XXIV World Congress of Neurology – Dubaï, October 27-31 2019
Teaching Course 12: NEUROMUSCULAR DISEASE
DIAGNOSIS AND TREATMENT OF HEREDITARY NEUROPATHIES
AND MOTOR NEURON DISEASE

Early Recognition of Amyloid Neuropathy

with a focus on hereditary transthyretin amyloidosis (hATTR)

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Disclosures

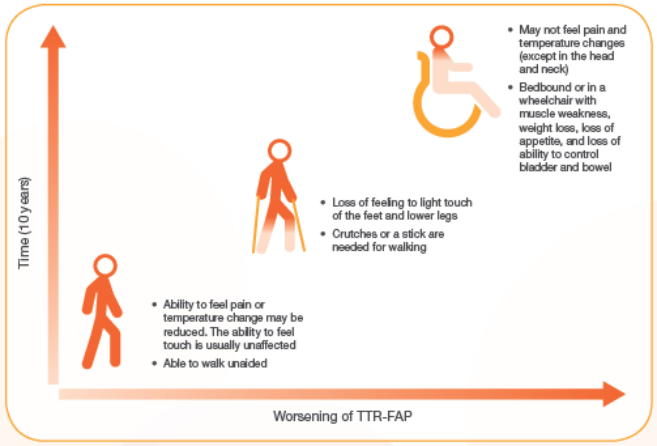
- Scientific Advisor for the development of the THAOS database (Pfizer Inc.), without financial support
- Pfizer and Alnylam supported expenses with travel and attendance to several scientific meetings (2016–2019)
- Consultant for Pfizer, Alnylam and Ionis Pharmaceuticals
- Has spoken on behalf Prothena,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

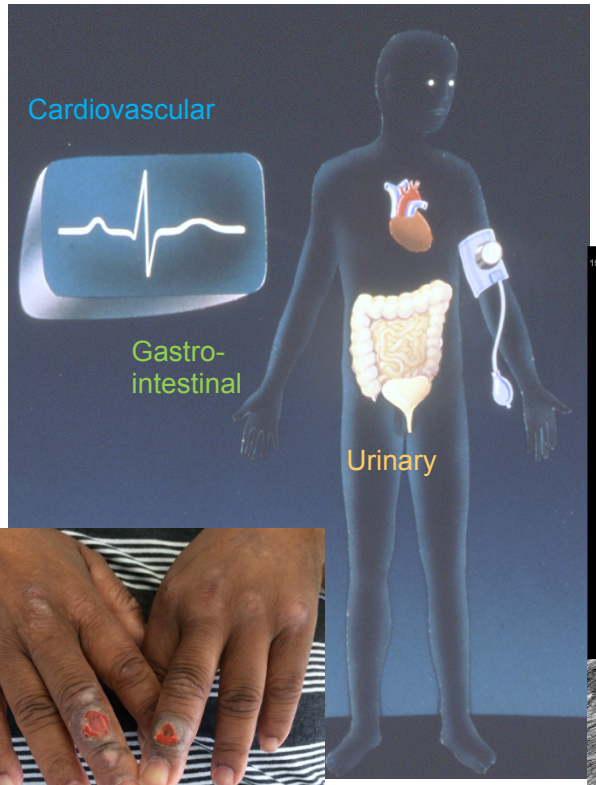
Learning objectives

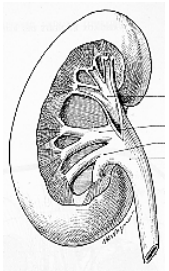
- Have an overview of the the amyloid polyneuropathy with a focus on the phenotypic and genotypic picture of the familial transthyretin amyloidosis (hATTR-PN)
- Get awareness on the therapeutic approaches available in this condition with a need to treat as early as possible
- Recognize the early clinical 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

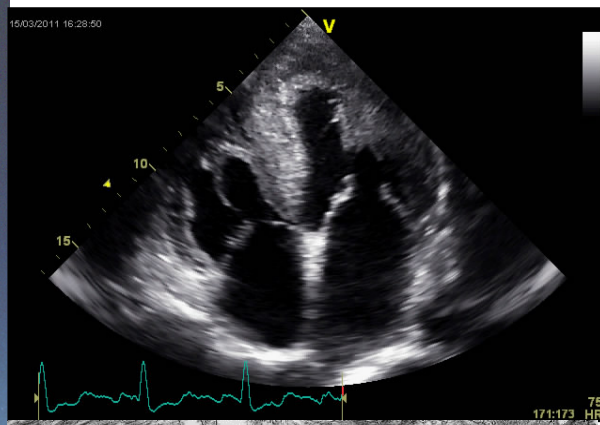
Hereditary Transthyretin Amyloid Polyneuropathy (hATTR-PN): a devastating disease

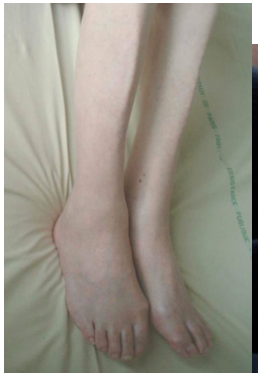
- Length-dependent **axonal sensory-motor and autonomic polyneuropathy**, associated with **systemic manifestations**
- Progressive amyloid deposition of TTR fibrils in organs

