Neuropatia da amiloidosi

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Dr P Guaraldi has been advisory board member of Alnylam and Sobi;

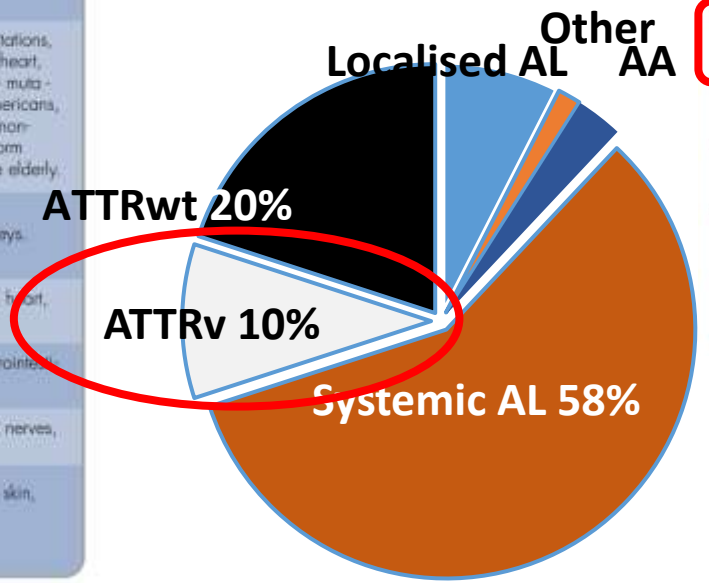
received speaker fees and honoraria from Alnylam, Theravance Biopharma, Akcea Therapeutic, Biogen and Chiesi.

received congress and travel accommodation expense compensations from Alnylam, Bial, Zambon and Abbvie.

Amyloidosis is an heterogeneous group of pathologies caused by the extracellular deposition of insoluble protein fibrils

The protein precursor, the underlying pathological process and clinical manifestations may differ considerably…

TYPE	SOURCE OF AMYLOID (Precursor Protein)	SYNDROME
AL, AH, ALH	**Plasma cells in the bone marrow** (Immunoglobulin light or heavy chains, or both)	Primary form of amyloidosis, similar to multiple myeloma, affecting the kidneys, heart, liver, gastrointestinal tract, and nerves.
AA	**Circulating inflammatory protein** (Serum amyloid A)	Secondary to chronic inflammatory and infectious diseases, affecting the kidneys and liver.
ALECT2	**White blood cells** (Leukocyte chemotactic factor 2)	Clinically resembles AL, affecting the kidneys and liver.
Aβ2M	**Circulating serum protein** (β2-microglobulin)	Dialysis-related, affecting the joints and tendons.
ATTR	**Mutant and wild-type protein produced in the liver** (Transthyretin)	Hereditary with over 100 mutations, affecting the nervous system, heart, and kidneys. The Val-122-Ile mutation is common in African Americans, causing cardiac disease. A non-hereditary, wild-type, senile form causes cardiac disease in the elderly.
AFib	**Mutant protein produced in the liver** (Fibrinogen A α-chain)	Hereditary, affecting the kidneys.
AApoAI	**Circulating serum protein** (Apolipoprotein AI)	Hereditary, affecting the liver, heart, kidneys, and nerves.
ALys	**Circulating serum protein** (Lysozyme)	Hereditary, affecting the gastrointestinal tract and kidneys.
AGel	**Circulating serum protein** (Gelsolin)	Hereditary, affecting the skin, nerves, and kidneys.
Localized	**Plasma cells in local tissues** (Immunoglobulin light chains)	Mostly occurs in the bladder, skin, and airways.



Clinical presentation of the most common forms of systemic amyloidosis

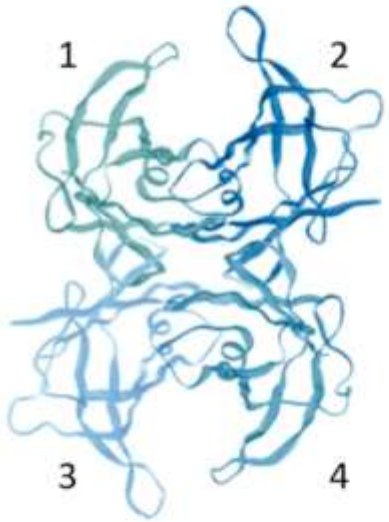
Amyloid type	Organ involvement					
	Heart	Kidney	Liver	PNS	ANS	GI
AL amyloidosis	++	++	+	+	+	+
Hereditary ATTR amyloidosis	++	±	-	++	+	+
AA (reactive) amyloidosis	±	++	+	-	+	+
Wild-type ATTR amyloidosis	++	-	-	-	-	-
Hereditary AApoAI amyloidosis	+	++	++	-	-	-
Hereditary lysozyme amyloidosis	-	+	++	-	-	++

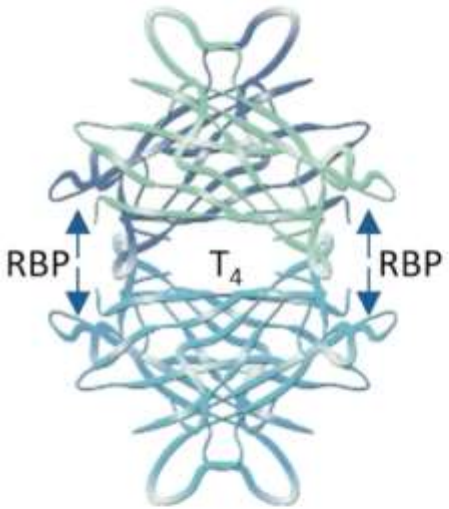
Palladini and Merlini, Blood. 2016M 12(2):159-168

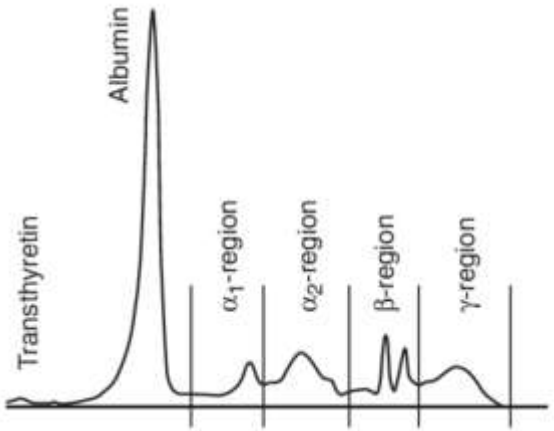
Thomas VE et al. Neurodegener Dis Manag 2019;9(6):289–99

Transthyretin is a transport protein of thyroxine and retinol-binding protein (RBP)/vitamin A

- Transthyretin is a tetramer with different binding sites for thyroxine (T4) and RBP / vitamin A[1,2]







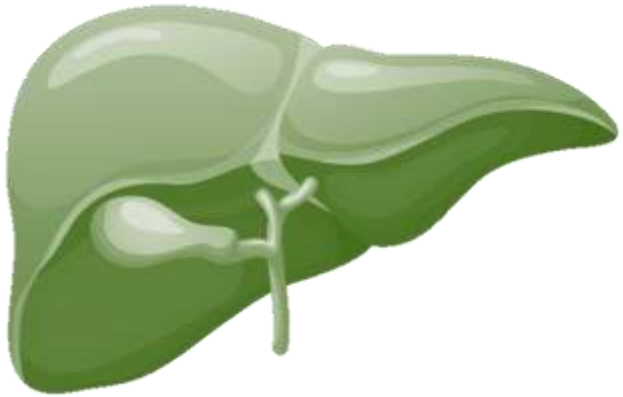
Transthyretin binds approximately 10% of T4 and 10% of T3. In addition
Transthyretin also binds retinol-binding protein, thereby being involved in vitamin A transport.
The bulk of thyroxine is carried by thyroxine-binding globulin and albumin

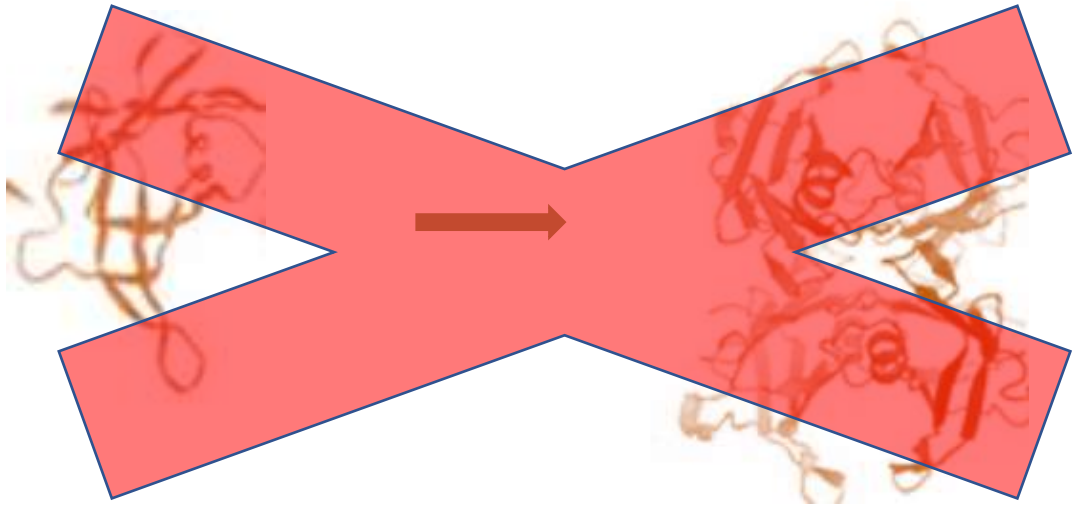
RBP: retinol-binding protein.
1. Benson MD, et al. *Muscle Nerve* 2007;36(4):411–423. 2. Sekijima Y, et al. *Curr Pharm Des* 2008;14:3219–3230.

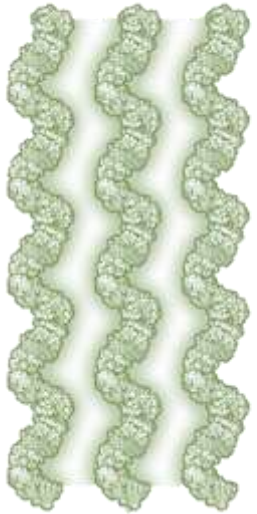
correctly folded protein

Transthyretin tetramer

TTR is formed in the Liver







misfolded protein

binds & form amyloid fibrils

•95% of TTR is produced by the **liver** and <5% is synthesised in the **choroid plexus** of the brain and the **retinal pgment** epithelium of the eyes

•The transthyretin tetramer transports retinol through the RBP, vitamin A complex and thyroxine

•The bulk of thyroxine is carried by thyroxine-binding globulin and albumin

•<1% of TTR bound to T4

CNS manifestations:

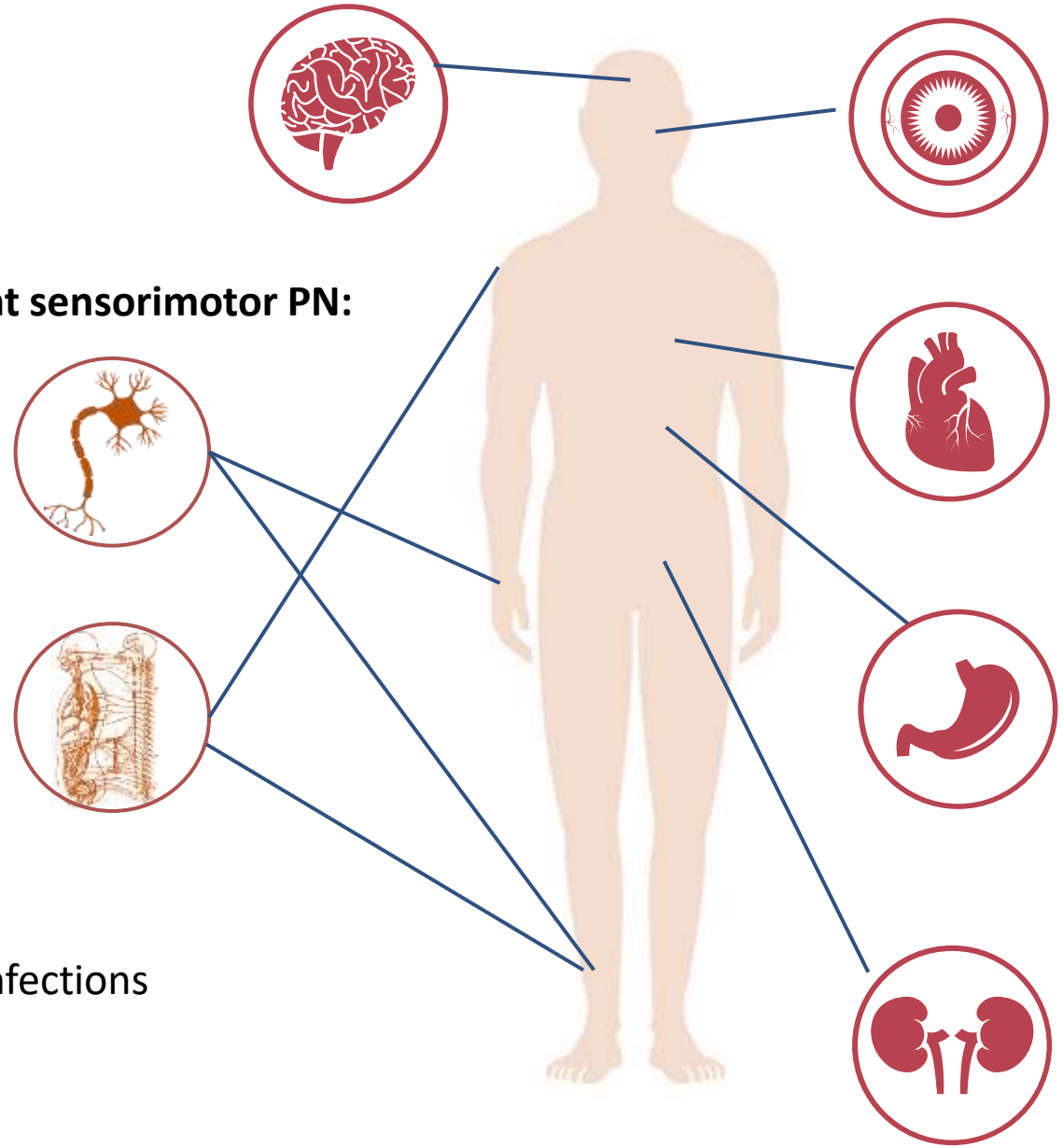
- Progressive dementia
- Ataxia
- Stroke-like episodes

Peripheral length-dependent sensorimotor PN:

- Neuropathic pain
- Paresthesia/sensory loss
- Weakness in LL & UL
- Areflexia
- Carpal tunnel syndrome
- Spinal stenosis

Autonomic dysfunction:

- Orthostatic hypotension
- Sweating disturbances
- Erectile failure
- Recurrent urinary tract infections



Ocular manifestations:

- Glaucoma
- pupil abnormalities
- vitreous opacities

Cardiovascular manifestations:

- Low/decreasing QRS voltage on ECG
- Thick interventricular septum, “speckled” myocardium by echocardiography
- HF with preserved ejection fraction (without hypertension)

GI manifestations:

- Constipation/Diarrhea
- Nausea /Vomiting
- Weight loss

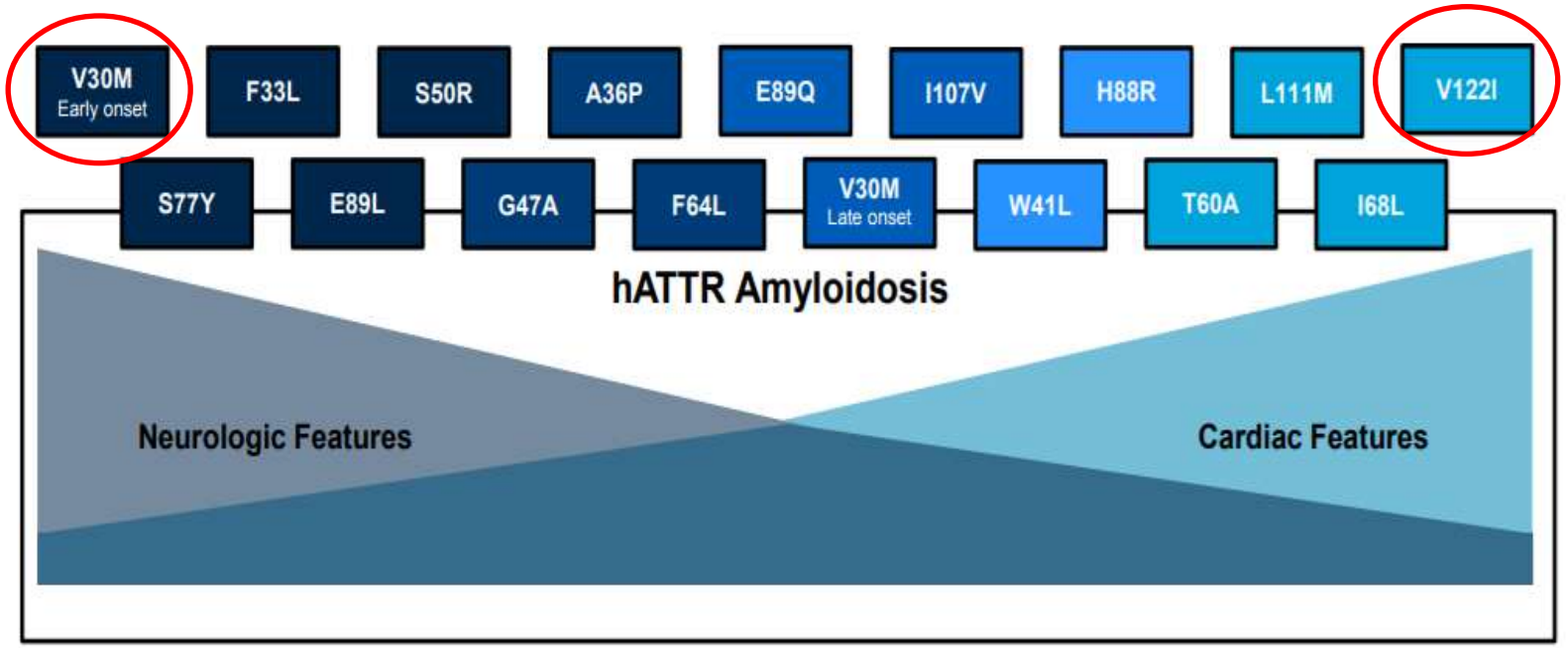
Nephropathy:

- Renal failure
- Microalbuminuria/Proteinuria

A broad genetic and phenotypic heterogeneity in ATTRv amyloidosis presents a diagnostic challenge for clinicians[1,2]

- Presentation can vary by TTR mutation, but mixed phenotype is often reported[1–3]

Type B deposits,[4] intact TTR monomers form the fibrils, common in early onset V30M polyneuropathy subjects.



Type A deposits[4] aggregates of intact monomers and monomer fragments present in most cardiomyopathic mutations and ATTRwt-associated cardiomyopathy.

Figure adapted from Maurer et al. 2019[1]

ATTRwt, wild-type amyloid transthyretin amyloidosis; hATTR, hereditary transthyretin amyloidosis; TTR, transthyretin

1. Maurer MS et al. Circ Heart Fail 2019;12:e006075; 2. Rowcenzio DM et al. Hum Mutat 2014;35:E2403–122; 3. Wixner J et al. Orphanet J Rare Dis 2014;9:61; 4. Suhr OB. PLOS ONE 2019;14:e0211

Geographical variability in hATTR amyloidosis genotypes

Early onset <50 years V30M (Neuropathic phenotype)[1,2]	Late onset >50 years V30M or Non-V30M (Mixed phenotype)[1,3]	Non-V30M (Cardiac phenotype)[1,4]
• Length-dependent sensorimotor PN (small fiber) • Severe autonomic dysfunction • GI disturbances • Cardiac involvement is rare and delayed	• Length-dependent sensorimotor PN (large fiber involvement) • Early motor involvement • Mild autonomic symptoms • Higher incidence of cardiac and ophthalmic involvement	• Cardiomyopathy • Mild neuropathy, autonomic symptoms • Ocular involvement

1. Conceição I et al. Amyloid 2019;26:3–9; 2. Conceição I. Clin Auton Res 2019;29(Suppl 1):11–17; 3. Conceição I et al. Muscle Nerve 2007;35:116–8; 4. Sekijima et al. Orphanet J Rare Diseases 2018;13:6.

Summary of diagnostic process

1

SUSPECT

Increased AWARENESS

- Family history of hATTR amyloidosis*
- Observation of **red flag** symptoms:
  - Peripheral sensory-motor neuropathy
  - Autonomic neuropathy
  - Gastrointestinal manifestations
  - Carpal tunnel syndrome
  - Cardiovascular manifestations
  - Nephropathy

2

DETECT & CONFIRM

- Neurological assessments
- Tissue biopsy
- Scintigraphy scan
- Cardiac assessments
- Genetic testing to identify specific TTR mutations

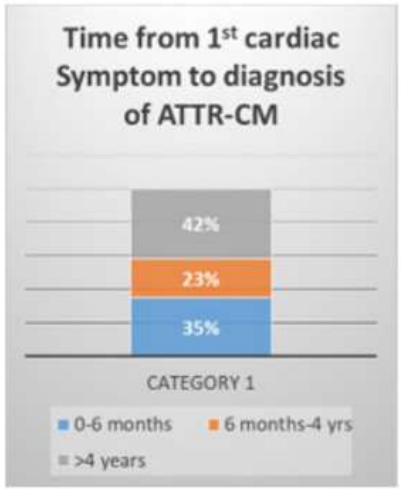
3

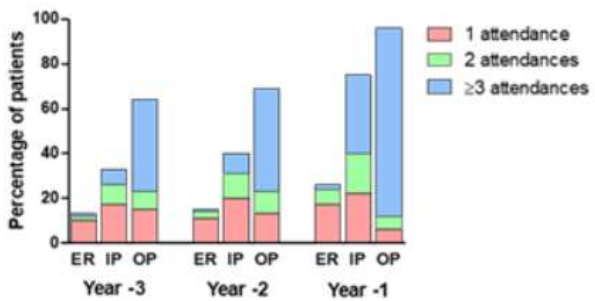
CLINICAL DIAGNOSIS OF DISEASE

ATTR AMYLOIDOSIS

MISDIAGNOSIS & DIAGNOSTIC DELAY

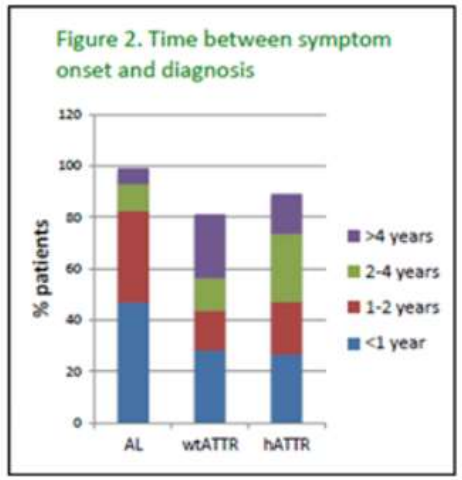
UK





Median 17 hospital attendances prior to diagnosis!
Median 3 hospital IP episodes prior to diagnosis

USA



Italy

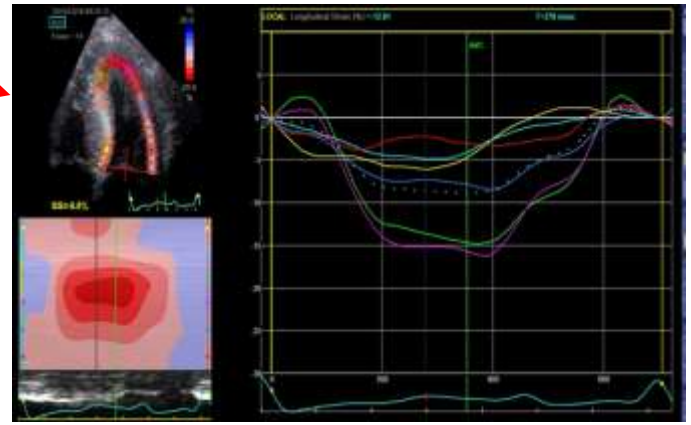
Table 1 Alternative diagnosis for patients with hereditary ATTR amyloidosis and variables associated with misdiagnosis of hereditary ATTR amyloidosis

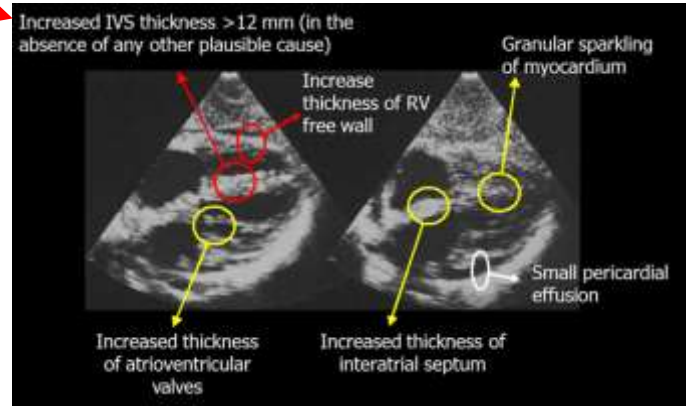
Misdiagnoses			n=49 (%)	
Chronic inflammatory demyelinating polyneuropathy			30 (61)	
Lumbar and sacral radiculopathy and lumbar canal stenosis			11 (22)	
Paraproteinaemic peripheral neuropathy			3 (6)	
AL amyloidosis			3 (6)	
Wild-type ATTR amyloidosis			1 (2)	
Toxic peripheral neuropathy			4 (8)	
Vasculitic peripheral neuropathy			1 (2)	
Motor neuron disease			1 (2)	
Fibromyalgia			2 (4)	
Other diagnosis			2 (4)	
Multiple misdiagnosis			9 (18)	
Variables associated with misdiagnosis of ATTR amyloidosis	**Misdiagnosed patients (n=49) (%)**	**Not misdiagnosed patients (n=101) (%)**	**OR (95% CI)*, p value**	**OR (95% CI)†, p value**
Late onset (after 50 years)	46 (94)	74 (73)	5.59 (1.60 to 19.49), p=0.007	3.89 (1.02 to 14.81), p=0.046
Absence of family history	28 (58)	36 (36)	2.4 (1.19 to 4.83), p=0.01	2.19 (1.01 to 4.89), p=0.049
Male gender	42 (86)	69 (68)	2.78 (1.12 to 6.86), p=0.02	2.67 (1.02 to 6.98), p=0.044
Absence of heart involvement (NYHA<2)	31 (63)	46 (46)	2.05 (1.02 to 4.14), p=0.04	2.60 (1.19 to 5.66), p=0.016
Negative tissue biopsy	14/36 (39)	8/40 (20)	2.5 (0.9 to 7), p=0.08	-

Lane T *et al,* Circulation 2019;140:16-26
Lousada I *et al, JACC* 2018;71:11(Abstract)
Cortese A *et al*, J Neurol Neurosurg Psychiatry 2017;88:457-458

An easier (or at least more linear) life for the cardiologist

- **Reduction in longitudinal strain with apical sparing**
- Discrepancy between left ventricular thickness and QRS voltage (with a lack of left ventricular hypertrophy on EKG)
- Atrioventricular block, in the presence of increased left ventricular wall thickness
- **Echocardiographic hypertrophic phenotype with associated infiltrative features, including increased thickness of the atrioventricular valves, interatrial septum and right ventricular free wall**
- Marked extracellular volume expansion, abnormal nulling time for the myocardium or diffuse late gadolinium enhancement on CMR
- **Symptoms of polyneuropathy and / or dysautonomia**
- **History of bilateral carpal tunnel syndrome**
- Mild increase in troponin levels on repeated occasions





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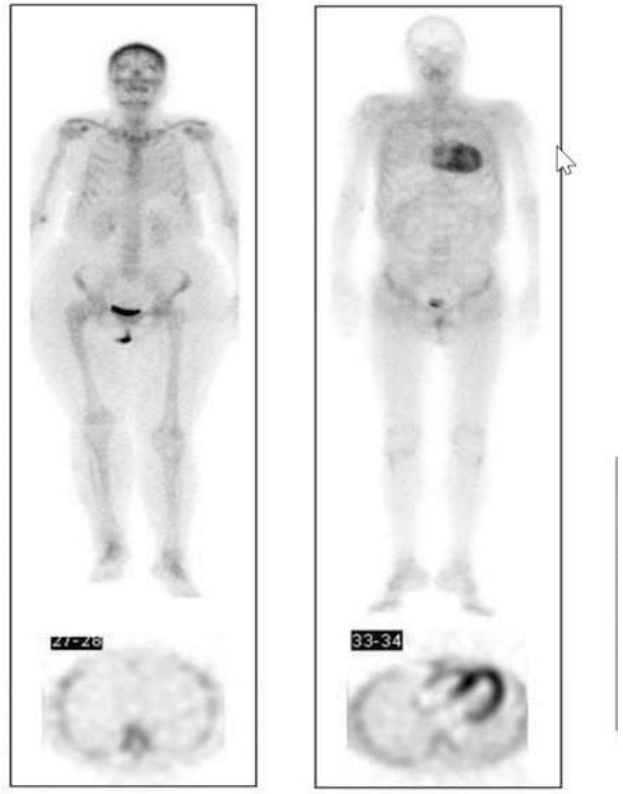
Noninvasive Etiologic Diagnosis of Cardiac Amyloidosis Using ^{99m}Tc-3,3-Diphosphono-1,2-Propanodicarboxylic Acid Scintigraphy



…but for the neurologist?

