Chiara Briani, University of Padova

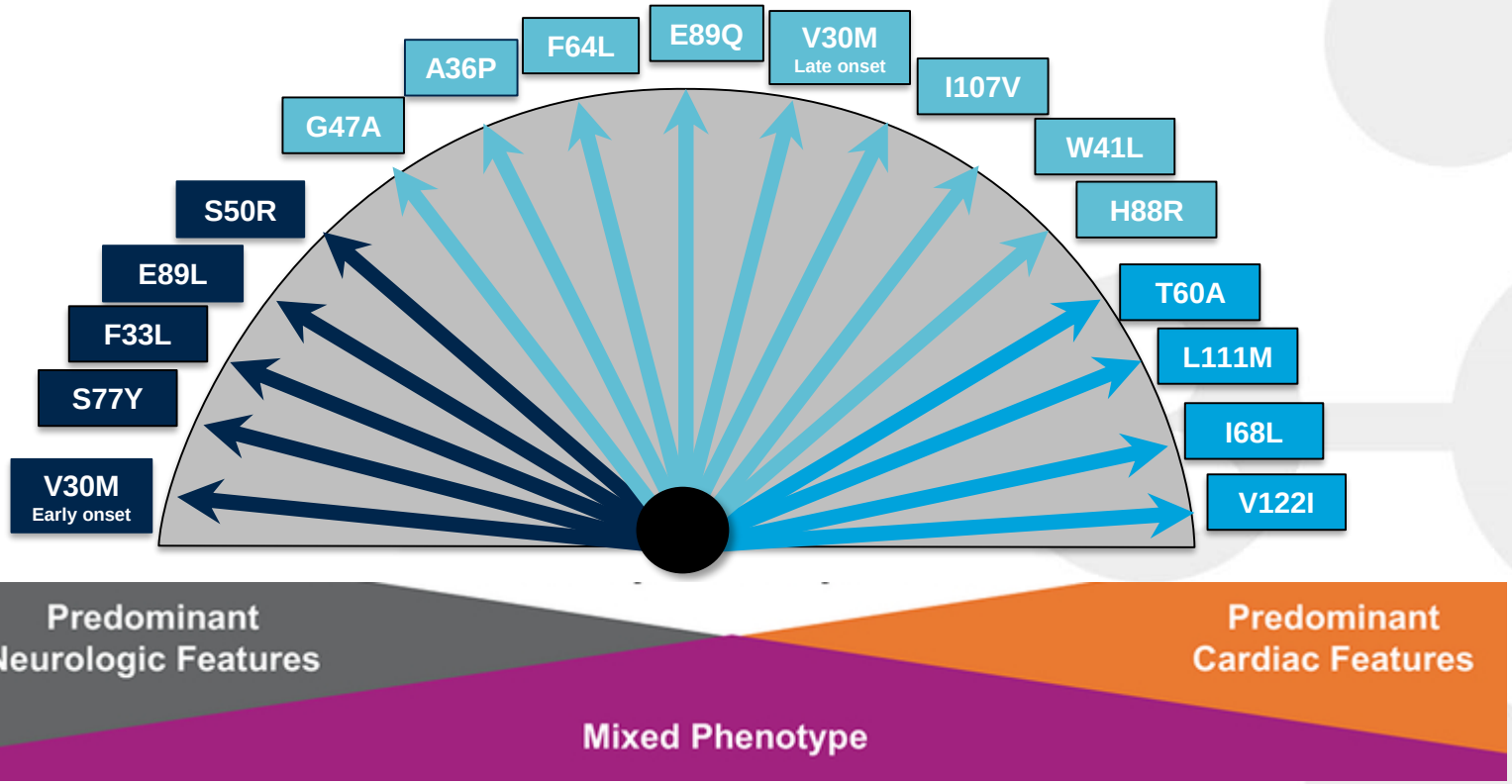
Titolo Le red flags neurologiche

Hereditary Transthyretin Amyloidosis (ATTRv)

- Rare, autosomal-dominant, progressive, often fatal disease caused by mutation in *TTR* gene
- Multisystem disease with heterogeneous clinical presentation
- ATTRv amyloidosis is relentless, with death occurring 10–15 years from diagnosis in untreated patients with ATTR polyneuropathy, and 2–5 years in untreated patients with TTR-amyloid cardiomyopathy
- Clinical manifestations (e.g., disease penetrance, rate of progression) are influenced by TTR genotype and geographical region
- Disease continuum includes predominantly polyneuropathy (formerly FAP) or cardiomyopathy symptoms (formerly FAC), yet many patients experience a variety of symptoms (mixed phenotype)