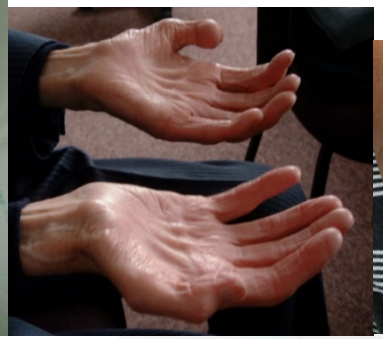


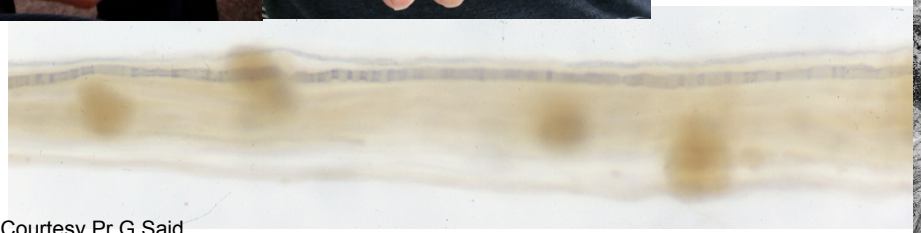


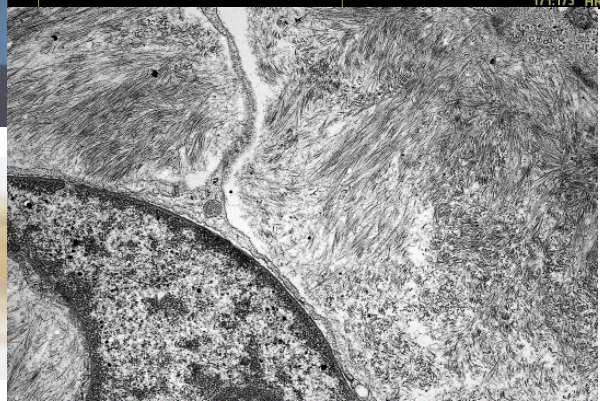










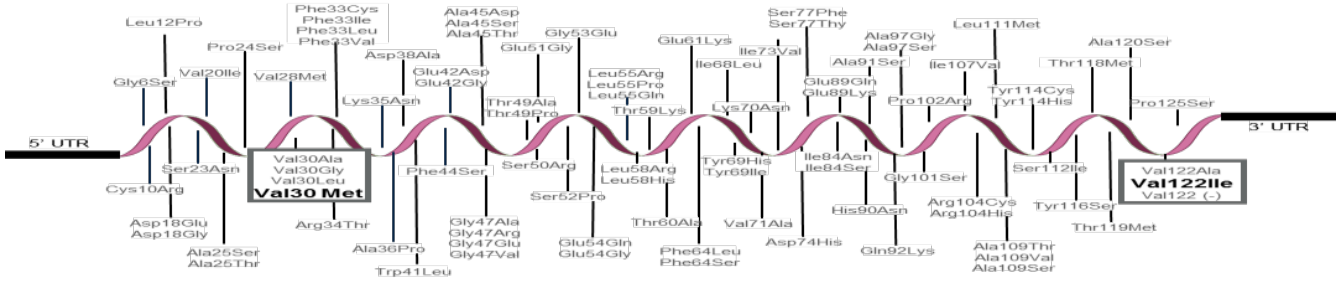


Planté-Bordeneuve et al. *Lancet Neurol* 2011, 10: 1090-1097;
Adams et al. *Nat Rev Neurol* 2019, 15: 387-404

Courtesy Pr G Said

hATTR-PN: the pheno-genotypic spectrum

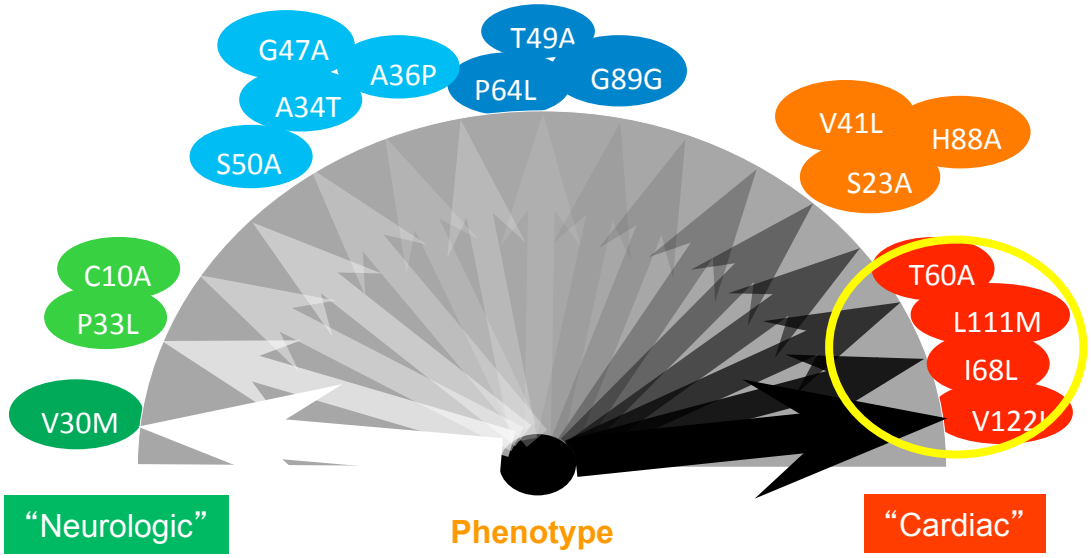
- Autosomal dominant transmission, *Gene TTR > 140 pathogenic variants*

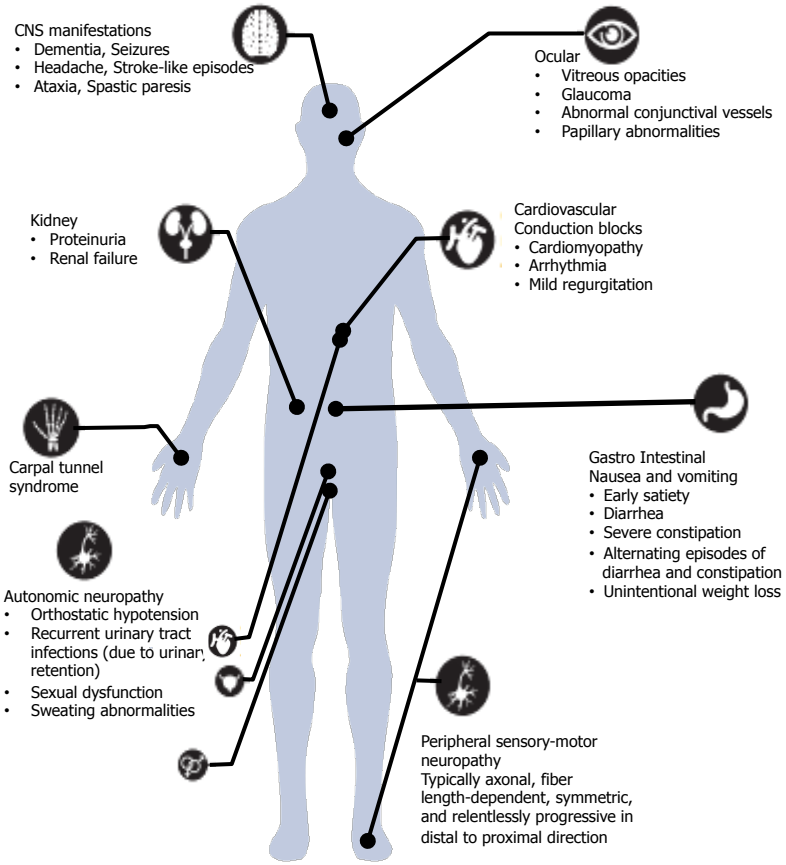


  - Significant geographic variation
  - Variable age of onset (AO)

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-Val122Ile + 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)

