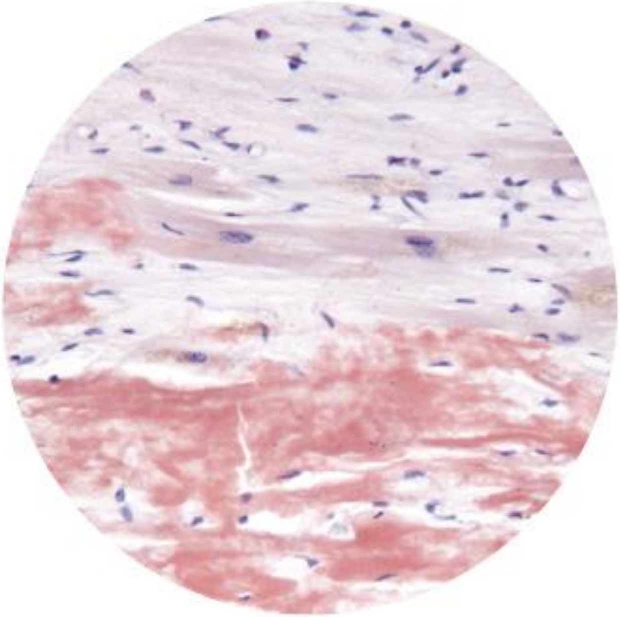
Asociación Española
Enfermedad de Andrade
(Amiloidosis Hereditaria por Transtirretina)

II JORNADAS
AMILOIDOSIS HEREDITARIA por TRANSTIRRETINA (AhTTR)



Viernes 5 de Octubre de 2018
Hospital Son Llàtzer (Salón de Actos)
Palma de Mallorca

II JORNADAS
AMILOIDOSIS HEREDITARIA
por TRANSTIRRETINA (AhTTR)

AEEA AhTTR
Asociación Española
Enfermedad de Andrade
(Amiloidosis Hereditaria por Transtirretina)

DIAGNÓSTICO PRECOZ EN LA AH-TTR: "PERSIGUIENDO LA NEUROPATIA DE FIBRA FINA".

•PRINCIPALES EXPLORACIONES NEUROFISIOLOGICAS.

Dra. CRISTINA DESCALS MOLL .
NEUROFISIOLOGIA CLINICA.SERVICIO DE NEUROLOGIA.
EQUIPO MULTIDISCIPLINAR AMILOIDOSIS POR TTR.
H.SON LLÀTZER.PALMA DE MALLORCA.

Son Llàtzer
HOSPITAL
UNIVERSITARI

INTRODUCCION:

- Ah-TTR/TTR-FAP:
  - Enfermedad sistémica, progresiva, neurodegenerativa, rara, severa, crónica (tratº), discapacitante, de HAD e inicio en edad adulta.
  - Descrita por 1ª vez en 1952 (Dr. Corino de Andrade).

  - Focos endémicos
    - Portugal, Suecia, Japón, España (Mallorca/Huelva).
  - PREVALENCIA GLOBAL: **10.000 personas**… Y SUS FAMILIAS.
    - Prevalencia en Portugal : **22.93/100.000**h. (1865 pacientes). (2016).
    - Mallorca :95 pacientes (2016).

Journal of the Peripheral Nervous System 21:352–356 (2016)

RESEARCH REPORT

Transthyretin familial amyloid polyneuropathy (TTR-FAP) in Mallorca: a comparison between late- and early-onset disease

Juan Buades-Reinés[1], Manuel Raya-Cruz[1], Cristina Gallego-Lezaún[1], Tomás Ripoll-Vera[2], Mercedes Usón-Martín[3], Hernán Andreu-Serra[4], and Eugenia Cisneros-Barroso[5]

[1]Department of Internal Medicine, Son Llàtzer Hospital, Carretera de Manacor; [2]Department of Cardiology, Son Llàtzer Hospital, Carretera de Manacor; [3]Department of Neurology, Son Llàtzer Hospital, Carretera de Manacor; [4]Department of Digestive Medicine, Son Llàtzer Hospital, Carretera de Manacor; and [5]Clinical Research Coordinator A-TTR Group, Son Llàtzer Hospital, Carretera de Manacor, Palma, Spain

Original Paper

Neuro epidemiology

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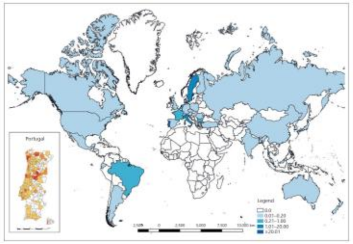
Published online: August 28, 2018

Epidemiology of Transthyretin Familial Amyloid Polyneuropathy in Portugal: A Nationwide Study

Mónica Inês[a] Teresa Coelho[b, c] Isabel Conceição[a, d] Filipa Duarte-Ramos[e] Mamede de Carvalho[a, d] João Costa[a, f]

[a]Instituto de Medicina Molecular, Faculdade de Medicina, Universidade de Lisboa, Lisboa, Portugal; [b]Andrade's Center for Familial Amyloidosis, Porto, Portugal; [c]Department of Neurosciences, Hospital de Santo António, Porto, Portugal; [d]Department of Neurosciences and Mental Health, Hospital de Santa Maria, Lisboa, Portugal; [e]Department of Social Pharmacy, Faculty of Pharmacy, University of Lisboa, Lisboa, Portugal; [f]Laboratório de Farmacologia Clínica e Terapêutica, Faculdade de Medicina, Universidade de Lisboa, Lisboa, Portugal