Genotypic–Phenotypic Association

Heterogeneous clinical presentation with variability based on TTR mutation



Genotypic–Phenotypic Association

♦ More than 150 mutations of the *TTR* gene have been identified, with the most common being the Val30Met (p.Val50Met)

♦ **Val30Met** incidence in Portugal: 1/538, with high penetrance (80% >50 yrs).
Prevalence of FAP in Europe <1/100000. Frequency of Val30Met 4%, low penetrance (11% >50 yrs).

Early-onset ATTR Val30Met: endemic areas (Portugal, Japan, Sweden, Brazil), onset < 50 yrs, high penetrance.
Pain and thermal sensation dysfunction and dysautonomia (gastrointestinal, cardiovascular, sexual and sweating disturbances).
The *progression* of amyloid deposits along the entire length of the nerve leads to a widespread involvement of nerve fibers including those of *large caliber.*

Late-onset ATTR Val30Met: nonendemic areas, onset > 60 yrs. Low penetrance, male prevalence.
Early impairment of the largest nerve fibers.
Autonomic neuropathy usually include erectile dysfunction, alternating diarrhea and constipation, and postural hypotension.

FAP – Familial Amyloidotic Polyneuropathy (V30M)

- ~~Early – onset~~
  - ~~endemic areas , high penetrance~~
  - ~~Small fibers~~
  - ~~Autonomic dysfynctions~~
  - ~~Cardiac arrhythmias~~
  - ~~Slowly progressive~~

- Late – onset
  - nonendemic areas, low penetrance
  - early impairment of the largest nerve fibers
  - Autonomic dysfynctions may remain underrecognized if not properly investigated.
  - Hypertrophic cardiomyopathy
  - Rapid course (death 7.3 years after onset)

In nonendemic areas (52–77% no family history):
20-40% incorrect diagnosis!

less frequent small fibers (33%)
length dependent neuropathies, areflexia, CIDP-like
ataxic neuropathy
rare motor neuropathy

Diagnostic pitfalls in sporadic transthyretin familial amyloid polyneuropathy (TTR-FAP)

Neurology® 2007;69:693-698

Diagnostic hallmarks and pitfalls in late-onset progressive transthyretin-related amyloid-neuropathy

Maike F. Dohrn · Christoph Röcken · Jan L. De Bleecker · Jean-Jacques Martin · Matthias Vorgerd · Peter Y. Van den Bergh · Andreas Ferbert · Katrin Hinderhofer · J. Michael Schröder · Joachim Weis · Jörg B. Schulz · Kristl G. Claeys

J Neurol (2013) 260:3093–3108

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

J Neurol Neurosurg Psychiatry May 2017 Vol 88 No 5

"Red-flag" symptom clusters in transthyretin familial amyloid polyneuropathy

Isabel Conceição[1], Alejandra González-Duarte[2], Laura Obici[3], Hartmut H.-J. Schmidt[4], Damien Simoneau[5], Moh-Lim Ong[6], and Leslie Amass[6]

Journal of the Peripheral Nervous System 21:5–9 (2016)

Diagnostic pitfalls in sporadic transthyretin familial amyloid polyneuropathy (TTR-FAP)

Neurology® 2007;69:693-698

V. Planté-Bordeneuve, MD, PhD
A. Ferreira, MD
T. Lalu, MD
C. Zaros, PhD
C. Lacroix, MD
D. Adams, MD, PhD
G. Said, MD

♦ Clinical and pathologic data of 90 patients (21 W, 69 M) with DNA-proven TTR-FAP who presented as sporadic cases

♦ Symptoms at onset: paresthesias in 68 patients, pain in 17, walking difficulties 8, GI disturbances 9, impotence 2

♦ Symptoms at referral:

All patients had a length-dependent sensory loss affecting

- the lower limbs in 2
- all four limbs in 20
- four limbs and anterior trunk in 68 patients.

Motor deficit predominated in distal lower limbs in 70 patients

♦ Autonomic dysfunction in 80/90 (90%) patients

♦ The mean interval to diagnosis: 4 years (range 1 to 10 years).

The diagnosis of CIDP was considered in 18 patients (20%),11 of whom received high doses of IVIg and corticosteroids.