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

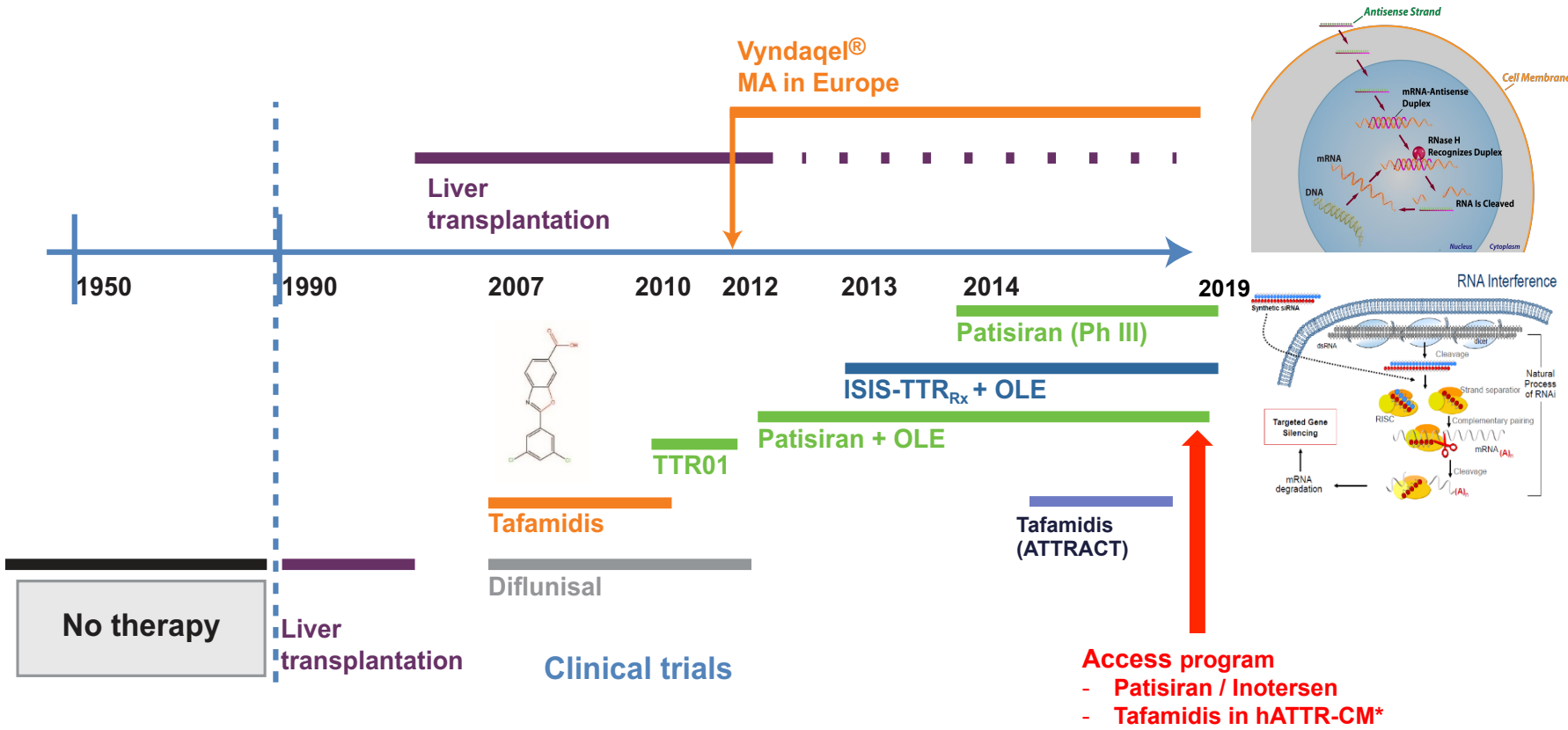
No family history
(« sporadic »)
in 60% of cases

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

Gertz M et al. *J Am Coll Cardiol.* 2015;66:2461-66; Planté-Bordeneuve V et al. *J Neurol.* 2018;265:976-983. Conceicao I, et al. *J Periph Nerv Syst* 2016;21:5–9.

hATTR-PN: a disease now treatable

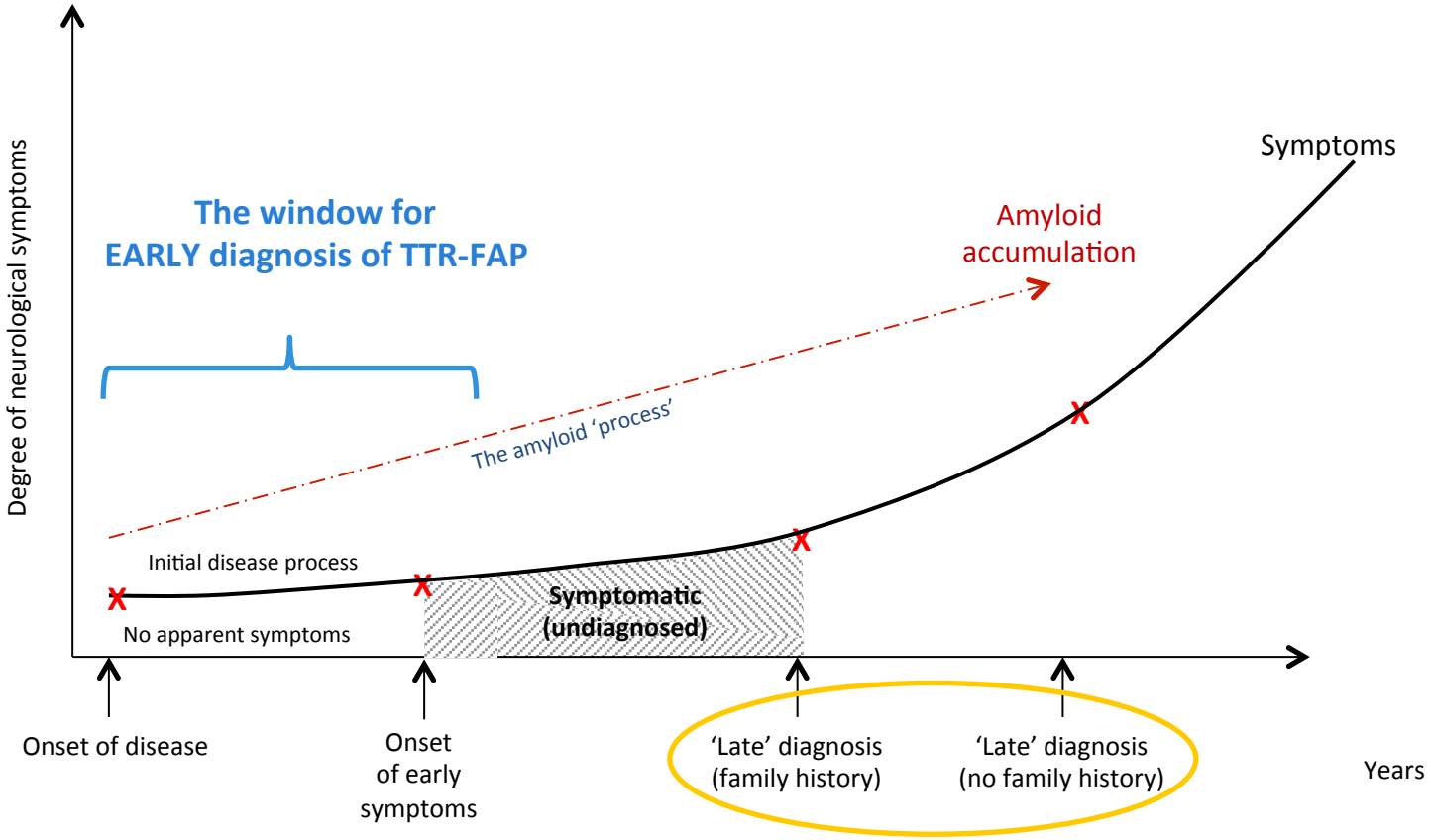
- Major therapeutic advances in the past decade
- Available treatments aim to prevent TTR amyloid deposition in organs and halt the progression of symptoms



* hATTR-CM: hereditary transthyretin amyloid cardiomyopathy

Ericzon et al. *Transplantation* 2015, 99: 1847-1854; Coelho et al. *J Neurol* 2013, 260: 2802-14; Waddington-Cruz et al. *Amyloid* 2016, 23: 178-183; Planté-Bordeneuve et al. *J Neurol* 2017, 264:264-268
Adams et al. NEJM 2018, 379: 11-21; Benson et al. NEJM 2018, 379: 22-31; Maurer et al. *NEJM* 2018, 379:1007–1016

hATTR – We should intervene much earlier in order to preserve the neurological function