Red flags currently identified in 2020

Endemic regions

Progressive sensory length dependent polyneuropathy

Autonomic dysfu
(e.g. GI compla
including chronic di
constipation or bo
erectile dysfunction,
postural h

+ ≥1 of the following

Family history of ATTR variant

Unexplained weight loss ≥ 5 kilos

ythm
s

acities

Renal abnormalities

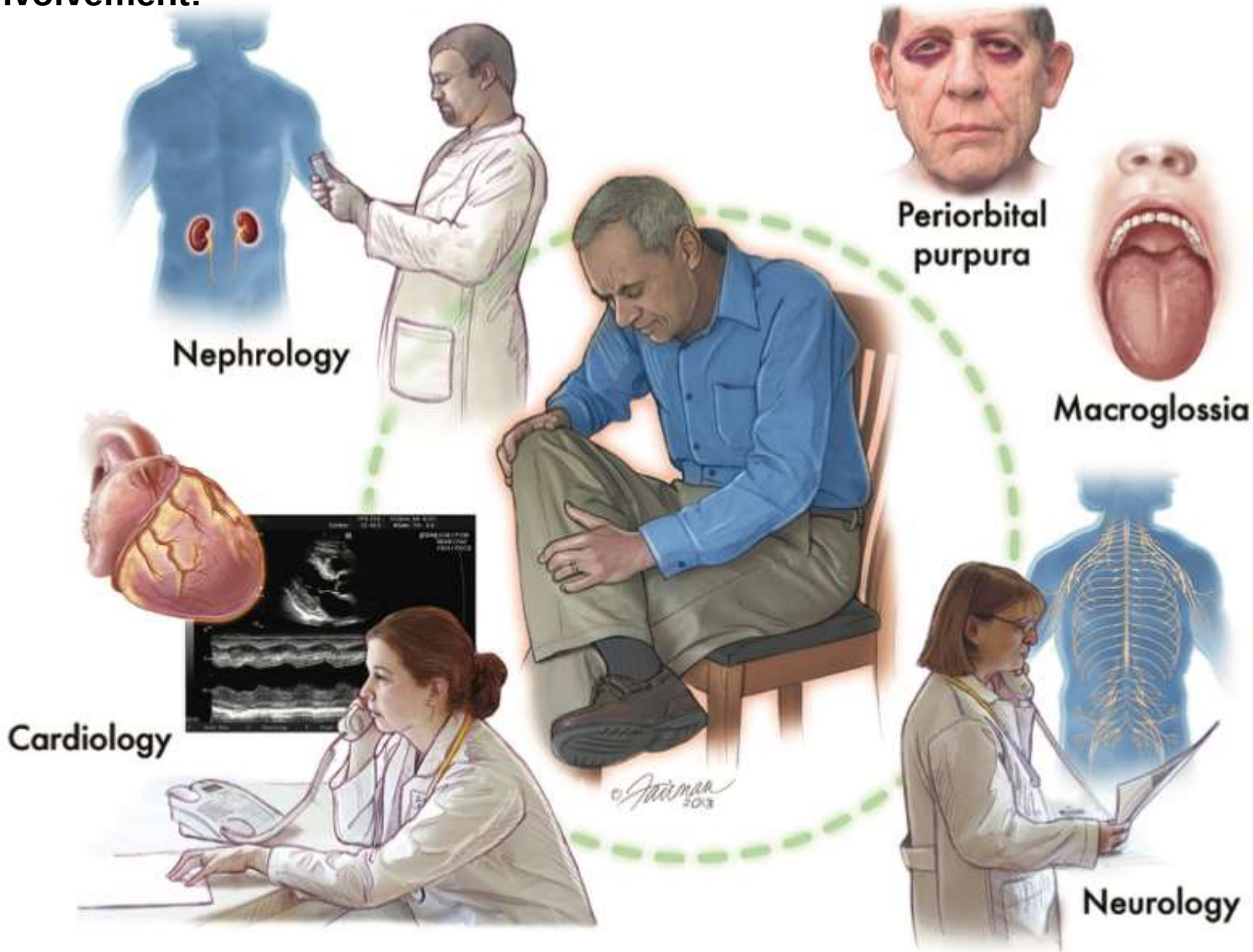
Non-endemic regions

Idiopathy rapidly progressive sensori-motor axonal neuropathy
Or
atypical CIDP

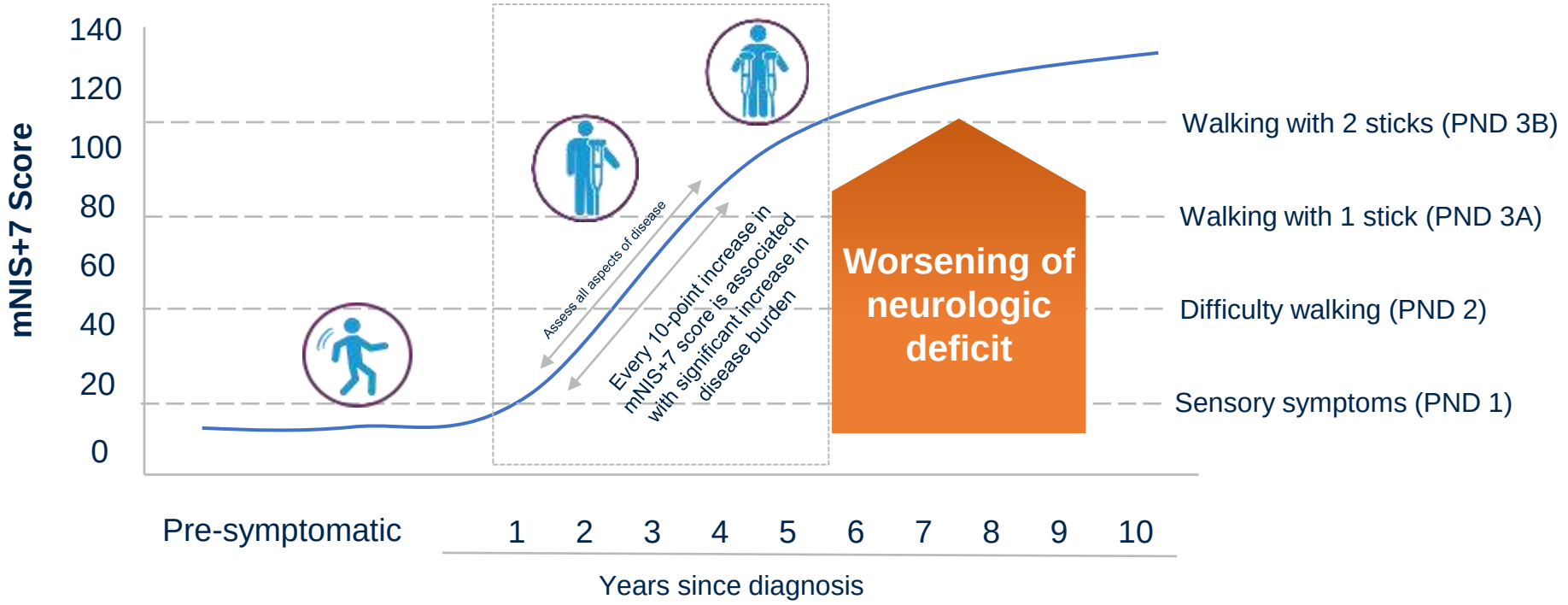
+ ≥1 of the following

- Family history
- Bilateral carpal tunnel syndrome
- Autonomic dysfunction e.g. GI complaints including chronic diarrhea, constipation or both, erectile dysfunction, orthostatic hypotension)
- Gait disorders
- Unexplained weight loss ≥ 5 kilos
- Cardiac hypertrophy Heart rhythm disorders
- Vitreous opacities
- Renal abnormalities

multiistemic involvement!



ATTRvPNP is a rapidly progressive multi-system disease



Corino Andrade (1906–2005)

Figure adapted from Adams D et al. 2015[2]

Natural history studies suggest

- PND stage increases every 12–18 months in patients with hATTR amyloidosis[2]
- Predicted neurologic progression: 14.3 points (NIS) and 17.8 points (mNIS +7) per year for subjects with an NIS score of 32 (typically at 19 months since symptom onset)[2]
- Without treatment, survival ranges between 6 and 12 years from symptom onset (depending on the genotype)[3]

hATTR, hereditary transthyretin amyloidosis; mNIS+7, modified Neuropathy Impairment Score plus 7; PND, polyneuropathy disability score

1. Adams D et al. Nature Rev Neurol 2019;15:387-404; 2. Adams D et al. Neurology 2015;85:675–82; 3. González-Duarte A et al. Neurol Ther 2020;9:135–49.

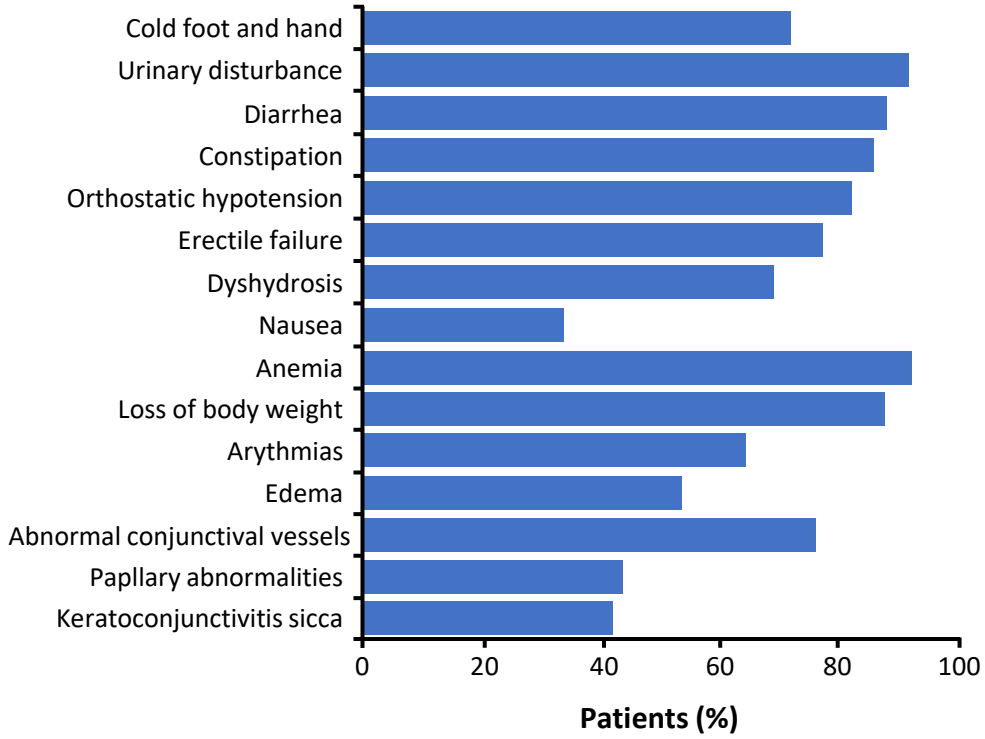
Autonomic dysfunction is a frequent, early, distinctive and disabling aspect of ATTRv!

Dysautonomia is more common in patients with hATTR amyloidosis than in those with AL or AA amyloidosis[1]

Autonomic Symptoms[1]

- Cardiovascular symptoms including orthostatic hypotension
- Gastrointestinal motility disorders
- Pupillomotor and sudomotor (sweat) dysfunction
- Genitourinary symptoms (e.g., neurogenic bladder, sexual dysfunction)

Clinical manifestations of Japanese ATTRv (n=138)[2]



Autonomic nerves are often affected before motor nerve impairment (presenting feature in about 10% of cases)

Gonzalez-Duarte. *Clin Auton Res.* 2019 Apr;29(2):245-251; 2. Ando & Suhr. *Amyloid* 1998;5:288–300

Autonomic dysfunction may vary in…

- **prevalence**:
  - higher in Val30Met mutations and lower in cardiac mutation
  - common in Ser50Arg, Ser52Pro, and Gly47Ala, Thr60Ala and Ser77Tyr.
  - Less prevalent in non-endemic areas

- **Severity:**
  - Severe in early onset, milder in non-endemic areas
  - Moderate in Glu89G and Phe64Leu
  - Severe in Thr49Ala mutation.

- **Timing:**
  - not present in Phe64Leu with new-onset symptoms, but occurred in all patients within 4 years following symptom onset.
  - presenting symptom in 50% of Thr49Ala mutation.
  - Val30Met had the shortest time from the first ATTR amyloidosis-related symptom to the first autonomic symptom, with a mean time from onset of 2.7 years.
  - different autonomic manifestations occur at different times: In early-onset disease, GI dysfunction and OH emerged in the early phase of the disease, whereas urinary manifestations appeared halfway through the course of the disease.

Ando Y (1994) Radiolabelled meta-iodobenzylguanidine in assessment of autonomic dysfunction. Lancet 343(8903):984–985
Ando Y, Suhr O (1998) Autonomic dysfunction in familial amyloidotic polyneuropathy. Amyloid Int J Exp Clin Invest 5:288–300
Delahaye N (2001) Myocardial muscarinic receptor upregulation and normal response to isoproterenol in denervated hearts by familial amyloid polyneuropathy. Circulation 104:2911–2916
Iklasson U (1989) Autonomic neuropathy in familial amyloidotic polyneuropathy. a clinical study based on heart rate variability. Acta Neurol Scand 79:182–187
Loavenbruck AJ (2016) Transthyretin amyloid neuropathy has earlier neural involvement but better prognosis than primary amyloid counterpart, Ann Neurol 80(3):401–411


Head-up tilt test
Valsalva maneuver
Deep breathing
Cold face test
Hand grip test

74% of the patients with ATTRv-wPN enrolled in this study had a cardiovascular autonomic dysfunction

Clinical Autonomic Research
https://doi.org/10.1007/s10286-022-00921-x

RESEARCH ARTICLE

Cardiovascular reflex tests detect autonomic dysfunction in symptomatic and pre-symptomatic subjects with hereditary transthyretin amyloidosis

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Received: 18 September 2022 / Accepted: 27 December 2022

Abstract

Purpose Autonomic dysfunction is a distinctive but undervalued feature of hereditary transthyretin amyloidosis (ATTRv). It may predate the onset of polyneuropathy and cardiomyopathy, thereby providing crucial prognostic and therapeutic information. The objective of this study was to assess autonomic function by means of the standardized cardiovascular autonomic reflex tests (CRTs) in a cohort of subjects with genetically proven ATTRv from non-endemic areas who were in the symptomatic and pre-symptomatic stages.

Methods All subjects enrolled in this cross-sectional study had genetically proven ATTRv. They underwent the head-up tilt test, Valsalva manoeuvre, deep breathing test, cold face test and handgrip test while under continuous blood pressure and heart rate monitoring. Based on the results of the nerve conduction study, the subjects were divided into two groups: those with polyneuropathy (ATTRv-wPN) and those without polyneuropathy (ATTRv-woPN). Age- and sex-matched healthy controls (HC) were used for comparison.

Results Thirty-seven ATTRv subjects (19 with ATTRv-wPN, 18 with ATTRv-woPN) and 41 HC performed the CRTs. Of these 37 subjects with ATTRv, four (11%) presented neurogenic orthostatic hypotension the during head-up tilt test. Based on the results of the CRTs, autonomic dysfunction characterized by either sympathetic or parasympathetic impairment was detected in 37% and 63% of ATTRv-wPN subjects, respectively. Subjects with ATTRv-woPN presented a significant impairment of autonomic responses to the Valsalva manoeuvre compared to the HC (overshoot $p=0.004$; Valsalva ratio $p=0.001$).

Conclusion Autonomic dysfunctions are frequent in subjects with ATTRv when investigated by means of standardized CRTs, and are also relevant in the pre-symptomatic stage. Cardiovagal functions are the primary functions affected, among others. This may be crucial in defining the proper diagnostic workout for early diagnosis and improving the likelihood of providing the patient with prompt administration of disease-modifying treatments.

Keywords Hereditary transthyretin amyloidosis · Autonomic dysfunction · Dysautonomia · Cardiovascular reflex tests · Familial amyloidotic polyneuropathy

37 ATTRv subjects (19 with ATTRv-wPN, 18 with ATTRv-woPN

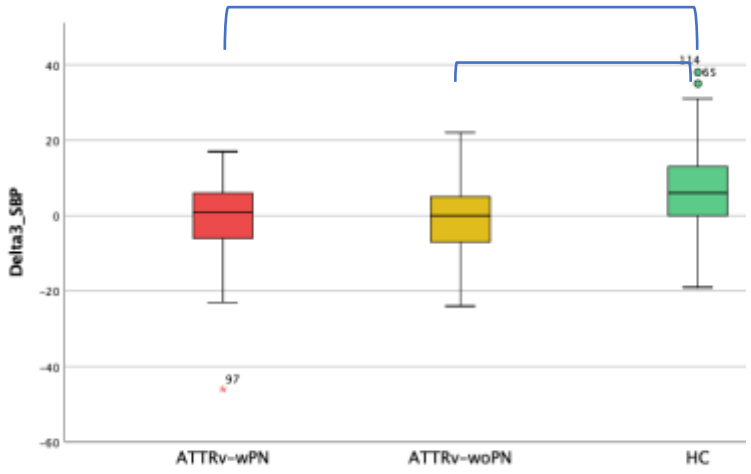
Cardiovascular reflex tests	ATTRv-wPN	ATTRv-woPN	HC	*p* value
Supine rest SPB (mmHg)	132 ± 25	128 ± 18	128 ± 16	0.927
Supine rest DBP (mmHg)	68 ± 9	66 ± 8	68 ± 8	0.891
Supine rest HR (bpm)	65 ± 24	63 ± 25	65 ± 8	0.186
Head-up tilt test				
Δ SBP (mmHg)	4 ± 23	17 ± 18	5 ± 10	0.141
Δ DBP (mmHg)	10 ± 20	18 ± 17*	7 ± 6	0.086
Δ HR (bpm)	3 ± 5*	8 ± 8	12 ± 7	< 0.001
Valsalva manoeuvre				
Valsalva ratio	1.16 ± 0.23*#	1.45 ± 0.35*	1.84 ± 0.33	< 0.001
Δ BP IIb-IIa	9 ± 11*	12 ± 9	17 ± 12	0.028
Δ BP IV (mmHg)	13 ± 21*#	31 ± 27*	43 ± 16	< 0.001
Deep breathing				
Δ IE (bpm)	7 ± 5*#	14 ± 9	17 ± 7	< 0.001
I/E ratio	1.12 ± 0.15*#	1.34 ± 0.30	1.28 ± 0.14	< 0.001
Cold face				
Δ SBP (mmHg)	19 ± 16*	23 ± 15	30 ± 18	0.048
Δ DBP (mmHg)	11 ± 10	18 ± 18	17 ± 14	0.199
Δ HR (bpm)	− 4 ± 6*	− 6 ± 6*	− 10 ± 6	0.007
Handgrip				
Δ SBP (mmHg)	20 ± 10*	26 ± 17	33 ± 17	0.013
Δ DBP (mmHg)	10 ± 5*	15 ± 10	17 ± 10	0.045
Δ HR (bpm)	4 ± 3*	6 ± 8*	14 ± 8	< 0.001

