WEBINAR ECM

LA POLINEUROPATIA HATTR: VERSO UN PROTOCOLLO DIAGNOSTICO REGIONALE - INSTANT FAP-Network

28 ottobre 2020

ore 17.00 - 18.30

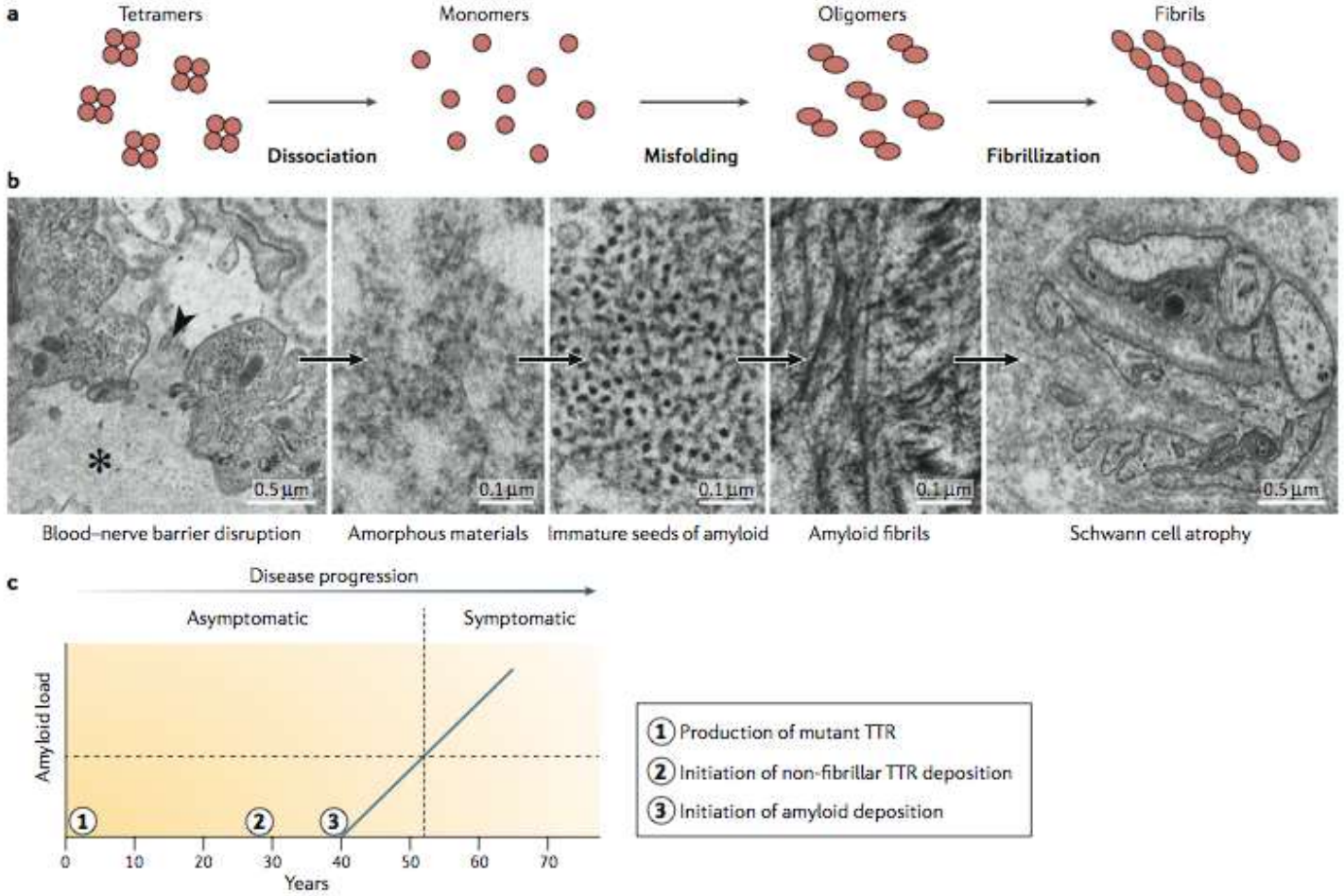
Come apprezzare la variabilità clinica

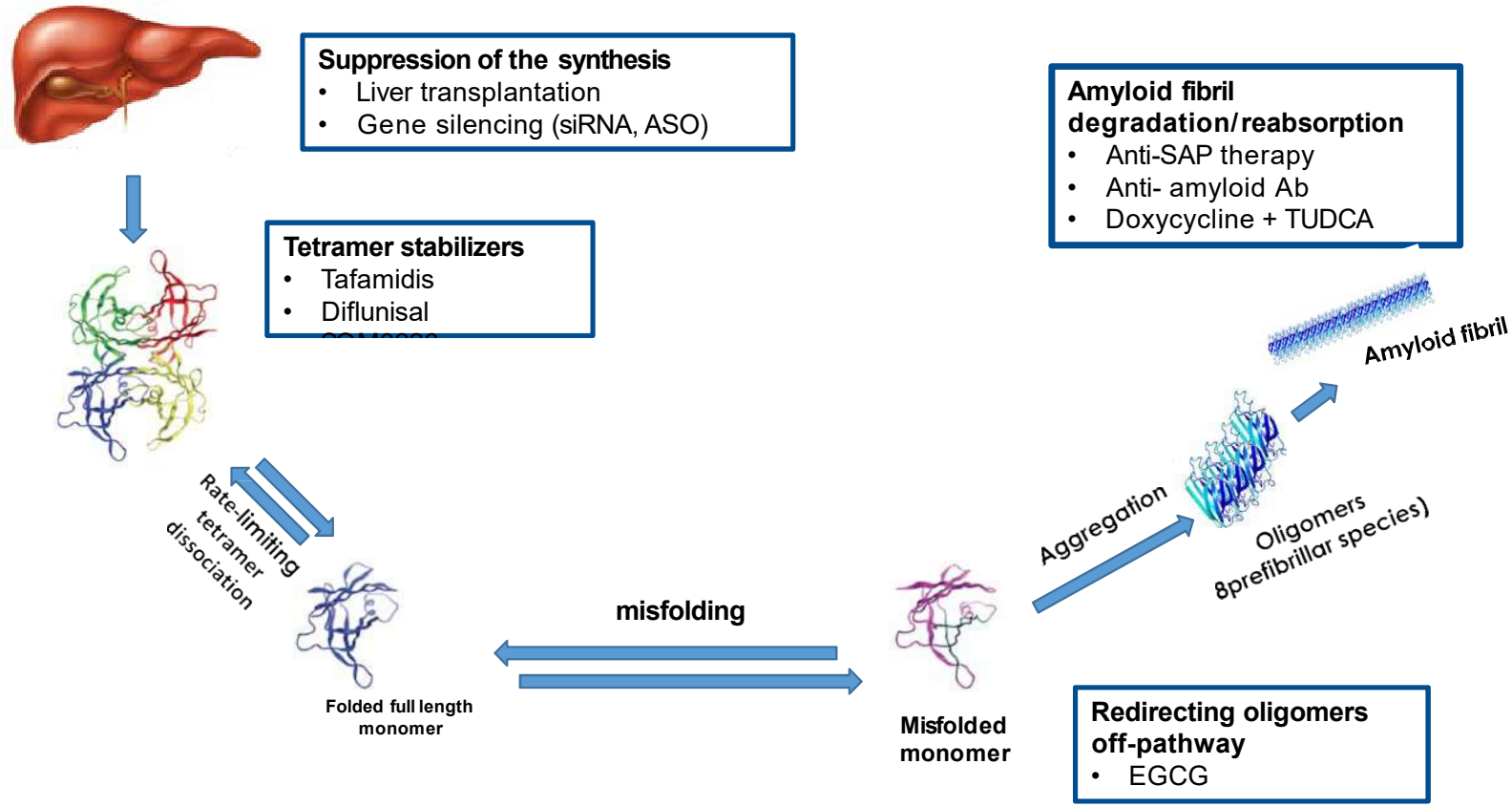
Dip. di Medicina Clinica e Sperimentale
Clinica Neurologica