The early recognition of hATTR is now a real challenge

Courtesy T Coelho

Early recognition of the hATTR neuropathy: clinical aspects

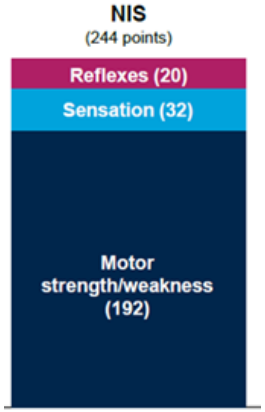
- Neurological examination including assessment of all sensory modalities
  - Temperature, pain
  - Vibration, position sense
- Autonomic manifestations
  - Can be difficult to assess
  - Test blood pressure in recumbent/standing position
  - CADT questionnaire to review the main autonomic manifestations

Table 1 Compound Autonomic Dysfunction Test (CADT)

	4	3	2	1	0
Postural hypotension	No	Asymptomatic	Lipothymia	Postural syncopes	Bedridden
Nausea preventing normal feeding, vomiting	No	Nausea/Slow digestion	Vomiting: Less than once a week	Vomiting: More than once a week	Vomiting: Daily
Diarrhea/Constipation	No	Once a month	Once a week	More than twice a week	Daily
Sphincter disturbances	No	Dysuria	Dysuria + episode of incontinence	Intermittent bladder catheterization	Permanent bladder catheterization
Erectile dysfunction	No	Difficulties	Impotency		
Total					

Denier C et al. *J Neurol.* 2007;254:1684-1688.

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



mPND

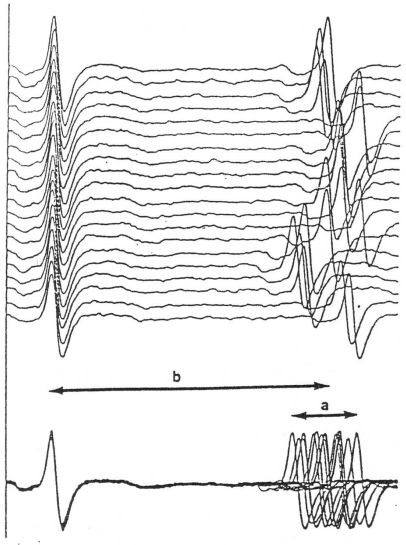
0	Normal
I	Sensory disturbances in the lower limbs, preserved walking capacity
II	Impaired walking, no need of aid or stick
IIIa	Walking with 1 stick
IIIb	Walking with 2 sticks
IV	Wheelchair or confined to bed

Denier C et al. *J Neurol.* 2007;254:1684-1688; Coelho et al. *Neurology* 2012 785-792.

Early recognition of the hATTR neuropathy: neurophysiological tests

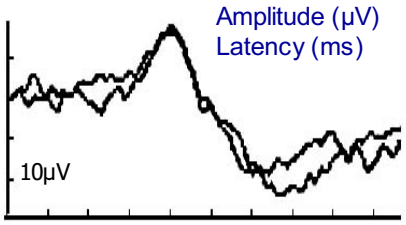
- Large nerve fibres
  - Motor and sensory nerve conduction in all 4 limbs
  - Normal at an early stage
  - A progressive decline of SNAP in the lower limbs may be a red flag !
- Small nerve fibre tests may be helpful at an early stage

Heart rate variability



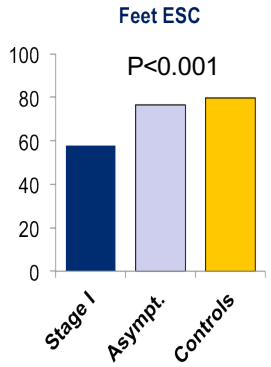
- R-R interval variation
- *During rest, hyperventilation, Valsalva maneuver,…*
- *Investigates* cardiac parasympathetic innervation

Laser Evoked Potential



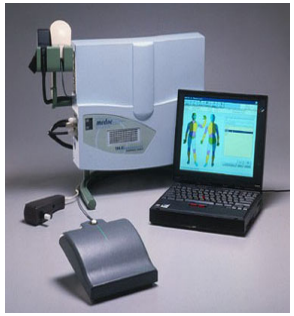
- *Hand or foot stimulation*
- *Cortical (vertex) recordings*
- *Investigates only Aδ fibres*

Electrochemical skin conductance (ESC)



Feet ESC showed 75% sensitivity and 85% specificity for detection of dysautonomia

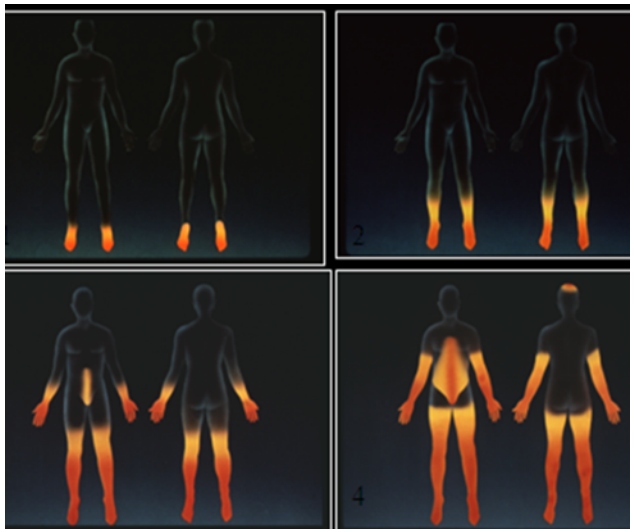
Quantitative Sensory Testing

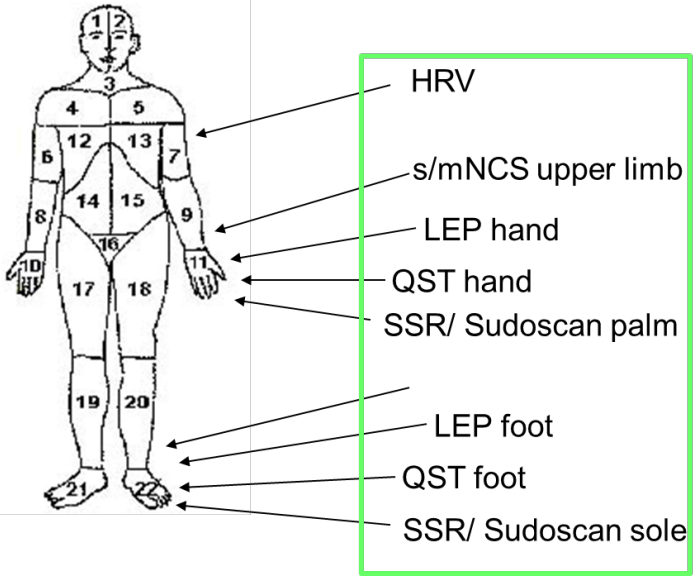


- *Cold, warm, pressure, heat-pain detection, pain, tolerance*
- *Threshold measurement*
- *Method of limits, levels,…*
- Investigates Aδ (cold) or C fibres (warm)

Castro J et al. *Clin Neurophysiol.* 2016;12:2222-2227; Lefaucheur JP et al. *Clin Neurophysiol.* 2018;129:1565-1569.

Small Nerve fibers assessment
Early neurophysiological markers….