ESTIMATING THE GLOBAL PREVALENCE OF TRANSTHYRETIN FAMILIAL AMYLOID POLYNEUROPATHY

HARTMUT H. SCHMIDT, MD,[1] MÁRCIA WADDINGTON-CRUZ, MD, PhD,[2] MARC F. BOTTEMAN, MSc, MA,[3]
JOHN A. CARTER, MS,[4] AVIJEET S. CHOPRA, PhD,[3] MARKAY HOPPS, MPH,[5] MICHELLE STEWART, PhD,[6]
SHARI FALLET, DO,[5] and LESLIE AMASS, PhD[7]

Muscle Nerve 57: 829–837, 2018

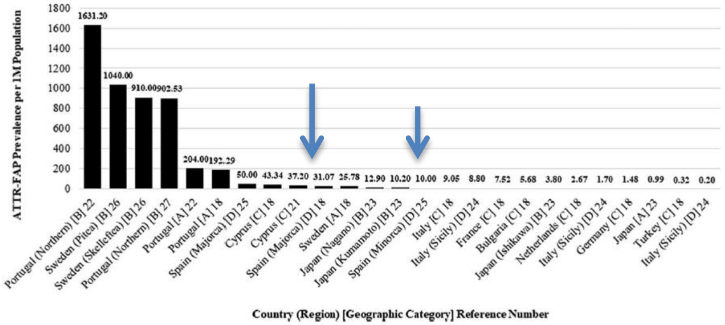


FIGURE 2. Extracted ATTR-FAP prevalence values per 1 million general population (1M). The highest and lowest prevalence values reported in the literature were for subnational regions. The highest prevalence was reported in Northern Portugal (1,631.20/1M), and the lowest was reported in Sicily (0.20/1M). Values are categorized as A (endemic country, national estimate), B (endemic country, regional estimate), C (nonendemic country, national estimate), and D (nonendemic country, regional estimate). ATTR-FAP, transthyretin familial amyloid polyneuropathy

Table 2. Prevalence estimates by country

Country	General population, M	Prevalence low	Prevalence mid	Prevalence high
Totals	4,582.3	5,526	10,186	38,468
Core	460.1	3,639	3,762	3884
Turkey	78.7	25	25	25
Bulgaria	7.2	41	41	41
Netherlands	16.9	45	45	45
Cyprus	1.2	51	51	51
Germany	81.4	121	121	121
Japan	127.0	111	123	135
Sweden	9.8	253	253	253
France	66.8	502	502	502
Italy	60.8	500	550	600
Portugal	10.3	1,990	2,051	2111
Extrapolated	4,122.2	1,887	6,424	3,4584
Luxembourg	0.6	0	1	4
Slovenia	2.1	1	3	16
Ireland (North)	1.9	1	3	14
New Zealand	4.6	1	7	35
Finland	5.5	2	8	41
Denmark	5.7	2	8	43
Israel	8.4	3	12	63
Switzerland	8.3	3	12	62
Austria	8.6	3	13	65
Hungary	9.8	3	15	74
Czech Republic	10.6	3	16	79
Greece	10.8	3	16	81
Belgium	11.3	4	17	85
Ecuador	16.1	5	24	121
Romania	19.8	6	29	149
Sri Lanka	21.0	7	31	158
Taiwan	23.5	8	35	177
Australia	23.8	8	35	179
Korea (South)	50.6	16	75	381
Malaysia	30.3	10	45	228
Canada	35.9	12	53	270
Poland	38.0	12	56	286
Argentina	43.4	14	64	326
Spain	46.4	15	69	349
UK	65.1	21	97	490
Mexico	127.0	41	188	955
Russia	144.1	46	214	1,084
Bangladesh	161.0	52	239	1,211
Brazil*	207.8	623	623	5,078
USA†	321.4	104	476	2,488
India	1,311.1	423	1,943	9,858
China	1,347.7	435	1,997	10,134

GENERALIDADES AhTTR

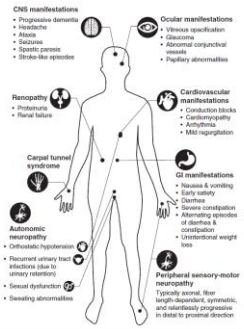
- FISIOPATOLOGÍA: Depósito extracelular de fibrillas de amiloide.
- SINTOMATOLOGÍA más característica:

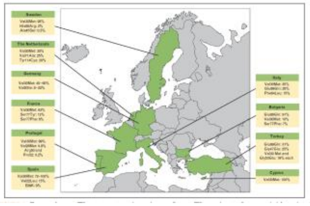
  PNP axonal sensitivo>motora progresiva .

  ☞ fibra fina > neuropatía autonómica > NFF (SFN)

  ⇨ fibra gruesa > PNP SM.