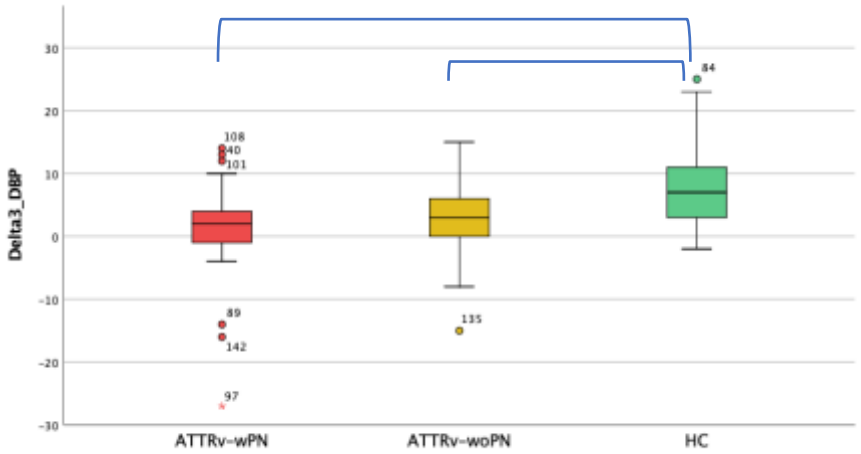
Data are expressed as the mean ± SD

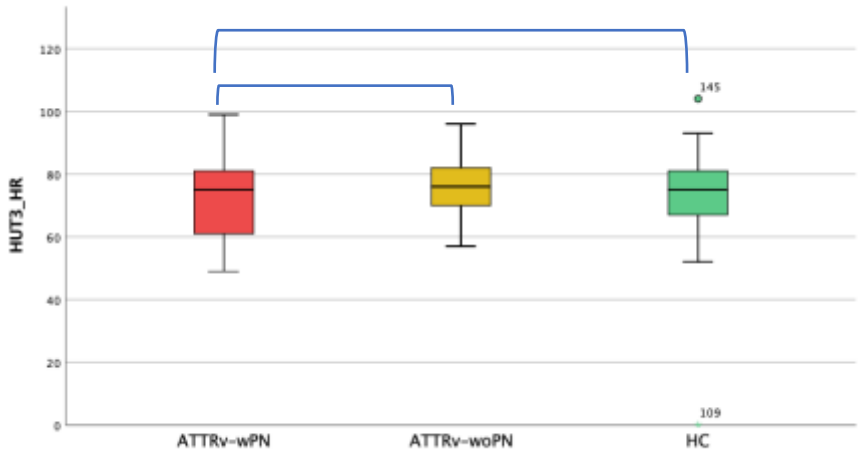
Asymptomatic carriers, may present **alterations that could represent the first signs of disease**

85 ATTRv subjects (35 ATTRv-wPN + 50 ATTRv-woPN) / 65 HCs

Head-up Tilt





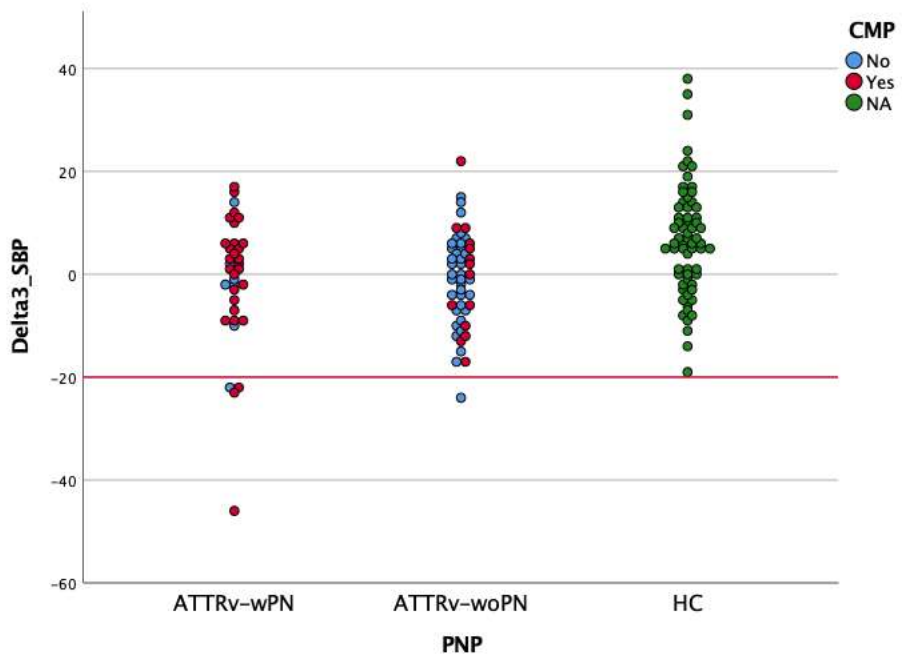


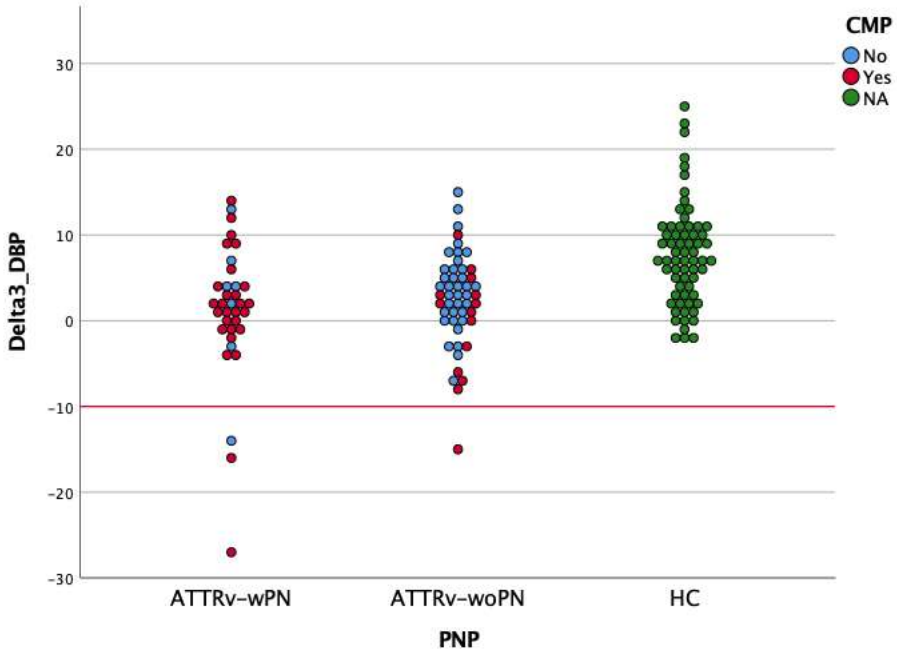
	ATTRv-wPN (n°35)	ATTRv-woPN (n°50)	HC (n°65)	p Value
Δ SBP (mmHg)	-1 ± 13*	-1 ± 9*	7 ± 11	<0.001
Δ DBP (mmHg)	1 ± 8*	3 ± 6*	8 ± 6	<0.001
Δ HR (bpm)	6 ± 6 *§	10 ± 7	11 ± 7	<0.003

Guaraldi P et al., In preparation

85 ATTRv subjects (35 ATTRv-wPN + 50 ATTRv-woPN) / 65 HCs

Head-up Tilt



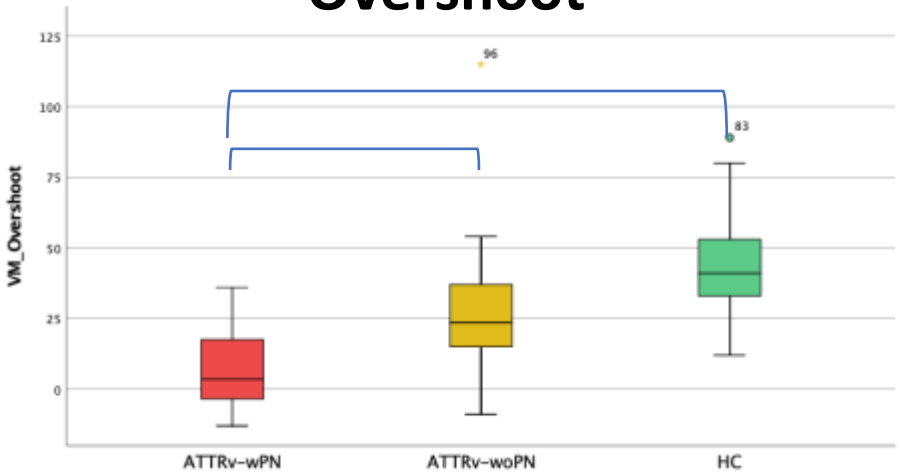


Guaraldi P et al., In preparation

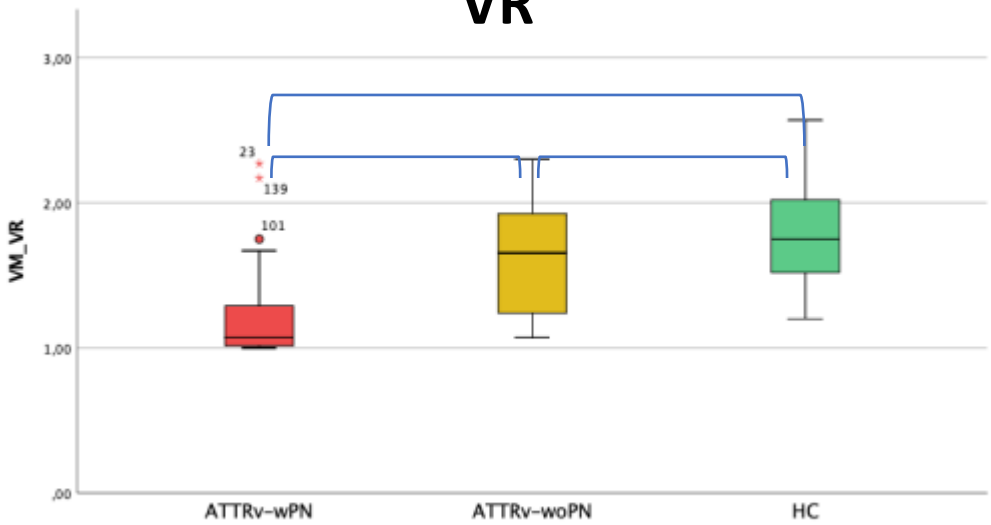
85 ATTRv subjects (35 ATTRv-wPN + 50 ATTRv-woPN) / 65 HCs

Valsalva Manoevure

Overshoot



VR



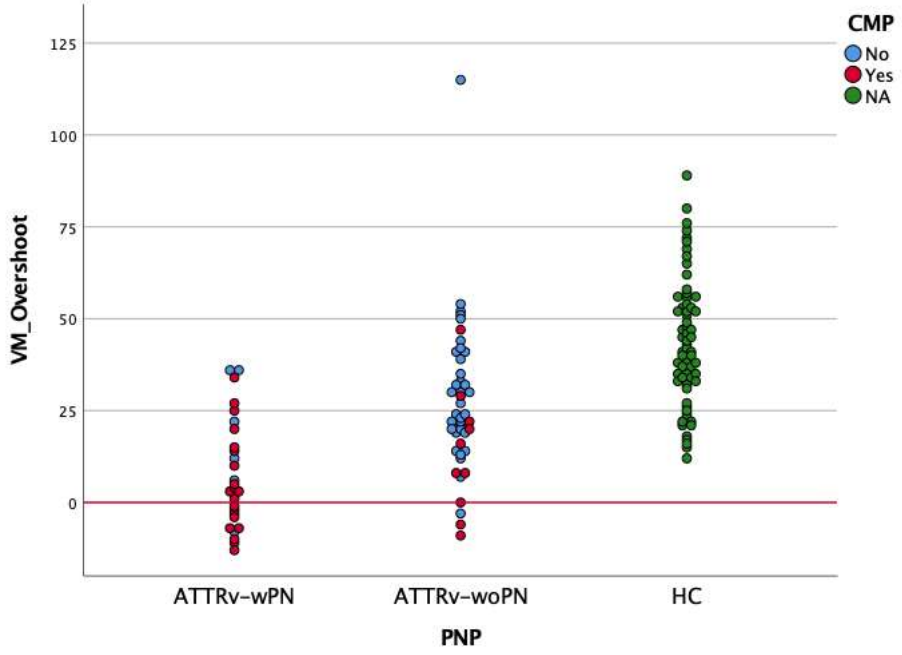
	ATTRv-wPN (n°35)	ATTRv-woPN (n°50)	HC (n°65)	p Value
VR	1.24 ± 0.35 *§	1.6 ± 0.37	1.78 ± 0.34	<0.001
Δ BP IV (mmHg)	7 ± 15 *§	27 ± 21*	43 ± 17	<0.001

Guaraldi P et al., In preparation

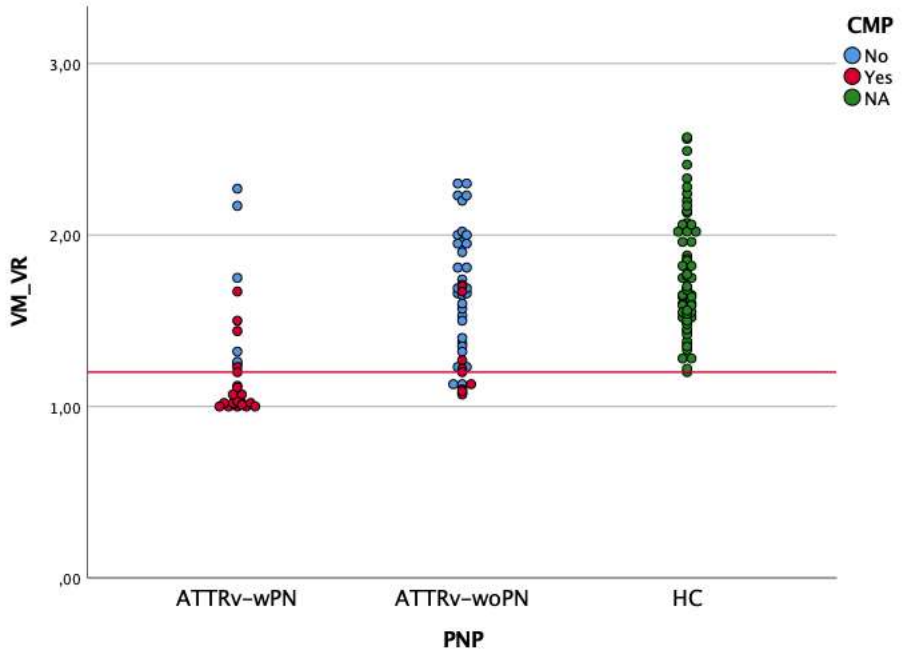
85 ATTRv subjects (35 ATTRv-wPN + 50 ATTRv-woPN) / 65 HCs