Università di Pisa

Dr.ssa Erika Schirinzi

Rare, inherited, rapidly progressive, debilitating, life-threatening, often fatal disease caused by mutation in transthyretin (TTR) gene resulting in misfolded TTR protein accumulating as amyloid fibrils in nerves, heart, and gastrointestinal tract

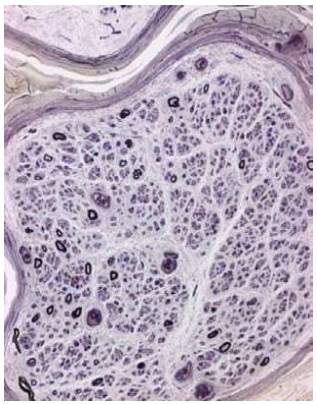
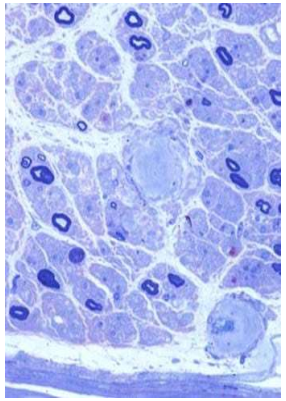
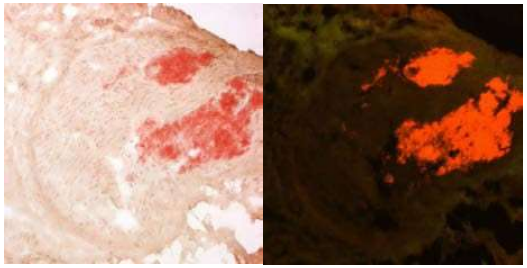
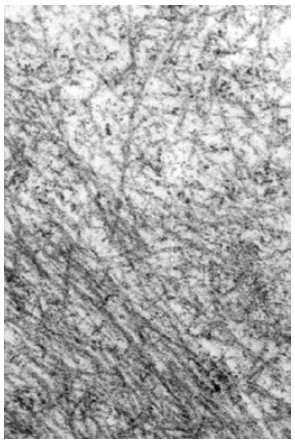


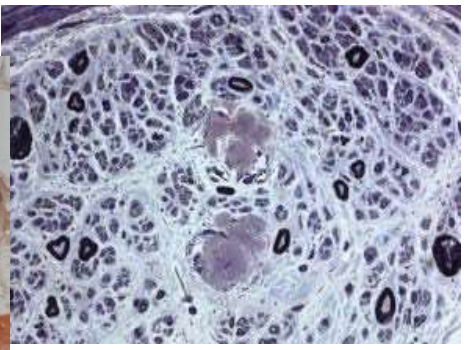

Suppression of the synthesis
• Liver transplantation
• Gene silencing (siRNA, ASO)
Tetramer stabilizers
• Tafamidis
• Diflunisal
Amyloid fibril degradation/reabsorption
• Anti-SAP therapy
• Anti- amyloid Ab
• Doxycycline + TUDCA
Amyloid fibril
Rate-limiting tetramer dissociation
Aggregation
Oligomers 8prefibrillar species)
misfolding
Folded full length monomer
Misfolded monomer
Redirecting oligomers off-pathway
• EGCG

Immunolocalization and Activation of Transcription Factor Nuclear Factor κB in Dysimmune Neuropathies and Familial Amyloidotic Polyneuropathy

ARCH NEUROL/VOL 61, JULY 2004

Anna Mazzeo, MD; Mohammed Aguennouz, PhD; Corrado Messina, MD; Giuseppe Vita, MD



Pathogenesis

1) **Axonal degeneration** (ganglia, nerves)

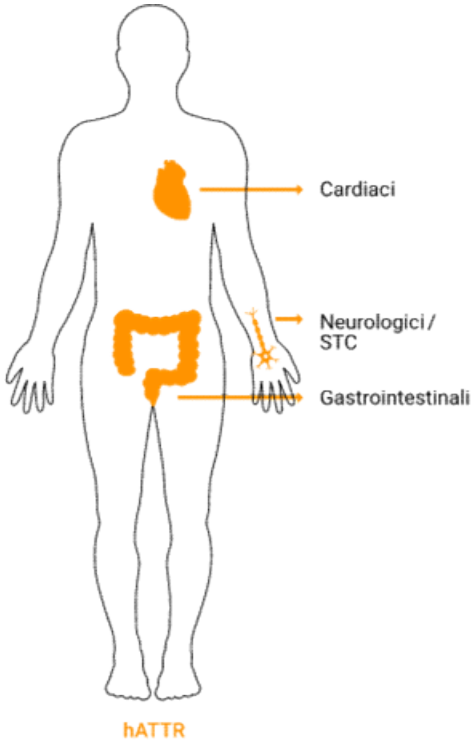
1) Amyloid: **mechanical and toxic effect**

1) **Endoneurial edema** slightly contributing to **nerve ischemia**

1) **Oxidative stress?**
Inflammation? Apoptosis?

h-ATTR amyloidosis

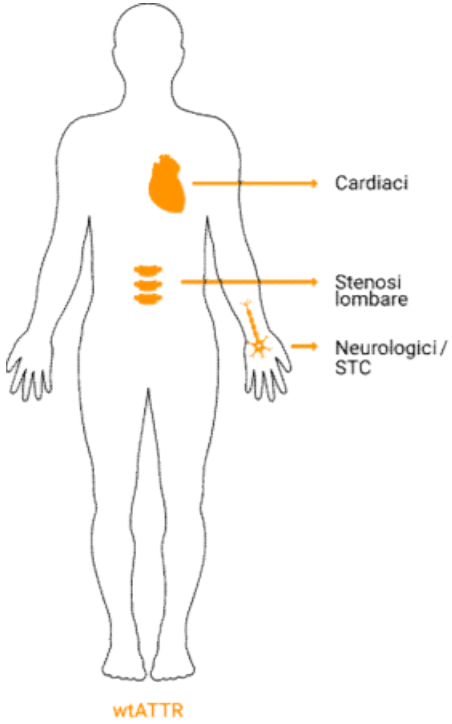
- → Inherited,
- → progressive disease
- → caused by the accumulation of mutant and wild-type amyloid fibrils
- → Multisystem disease that can include sensory and motor, autonomic, and cardiac symptoms