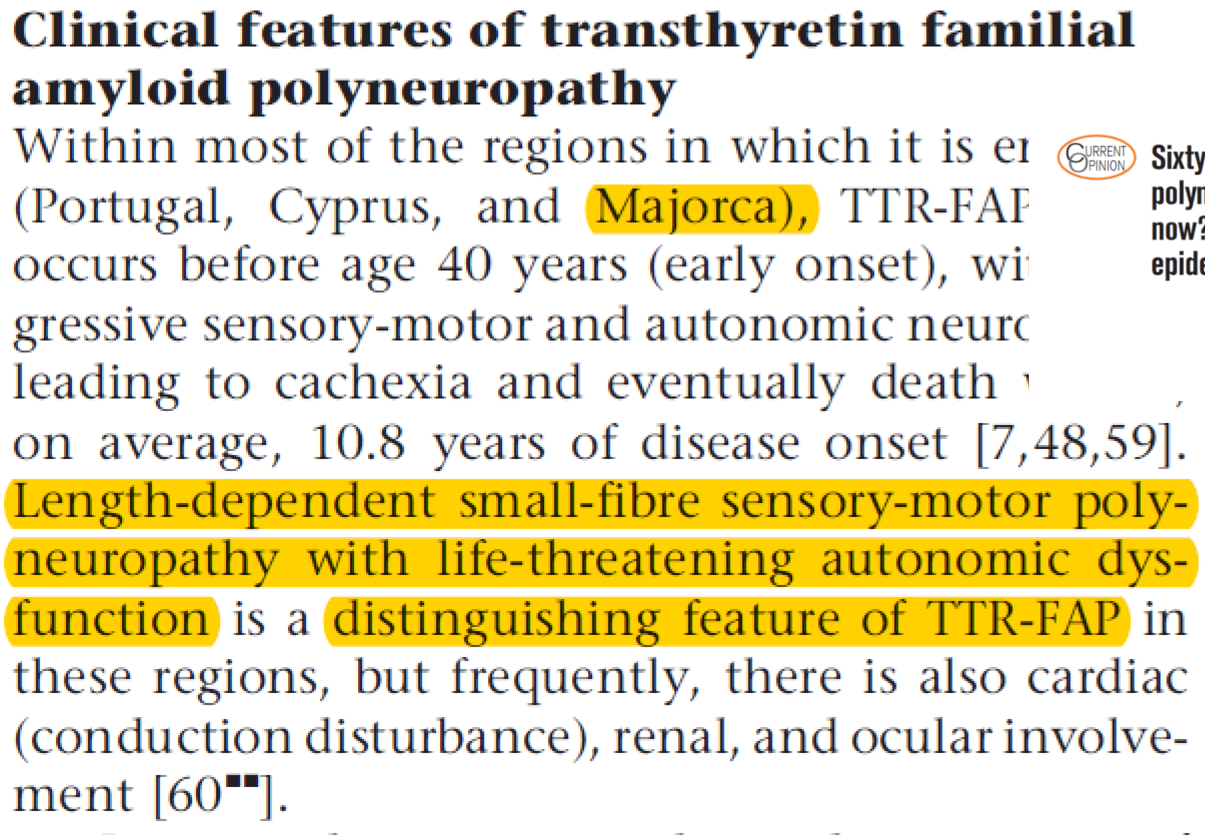
  - ASOCIA: afectación cardiaca, GI, ocular , STC y renal.
    - Heterogenicidad fenotípica y genética (> 120 mutaciones).
      - Retraso en el diagnóstico.


CNS manifestations
• Progressive dementia
• Headache
• Ataxia
• Seizures
• Spastic paresis
• Stroke-like episodes
Ocular manifestations
• Vitreous opacification
• Glaucoma
• Abnormal conjunctival vessels
• Papillary abnormalities
Renopathy
• Proteinuria
• Renal failure
Cardiovascular manifestations
• Conduction blocks
• Cardiomyopathy
• Arrhythmia
• Mild regurgitation
Carpal tunnel syndrome
GI manifestations
• Nausea & vomiting
• Early satiety
• Diarrhea
• Severe constipation
• Alternating episodes of diarrhea & constipation
• Unintentional weight loss
Autonomic neuropathy
• Orthostatic hypotension
• Recurrent urinary tract infections (due to urinary retention)
• Sexual dysfunction
• Sweating abnormalities
Peripheral sensory-motor neuropathy
Typically axonal, fiber length-dependent, symmetric, and relentlessly progressive in distal to proximal direction



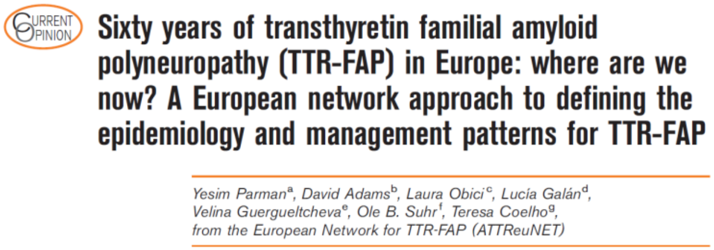
PUNTOS CLAVE :

- El diagnóstico está frecuentemente retrasado de 2,8-4,3 años TRAS EL PRIMER SÍNTOMA.
- El pronóstico es FATAL entre los 2 a 15 desde el inicio.
- La PNP progresa en 3 a 5 años.
  - Primero FF autonómicas >FF termoalgésica> FG (S>M).
  - Distal a proximal de EEII a EESS.
- Forma de inicio PRECOZ (<50 a.) : predomina la PNP y el inicio con la neuropatía de fibra fina.
- Forma de inicio TARDÍO (>50 a.) : predomina la afectación cardiaca +PNP (más difusa).
- TRATAMIENTOS EMERGENTES : **DIAGNÓSTICO PRECOZ**.



Clinical features of transthyretin familial amyloid polyneuropathy

Within most of the regions in which it is e
(Portugal, Cyprus, and Majorca), TTR-FA
occurs before age 40 years (early onset), wi
gressive sensory-motor and autonomic neur
leading to cachexia and eventually death
on average, 10.8 years of disease onset [7,48,59].
Length-dependent small-fibre sensory-motor polyneuropathy with life-threatening autonomic dysfunction is a distinguishing feature of TTR-FAP in these regions, but frequently, there is also cardiac (conduction disturbance), renal, and ocular involvement [60▪▪].