Bilateral investigation
(About 45 min.)

Comparison with normative data for diagnosis

Use of cumulative indexes for follow-up

HRV: heart rate variability, NCS: nerve conduction study, LEP: laser evoked potential, QST: quantitative sensory testing, SSR: sympathetic sensory testing

J Neurol
DOI 10.1007/s00415-012-6816-8

ORIGINAL COMMUNICATION

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

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

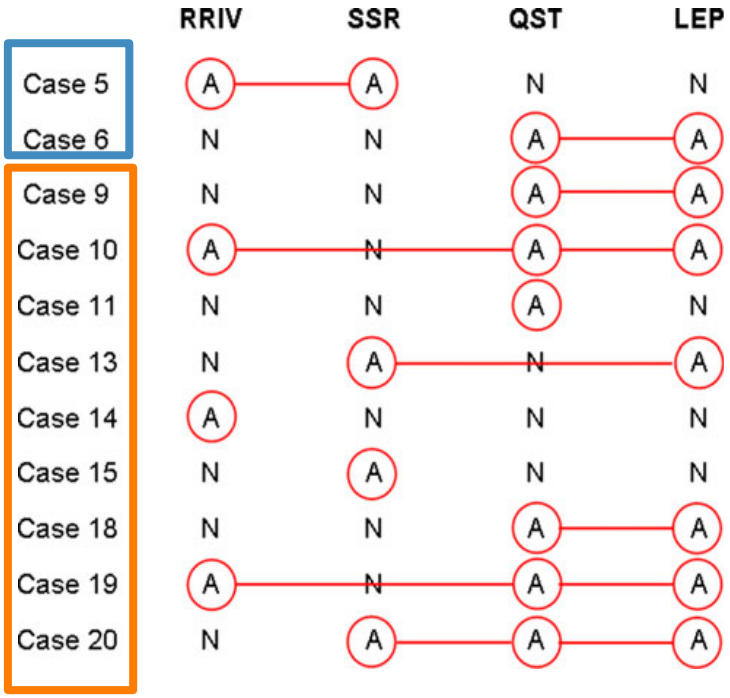
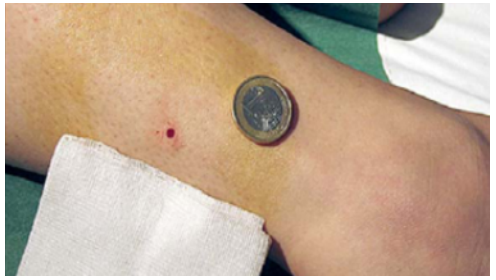


Fig. 1 The various combinations of small-fibre neurophysiological test results in the 11 patients presenting at least one abnormality of these tests. *A* abnormal result, *N* normal result. *RRIV* RR interval variation, *SSR* sympathetic skin response, *QST* quantitative sensory testing, *LEP* laser-evoked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

JP Lefaucheur et al *J neuro*l 2013 260(6):1497-503

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



RESEARCH ARTICLE
ANN NEUROL 2017;82:44–56

Cutaneous Nerve Biomarkers in Transthyretin Familial Amyloid Polyneuropathy

Gigi J. Ebenezer, MBBS, MD,[1] Ying Liu, MD, PhD,[1] Daniel P. Judge, MD,[2] Kelly Cunningham, MS,[1] Shaun Truelove, PhD,[3] Noel D. Carter, MLS,[1] Blessan Sebastian, BS,[1] Kelly Byrnes, MS,[1] and Michael Polydefkis, MD, MHS[1]

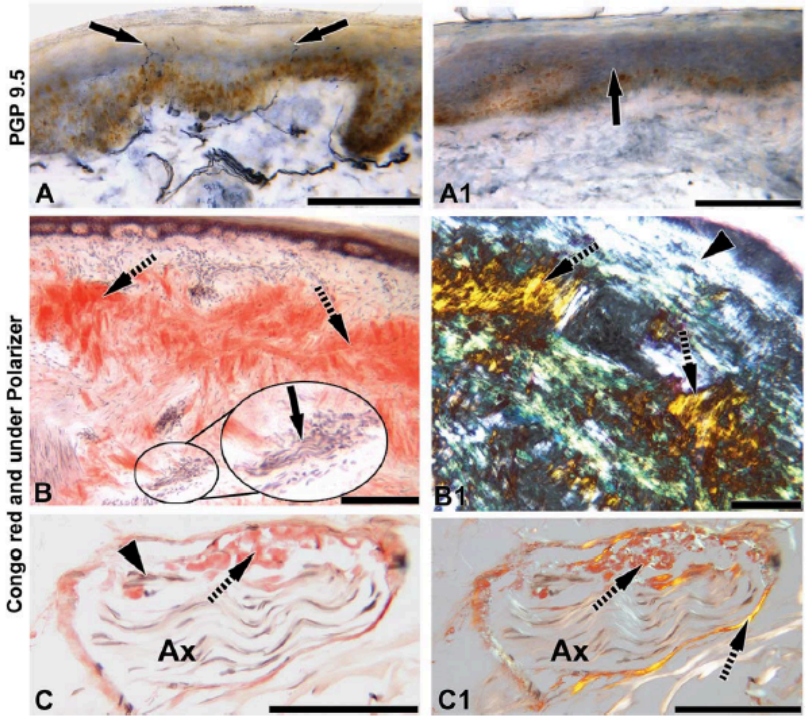


TABLE Demographics and Baseline Characteristics

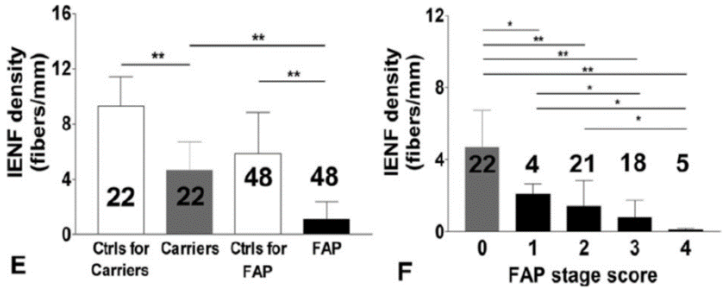
Characteristic	TTR		Controls		
	TTR-FAP	TTR-noPN	Healthy	Disease	AL
No.	20	10	20	20	2
Skin biopsy + amyloid, No.	14/20	2/10	0/20	0/20	2/2
Age, yr, median, range	65, 27–76	47.5, 17–83	58, 30–72	59, 30–73	70
Female, No. (%)	7 (35)	8 (80)	7 (35)	7 (35)	2 (100)
V30M mutation, No. (%)	13 (65)	5 (50)			
NIS-LL, mean [SD]	31.8 [23.2]	4.4 [1.8]	0.2 [0.2]	16.0 [3.6]	
NIS sensory score, mean [SD]	11.3 [5.9]	1.6 [2.9]	0.2 [0.2]	15.5 [3.5]	
IENFD, fibers/mm, mean [SD]					
Distal leg	6.4 [11.1][a]	14.6 [12.6][b]	16.0 [6.9]		
Proximal thigh	14.8 [12.3][c]	22.1 [12.0]	23.9 [7.1]		

[a] $p < 0.0001$, TTR-FAP vs healthy controls.
[b] $p < 0.05$, TTR-FAP vs TTR-noPN.
[c] $p < 0.05$, TTR-FAP vs healthy controls.
[d] $p < 0.001$, TTR-FAP vs healthy controls.
AL = light-chain amyloidosis; FAP = familial amyloidotic polyneuropathy; IENFD = intraepidermal nerve fiber density; NIS = Neuropathy Impairment Score; NIS-LL = NIS in the Lower Limbs; noPN = without peripheral neuropathy; PMNFD = pilomotor nerve fiber density; SD = standard deviation; SGNFD = sweat gland nerve fiber density; TTR = transthyretin.