wt-ATTR amyloidosis

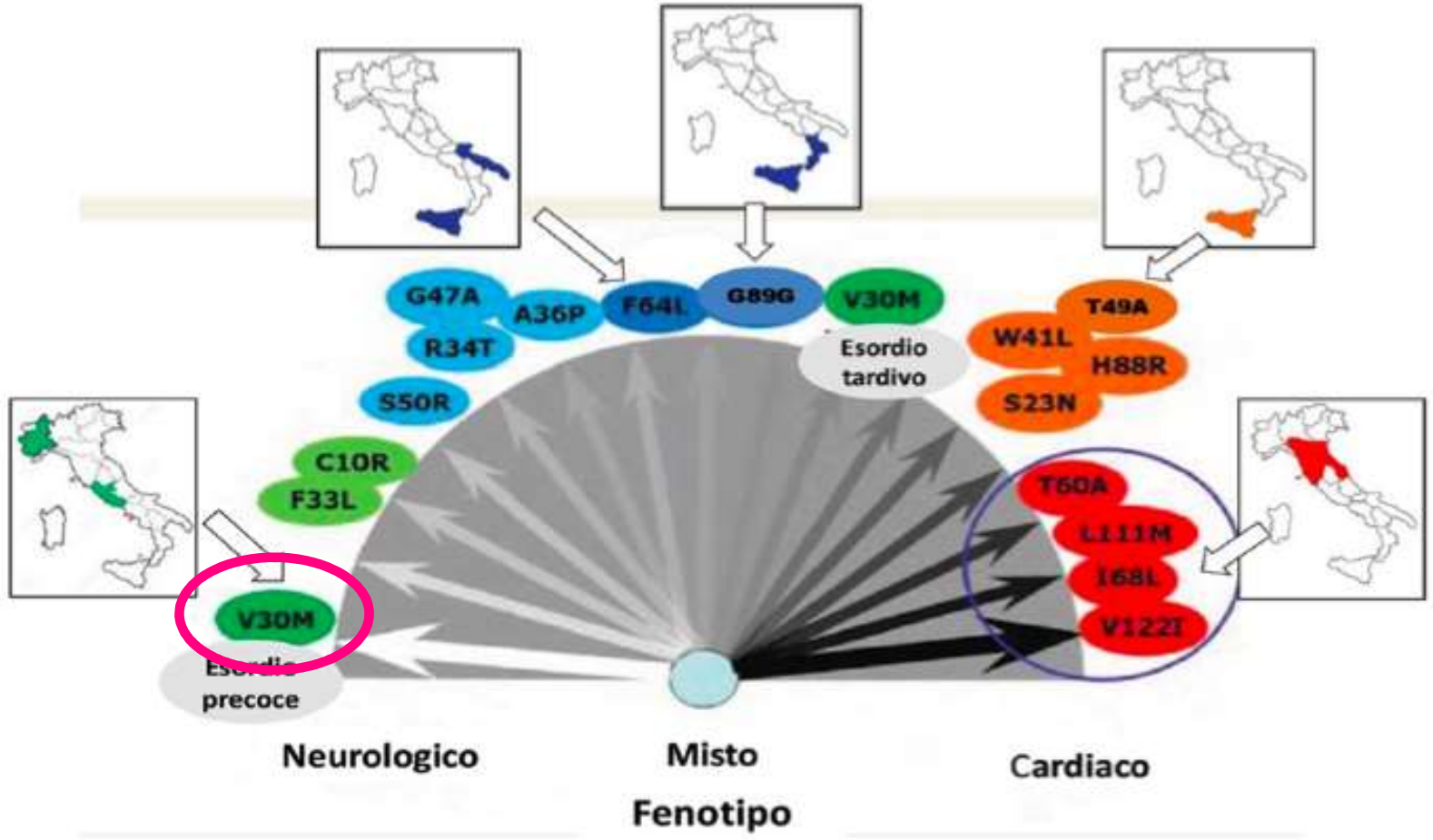
- → Non-hereditary
- → progressive disease
- → of undefined etiology caused by the accumulation of wild-type amyloid fibrils

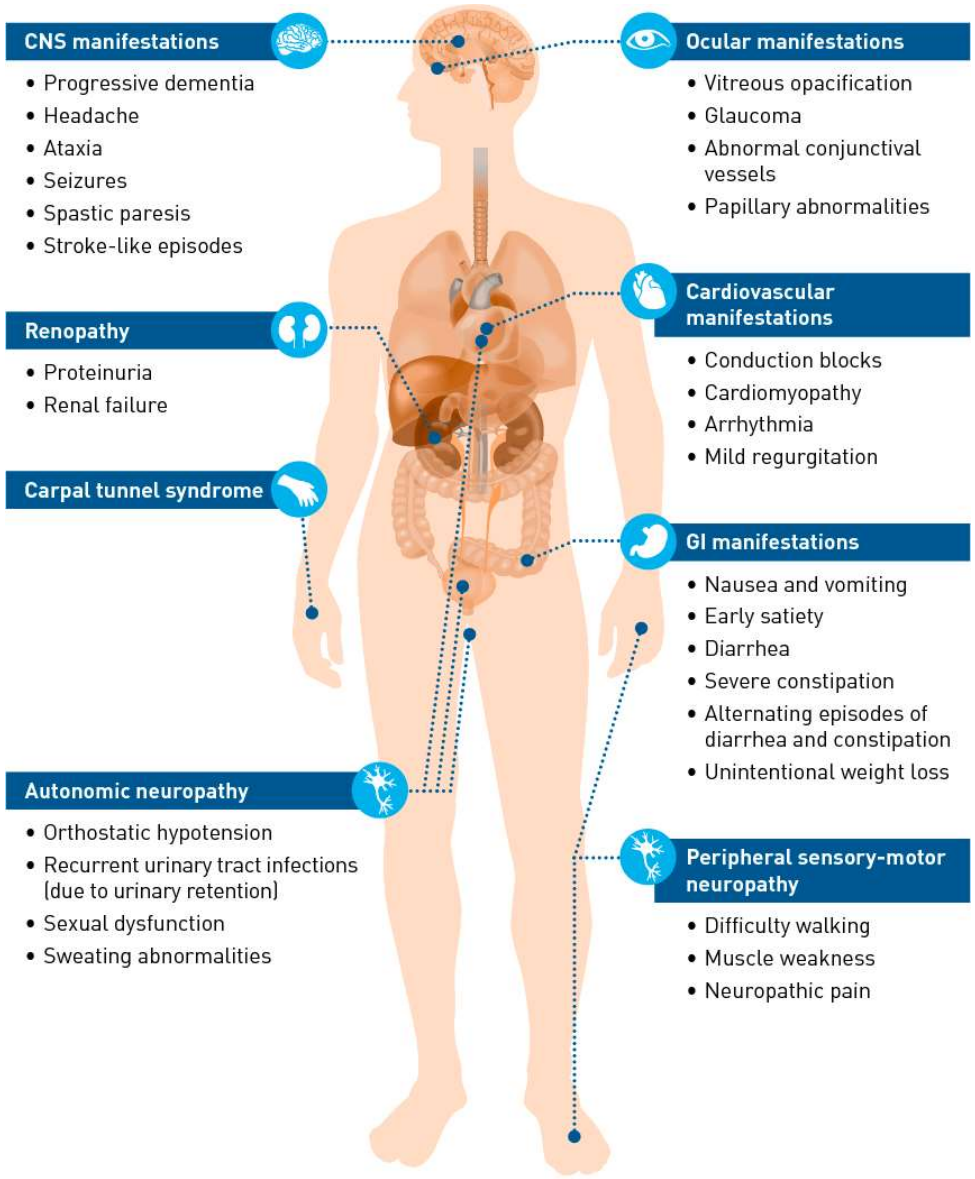
→ **Predominantly manifests as cardiac symptom**s, but other systems can be involved



→ Median survival is 4.7 years following diagnosis with a reduced survival (3.4 years) for patients presenting with cardiomyopathy