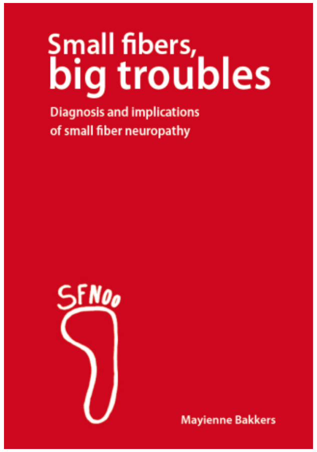


CURRENT OPINION

Sixty years of transthyretin familial amyloid polyneuropathy (TTR-FAP) in Europe: where are we now? A European network approach to defining the epidemiology and management patterns for TTR-FAP

Yesim Parman[a], David Adams[b], Laura Obici[c], Lucía Galán[d], Velina Guergueltcheva[e], Ole B. Suhr[f], Teresa Coelho[g], from the European Network for TTR-FAP (ATTReuNET)

“HABRA QUE BUSCARLA Y DEMOSTRARLA”…



Small fibers,
big troubles

Diagnosis and implications
of small fiber neuropathy

SFN

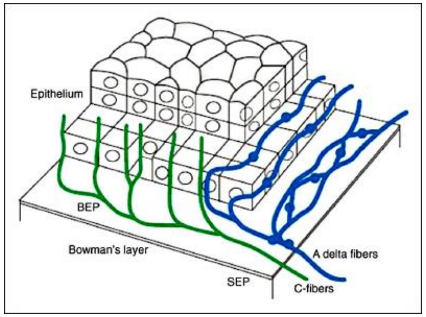
Mayienne Bakkers

NUESTRA EXPERIENCIA.

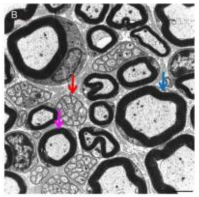
☞ESTUDIO DE SEGUIMIENTO EN PORTADORES VAL30MET EN LA UNIDAD MULTIDISCIPLINAR DE AMILOIDOSIS.

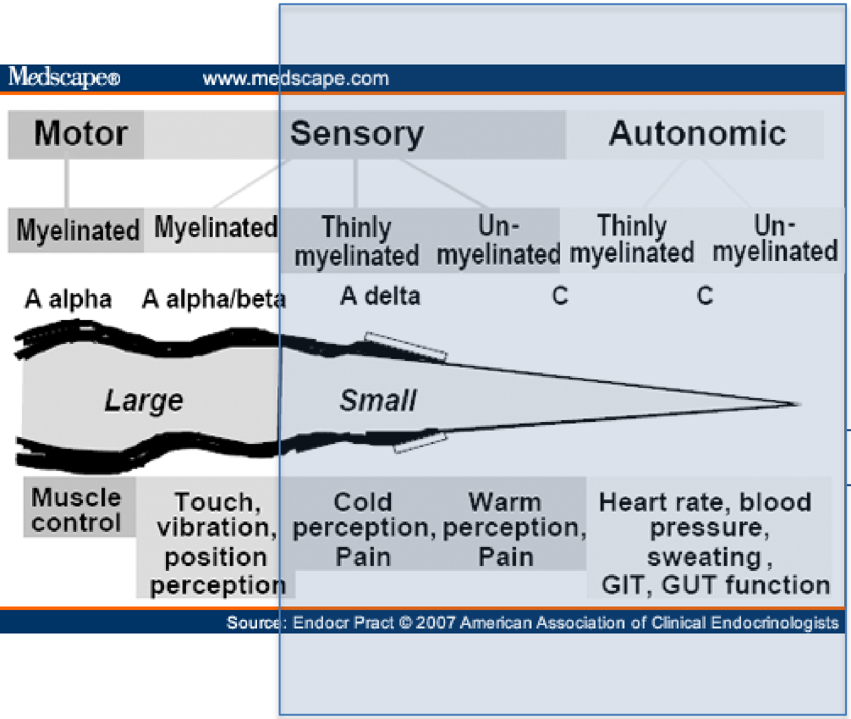
☞PRINCIPALES PRUEBAS NEUROFISIOLÓGICAS.

“PERSIGUIENDO LA NEUROPATIA DE FIBRA FINA”.