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Clinical pitfalls

- Manifestations: symmetric paresthesias in distal lower limbs, symptoms common in CIDP which is a far more common condition than FAP.
- Conversely, motor deficit, which is observed in approximately 80% of CIDP patients, was absent at early stages of FAP. Roughly 17% of CIDP patients present with pure sensory deficit.

Attention to autonomic dysfunction, impotence, and intracardiac conduction abnormalities, which do not occur in CIDP!

Laboratory pitfalls

- Increased CSF protein content (7 patients)
- Marked decrease of nerve conduction velocity (8 patients)
- Negative findings of salivary gland, rectal, or nerve biopsies in 11 patients led to reject the diagnosis.

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

We reviewed the medical records of **150 patients** with ATTR diagnosed between 1999 and 2013

Misdiagnosis in 49/150 (32%) cases

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)

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♦ 30 (61%) patients received immune therapy:
- intravenous immunoglobulins (22 patients, 45%)
- steroids (25 patients, 51%)
- immune suppressors (6, 12%)
- combination of them (22 cases, 45%)

without clinical improvement → **In any CIDP who fails all proven first line therapies reconsider the diagnosis!**

♦ 11 patients (22%) diagnosed with lumbar spinal stenosis underwent spine surgery with no or only transient clinical improvement

♦ In 76 pts tissue biopsy failed to show amyloid deposit in 9/35 (25%) nerve biopsy, 15/32 (47%) fat biopsies, 7/16 (43%) in other sites

♦ Delay from disease onset to diagnosis was significantly longer in misdiagnosed patients compared with those not misdiagnosed (46.4±25.4 months vs 34.7±26 months; p=0.01).

Sporadic hereditary neuropathies misdiagnosed as chronic inflammatory demyelinating polyradiculoneuropathy: Pitfalls and red flags

Marta Campagnolo[1] | Federica Taioli[2] | Mario Cacciavillani[3] | Marta Ruiz[1] | Marco Luigetti[4] | Alessandro Salvalaggio[1] | Francesca Castellani[1] | Silvia Testi[2] | Moreno Ferrarini[2] | Tiziana Cavallaro[2] | Roberto Gasparotti[5] | Gian Maria Fabrizi[2] | Chiara Briani[1]

J Peripher Nerv Syst. 2020;25:19–26.

CSF protein: frequent misleading finding!

Lack of response to immunomodulatory therapies and weight loss: red flags

TABLE 2 Red flags for CIDP misdiagnosis

	Diagnosis EFNS/PNS 2010	Variant	Misleading features: NCS	Misleading features: Clinical-CSF	Red flags
1	Definite	Typical	Severe secondary axonal damage Marked temporal dispersion	CSF proteins 0.70 g/L	No response to IV Ig
2	Definite	Typical	Severe secondary axonal damage	CSF oligoclonal bands Transient response to steroids	Clinical phenotype Reduced motor CVs, both proximal and distal
3	Possible	Typical			No response to IV Ig
4	Definite	Typical	Severe secondary axonal damage	CSF proteins 1.5 g/L	Markedly reduced motor CVs (7-16 m/s) with prolonged DLs Nerve US: diffuse ⇑ CSA in all nerves, involving the entire length of the nerve without focal enlargement
5	Definite	Typical	Conduction blocks Marked temporal dispersion	CSF proteins 0.57 g/L; oligoclonal bands Transient response to steroids	Long history (since childhood) Markedly reduced motor CVs, both proximal and distal Nerve US and MR-neurography: diffuse ⇑ CSA in all nerves, involving the entire length of the nerve without focal enlargement
6	Definite	Typical	Severe secondary axonal damage	CSF proteins 0.72 g/L Inconstant response to steroids	Clinical phenotype
7	Definite	Typical	Severe axonal damage	Transient response to steroids and IV Ig	Unexplained weight loss
8	Possible	Typical		Mild improvement of NCS parameters and resolution of CBs after oral steroids	
9	Possible	Typical		Proteins 0.57 g/L	Weight loss

Abbreviations: CB, conduction block; CSA, cross-sectional area; CSF, cerebrospinal fluid; CVs, conduction velocities; DLs, distal latencies; IVIg, intravenous immunoglobulins; NCS, nerve conduction studies; nerve US, nerve ultrasound.