→ Clinical manifestations are influenced by TTR genotype (greater than 120 known pathogenic mutations) and geographical region





Progressive symmetric sensorimotor neuropathy

+ ≥1 of

Family history of hATTR amyloidosis symptoms

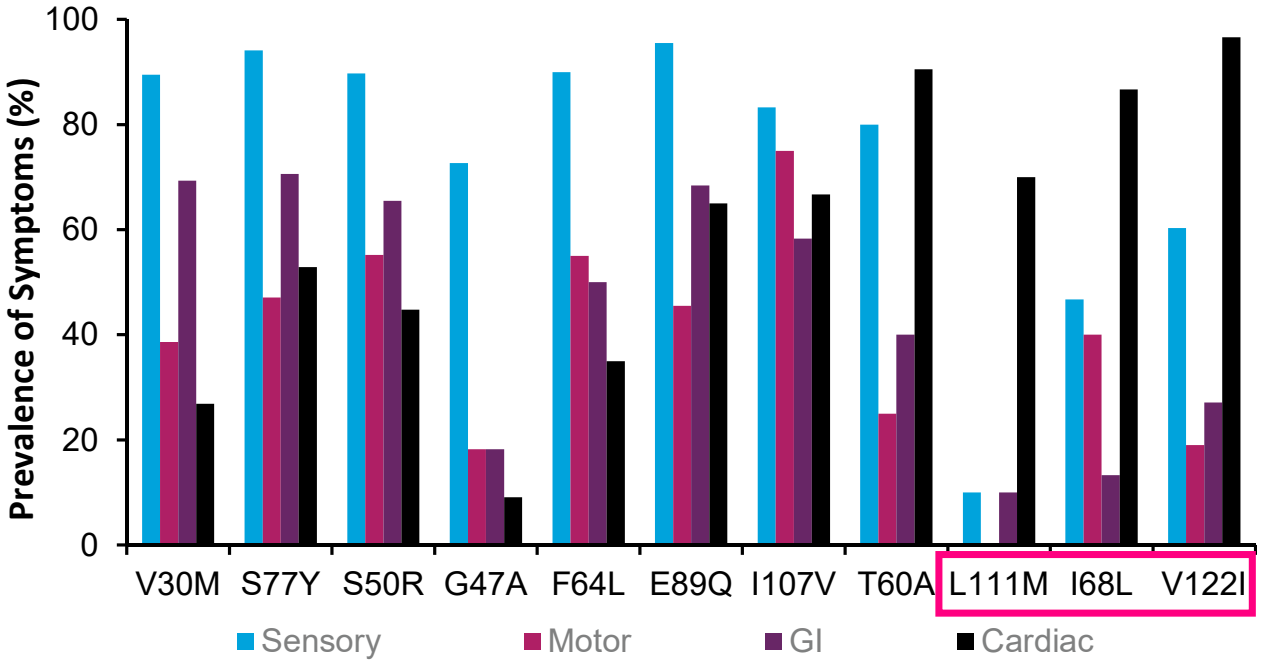
- Neuropathy and sensory involvement
- Renal abnormalities
- Bilateral CTS
- Early autonomic dysfunction and GI complaints
- HFpEF (without hypertension)
- Cardiac hypertrophy, arrhythmias, ventricular blocks, right-sided or biventricular HF, or cardiomyopathy
- Vitreous opacities

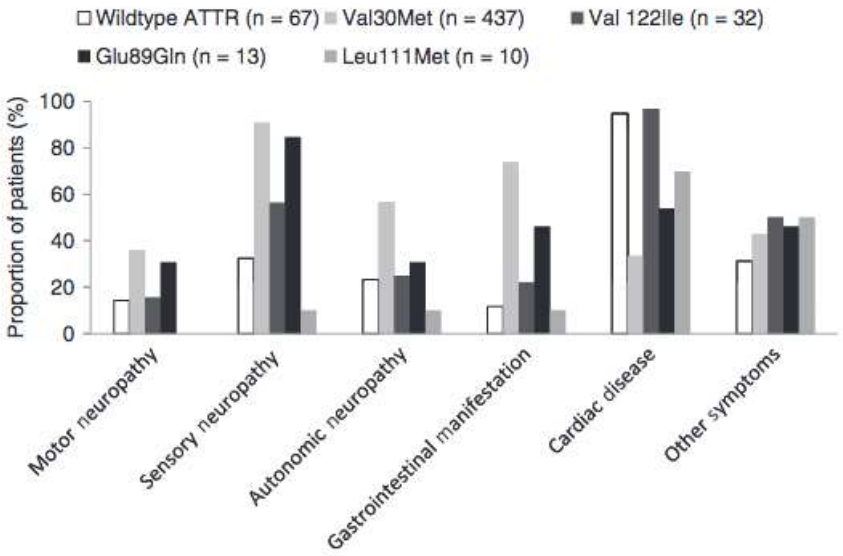
HFpEF, heart failure with preserved ejection fraction

THAOS – The Transthyretin Amyloidosis Outcomes Survey: initial report on clinical manifestations in patients with hereditary and wild-type transthyretin amyloidosis

Current Medical Research & Opinion Vol. 29, No. 1, 2013, 63–76

Teresa Coelho, Mathew S. Maurer & Ole B. Suhr





Neurologic
Cardiac

Epidemiological and clinical characteristics of symptomatic hereditary transthyretin amyloid polyneuropathy: a global case series

Orphanet Journal of Rare Diseases (2019) 14:34

Márcia Waddington-Cruz[1,8*], Hartmut Schmidt[2], Marc F. Botteman[3], John A. Carter[4], Michelle Stewart[5], Markay Hopps[6], Shari Fallet[6] and Leslie Amass[7]

542 cases identified through a review of the literature between 2005 and 2016

→ Approximately 18% of the cases from countries traditionally considered to be endemic
→ Approximately 37% of the cases from East Asia
→ Val30Met the most common mutation

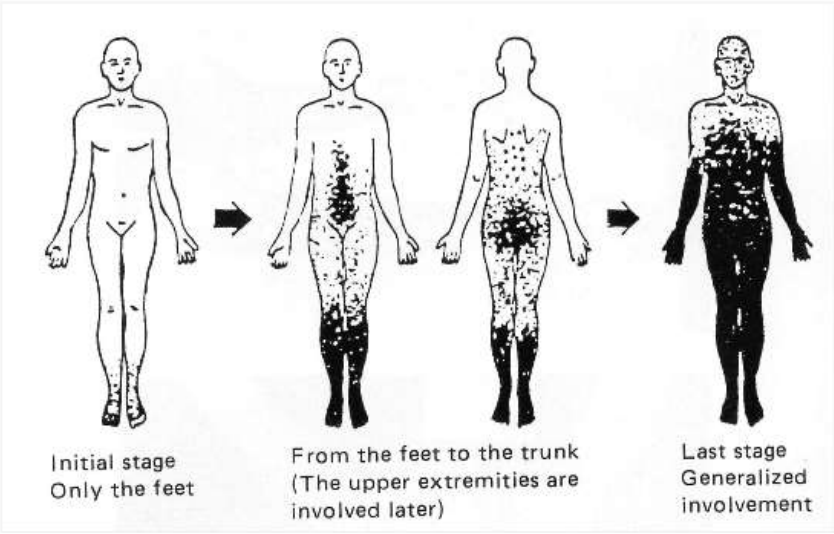
	Country Total	Ala97Ser	Phe64Leu	Ser77Tyr	Val30Met	Other
Italy	58 (10.7%)	0 (0%)	24 (41.4%)	0 (0%)	21 (36.2%)	13 (22.4%)