Valsalva Manoevure

Overshoot



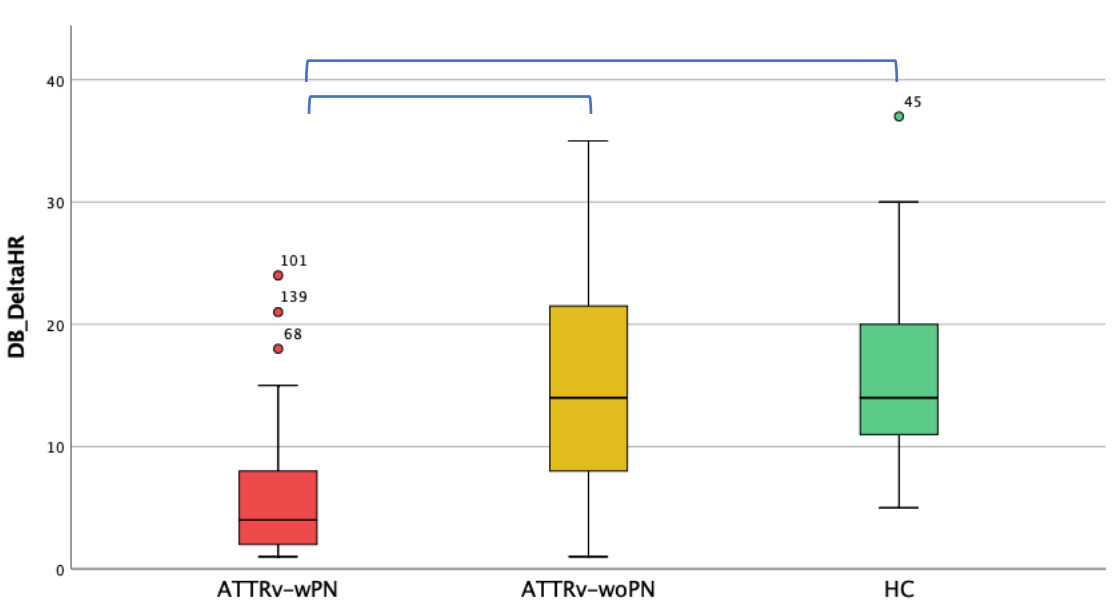
VR

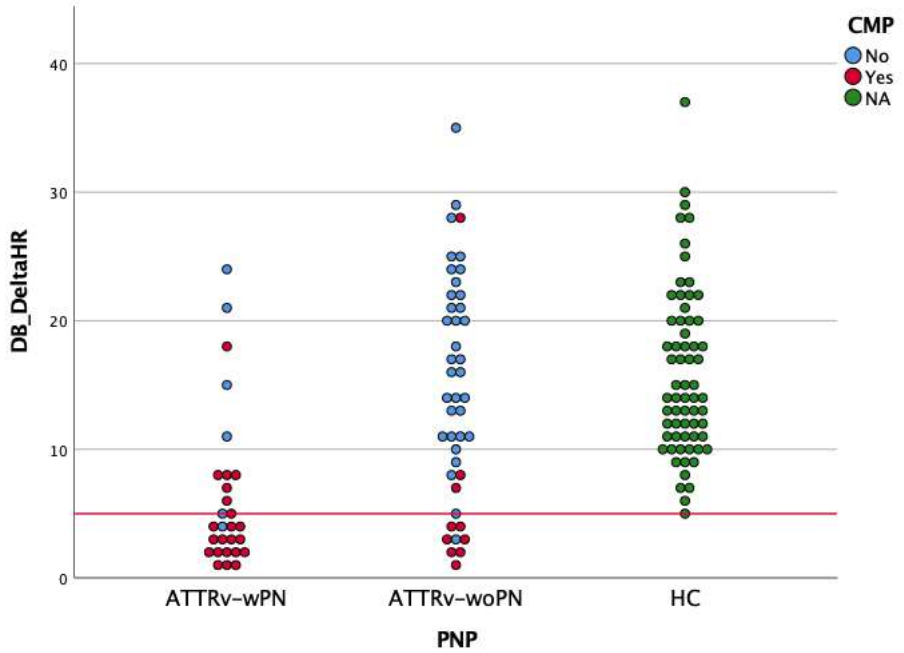


Guaraldi P et al., In preparation

85 ATTRv subjects (35 ATTRv-wPN + 50 ATTRv-woPN) / 65 HCs

Deep Breathing





	ATTRv-wPN (n°35)	ATTRv-woPN (n°50)	HC (n°65)	p Value
Δ IE (bpm)	6 ± 6*§	15 ± 9	16 ± 7	<0.001

Guaraldi P et al., In preparation

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RESEARCH ARTICLE

Cardiovascular autonomic failure in hereditary transthyretin amyloidosis and *TTR* carriers is an early and progressive disease marker

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Abstract

Background The cardiomyopathic and neuropathic phenotype of hereditary transthyretin amyloidosis are well recognized. Cardiovascular autonomic dysfunction is less systematically and objectively assessed.

Methods Autonomic and clinical features, quantitative cardiovascular autonomic function, and potential autonomic prognostic markers of disease progression were recorded in a cohort of individuals with hereditary transthyretin amyloidosis and in asymptomatic carriers of *TTR* variants at disease onset (T0) and at the time of the first quantitative autonomic assessment (T1). The severity of peripheral neuropathy and its progression was stratified with the polyneuropathy disability score.

Results A total of 124 individuals were included (111 with a confirmed diagnosis of hereditary transthyretin amyloidosis, and 13 asymptomatic carriers of *TTR* variants). Symptoms of autonomic dysfunction were reported by 27% individuals at T0. Disease duration was 4.5 ± 4.0 years [mean ± standard deviation (SD)] at autonomic testing (T1). Symptoms of autonomic dysfunction were reported by 78% individuals at T1. Cardiovascular autonomic failure was detected by functional testing in 75% individuals and in 64% of *TTR* carriers. Progression rate from polyneuropathy disability stages I/II to III/IV seemed to be shorter for individuals with autonomic symptoms at onset [2.33 ± 0.56 versus 4.00 ± 0.69 years (mean ± SD)].

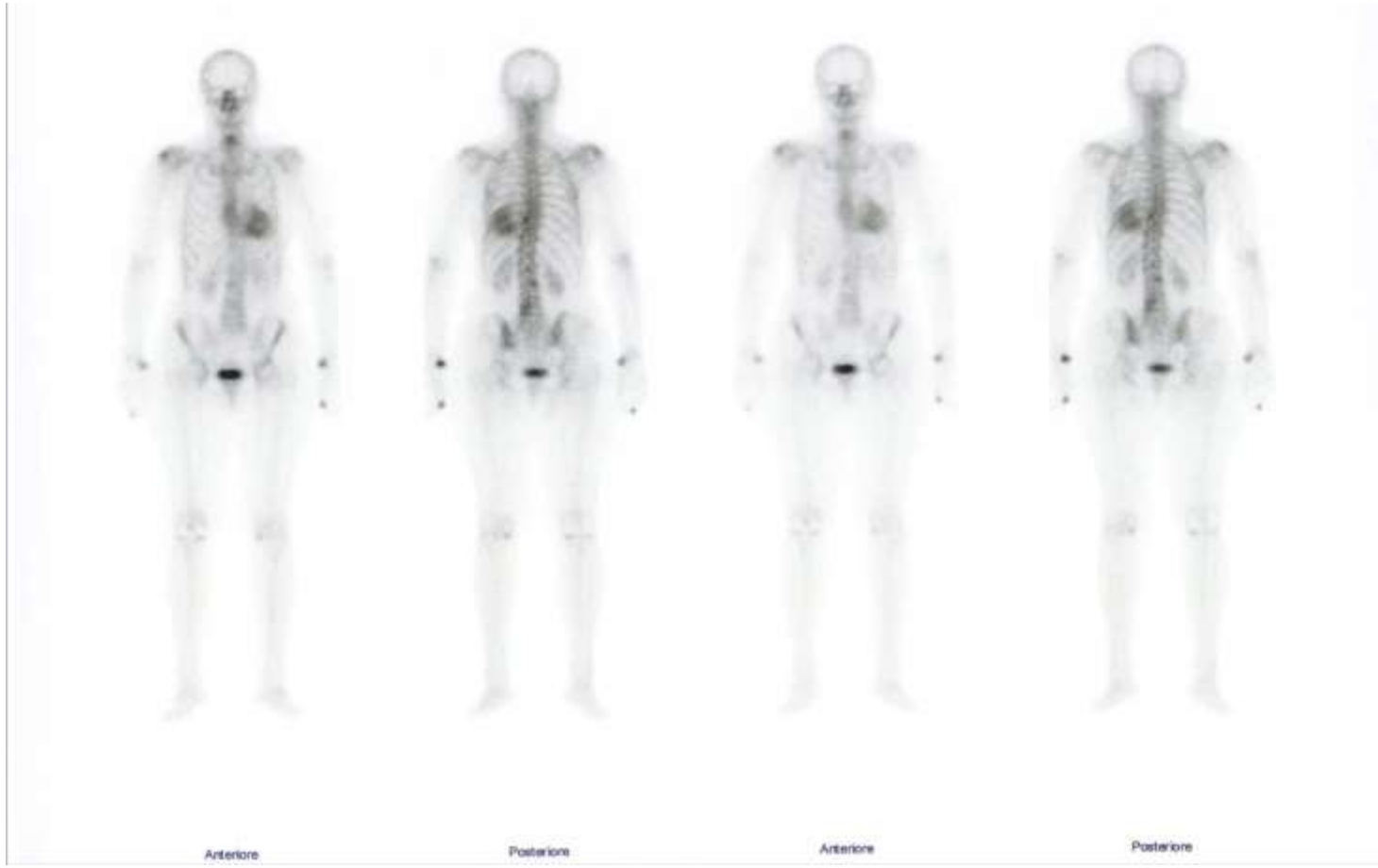
Conclusions Cardiovascular autonomic dysfunction occurs early and frequently in individuals with hereditary transthyretin amyloidosis within 4.5 years from disease onset. Cardiovascular autonomic failure can be subclinical in individuals and asymptomatic carriers, and only detected with autonomic function testing, which should be considered a potential biomarker for early diagnosis and disease progression.

Keywords ATTRv amyloidosis · Cardiovascular autonomic failure · Autonomic function testing · TTR carriers · Disease-modifying treatment

L.O. ♀1942

- Ipertensione arteriosa, ipercolesterolemia, ex fumatrice.
- Intolleranze a vari farmaci (mialgie).
- Rizoartrosi e pregresso intervento per tunnel carpale dx.
- Nel 2001 intervento per ernia discale cervicale.
- Nel 2005 stent carotideo sinistro.
- Nel 2013 clipping per aneurisma intatto della ACoA (riscontro accidentale durante RM eseguita per sndr vertiginosa)
- Artroprotesi al ginocchio destro gennaio 2017 per frattura rotula omolaterale evoluta in pseudoartrosi.

2019: sospetta mobilizzazione PTG



L’esame scitigrafico NON è indicativo di mobilizzazione di protesi di ginocchio dx ma come reperto collaterale si segnala diffuso iperaccumolo del tracciante a livello cardiaco

2019: v cardiologica

ECG

- RS
- FC: 68 b/m
- Scarsa progressione onda R
- IVSn

ECO-CUORE

- SIV TD 17 mm
- PP TD 14 mm
- FE 60 %
- lieve versamento pericardico.

- **Cardiopatia ipertofico-ipertensiva**, in base a Scintigrafia, Eco e ECG si pone il sospetto di **amiloidosi cardiaca in paziente asintomatica**
- Si richiede RM cardiaca

2019: RM CUORE CON MDC

- Vsn TD 48 mm Volume TDV s 110 ml (v.n. 82-174 ml)
- SIV TD 17 mm Volume TS Vsn 70 ml (v.n. 16-64 ml)
- PP TS 17 mm
- EF 83%
- Cardiomiopatia ipertrofica concentrica con obliterazione sistolica medio-apicale del ventricolo sinistro ipercinetico
- Versamento pericardico lieve
- **Quadro compatibile con cardiomiopatia infiltrativa di origine amiloide**

MOD-002-UOGMMol
Ferrara, 18.08 2020

LABORATORIO DI GENETICA MOLECOLARE

ANALISI MOLECOLARE DEL GENE TRANSTIRETINA (TTR, MIM *176300)

[redacted]

Indicazione all'esame: possibile amiloidosi TTR-relata

Metodiche utilizzate: SEQUENZIAMENTO DIRETTO (ABI PRISM 3130)
Sensibilità e specificità analitiche > 99%

Regioni geniche esplorate (Numero di accesso GenBank NG_009490.1, NM_000371.3)
Intera regione codificante e regioni fiancheggianti introniche

RISULTATO
Esone 2: variazione di sequenza nucleotidica in eterozigosi c.148G>A, corrispondente alla mutazione p.Val50Met (Val30Met).
Tipo di mutazione:
-missenso

CONCLUSIONI
Genotipo eterozigote per la mutazione p.Val50Met (Val30Met) nel gene TTR.
E' appropriata consulenza genetica
La sensibilità diagnostica è 99%

Biologo Dirigente
Dr.ssa Paola Rimessi

Biologo Dirigente
Dr.ssa Anna Venturoli

Si sottolinea l'appropriatezza della consulenza genetica per l'interpretazione dei test genetici

2020 (77a): v neurologica

- *Lamenta disestesie ai 4 arti e ipoestesia tattile e termodolorifica distale*; stipsi e oliguria.
- Ha eseguito una EMG arti inferiori l'11/2/19: nella norma i parametri di conduzione.
- EON: lieve ipostenia di prensione delle mani; *ipoestesia ai piedi; ROT stiloradiali, cubitopronatori assenti; achilleo sinistro assente, torpido a destra;* patellare destro torpido; *ipopallestesia arti inferiori.*Marcia lievemente difficoltosa in tandem.
- Conclusioni: **Possibile polineuropatia sensitiva**.

2020: ENG

Dati motoria									
Nervo	Lat ms	Amp mV	VCM m/s	Distanza mm	Diff Amp %	Area mV*ms	Diff Area %	durata ms	Int Stim mA
Medianus Motoria Destra									
Wrist - APB	3.75	7.5				27.5		16.8	51.8
Elbow-Wrist	7.44	7.2	51.5	190	-4.0	27.4	-0.36	21.5	51.8
Peroneus Motoria Sinistra									
Ankle - EDB	4.11	7.6				28.9		13.7	50.8
Bl. knee-Ankle	11.2	7.2	42.7	303	-5.3	28.4	-1.73	23.8	50.8
Peroneus Motoria Destra									
Ankle - EDB	3.80	4.4				16.6		11.9	99.0
Bl. knee-Ankle	11.3	4.1	41.1	308	-6.8	20.1	21.1	27.1	99.0
Tibialis Motoria Sinistra									
Ankle - Abd hal	4.22	8.6				21.9		13.1	58.6
Knee-Ankle	12.8	7.7	41.7	358	-10.5	22.1	0.91	20.2	99.0
Tibialis Motoria Destra									
Ankle - Abd hal	3.74	8.2				22.8		15.2	64.2
Knee-Ankle	12.3	6.4	44.4	380	-22.0	24.1	5.7	34.7	99.0
Ulnaris Motoria Destra									
Wrist - ADM	3.04	10.5				40.9		18.2	37.6
Bl. elbow-Wrist	6.35	10.2	58.9	195	-2.9	41.3	0.98	19.5	37.6