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]

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Multiple misdiagnosis	9 (18)

Sporadic transthyretin amyloidosis with a novel *TTR* gene mutation misdiagnosed as primary amyloidosis

Chiara Briani · Tiziana Cavallaro · Sergio Ferrari · Federica Taioli · Sara Calamelli · Laura Verga · Fausto Adami · Gian Maria Fabrizi

J Neurol (2012) 259:2226–2228

- A 75-year-old man with diabetes, coronary artery disease, presented with signs and symptoms of right-sided heart failure.
- Echocardiogram: left ventricular wall thickening, mild systolic dysfunction and restrictive diastolic pattern.
  Cardiac MRI findings were suggestive of amyloid deposition.

- Abdominal fat fine needle aspiration was negative.
- Endomyocardial biopsy was positive at Congo Red stain and anti-λ chain immunohistochemistry.
- A mild IgG/λ monoclonal gammopathy was present (2.5 g/L); no Bence-Jones protein was detected but a slightly abnormal κ/λ serum free light chain ratio was present
- Cardiac Troponin I was increased as well as NTproBNP.

- Started on melphalan and dexamethasone, cardiac markers the κ/λ FLC chain ratio did not improve.
  A shift to bortezomib-dexamethasone was not effective and a possible hereditary amyloidosis was considered.

♦ Mutational analysis of *TTR* gene demonstrated a heterozygous c.183G>A transition in exon 3 that substituted a glutammic acid with a lysine at residue 62 (p.Glu62Lys) of the mature protein.

♦ After re-evaluating the endocardial biopsy, immunohistochemistry demonstrated a weak TTR positivity. Due to the paucity of bioptic cardiac specimen, electron microscopy studies could not be performed.

.

♦ Neurophysiology revealed a sensory-motor peripheral polyneuropathy and bilateral carpal tunnel syndrome.

♦ Sural nerve biopsy: axonal neuropathy with slight loss of myelinated fibers and few fibers with wallerian-like degeneration. On serial sections a singleton amyloid deposit within a perineurial venule stained positively at TTR immunohistochemistry.

Direct immunofluorescence of cryostatic sections did not show IgG, IgA, IgM, κ- or λ-chains, or C3d deposition.

Following a progressive worsening of the cardiac failure, the patient died.

♦ Autopsy was performed and heart specimen analyzed.

At post-embedding immunogold electron microscopy, the amyloid fibrils were positive for TTR and negative for anti-κ- and λ-chains.

J Neurol (2012) 259:2226–2228

Monoclonal gammopathy of undetermined significance in systemic transthyretin amyloidosis (ATTR)

Amyloid. 2018 March ; 25(1): 62–67.

Pooja Phull[1], Vaishali Sanchorawala[1,2], Lawreen H. Connors[1,3], Gheorghe Doros[1,6], Frederick L. Ruberg[1,4], John L. Berk[1,5], and Shayna Sarosiek[1,2]

♦ **Given the increasing incidence of both TTRwt amyloidosis and monoclonal gammopathies in the elderly population, it is not uncommon to discover a monoclonal protein in elderly patients with amyloidosis.**

♦ **Aim**: retrospective analysis of biopsy-proven ATTRwt and ATTR V122I amyloidosis patients

♦ 140 patients with ATTRwt and 57 V122I ATTR subjects, were included

♦ 55 patients (39%) in the ATTRwt cohort and 28 patients (49%) in the ATTR V122I cohort had a MGUS, as indicated by an abnormality in the serum-free light-chain ratio and/or serum immunofixation electrophoresis.

Monoclonal gammopathy plus positive amyloid biopsy does not always equal AL amyloidosis

MH Sidiqi, S Dasari, ED McPhail, *et al.*

Am J Hematol, 94 (2019), pp. E141-E143

142/495 (29%) wtTTR had a plasma cell disorder

129/142 (90%) wtTTR had a MGUS

RESEARCH

Carpal tunnel syndrome and associated symptoms as first manifestation of hATTR amyloidosis

Chafic Karam, MD, Diana Dimitrova, PhD, Megan Christ, ND, and Stephen B. Heitner, MD

Neurology: Clinical Practice August 2019 vol. 9 no. 4 1-5 doi:10.1212/CPJ.0000000000000640

- **Aim:** to assess whether CTS, when associated with systemic manifestations, could help screen for TTR gene mutation
- **Methods:** We reviewed the charts and interviewed the patients with hATTR seen between 2017 and 2018.