Table 3 Clinical Characteristics at Presentation

Feature	All	Ala97Ser	Phe64Leu	Ser77Tyr	Val30Met	Other
Any Reported	374 (69%)	35 (9%)	22 (6%)	48 (13%)	141 (38%)	128 (34%)
Autonomic	199 (53%)	27 (77%)	18 (82%)	5 (10%)	74 (52%)	75 (59%)
Unspecified	47	0	7	1	22	17
Urinary	36	7	3	0	16	10
Gastrointestinal	114	22	6	3	39	44
Cardio	96	15	7	1	34	39
Respiratory	3	0	0	0	0	3
Impotence	51	18	5	1	13	14
Sweat	20	7	3	1	4	5
Sensory	326 (87%)	25 (71%)	22 (100%)	45 (94%)	127 (90%)	107 (84%)
Unspecified	76	21	5	0	25	25
Lower Limbs	219	2	15	37	100	65
Upper Limbs	133	2	10	35	48	38
Carpal Tunnel	42	4	4	0	7	27
Motor	215 (57%)	10 (29%)	15 (68%)	32 (67%)	79 (56%)	79 (62%)
Unspecified	67	9	4	0	33	21
Lower Limbs	138	0	11	28	46	53
Upper Limbs	83	1	10	10	33	29
Other	1	0	0	0	0	1
Miscellaneous	155 (41%)	4 (11%)	17 (77%)	14 (29%)	39 (28%)	81 (63%)
Cardiomyopathy	93	4	15	2	28	44
Visual (Non-Motor)	49	0	2	13	9	25
Weight Loss	35	0	2	2	9	22

Specific genotypes shown are those with ≥4% representation among the included cases. Genotypes with < 4% representation are listed as "Other". Refer to Additional file 1: Appendix A for a list of genotypes included in the "Other" category

Familial amyloid polyneuropathy (FAP): red flags…or confounders?



Symmetric, ascending length–dependent, sensorimotor, axonal polyneuropathy

ATTR V30M variant:

↓

→ Lower extremity weakness, pain, and/or impaired sensation;

→ autonomic dysfunction, often manifesting as sexual or urinary dysfunction

→ Carpal ligament deposits (eg, variant *TTR* L58H, normal-sequence TTR); **localized symptomatic carpal ligament deposition sometimes precedes other clinical manifestations by as long as 20 years!!!!!**

→ Small fiber neuropahy

	Early-onset *Val30Met* [7, 19]	Late-onset *Val30Met* [8, 19, 20]
Age at onset, years	<50	≥50
Country	Portugal, Japan[a], Brazil, Sweden[b]	Sweden[b], France, UK, Italy, Japan, USA
Positive family history, %	94	48
Peripheral neuropathy, %	57	81
Autonomic neuropathy, %	48	10
Weight loss, %	5	0
Disease course		
Mean delay in need for aid in walking, years	>5.6	3
Mean delay for wheelchair bound, years	10	6
Cardiac events	Progressive conduction disorders	Restrictive cardiomyopathy Cardiac insufficiency Progressive conduction disorders
Median survival, years	11	7.3
Cause of death	Cachexia Infection	Cardiac insufficiency Sudden death Cachexia or secondary infection

Small fibre neuropathy assessments in early stages of hATTR amyloidosis

Alejandra González-Duarte[a], Karla Cárdenas-Soto[a], Omar Fueyo[a], Carlo-Enrico Bañuelos[a], Christopher Gibbons[b] and Roy Freeman[b]

AMYLOID
2019, VOL. 26, NO. S1, 55–56

SCREENING FOR FABRY DISEASE AND HEREDITARY ATTR AMYLOIDOSIS IN IDIOPATHIC SMALL-FIBER AND MIXED NEUROPATHY

KRISTIN SAMUELSSON, PhD, MD,[1] ANA RADOVIC, MD,[2] RAYOMAND PRESS, PhD, MD,[1] MARI AURANEN, PhD, MD,[3] EMIL YLIKALLIO, PhD, MD,[3] HENNA TYYNISMAA, PhD,[3] MIKKO KÄRPPÄ, PhD, MD,[4] MATILDA VETELÄINEN, MD,[4] NIINA PELTOLA, MD,[5] SVEIN IVAR MELLGREN, PhD, MD,[6] ÅSE MYGLAND, PhD, MD,[7] CHANTAL TALLAKSEN, PhD, MD,[8] HENNING ANDERSEN, PhD, MD,[9] ASTRID JUHL TERKELSEN, PhD, MD,[9] FREJA FONTAIN, MD,[9] and AKI HIETAHARJU, PhD, MD[5]

ABSTRACT: *Introduction*: In this study we assessed the value of genetic screening for Fabry disease (FD) and hereditary ATTR amyloidosis in patients with idiopathic small-fiber neuropathy (SFN) or mixed neuropathy in a clinical setting. *Methods*: This was a Nordic multicenter study with 9 participating centers. Patients with idiopathic SFN or mixed neuropathy were included. Genetic sequencing of the *TTR* and *GLA* genes was performed. *Results*: There were 172 patients enrolled in the study. Genetic screening was performed in 155 patients. No pathogenic mutations in the *TTR* gene were found. A single patient had a possible pathogenic variant, R118C, in the *GLA* gene, but clinical investigation showed no firm signs of FD. *Discussion*: Screening for hereditary ATTR amyloidosis and FD in patients with idiopathic SFN or mixed neuropathy without any additional disease-specific symptoms or clinical characteristics in a Nordic population appears to be of little value in a clinical setting.

Muscle Nerve 59:354–357, 2019

Diagnostic challenges in hereditary transthyretin amyloidosis with polyneuropathy: avoiding misdiagnosis of a treatable hereditary neuropathy

Andrea Cortese,[1,2] Elisa Vegezzi,[3,4] Alessandro Lozza,[1] Enrico Alfonsi,[1] Alessandra Montini,[1] Arrigo Moglia,[1,5] Giampaolo Merlini,[6] Laura Obici[6]

J Neurol Neurosurg Psychiatry May 2017 Vol 88 No 5

Pavia Amyloidosis Center

Circa 1/3 dei casi non riconosciuti (49/150)

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	-

*Univariate logistic regression.
†Variables significantly associated with misdiagnosis in the univariate model were tested in a multivariate logistic regression model.
NYHA, New York Heart Association.

CIDP

CMT

Amyotrophic lateral sclerosis

Other form of amyloidoses

Lumbar spinal stenosis

Diabetic neuropathy

Idiopathic neuropathy

Alcoholic neuropathy

Misdiagnosis	Incidence, %	Misleading features	Red flags
CIDP	13–15	SM 4 limbs Diffuse areflexia Albuminocytologic dissociation Demyelination on biopsy Demyelinating NCS	Pain Sensory loss (wrists) Autonomic dysfunction Upper limb weakness NCS
Chronic axonal idiopathic PN	24–33	Axonal neuropathy in the elderly, seemingly idiopathic	Severity, disability, rapid Difficulties in walking
CTS	11	Paresthesia in the hands	No relief after surgery
Lumbar spinal stenosis	7.3	Progressive difficulty walking in the elderly Spinal stenosis on lumbar CT or MRI	Abnormal NCS Worsening in spite of surgery
Motor neuron disease Motor neuropathy, ALS	<1	Upper limb and tongue amyotrophy Dysarthria Hand weakness	Abnormal sensory SNAP (NCS) No symptoms of upper motor neuron involvement
Miscellaneous			
Alcoholic PNP		Small-fiber length-dependent PN	Alcoholism
Diabetic PNP		Small-fiber length-dependent PN Autonomic dysfunction	Rapid severity/duration of diabetes Difficulties in walking
Paraneoplastic neuropathy		Non-length-dependent sensory loss + ataxia Weight loss	No anti-onconeuronal antibody Negative findings on whole-body PET

Carpal tunnel syndrome and spinal canal stenosis: harbingers of transthyretin amyloid cardiomyopathy?