Epithelium
BEP
Bowman's layer
A delta fibers
SEP
C-fibers

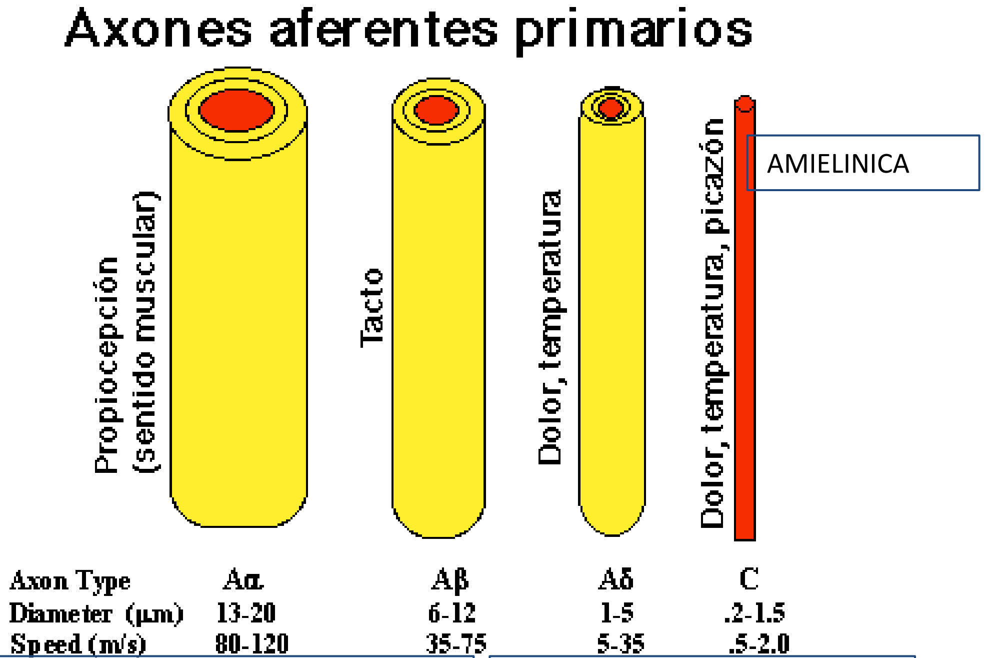
TIPOS DE FIBRAS NERVIOSAS




Medscape®
www.medscape.com
Motor
Sensory
Autonomic
Myelinated
Myelinated
Thinly myelinated
Un-myelinated
Thinly myelinated
Un-myelinated
A alpha
A alpha/beta
A delta
C
C
Large
Small
Muscle control
Touch, vibration, position perception
Cold perception, Pain
Warm perception, Pain
Heart rate, blood pressure, sweating, GIT, GUT function

Source: Endocr Pract © 2007 American Association of Clinical Endocrinologists

Axones aferentes primarios


Propiocepción (sentido muscular)
Tacto
Dolor, temperatura
Dolor, temperatura, picazón

AMIELINICA

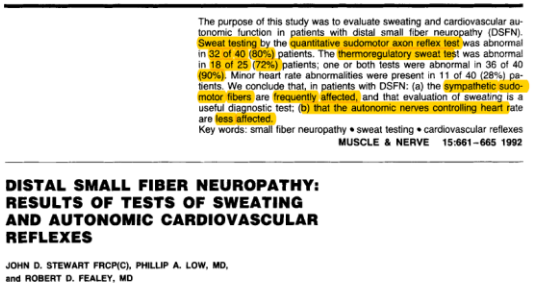
Axon Type	Aα	Aβ	Aδ	C
Diameter (µm)	13-20	6-12	1-5	.2-1.5
Speed (m/s)	80-120	35-75	5-35	.5-2.0

CALIBRE GRUESO

CALIBRE FINO

NEUROPATIA de FIBRA FINA:

- Descrita en 1992: **Stewart et al**.



The purpose of this study was to evaluate sweating and cardiovascular autonomic function in patients with distal small fiber neuropathy (DSFN). Sweat testing by the quantitative sudomotor axon reflex test was abnormal in 32 of 40 (80%) patients. The thermoregulatory sweat test was abnormal in 18 of 25 (72%) patients; one or both tests were abnormal in 36 of 40 (90%). Minor heart rate abnormalities were present in 11 of 40 (28%) patients. We conclude that, in patients with DSFN: (a) the sympathetic sudomotor fibers are frequently affected, and that evaluation of sweating is a useful diagnostic test; (b) that the autonomic nerves controlling heart rate are less affected.

Key words: small fiber neuropathy • sweat testing • cardiovascular reflexes

MUSCLE & NERVE 15:661–665 1992

DISTAL SMALL FIBER NEUROPATHY: RESULTS OF TESTS OF SWEATING AND AUTONOMIC CARDIOVASCULAR REFLEXES

JOHN D. STEWART FRCP(C), PHILLIP A. LOW, MD,
and ROBERT D. FEALEY, MD

- Aquella neuropatía periférica en la que se afectan las fibras nerviosas de pequeño calibre : **Aδ y C.**
  - La mayoría de PNP afectan en su evolución los dos tipos de fibras (f+g).
    - Los nervios sensitivos están formados por fibras g+f con diferentes umbrales de estímulo y receptores.
  - Si existe > afectación del SNA (fibras amielínicas C):
    - NEUROPATÍA AUTONÓMICA.
  - Si existe > afectación difusa de FF (Aδ y C : termoelgésica+autonómica) :
    - NEUROPATÍA DE FIBRA FINA.

NEUROPATIA de FIBRA FINA:

- FISIOPATOLOGÍA:
  - Degeración axonal de esas terminaciones nerviosas.
  - Hiperexcitabilidad (canales Na+).
- ETIOLOGÍA:
  - Idiopática.
  - Secundaria.