- **Results: 17/23** patients had CTS.
  CTS was the first manifestation of the disease in 10 of 17 patients.
  CTS symptoms occurred 10.4 years before their diagnosis of hATTR amyloidosis.

- In 6 of 10 patients with CTS, the following systemic symptoms were present as the first manifestation: erectile dysfunction, dysautonomia, polyneuropathy, exercise intolerance, and gastrointestinal and ocular symptoms.

→ Most patients with CTS preceding hATTR diagnosis have systemic features. Recognizing systemic features at the time of CTS presentation may help in early diagnosis of hATTR amyloidosis.

Screening Of Hereditary Amyloidosis In Non Endemic Areas: One Step Ahead Of Symptoms

Tiziana Rosso[1], Raffaele Del Colle[2], Mirco Albanese[1], Alessandro Burlina[1], Alessandro Salvalaggio[3]

[1]Neurologia Ospedale San Bassiano, Bassano del Grappa, Italy, [2]Neurologia Ospedale Legnago, Legnago, Italy, [3]Department of Neuroscience, University of Padova, Padova, Italy, Padova, Italy

Methods:

We developed a questionnaire to be applied by neurophysiology technicians and neurophysiologists in the routinary setting of the neurophysiological laboratory while performing an electrodiagnostic test for carpal tunnel syndrome, to screen for hereditary amyloidosis in non endemic areas. **The items investigate signs and symptoms of neuropathy, vertebral stenosis, autonomic neuropathy, cardiac disorders or biceps brachialis tendon fracture**. If 2 red flags are present in a patient affected by bilateral carpal syndrome, neurologists can recommend the oral swab for genetic testing (to be done immediately).

In the medical report itis advisable to extend differential diagnosis, by suggestion of serum protein electrophoresis for AL-Amy and/or cardiological evaluation.

Results:

We identified 3 TTR-mutated patients among 63 screened patients (from the 1600 who underwent proper questionnaire).

PNS PERIPHERAL NERVE SOCIETY
2024 ANNUAL MEETING
PALAIS DES CONGRÈS DE MONTRÉAL
22-25 JUNE 2024

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

Expert consensus recommendations to improve diagnosis of ATTR amyloidosis with polyneuropathy

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]

In non endemic areas

Expert consensus recommendations to improve diagnosis of ATTR amyloidosis with polyneuropathy

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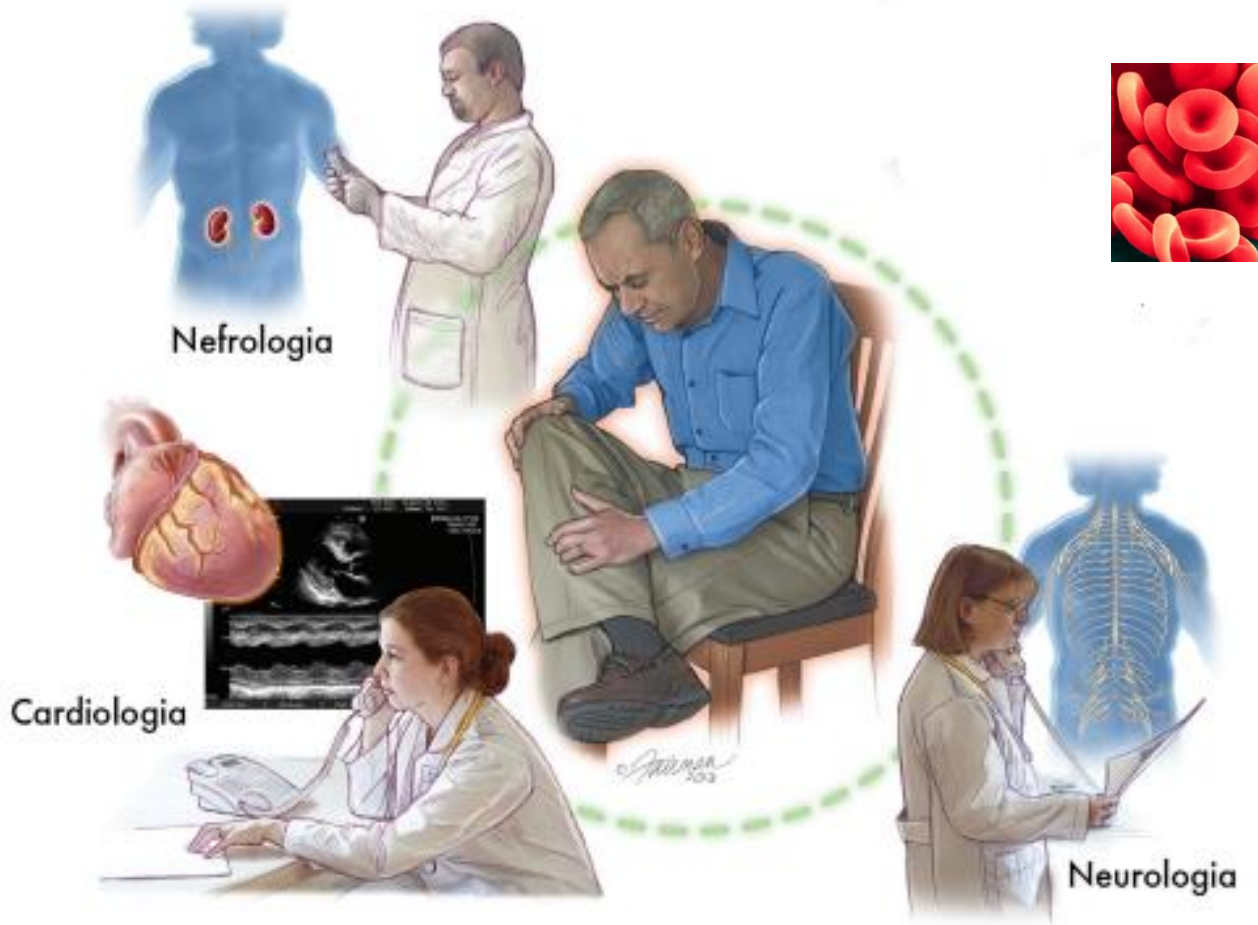
Idiopathic rapidly progressive sensory motor axonal neuropathy
Or
Atypical CIDP