RESEARCH ARTICLE
ANN NEUROL 2019;85:560–573

Skin Nerve Pathology: Biomarkers of Premanifest and Manifest Amyloid Neuropathy

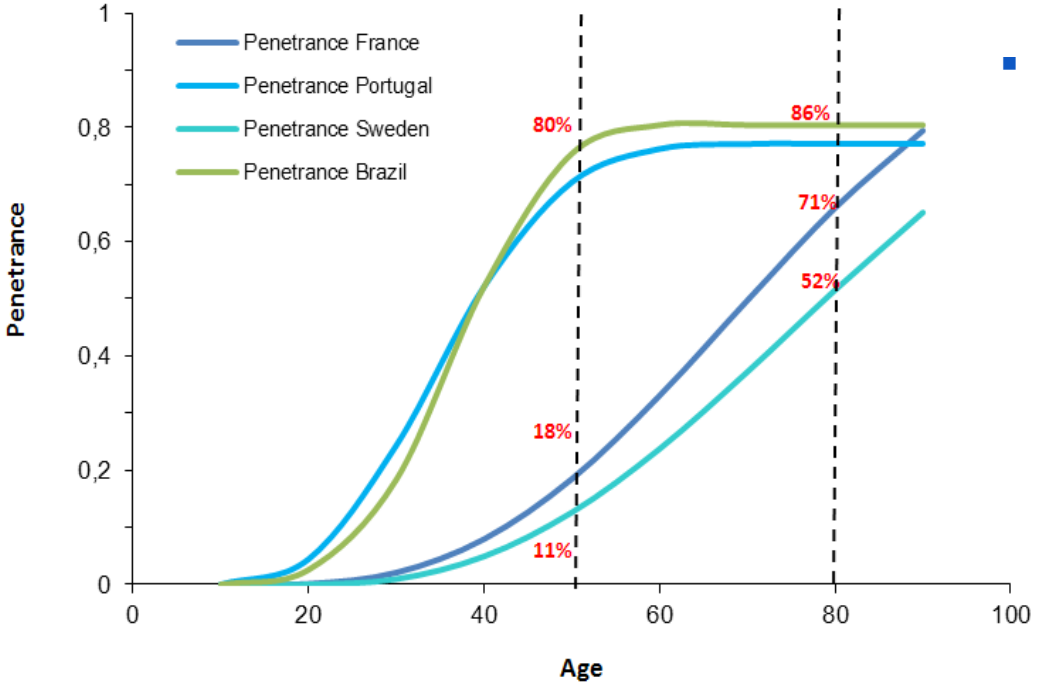
Chi-Chao Chao, MD, PhD,[1] Hsueh-Wen Hsueh, MD,[1] Hung-Wei Kan, PhD,[2] Chun-Hua Liao, MD,[2] Hao-Hua Jiang, MS,[2] Hao Chiang, PhD,[2] Whei-Min Lin, MS,[2] Ti-Yen Yeh, PhD,[2] Yea-Huey Lin, BS,[1] Ya-Yin Cheng, MS,[2] and Sung-Tsang Hsieh, MD, PhD[1,2,3,4,5]



TTR gene carriers monitoring for an early diagnosis: when and how to do ?

- 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

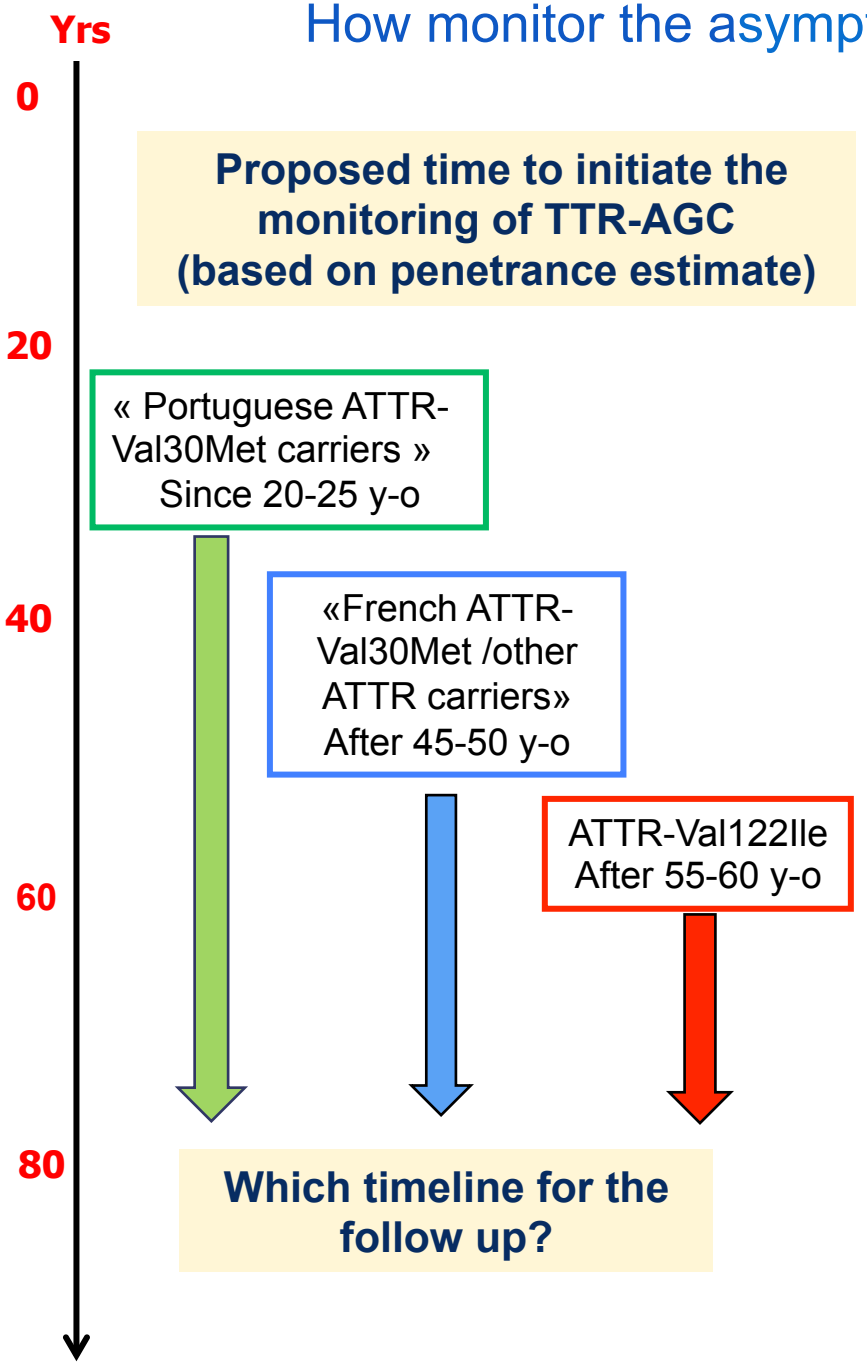
- **Penetrance studies give insights on the appropriate time to monitor TTR-AGC**
  - Estimates the risk of being affected for TTR gene mutation carriers according the age



- 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

Plante-Bordeneuve et al. *J Med Genet* 2003, Hellman et al. *Amyloid* 2008; Sapporta et al *Eur J Hum genet* 2009

How monitor the asymptomatic gene carriers ?