Fabian aus dem Siepen[1] · Selina Hein[1] · Sofie Prestel[1] · Christian Baumgärtner[1] · Stefan Schönland[2] · Ute Hegenbart[2] · Christoph Röcken[3] · Hugo A. Katus[1,4] · Arnt V. Kristen[1]

Received: 17 October 2018 / Accepted: 19 January 2019

Methods Medical records of 253 patients diagnosed with wt-ATTR, 136 patients with mt-ATTR and 77 asymptomatic gene carriers were screened for history of CTS and spinal canal stenosis and laboratory analysis, electrocardiography and echocardiographic results, respectively. Clinical follow-up was performed by phone assessment.

	Asymptomatic gene carriers ($n=77$)	mt-ATTR ($n=136$)	wt-ATTR ($n=253$)	p value (ANOVA/χ^2)
Male gender (n, %)	17 (49%)	124 (70%)	232 (92%)	<0.001
Age (years)	38 ± 11	59 ± 12	74 ± 6	<0.001
Height (cm)	174 ± 10	173 ± 8	175 ± 8	0.04
Weight (kg)	81 ± 19	76 ± 16	81 ± 19	0.03
mBMI	1206 ± 237	1098 ± 246	1120 ± 180	0.02
Karnofsky index (%)	97 ± 9	80 ± 16	82 ± 9	ns
Carpal tunnel syndrome (n, %)	10 (13%)	77 (57%)	152 (60%)	<0.001
Unilateral	10 (13%)	51 (38%)	90 (36%)	
Bilateral	0 (0%)	26 (19%)	62 (25%)	
Latency between carpal tunnel surgery and diagnosis of cardiac amyloidosis (months)	–	66 ± 73	117 ± 179	0.02
Spinal canal stenosis (n, %)	0 (0%)	7 (5%)	36 (14%)	<0.001

J Neuromuscul Dis. 2019;6(2):267-270. doi: 10.3233/JND-180348.

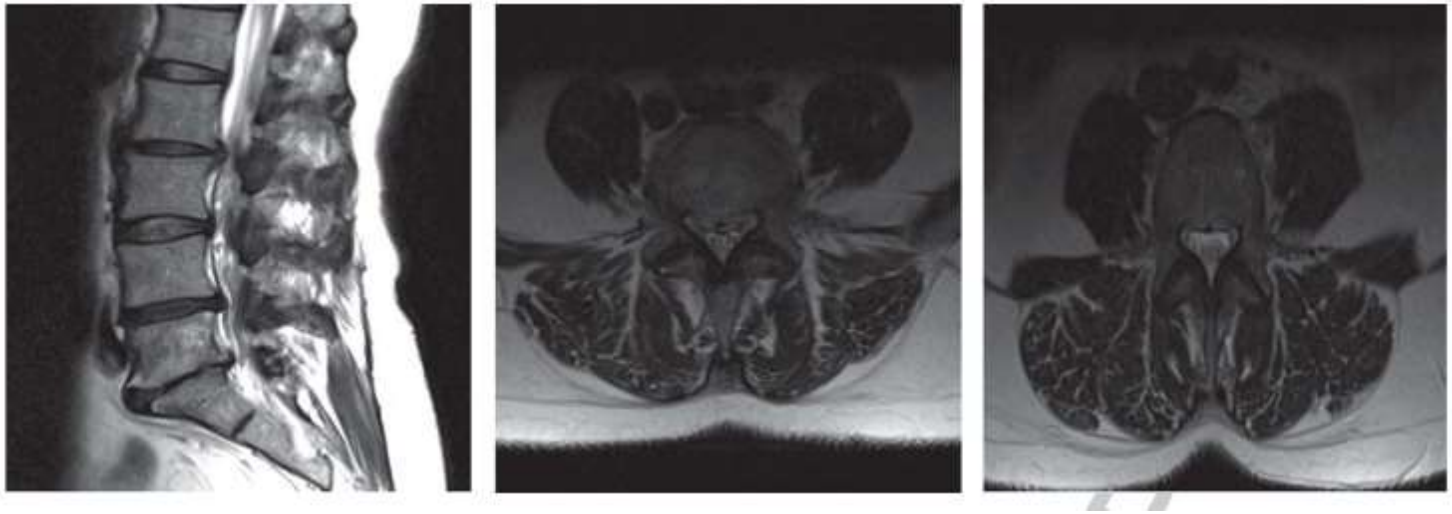
Spinal Stenosis in Familial Transthyretin Amyloidosis.

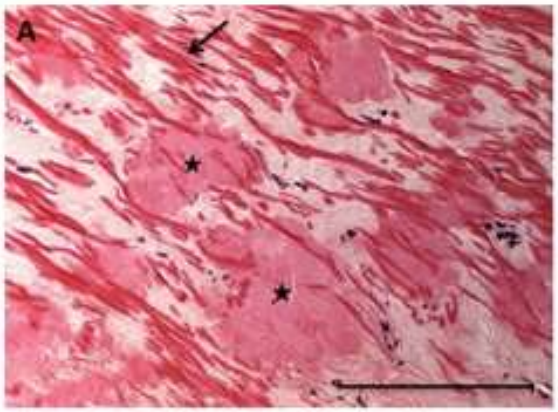
Carr AS[1], Shah S[2], Choi D[3], Blake J[1,4], Phadke R[5], Gilbertson J[6], Whelan CJ[6], Wechalekar AD[6], Gillmore JD[6], Hawkins PN[6], Reilly MM[1].

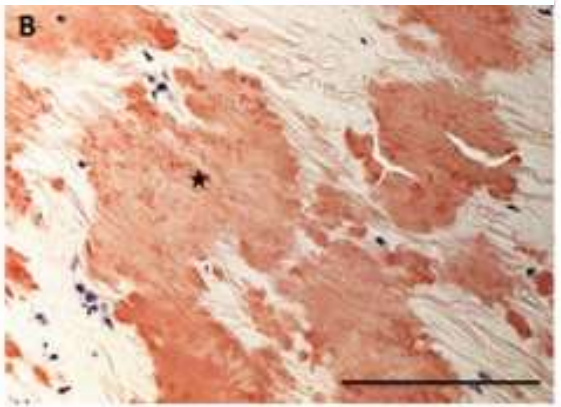
⊕ Author information

Abstract

Here we describe a patient with genetically confirmed ATTR, a family history of the disease and histological confirmation following carpal tunnel release surgery but no other manifestations. The first major neurological or systemic manifestation was cauda equina syndrome with ATTR deposits contributing to lumbar spinal stenosis. Recent gene therapy trials showed improvement in the neuropathy in TTR amyloidosis. This case highlights the need for awareness of the heterogeneous neurological phenotype seen in ATTR to aid earlier diagnosis especiall now that disease modifying therapies are available.