+ ≥1 of the following

- **Family story**
- **Bilateral carpal tunnel syndrome**
- **Autonomic dysfunction (GI complaints (constipation, chronic diarrhea, or both), erectile dysfunction, OH)**
- **Gait disorders**
- **Unexplained weight loss ≥5 kilos**
- **Cardiac hypertrophy Heart rhythm disorders**
- **Vitreous opacities**
- **Renal abnormalities**

Journal of Neurology (2021) 268:2109–2122

Multidisciplinary approach




Thank You

Transthyretin amyloid polyneuropathies mimicking a demyelinating polyneuropathy

Pierre Lozeron, MD, PhD, Louise-Laure Mariani, MD, Pauline Dodet, MD, Guillemette Beaudonnet, MD, Marie Théaudin, MD, PhD, Clovis Adam, MD, Bertrand Arnulf, MD, PhD, and David Adams, MD, PhD

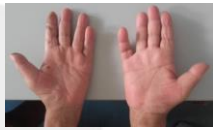
Neurology® 2018;91:e143-e152. doi:10.1212/WNL.0000000000005777

- A retrospective study of patients referred to the French National Reference Center for FAP between 1988 and 2010.
- 13/84 (15%) pts of French ancestry had late-onset dFAPs irrespective of TTR variants.
- The authors compared clinical presentation and electrophysiology to a cohort of CIDP and POEMS pts.
- **Clinical markers** that should alert to possible FAP in patients with suspected CIDP:

→ **Pain** (at 4 limbs) was one of the major complaints.
In CIDP, pain is mild or moderate and rare (7%–8%), in treatment-resistant up to 30%

→ **Dysautonomic features** provide a clue toward the diagnosis of FAP but are less common in late-onset FAP and can be overlooked

→**Distal upper limb motor deficits** were observed in two-thirds of our patients with dFAP



→ **Small fibers sensory loss above the wrist**

Transthyretin amyloid polyneuropathies mimicking a demyelinating polyneuropathy

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Neurology® 2018;91:e143-e152. doi:10.1212/WNL.0000000000005777

♦ Electrophysiologic markers that should alert to possible FAP in patients with suspected CIDP:

♦ No conduction blocks
♦ Axonal loss in the upper limbs is greater in dFAPs than in CIDP and in POEMS

♦ Given that reduced CMAP amplitude in the lower limbs can be blurred by the proportion of nonrecordable nerves, and in the median nerve by a superimposed carpal tunnel syndrome, ulnar nerve CMAP amplitude <5.4 mV would appears to be the most reliable early electrophysiologic clue for suspecting FAP in patients with suspected CIDP.