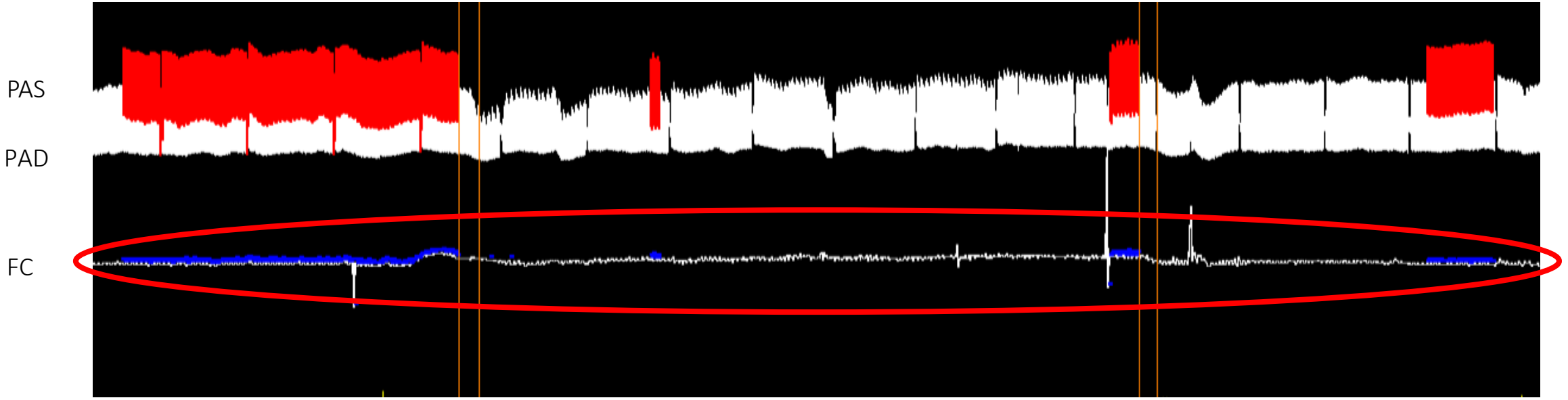
Dati sensitiva				
Nervo	Lat ms	Amp uV	VCS m/s	Distanza mm
- Sensitiva Destra				
I RAD - -	3.04	10.9	56.8	130
III MED - -	3.44	26.8	49.3	134
III MED gom - -	7.33	7.0	--	
V ULN - -	2.85	18.6	62.8	130
III MED - -			49.6	134
V ULN - -			61.9	130
III MED gom-III MED			60.7	193
Suralis Sensitiva Sinistra				
Mid. lower leg - Lat. Malleolus	4.25	15.6	42.0	145
Mid. lower leg - Lat. Malleolus			41.4	145
Suralis Sensitiva Destra				
Mid. lower leg - Lat. Malleolus	3.94	16.4	42.3	135
Mid. lower leg - Lat. Malleolus			42.2	135

Nella norma le conduzioni sensitive

Nella norma le conduzioni motorie

Conclusioni:Quadro neurofisiologico esaminato ai limiti di norma, non segni di neuropatia

2021: Tilt test

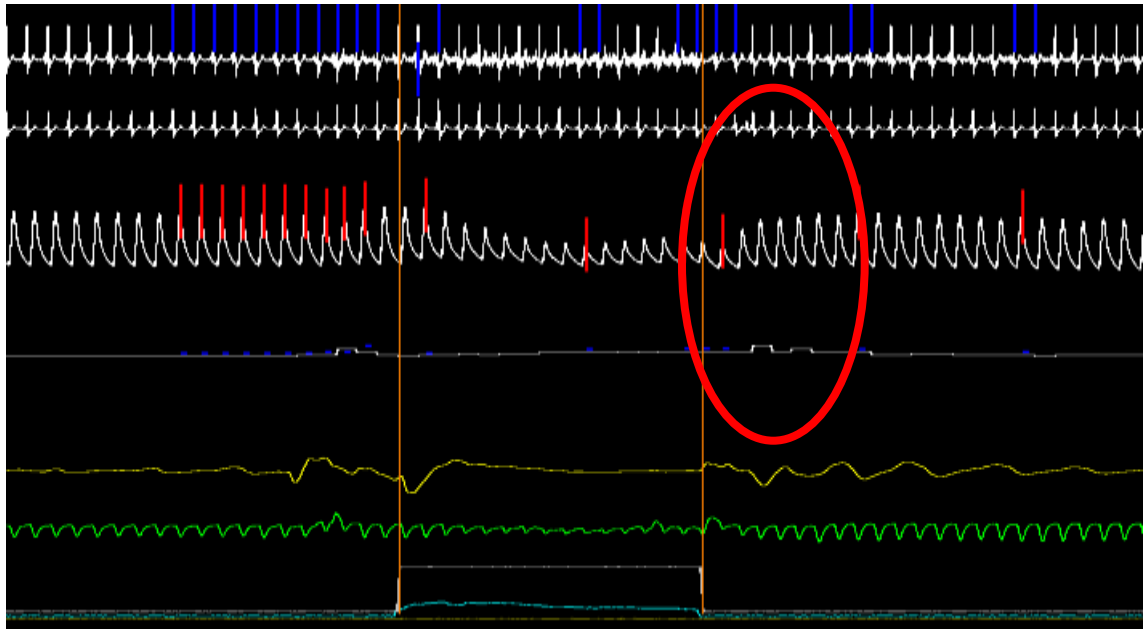


	PAS (mmHg)	*PAD (mmHg)*	*FC (bpm)*
Base	203	85	57
3' min	194	86	59
Delta 3'	-9	**1**	2
10 min : 5 s	217	95	61
Delta last	**14**	**10**	**4**
Post 5'	217	89	56
RR30/RR15 = 1,045			

Commento: nella norma

- Ipertensione arteriosa a riposo.
- Assenza di ipotensione ortostatica

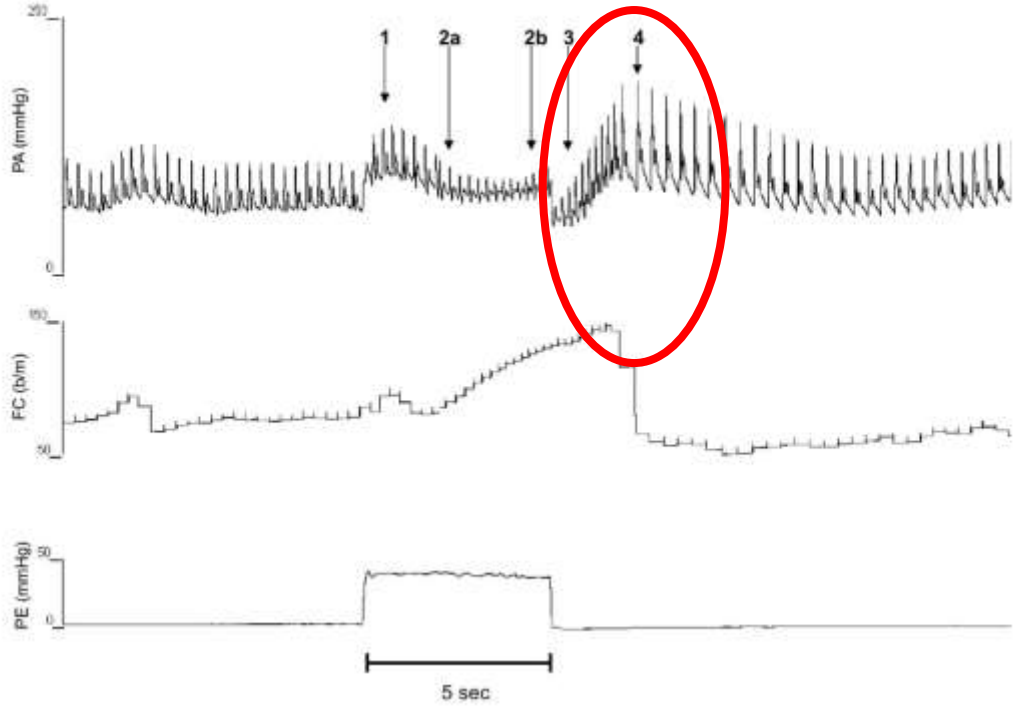
2021: manovra di Valsalva



Manovra di VALSALVA 2 (40 mmHg x 15 s)

	Base	*I*	*IIa*	*IIb*	*III*	*IV*
PAS (mmHg)	209	225	136	157	143	208
PAD (mmHg)	87	102	87	94	81	87
FC (bpm)	56	54	57	59	58	56
Time (s)		1,4	9,9	15,0	1,1	8,2

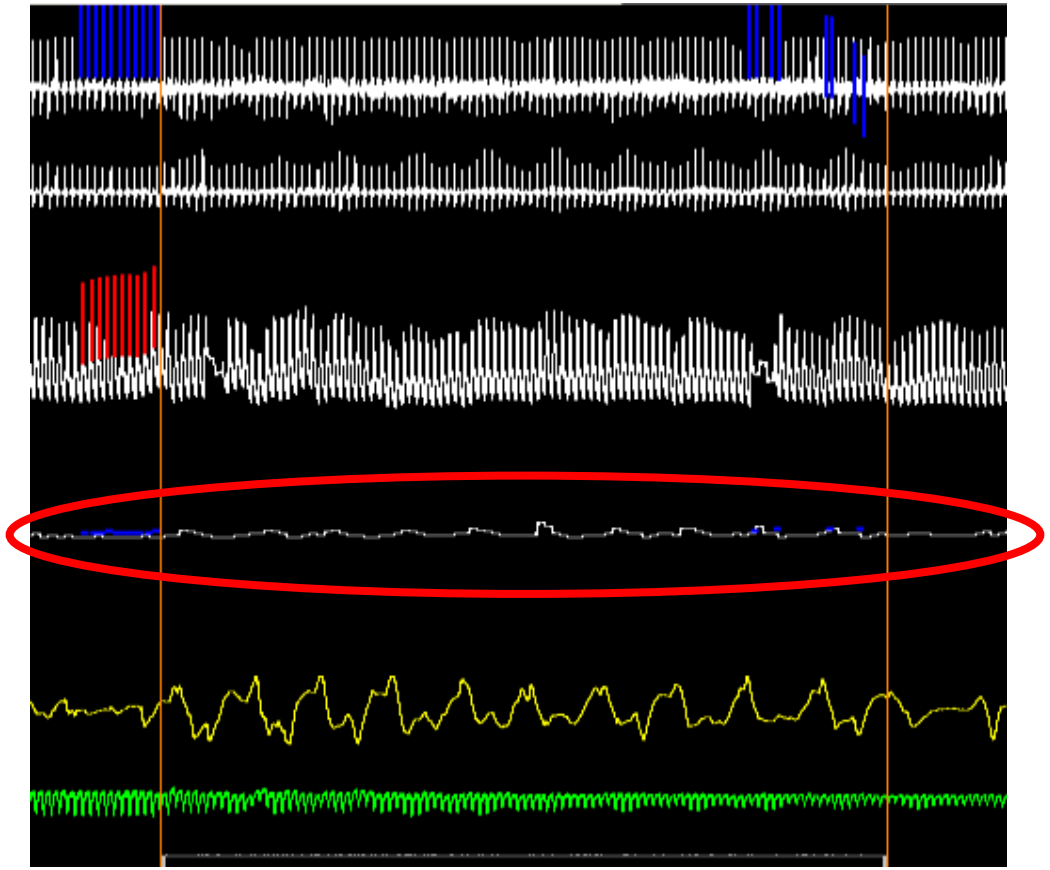
Overshoot: assente - VR: 1,07 - Max bradi: 55 bpm a 16,9 s

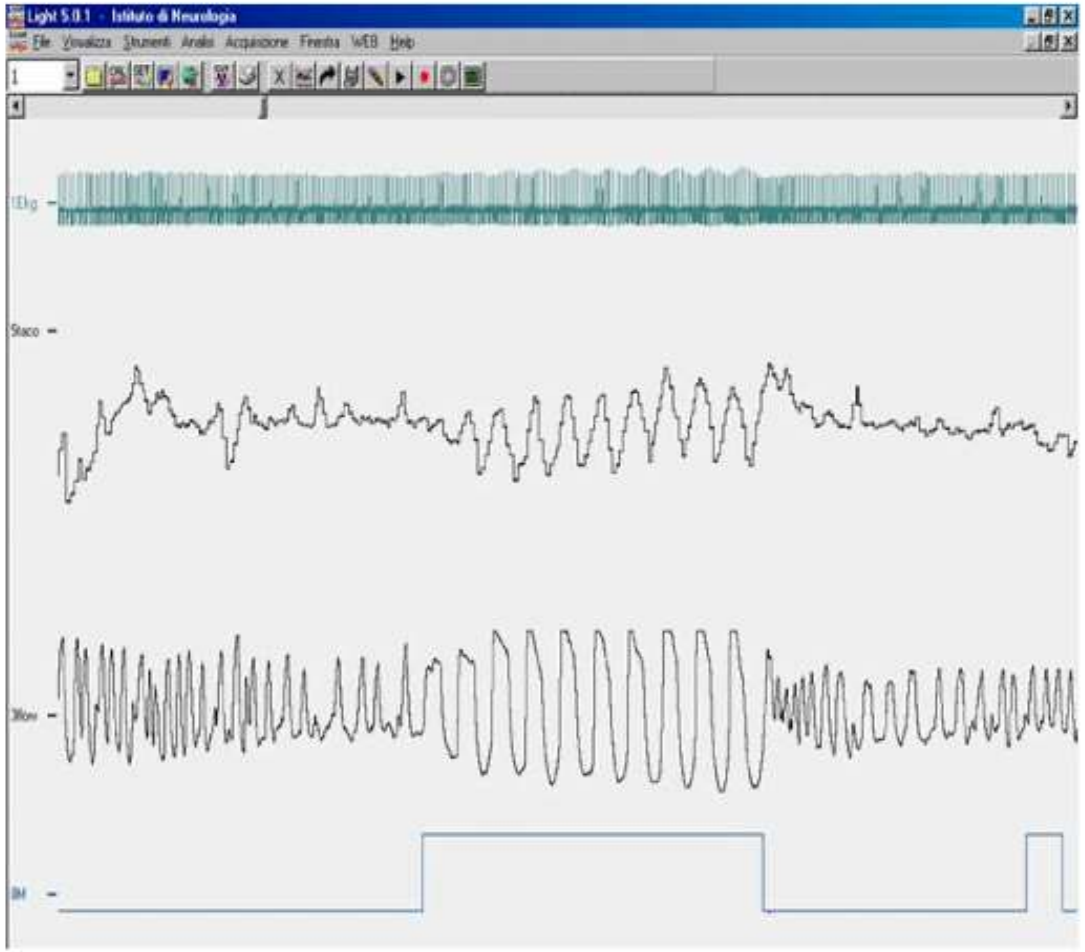


Manovra di Valsalva patologica per assenza di overshoot e VR ridotto.

2021: respiro profondo

CNT





RESPIRO PROFONDO 1 - (6 atti al minuto)

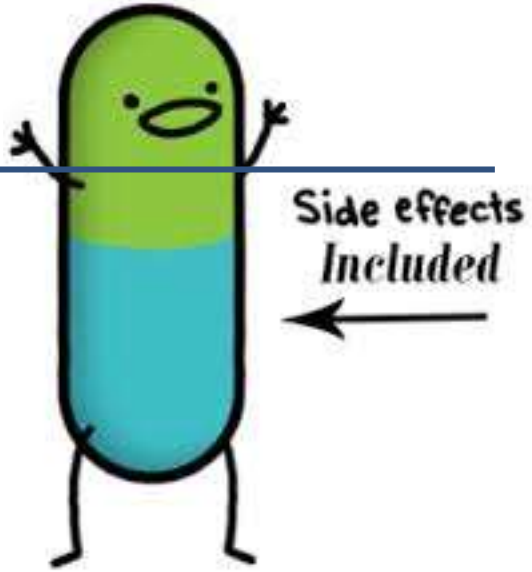
	Base	I	E	Delta (I-E)	I/E	Delta %
FC (bpm)	55	60	55	5	1,09	2,58

Ridotta aritmia respiratoria

Aprile 2021

- FAP 1,
- NIS: 16
- Norfolk 82
- Karnofsky: 90%
- PLT: 289
- **inizia inotersen**

…scarsa tollerabilità



- 30/4 (1°somministrazione)>> dolori diffusi con allodinia temperatura >38 per 48h.
- 7/5 e 14/5: Non complicazioni
- 21/5 (4° somministrazione) >> intenso dolore a tutto li rachide, capogiro successiva comparsa di reazione eritematosa con ponfo nella sede di iniezione.
- Pausa
- 11/6 (5° somministrazione) >> edema e prurito intenso

GIUGNO 2021

STOP INOTERSEN >> TAFAMIDIS 20

Gennaio 2022: ENG (6 mesi dopo Tafamidis)

Dati motoria Nervo	Lat ms	Amp mV	VCM m/s	Distanza mm	Diff Amp %	Area mV*ms	Diff Area %	durata ms	Int Stim mA
Peroneus Motoria Sinistra									
Ankle - EDB	5.46	8.2				30.6		15.3	99.0
Bl. knee-Ankle	11.7	7.4	43.6	272	-9.8	28.6	-6.5	16.6	98.8
Peroneus Motoria Destra									
Ankle - EDB	5.26	7.2				30.9		17.1	98.8
Bl. knee-Ankle	12.5	7.6	40.6	294	5.6	34.0	10.0	17.2	99.0
Tibialis Motoria Sinistra									
Ankle - Abd hal	3.10	10.4				25.7		10.8	99.0
Knee-Ankle	12.0	7.6	42.1	375	-26.9	27.6	7.4	17.4	99.0
Tibialis Motoria Destra									
Ankle - Abd hal	3.84	10.1				27.0		12.2	99.0
Knee-Ankle	12.7	8.1	41.5	368	-19.8	29.3	8.5	19.6	99.0