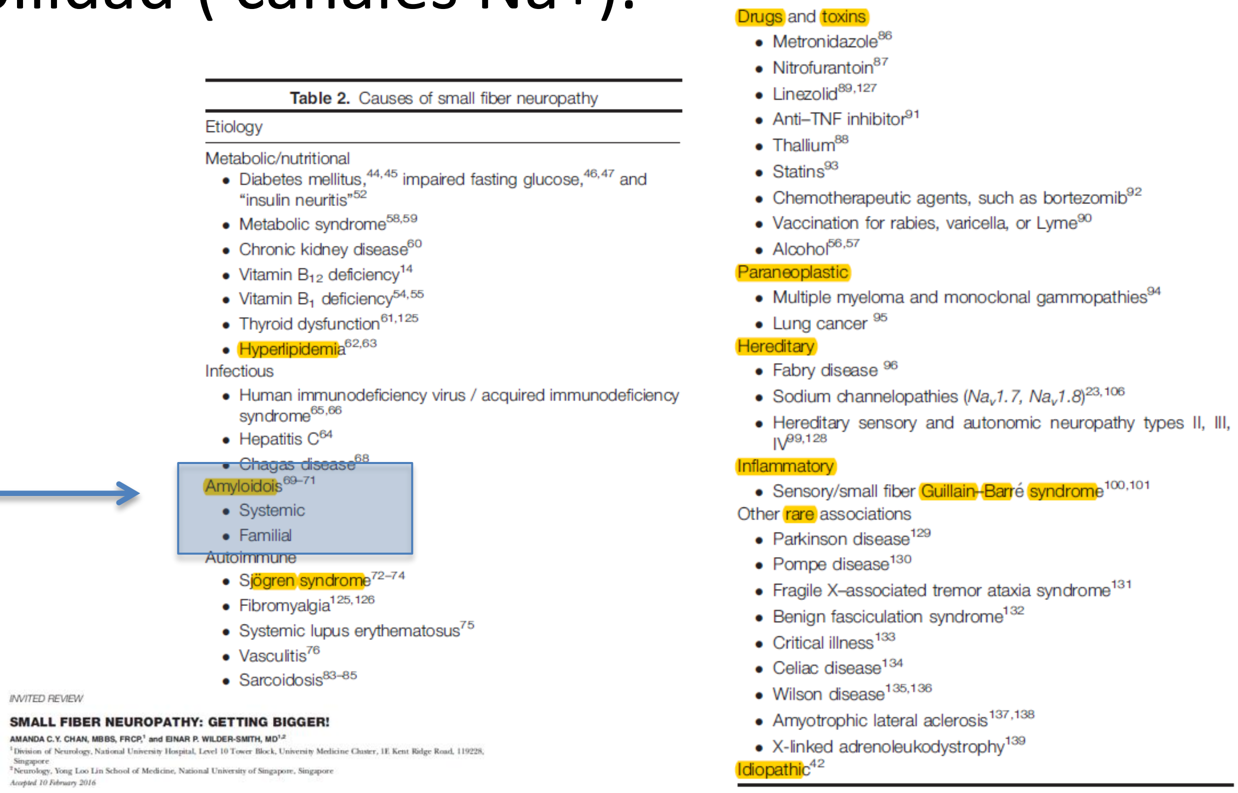


Table 2. Causes of small fiber neuropathy

Etiology

Metabolic/nutritional
- Diabetes mellitus,[44,45] impaired fasting glucose,[46,47] and "insulin neuritis"[52]
- Metabolic syndrome[58,59]
- Chronic kidney disease[60]
- Vitamin B_{12} deficiency[14]
- Vitamin B_1 deficiency[54,55]
- Thyroid dysfunction[61,125]
- Hyperlipidemia[62,63]

Infectious
- Human immunodeficiency virus / acquired immunodeficiency syndrome[65,66]
- Hepatitis C[64]
- Chagas disease[68]

Amyloidois[69–71]
- Systemic
- Familial

Autoimmune
- Sjögren syndrome[72–74]
- Fibromyalgia[125,126]
- Systemic lupus erythematosus[75]
- Vasculitis[76]
- Sarcoidosis[83–85]

Drugs and toxins
- Metronidazole[86]
- Nitrofurantoin[87]
- Linezolid[89,127]
- Anti–TNF inhibitor[91]
- Thallium[88]
- Statins[93]
- Chemotherapeutic agents, such as bortezomib[92]
- Vaccination for rabies, varicella, or Lyme[90]
- Alcohol[56,57]

Paraneoplastic
- Multiple myeloma and monoclonal gammopathies[94]
- Lung cancer [95]

Hereditary
- Fabry disease [96]
- Sodium channelopathies ($Na_v1.7$, $Na_v1.8$)[23,106]
- Hereditary sensory and autonomic neuropathy types II, III, IV[99,128]

Inflammatory
- Sensory/small fiber Guillain–Barré syndrome[100,101]

Other rare associations
- Parkinson disease[129]
- Pompe disease[130]
- Fragile X–associated tremor ataxia syndrome[131]
- Benign fasciculation syndrome[132]
- Critical illness[133]
- Celiac disease[134]
- Wilson disease[135,136]
- Amyotrophic lateral aclerosis[137,138]
- X-linked adrenoleukodystrophy[139]

Idiopathic[42]

INVITED REVIEW

SMALL FIBER NEUROPATHY: GETTING BIGGER!

AMANDA C.Y. CHAN, MBBS, FRCP,[1] and EINAR P. WILDER-SMITH, MD[1,2]

[1] Division of Neurology, National University Hospital, Level 10 Tower Block, University Medicine Cluster, 1E Kent Ridge Road, 119228, Singapore

[2] Neurology, Yong Loo Lin School of Medicine, National University of Singapore, Singapore

Accepted 10 February 2016

NFF: SINTOMAS y SIGNOS

DOLOR-DISESTESIAS

- Severo, limitante
  - > espontáneo.
  - Evocado (sábanas en la cama, calcetines).
  - Ejercicio o calor (Canalopatías, Fabry).
- Distribución longitud-dependiente (pies>manos).
- Ocasionalmente distribución focal (inmunomediadas).
- Quemazón, pinchazos, prurito.
- HIPOESTESIA (<frecuente).

ALTERACIÓN SENSIBILIDAD A LA TEMPERATURA

- Hipoestesia al frío, calor.
- Hiperalgesia al frío, calor.

SÍNTOMAS AUTONÓMICOS (<20%)

- Hipotensión ortostática.
- Disfunción gastrointestinal-urinaria.
- Disfunción sexual.
- Ojo seco.