APR

- Stenosi del rachide lombo-sacrale L4-L5 sottoposto a intervento di decompressione in marzo 2017
- Trauma stradale con frattura dello sterno, metacarpo e V dito mano destra
- ipertensione arteriosa, ipercolesterolemia
- aneurisma dell'aorta ascendente (in follow-up)
- extrasistolia ventricolare

EO

- Lieve ipotrofia del I interosseo delle mani bilateralmente
- Modesta ipostenia nei movimenti di abdu/adduzione delle dita delle mani
- Sfumate oscillazioni pluridirezionali del tronco in posizione di Romberg ad occhi chiusi.
- Deambulazione eseguita con note talloneggianti.
- Cavismo di piede bilaterale

APP

- Algie agli arti inferiori, non migliorate dopo intervento NCH
- Parestesie a tipo formicolio alle mani

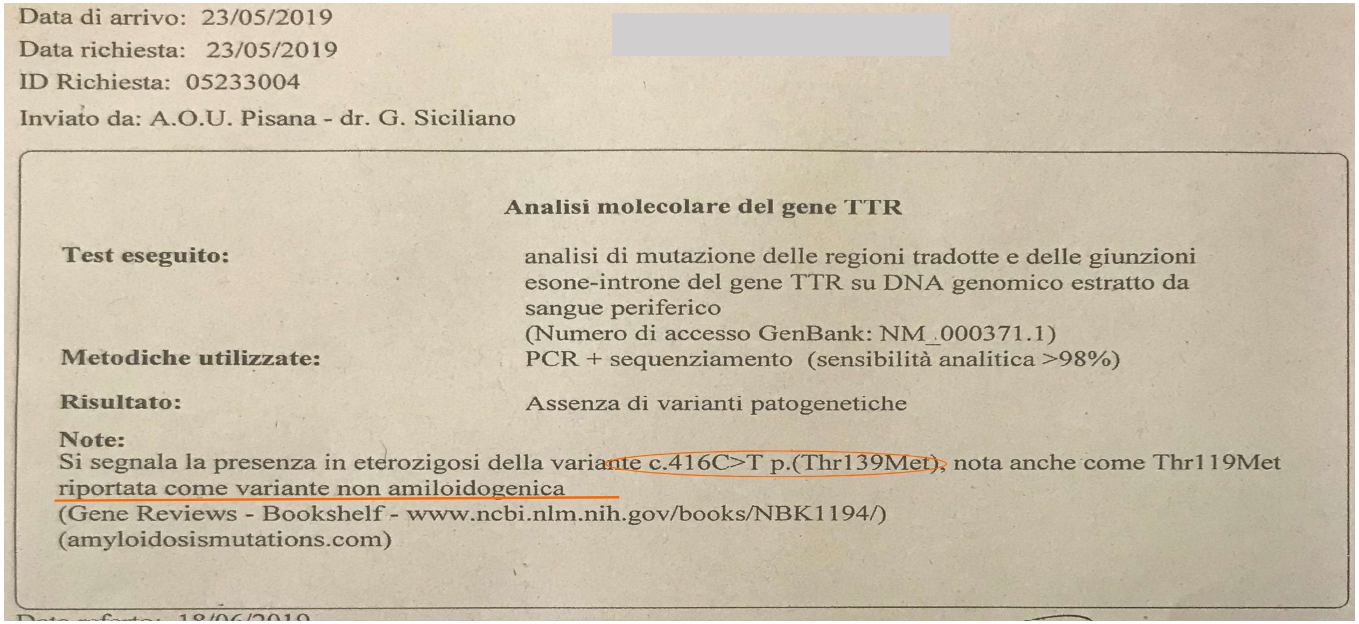
VDC

polineuropatia sensitivo-motoria
prev assonale
ai quattro arti

Biopsia grasso peri-ombelicale — negativa

Anticorpi antigangliosidi — negativi

Genetica CMT (NGS) — negativa



Data di arrivo: 23/05/2019
Data richiesta: 23/05/2019
ID Richiesta: 05233004
Inviato da: A.O.U. Pisana - dr. G. Siciliano

Analisi molecolare del gene TTR

Test eseguito: analisi di mutazione delle regioni tradotte e delle giunzioni esone-introne del gene TTR su DNA genomico estratto da sangue periferico
(Numero di accesso GenBank: NM_000371.1)

Metodiche utilizzate: PCR + sequenziamento (sensibilità analitica >98%)

Risultato: Assenza di varianti patogenetiche

Note:
Si segnala la presenza in eterozigosi della variante c.416C>T p.(Thr139Met), nota anche come Thr119Met riportata come variante non amiloidogenica
(Gene Reviews - Bookshelf - www.ncbi.nlm.nih.gov/books/NBK1194/)
(amyloidosismutations.com)

Expert consensus recommendations to improve diagnosis of ATTR amyloidosis with polyneuropathy

Journal of Neurology 2020

David Adams[1] · Yukio Ando[2] · João Melo Beirão[3] · Teresa Coelho[4] · Morie A. Gertz[5] · Julian D. Gillmore[6] · Philip N. Hawkins[6] · Isabelle Lousada[7] · Ole B. Suhr[8] · Giampaolo Merlini[9,10]

Clinical suspicion of amyloid neuropathy (*refer to Figure 2*)

→ **Confirmation of ATTRv amyloidosis**

DNA sequencing
Analysis of the amyloidogenic *TTR* variant

Amyloid typing
Immunohistochemistry or mass spectrometry

Biopsy of amyloid deposition

Possible biopsy sites: Labial salivary gland; subcutaneous fatty tissue of abdominal wall; skin; kidney; nerve; gastrointestinal tract including submucosa

Congo red staining with characteristic green birefringence under polarized light

→ **Patient follow-up after diagnosis**

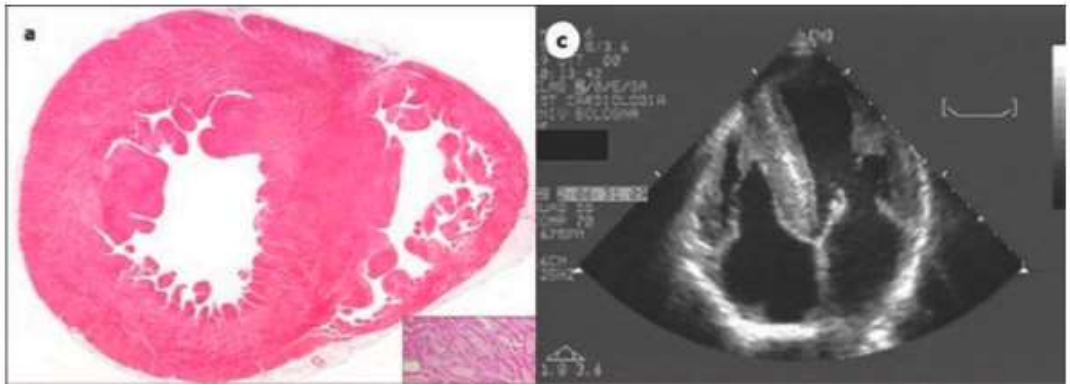
Clinical examination every 6 months (every 3 months for stages II/III) unless responding well to treatment