What are the appropriate tests?

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

Neurological

?

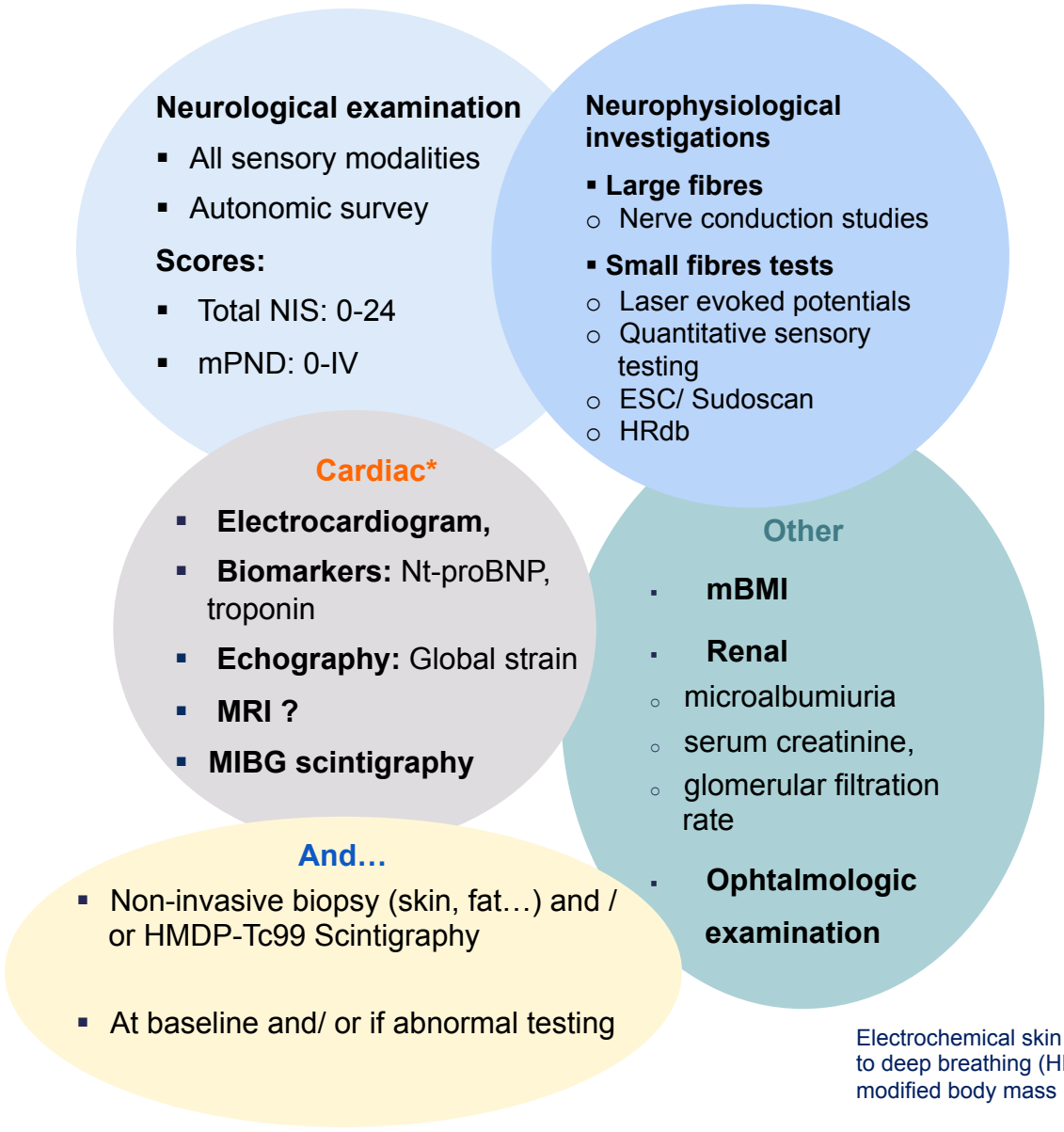
Cardiac

?

Other

?

Proposed tools to assess TTR-AGC
A multidisciplinary approach is necessary

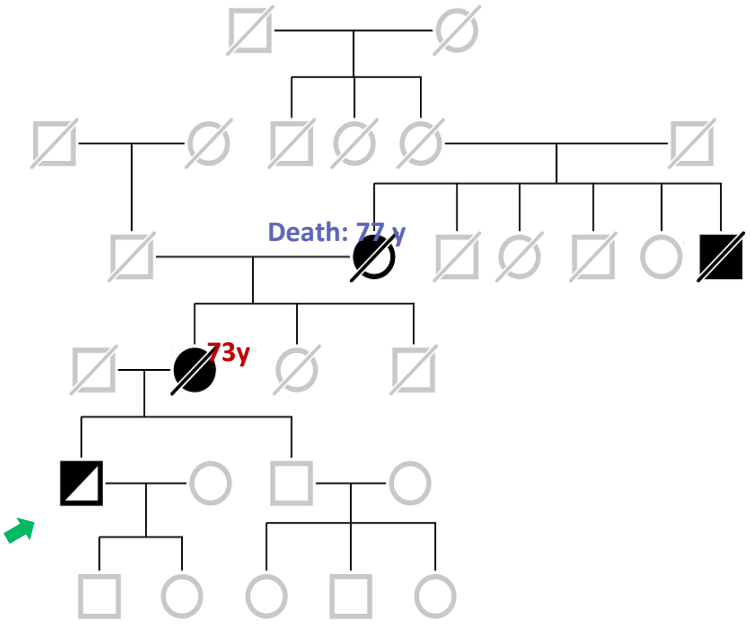


Electrochemical skin conductance (ESC); Heart rate variability to deep breathing (HRDB), magnetic resonance imaging (MRI); modified body mass index (mBMI)

Schmidt H et al. *Muscle & Nerve*, 54: 353-360 (2016); Obici L et al. *Curr op Neurol* 29, Supp 1, S1-S8 (2016); Conceiçao I et al. *Amyloid* 2019, 26 (1): 3-9; personnal experience
* Maurer M et al. *Circ Heart Fail* 2019, 12: e006075; Piekarski E et al, *Eur J Nucl Med* 2018, 45: 1108-18 *;* Gillmore J et al. *Circulation* 2016, 133: 2404-2412

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 »