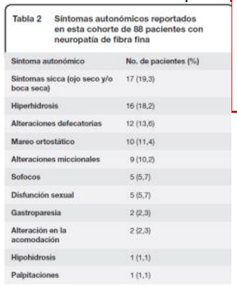


Tabla 2 Sintomas autonómicos reportados en esta cohorte de 88 pacientes con neuropatía de fibra fina

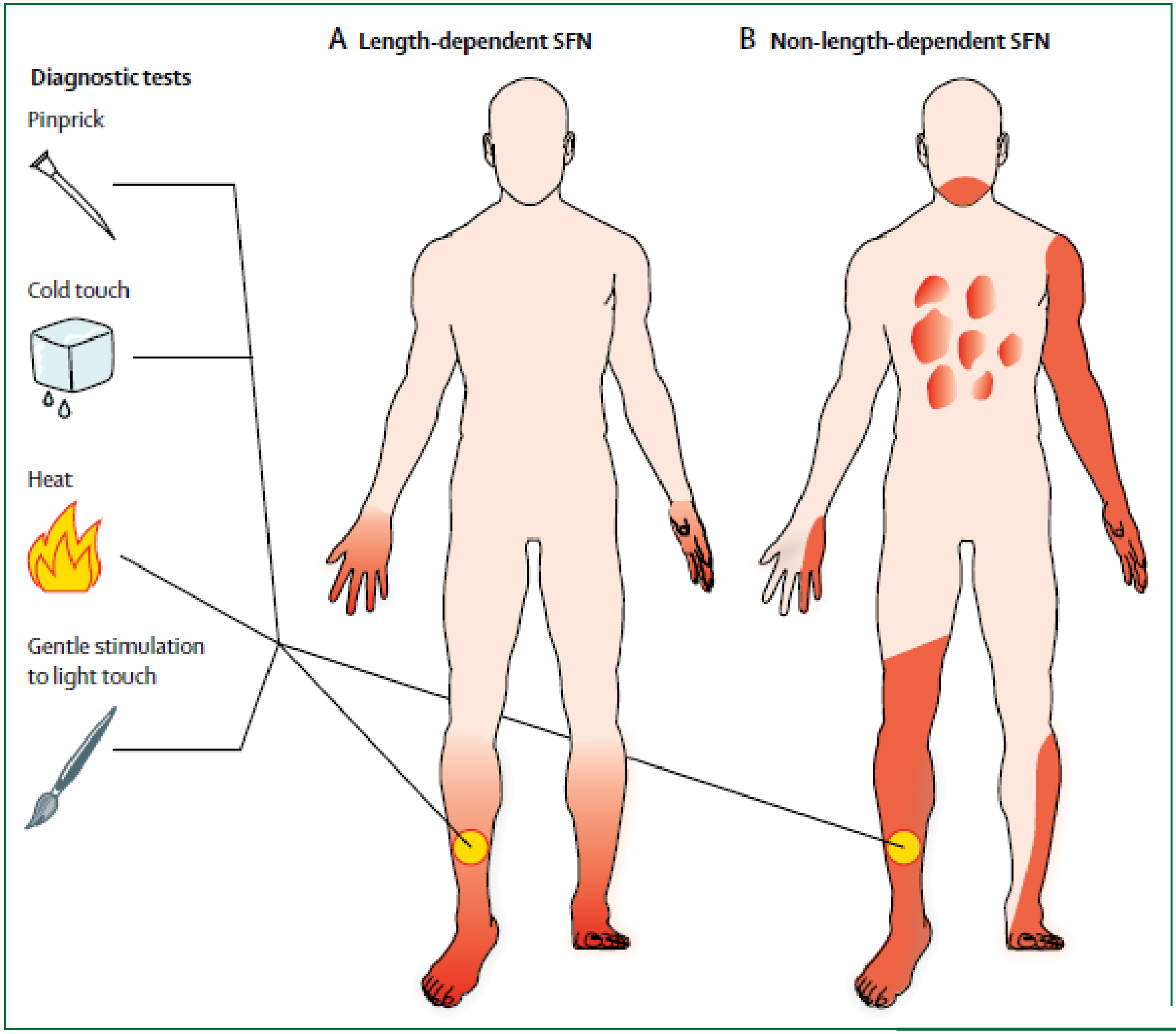
Sintoma autonómico	No. de pacientes (%)
Sintomas sicca (ojo seco y/o boca seca)	17 (19,3)
Hiperhidrosis	16 (18,2)
Alteraciones defecatorias	12 (13,6)
Mareo ortostático	10 (11,4)
Alteraciones miccionales	9 (10,2)
Sofocos	5 (5,7)
Disfunción sexual	5 (5,7)
Gastroparesia	2 (2,3)
Alteración en la acomodación	2 (2,3)
Hipohidrosis	1 (1,1)
Palpitaciones	1 (1,1)

- Cambios tróficos piel: seca, agrietada o brillante.
- Normalidad función motora.
- Normalidad función sensitiva de fibra gruesa: tacto, vibración y propiocepción.

- Disminución sensibilidad punzante y térmica.
- Hiperalgesia al pinchazo.
- Alodinia al pincel.

- Disminución TA cambio postural con aumento FC.

