<td>7 (35)</td>
<td>2 (100)</td>
</tr>
<tr>
<td>V30M mutation, No. (%)</td>
<td>13 (65)</td>
<td>5 (50)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>NIS-LL, mean (SD)</td>
<td>31.8 [23.2]</td>
<td>4.4 [1.8]</td>
<td>0.2 [0.2]</td>
<td>16.0 [3.6]</td>
<td></td>
</tr>
<tr>
<td>NIS sensory score, mean (SD)</td>
<td>11.3 [5.9]</td>
<td>1.6 [2.9]</td>
<td>0.2 [0.2]</td>
<td>13.5 [3.3]</td>
<td></td>
</tr>
</tbody>
</table>

- IENFD, fibers/mm, mean (SD)
  - Proximal thigh: 14.8 [12.3] vs. 22.1 [12.0] vs. 23.9 [7.1]

*P < 0.0001, TTR FAP vs healthy controls.
*P < 0.005, TTR FAP vs TTR noFAP.
*P < 0.05, TTR FAP vs healthy controls.
*P < 0.0001, TTR FAP vs healthy controls.

AL = Light-chain amyloidosis; FAP = Familial amyloidotic polyneuropathy; IENFD = Intraepidermal nerve fiber density; NIS = Nerve Impairment Score; NIS-LL = NIS in the Lower Limbs; noFAP = without peripheral neuropathy; PanFND = Pancreatic nerve fiber density; SD = standard deviation; SGNFD = Sweat gland nerve fiber density; TTR = Transthyretin.
The monitoring of asymptomatic TTR gene carrier (TTR-AGC) is the main option to detect first symptoms
- TTR presymptomatic gene testing performed in the frame of genetic counselling by a multidisciplinary team

Penetrance studies give insights on the appropriate time to monitor TTR-AGC
- Estimates the risk of being affected for TTR gene mutation carriers according the age

In hATTR-Val30Met kindreds of different origin:
- Incomplete penetrance at age 80 y-o, in all areas
- Variable risks at intermediate ages, increasing
  - From 25-30 y-o in Portuguese or Brazilian carriers
  - After 45-50 y-o in French and Swedish carriers
How monitor the asymptomatic gene carriers?

Proposed time to initiate the monitoring of TTR-AGC (based on penetrance estimate)

- « Portuguese ATTR-Val30Met carriers »
  - Since 20-25 y-o

- « French ATTR-Val30Met /other ATTR carriers »
  - After 45-50 y-o

- ATTR-Val122Ile
  - After 55-60 y-o

What are the appropriate tests?

- Need to investigate the different facets of the disease
  - Multidisciplinary approach
  - Non invasive tests

Neurological

Cardiac

Other

Which timeline for the follow up?
Proposed tools to assess TTR-AGC
A multidisciplinary approach is necessary

**Neurological examination**
- All sensory modalities
- Autonomic survey

**Scores:**
- Total NIS: 0-24
- mPND: 0-IV

**Neurophysiological investigations**
- **Large fibres**
  - Nerve conduction studies
- **Small fibres tests**
  - Laser evoked potentials
  - Quantitative sensory testing
  - ESC/Sudoscan
  - HRdb

**Cardiac**
- Electrocardiogram
- **Biomarkers:** Nt-proBNP, troponin
- **Echography:** Global strain
- MRI?
- MIBG scintigraphy

**Other**
- **mBMI**
- Renal
  - microalbuminuria
  - serum creatinine,
  - glomerular filtration rate
- **Ophtalmologic examination**

And...
- Non-invasive biopsy (skin, fat… and/or HMDP-Tc99 Scintigraphy
- At baseline and/ or if abnormal testing

Electrochemical skin conductance (ESC); Heart rate variability to deep breathing (HRDB), magnetic resonance imaging (MRI); modified body mass index (mBMI)

Case study: Mr R. 60 years old

- Ask for ATTR presymptomatic genetic test
- Family history: the patient’s mother died of documented TTR-FAP in 2010
  - Diagnosed at 76 years old, 4 years after the inaugural symptoms
- One maternal uncle died at 74 years of age of « amyloidosis »

- Genetic counselling: TTR genetic testing showed heterozygous ATTR- Ile107Val

- Baseline evaluation
  - Surgery for carpal tunnel syndrome (2005)
  - Neurological examination: normal
  - Nerve conduction studies and small-fibre neurophysiological tests
    (*LEP, QST, ESC, HRDB): normal
  - Blood tests
  - Cardiac workup: normal

- Recommended follow up every 2 years in an expert center

*Quantitative sensory testing (QST); Laser evoked potentials (LEP); Electrochemical skin conductance (ESC / Sudoscan); Heart rate variability to deep breathing (HRDB)
Case study: Follow up evaluation (2015)

- **Intermittent numbness in his feet**, no other complains, active
- Neurological examination:

  - Temperature
  - Pin-Prick

  ![Diagram showing body with temperature and pin-prick areas marked]

- Isolated thermoalgic sensory loss (**NIS =2**)
- **CADT : 2** (intermittent diarrhea)
- Walk unlimited (**mPND = I**), stable weight (**BMI = 24.6**)
- Cardiac work up; Blood tests all normal

- Salivary gland biopsy: normal, skin biopsy positive AD

- **Final diagnosis: hATTR sensory neuropathy**

- Nerve conduction studies - small nerve fibers tests

<table>
<thead>
<tr>
<th></th>
<th>2010</th>
<th>2015</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SNAP (µV)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sup. peroneal</td>
<td>26</td>
<td>17</td>
</tr>
<tr>
<td>Sural</td>
<td>39</td>
<td>25</td>
</tr>
</tbody>
</table>

- **Sudoscan**
  - Palm: N
  - Feet: N
  - LEP: Hand N, Feet A

- **QST (Heat/Cold)**
  - Hand: N
  - Feet: N, A
  - HRDB: N, A
Case study: Mrs LEM…, 56 y-o

Family history:
- Her elder brother first diagnosed with ATTR-Ser77Tyr (2015)
  - Mixed cardiac and neurologic phenotype, onset 57 y-o,
  - Diagnosis delay 3 years, now treated
- Her father died at 74 y-o, her mother, age 86 y-o is healthy, no history suggesting ATTR
- 2017, her 2\textsuperscript{nd} brother, 58 years presented a syncope
  - Subsequently diagnosed with a hATTR-Ser77Tyr hypertrophic cardiomyopathy
  - Work up showed a mild sensory axonal neuropathy with amyloid deposits on salivary gland biopsy

- 2018: Mrs Lem. 56 y-o, asked for genetic counselling and TTR genetic test
  - Heterozygous ATTR-Ser77Tyr

- Advised to perform a baseline assessment
  - Relevant Past medical history: carpal tunnel syndrome surgery (2010), investigated (2015) for pains in her lower limbs (cramps), knees arthralgia: Negative work up (biological tests, NCS, radiography), diagnosis of «fibromyalgia»
Case study: Mrs LEM…, ATTR-Ser77Tyr carrier: assessment

- Presently: intermittent pains in her lower limbs, worse with effort, avoid to walk on long distances, stopped all sports
  - Good general health, BMI= 19.3 kg/m², autonomic survey*, blood pressure: normal
- Examination, nerve conduction study (NCS) and small nerve fibre tests (SNFT)
  - Strength: normal; reflexes: weak in her lower limbs
  - Sensation: vibration decreased in toes, position sense and light touch normal
  - Thermo-algetic sensation:

<table>
<thead>
<tr>
<th>NCS</th>
<th>SNFT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lower limbs</td>
<td>SNAP (µV)</td>
</tr>
<tr>
<td>Sup. peroneal nerve</td>
<td>35</td>
</tr>
<tr>
<td>Sural nerve</td>
<td>30</td>
</tr>
</tbody>
</table>

- Biological tests, NT-proBNP, troponin: normal
- Salivary gland + skin biopsies: Normal
- Cardiac work up: normal except

99mTc-HMPD Scintigraphy: cardiac hyperfixation

Final diagnosis: ATTR-Ser77Tyr polyneuropathy and cardiomyopathy
Conclusions - Take home messages

- hATTR polyneuropathy is a severe systemic disease now treatable
- Early diagnosis and treatment is a real challenge in hATTR, to stop the disease progression and preserve the neurological function
- To this end, a careful clinical evaluation is necessary including the assessment of all sensory modalities along with autonomic manifestations
  - Nerve conduction studies remain normal at the stage of pure small fibers sensory neuropathy
  - Neurophysiological and skin biomarkers can be contributive to detect alterations of small nerve fibers
    - Require a high level of expertise
- In this context, the identification, through genetic counselling and the monitoring of TTR asymptomatic carrier are desirable
  - Timelines adapted to the penetrance estimates
  - Using non invasive tests and a multidiciplinary approach to evaluate all facets of the disease
    - Importance of the cardiac evaluation
    - Non invasive biopsies, cardiac scintigraphy with bone tracers may help detect amyloid deposition
Thank you ...

• Neurology
  • Violaine Planté-Bordeneuve
  • Thierry Gendre
  • Abir Wahab
  • Farida Gorram

• Neurogenetics
  • Benoît Funalot
  • Bérénice Hebrard
  • Jodie Drevet

• Neurophysiology
  • Jean-Pascal Lefaucheur
  • Samar Ayache
  • Tarik Nordine

• Neuropathology
  • Jérôme Authier

• Cardiology
  • Laura Ernande
  • Geneviève Derumeaux
  • Thibaud Damy

• Nuclear Medicine
  • Emmanuel Itti

violaine.plante@aphp.fr ; www.reseau-amylose-chu-mondor.org