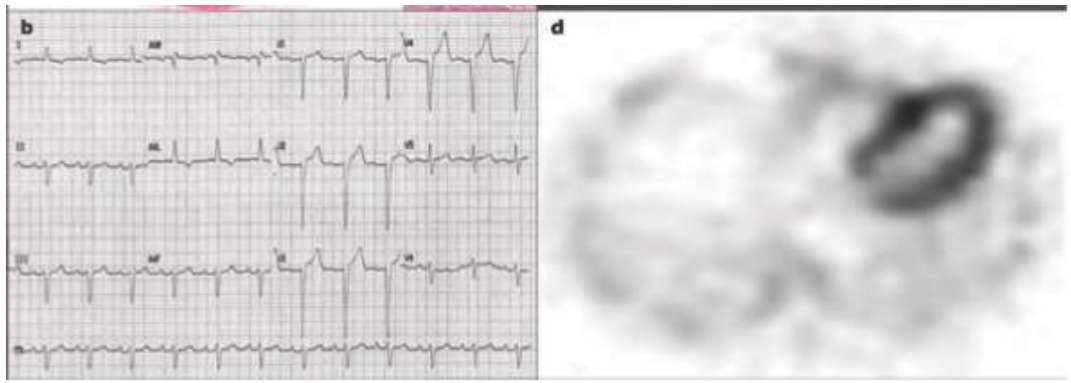
Neurology
- New or progressed symptoms
- Functional scores (eg, walking ability, polyneuropathy disability, neurological impairment score)
- Autonomic (eg, bladder/urinary tract infection, orthostatic hypotension, erectile dysfunction, and gastrointestinal disturbances including diarrhea and early satiety)

Cardiology
- Electrocardiography
- Echocardiography and NT-proBNP

Ophthalmology

Modified body mass index, weight





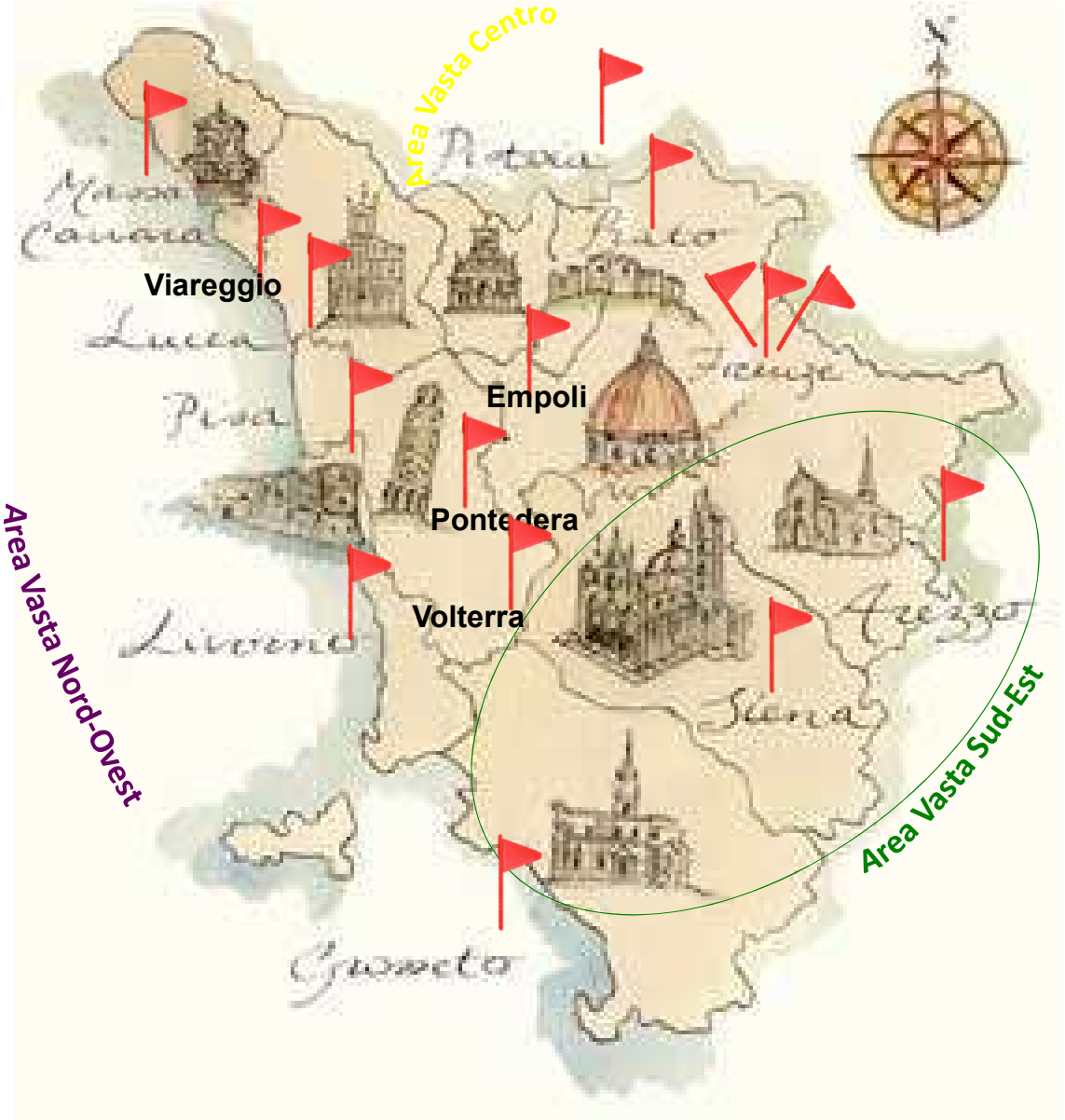
Feature	ATTR	AL	SSA
Ventricular wall thickness	Moderately increased (1.5–2.0 cm)	Mildly increased (1.2–1.5 cm)	Greatly increased (1.8–2.2 cm)
Type of LV "hypertrophy"	Symmetric	Symmetric	Symmetric
Increased RV wall thickness	Frequent	Frequent	Frequent
Increased thickness of interatrial septum	Frequent	Frequent	Frequent
LV ejection fraction	Slightly reduced	Normal or slightly reduced	Moderately reduced
Diastolic dysfunction	Frequent	Frequent	Frequent
Increased thickness of atrio-ventricular valve leaflets	Frequent	Possible	Frequent
Pericardial effusion	Frequent	Frequent	Frequent
Low QRS voltage (%)	<25% of cases	Frequent	<25% of cases
^{99m}Tc-DPD myocardial uptake	Strong	Absent or weak	Strong
NT-proBNP and cardiac troponin	Moderately increased	Severely increased	Moderately increased

Ile68Leu is endemic in some Italian regions . The predominant phenotypic feature associated with these mutations is a severe **restrictive cardiomyopathy with a late onset** (generally in the fifth-seventh decade of life) **with no or minimal neurologic involvement**

Val30Met mutation from endemic areas (Portugal, Sweden and Japan) tend to have a less severe cardiac involvement compared to individuals with the same mutation but from a non-endemic area or with non-Val30Met mutations

Key concepts

- hATTR amyloidosis is a multisystem disease with a heterogeneous clinical presentation in which majority of patients develop a mixed phenotype of both polyneuropathy and cardiomyopathy
- There is frequently a delay in diagnosis of hATTR amyloidosis, due to non-specific symptomatology of the disease
- Patient symptoms worsen significantly throughout the disease course
- In addition to variant TTR, the deposition of wild-type TTR plays a significant role even in ATTRv amyloidosis, particularly in patients with late-onset Val30Met ATTR amyloidosis.
- Due to rapid progression of the disease, there is a need for earlier suspicion and diagnosis of patients with hATTR amyloidosis



3,737 milioni di abitanti, di cui
1,950 mil circa femmine
(dati EUROSTAT 2018)

UO Neurologia

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