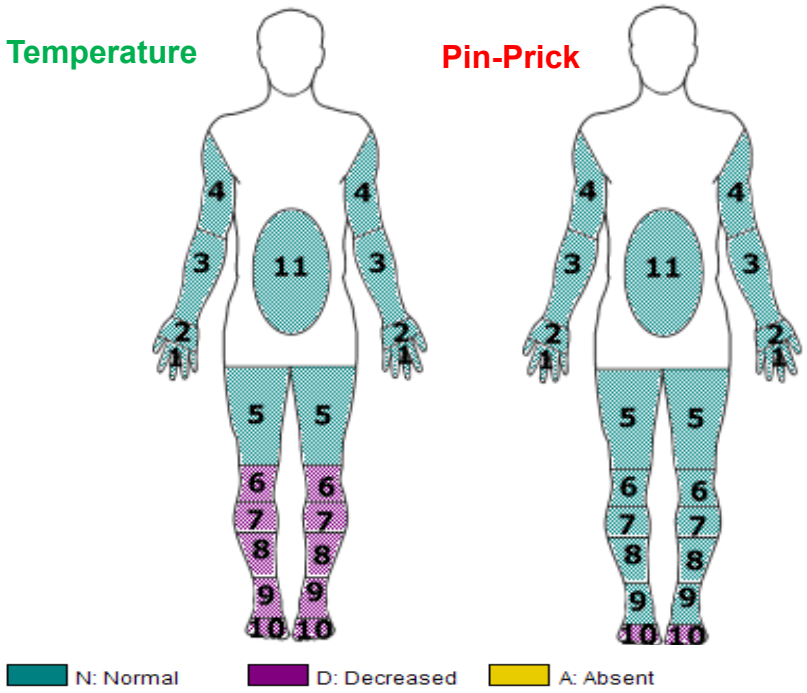


- Genetic couselling: TTR genetic testing showed heterozygous ATTR- Ille107Val
- Baseline evaluation
  - Surgery for carpal tunnel syndrome (2005)
  - Neurological examination: normal
  - Nerve conduction studies and small-fibre neurophysiological tests (*LEP, QST, ESC, HRDB): normal
  - Blood tests
  - 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:



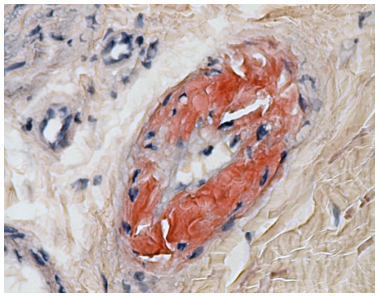
- Nerve conduction studies - small nerve fibers tests

	2010	2015
SNAP (µV)		
Sup. peroneal n.	**26**	**17**
Sural n.	**39**	**25**
Sudoscan		
Palm	**N**	**N**
Feet	**N**	**N**
LEP		
Hand	**N**	**N**
Feet	**N**	**A**
QST (Heat/Cold)		
Hand	**N**	**N**
Feet	**N**	**A**
HRDB	**N**	**A**

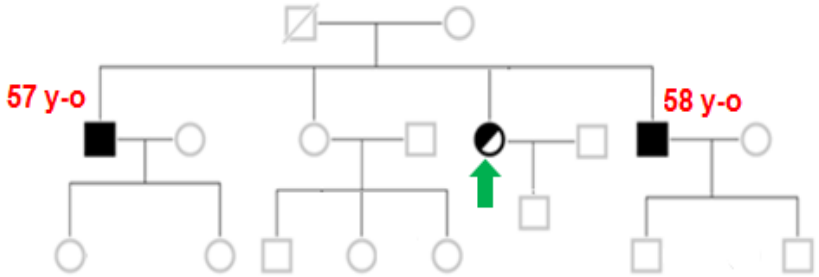
- **Isolated thermoalgic sensory loss (NIS =2)**
- **CADT : 2 (intermittent diarrhea)**
- Walk unlimited **(mPND = I)**, stable weight **(BMI = 24.6)**
- Cardiac work up; Blood tests all normal

- **Salivary gland biopsy: normal, skin biopsy positive AD**

- **Final diagnosis: hATTR sensory neuropathy**



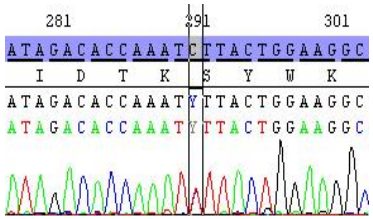
Case study: Mrs LEM…, 56 y-o



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 2nd brother, 58 years presented a syncopae
  - Subsequently diagnosed with a hATTR-Ser77Tyr hypertrophic cardiomyopathy
  - Work up showed a mild sensory axonal neuropathy with amyloid deposits on salivary gland biopsy

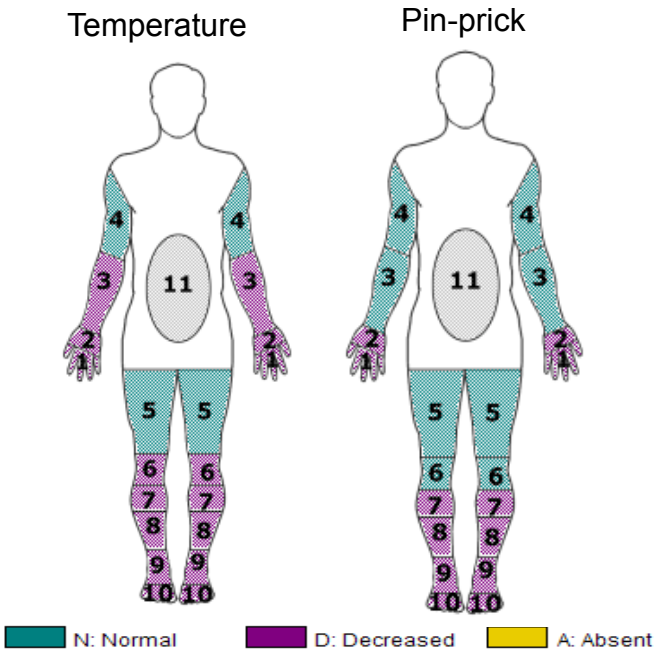
- **2018**: Mrs Lem. 56 y-o, asked for genetic counselling and TTR genetic test
  - Heterozygous ATTR-Ser77Tyr



- 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

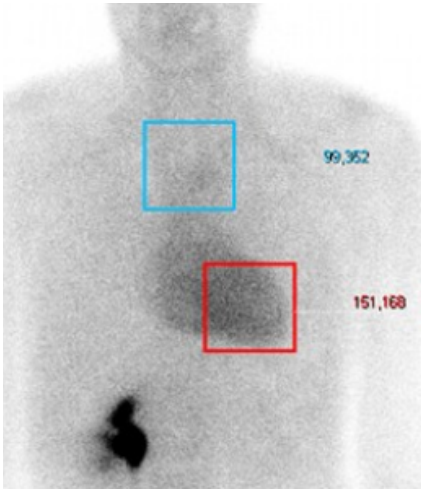
- **Presently: intermittent pains in her lower limbs, worse with effort,** avoid to walk on long distances, stopped all sports
  - Good general health, BMI= 19.3 kg/m^2, autonomic survey*, blood pressure: normal
- **Examination, nerve conduction study (NCS) and small nerve fibre tests (SNFT)**
  - Strength: normal; reflexes: weak in her lower limbs
  - Sensation: vibration decreased in toes, position sense and light touch normal
  - Thermo-algic sensation:



NCS		SNFT				
Lower limbs	**SNAP (µV)**	**Site**	**Sudoscan**	**LEP**	**QST**	**HRDB**
Sup. peroneal nerve	**35**	**Feet**	**N**	**N**	**N**	**A**
Sural nerve	**30**	**Hand**	**N**	**A**	**N**	

- 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 …

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