Dati sensitiva Nervo	Lat ms	Amp uV	VCS m/s	Distanza mm
Suralis Sensitiva Sinistra				
Mid. lower leg - Lat. Malleolus	4.60	16.7	37.2	140
Mid. lower leg - Lat. Malleolus			36.8	140
Suralis Sensitiva Destra				
Mid. lower leg - Lat. Malleolus	4.50	18.8	38.1	140
Mid. lower leg - Lat. Malleolus			37.8	140

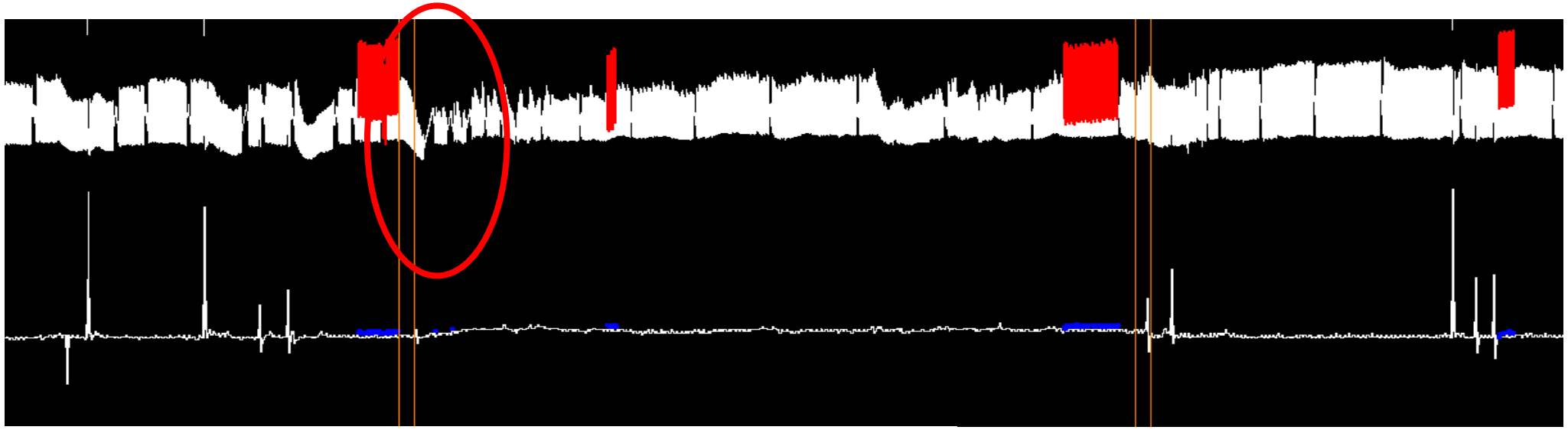
n.surale destro e sinistro: SAP di ampiezza regolare e latenza lievemente aumentata con VCS lievemente ridotta

Gennaio 2022:

- FAP 1,
- NIS: 27 (+11)
- Norfolk 66
- Karnofsky: 90%

- Buone condizioni di compenso cardiovascolare ad interessamento cardiaco e neurologico, in terapia con Tafamidis 20 mg/die.
- In anamnesi, non si segnalano ricoveri per scompenso cardiaco congestizio.
- Attualmente, non sintomi riferibili a cardiomiopatia.
- Si consiglia prosecuzione della terapia in atto

2022: Tilt test

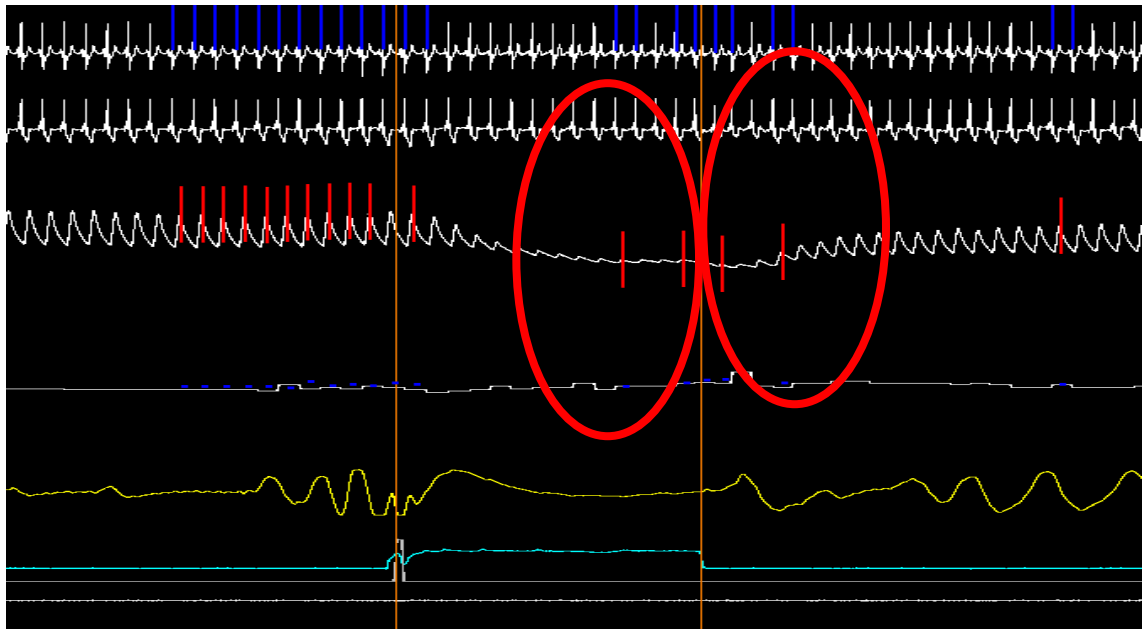


TILT 1 (65° - 10 min)

	PAS (mmHg)	*PAD (mmHg)*	*FC (bpm)*
Base	162	80	56
3' min	151	79	60
Delta 3'	**-11**	**-1**	**4**
10 min : 7 s	162	82	60
Delta last	**0**	**3**	**4**
Post 5'	181	81	57
RR30/RR15 = 0,953			

assenza di ipotensione ortostatica
Rispetto alla precedente esame del 2021 si segnala ipotensione ortostica transitoria iniziale

2022: manovra di Valsalva



Manovra di VALSALVA 1 (40 mmHg x 15 s)

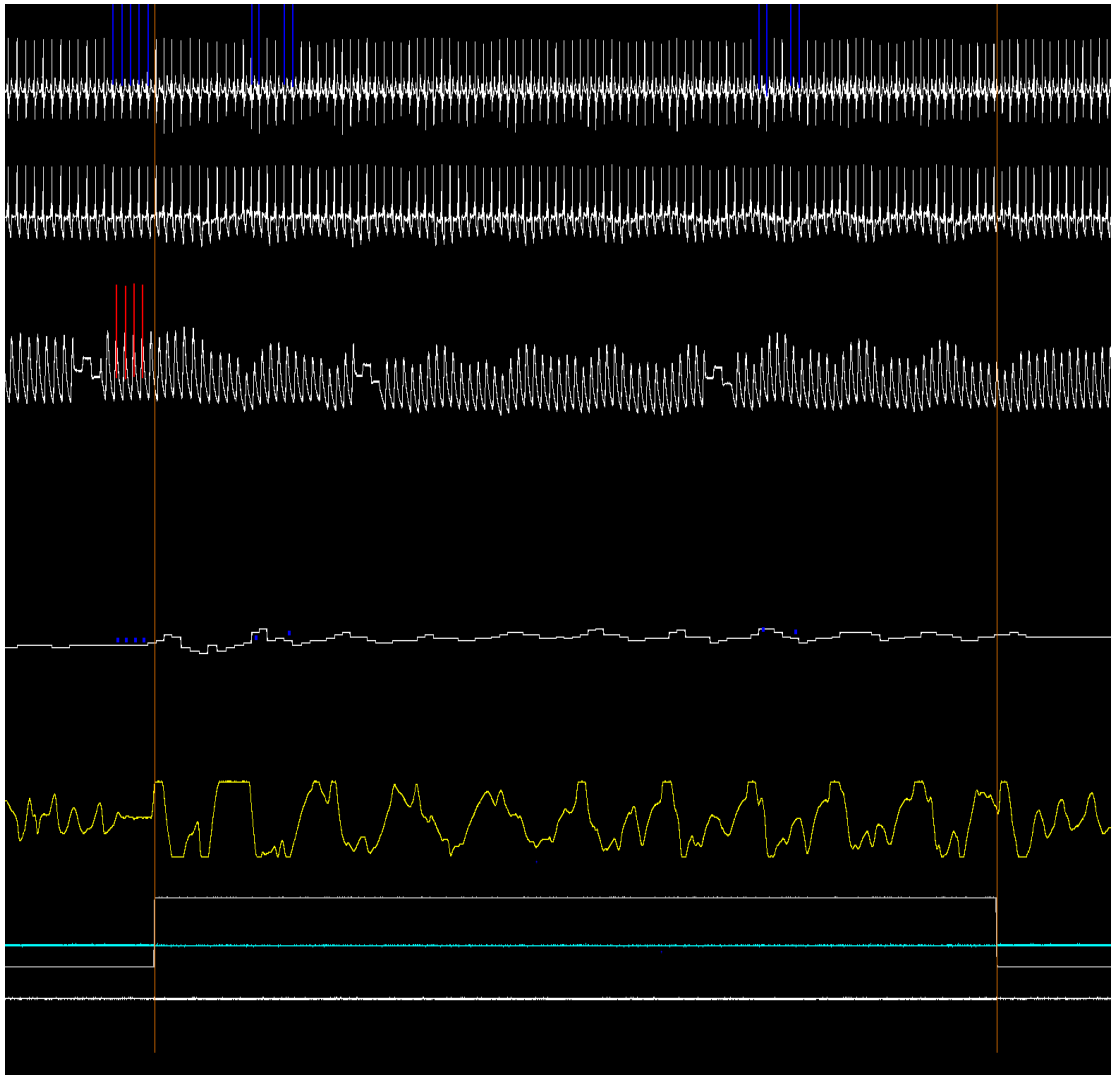
	Base	*I*	*IIa*	*IIb*	*III*	*IV*
PAS (mmHg)	133	131	42	42	33	57
PAD (mmHg)	67	67	35	36	26	30
FC (bpm)	57	53	59	61	70	61
Time (s)		0,9	11,4	14,5	1,0	4,0

Overshoot: assente - VR: 1,06 - Max bradi: 58 bpm a 18,0 s

Commento: patologica per assenza di overshoot, della fase IIb; ridotte modificazioni della FC

Deficit al Valsalva per assenza delle fisiologiche risposte pressorie e in FC.
Rispetto alla precedente esame del 2021 si segnala perdita della risposta pressoria alla fase 2b

2022: respiro profondo

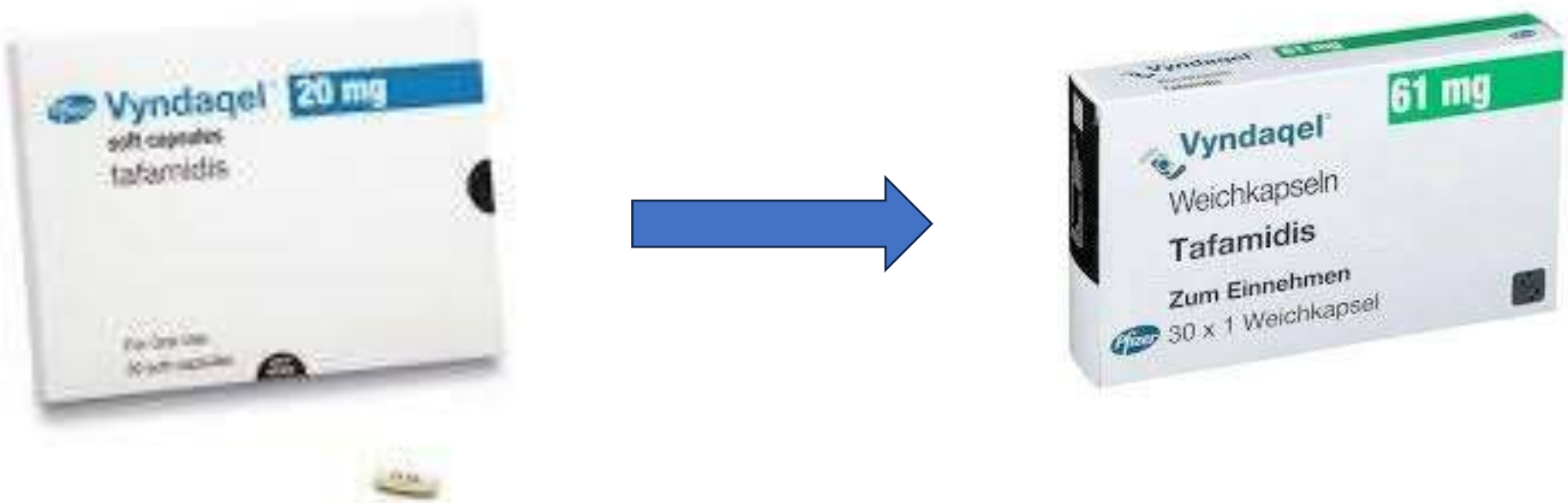


RESPIRO PROFONDO 1 - (6 atti al minuto)

	Base	*I*	*E*	*Delta (I-E)*	*I/E*	*Delta %*
FC (bpm)	58	66	58	7	1,12	3,33

Commento: ridotta aritmia respiratoria

2023

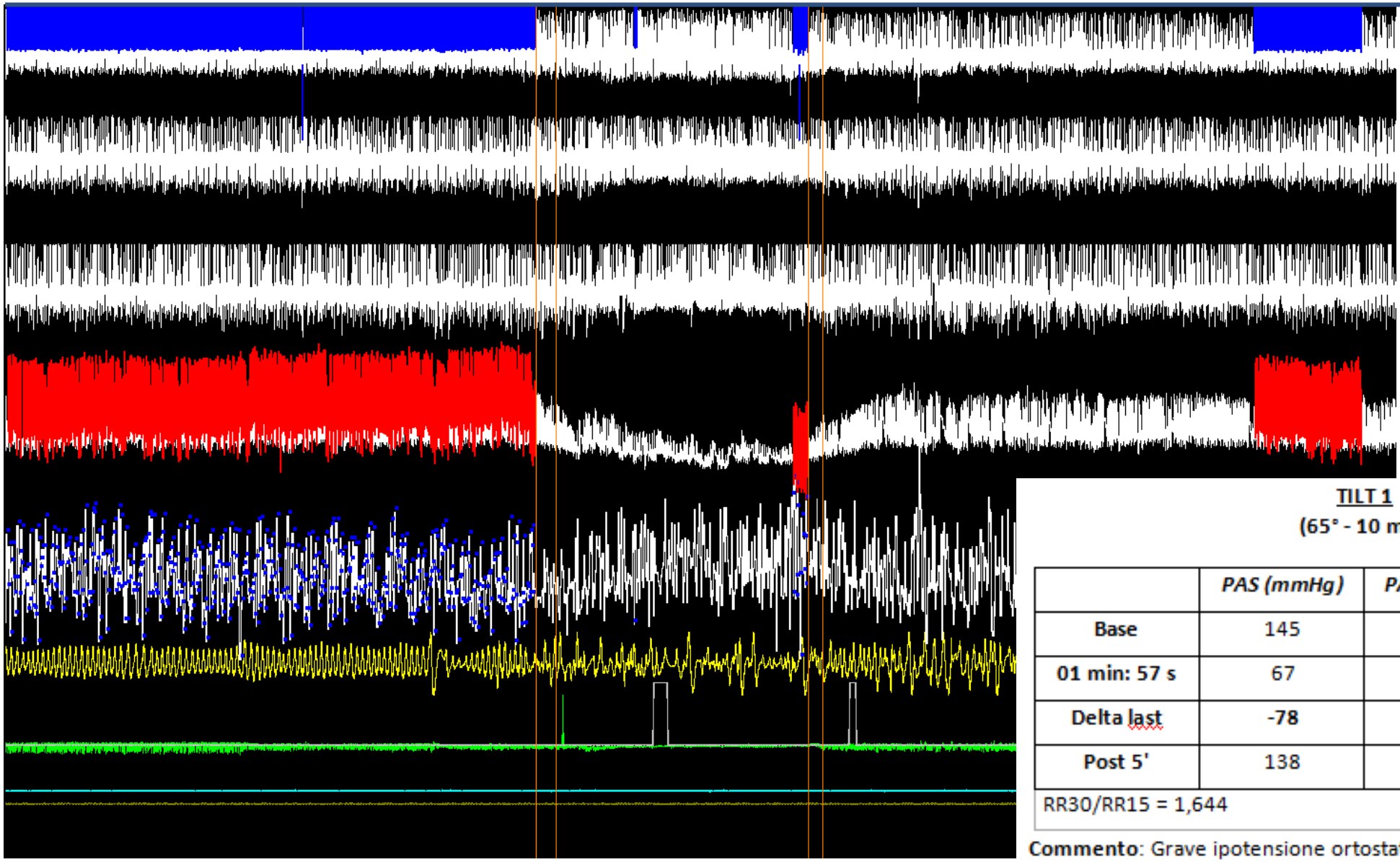

Vyndaqel
20 mg
tafamidis
Vyndaqel
61 mg
Weichkapseln
Tafamidis
Zum Einnehmen
30 x 1 Weichkapsel

2024

- EON: 160cm × 56K g . Lieve ptosi OS. Macroglossia. Non altri deficit al distretto cranico. Barrè e Mingazzini mantenuti con oscillazioni. Prensione lievemente ipovalida mano dx Alle prove di forza segmentarie segnalo lieve ipostenia 4/5 di EBP s xe interossei bil. Ipotrofia eminenza tenar bil. Ipostenia ileopsoas SX>dx e tricipite sn e estensori alluce Sx >Dx. ROT achilleo e medio-plantare assenti bil. Apallestesia a calza sx e ipopallestesia a dx. Autonoma nei passaggi. Deambulazione cauta ma autonoma. Difficoltà alla marcia in tandem e sui talloni. Oscillazioni in Romberg
- NIS: 22
- FAP1, PND 1
- PA supina 131/83 mmHg Fc 84 bpm
- PA in piedi 1° min 96/68 mmHg 86 bpm
- PA in piedi 3° min 121/70 mmHg 89 bpm

2024: Tilt test

FAC. Grave ipotensione ortostatica sintomatica.



TILT 1

(65° - 10 min)

	PAS (mmHg)	*PAD (mmHg)*	*FC (bpm)*
Base	145	81	n.v.
01 min: 57 s	67	51	n.v.
Delta last	-78	-29	n.v.
Post 5'	138	78	n.v.
RR30/RR15 = 1,644			

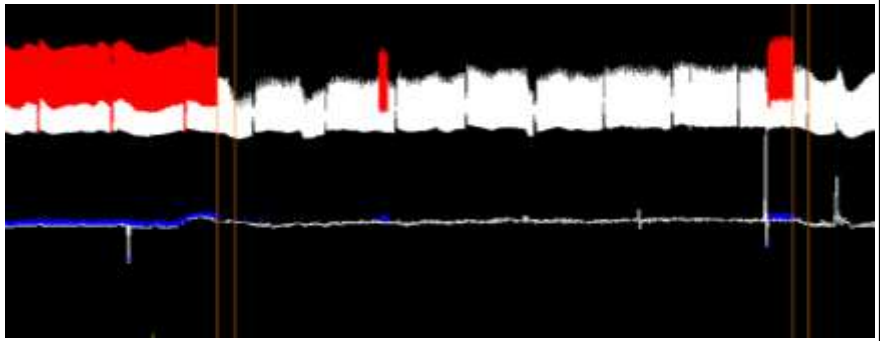
Commento: Grave ipotensione ortostatica sintomatica.

2024

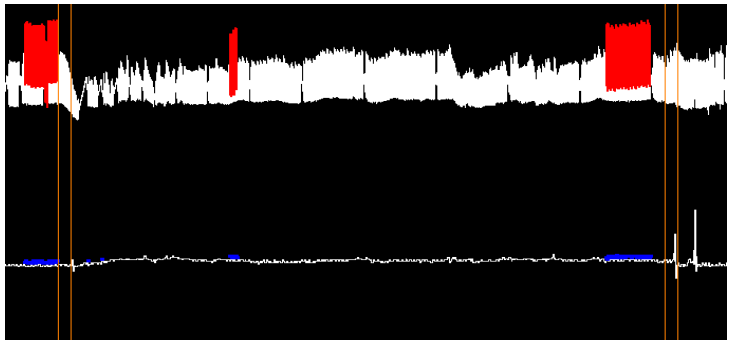

61 mg
Vyndaqel
Weichkapseln
Tafamidis
Zum Einnehmen
30 x 1 Weichkapsel


amvuttra

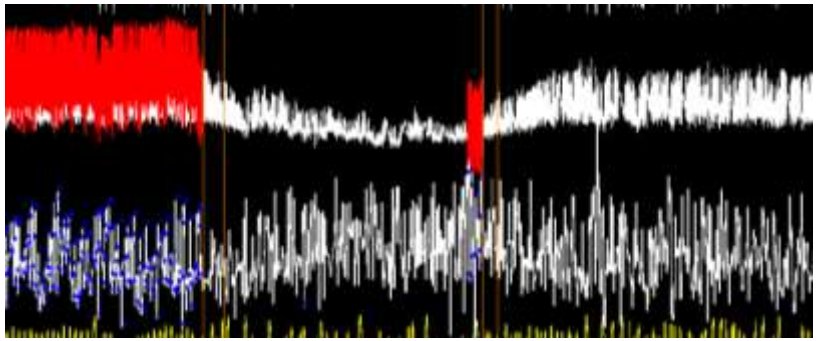
2021

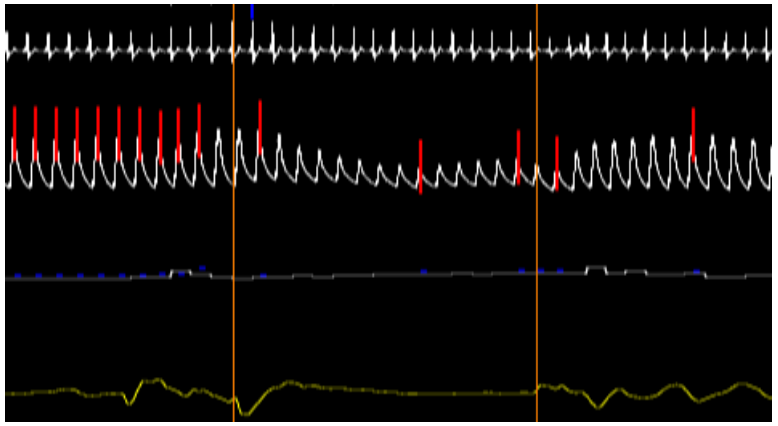


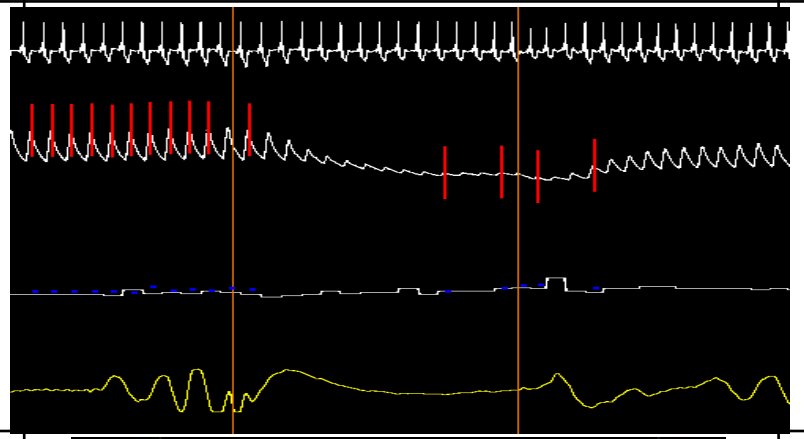
2022

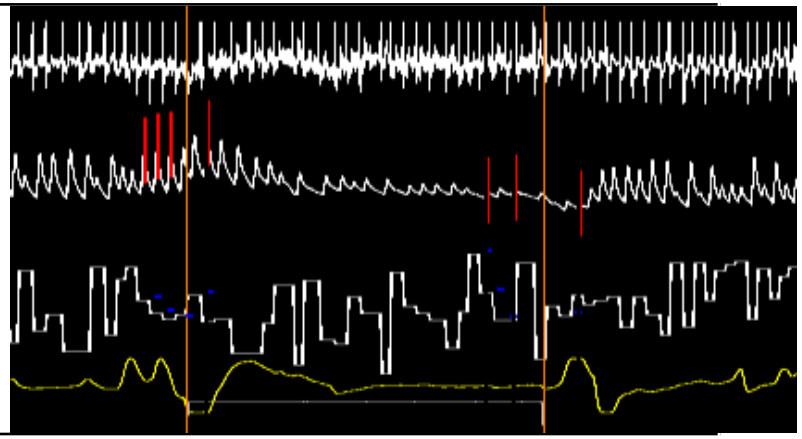


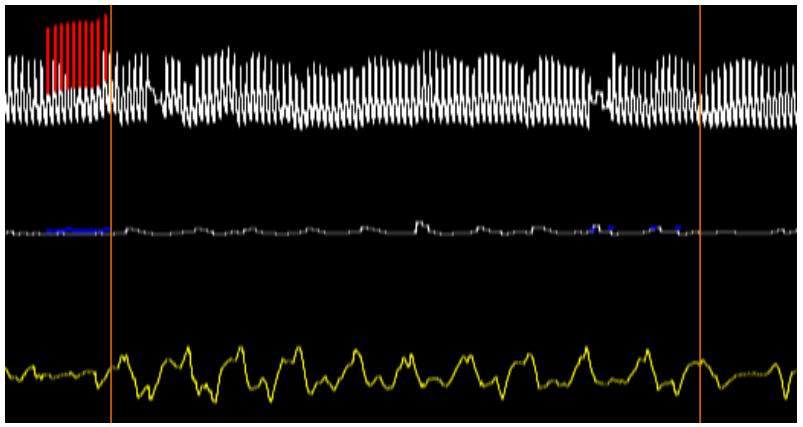
2024

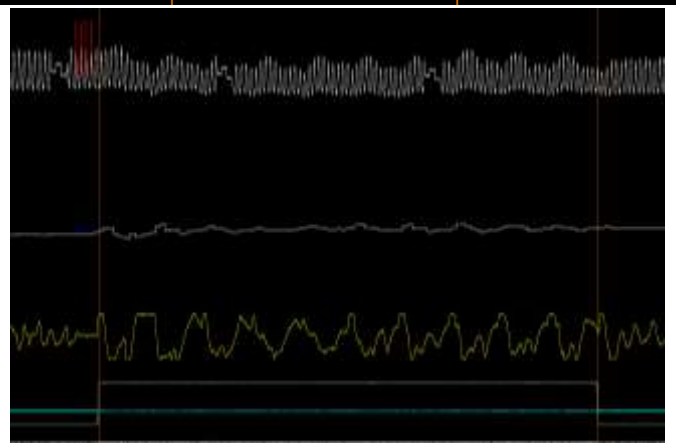








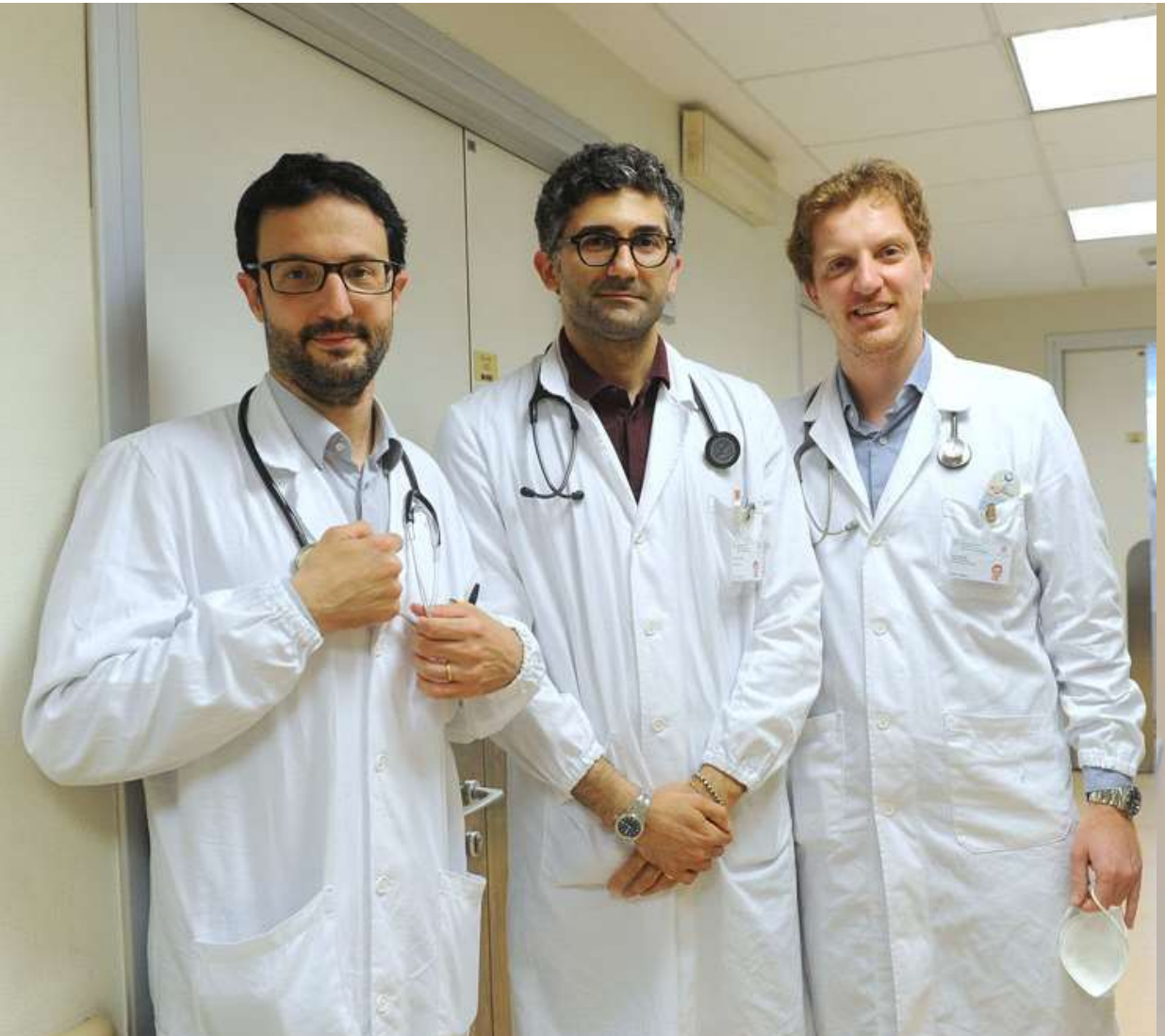




Conclusions

- Awareness is the key for the diagnosis of hATTR amyloidosis
- Autonomic dysfunction is an early, distinctive and disabling aspect of the disease.
- Autonomic dysfunction is still undervalued in ATTRv.
- Standardized CRTs confirmed that cardiovascular autonomic dysfunction was frequent in patients with ATTRv-wPN even in non-endemic areas
- Pre-symptomatic subjects (ATTRv-woPN) presented a significant impairment of sympathetic and cardiovagal responses suggesting an initial autonomic involvement.
- The detection of an early autonomic dysfunction could become a key feature for anticipating the administration of specific treatments that may revolutionize the disease progression

Thanks to..



GRAZIE