- SPI
- CALAMBRES

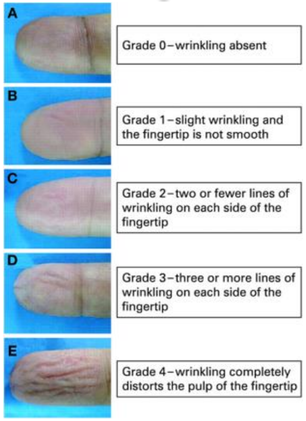

A Length-dependent SFN
B Non-length-dependent SFN
Diagnostic tests
Pinprick
Cold touch
Heat
Gentle stimulation to light touch

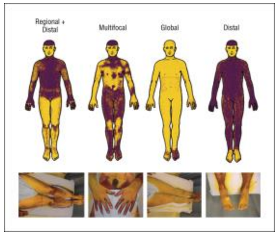
The diagnostic challenge of small fibre neuropathy: clinical presentations, evaluations, and causes

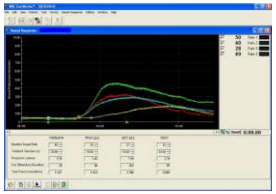
Astrid J Terkelsen*, Páll Karlsson*, Giuseppe Lauria, Roy Freeman, Nanna B Finnerup, Troels S Jensen

Lancet Neurol 2017; 16: 934–44

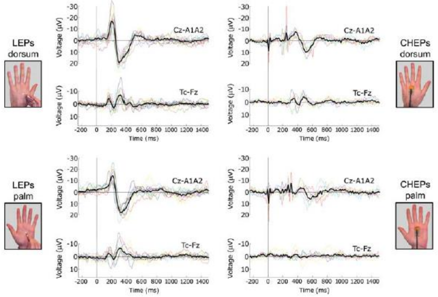
DIAGNÓSTICO: Exploraciones Complementarias

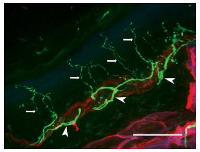

A
Grade 0–wrinkling absent
B
Grade 1–slight wrinkling and the fingertip is not smooth
C
Grade 2–two or fewer lines of wrinkling on each side of the fingertip
D
Grade 3–three or more lines of wrinkling on each side of the fingertip
E
Grade 4–wrinkling completely distorts the pulp of the fingertip

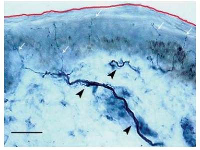

Regional + Distal
Multifocal
Global
Distal

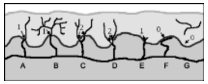


- CUESTIONARIOS PARA VALORAR NFF.
- PRUEBAS VALORACIÓN FUNCIONAL SNA:
  - CARDIOVASCULAR: HRV, Tilt Test, Hipotension postural (TA).
    - MN: SPECT (I-MIBG).
  - PRUEBAS DE VALORACION FUNCION SUDOMOTORA:
    - QSART.
    - SUDOSCAN (ESC).
    - STIMULATED SKIN WRINKLING
    - TEST de SUDOR TERMORREGULADO, MOLDES DE "SWEAT IMPRINT",..
- PRUEBAS NEUROFISIOLÓGICAS: ENG por definición debe ser NORMAL.
  - QST.
  - RSC.
  - Intervalo R-R.
  - POTENCIALES EVOCADOS LASER/CALOR (CHEPs /LEPs).
  - Microneurografía.
- PRUEBAS DE A.P.: Biopsia cutánea (DFNIE).
- MICROSCOPÍA CONFOCAL (Oftalmología).









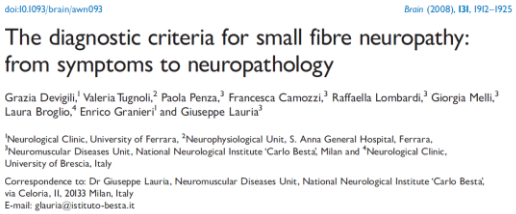
DIAGNÓSTICO

- **DIAGNÓSTICO de la NEUROPATÍA DE FIBRA FINA:**
  - **CLÍNICO con el soporte de UNA TÉCNICA DIAGNÓSTICA ESPECÍFICA para el estudio de LA FIBRA FINA > TERMOALGÉSICA.**
    - Criterios diagnósticos.

- **Las exploraciones complementarias para el estudio específico de las fibras de pequeño calibre son MUY LABORIOSAS ("time-consuming"), y están disponibles en pocos centros hospitalarios.**
  - PEL/CHEP/microneurografía.
  - Unidades de estudio de DISAUTONOMIA.
  - Biopsia cutánea para valorar la DFNIE.

CRITERIOS DIAGNÓSTICOS

AL MENOS 2 (2006):



doi:10.1093/brain/awn093 *Brain* (2008), **131**, 1912–1925

The diagnostic criteria for small fibre neuropathy: from symptoms to neuropathology

Grazia Devigili,[1] Valeria Tugnoli,[2] Paola Penza,[3] Francesca Camozzi,[3] Raffaella Lombardi,[3] Giorgia Melli,[3] Laura Broglio,[4] Enrico Granieri[1] and Giuseppe Lauria[3]

[1]Neurological Clinic, University of Ferrara, [2]Neurophysiological Unit, S. Anna General Hospital, Ferrara, [3]Neuromuscular Diseases Unit, National Neurological Institute 'Carlo Besta', Milan and [4]Neurological Clinic, University of Brescia, Italy

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E-mail: glauria@istituto-besta.it

- 1) **SINTOMAS CLÍNICOS** DE AFECTACIÓN DE FIBRA FINA:
  - Alodinia y/o hiperalgesia y/o alteración s. termoalgésica.
  - Distribución de neuropatía periférica.
- 2) **QST** patológico (para umbral de frío y calor).
- 3) Disminución de la densidad distal EEII de fibras (biopsia piel) : **IENF**.

- **DESCARTAR**: PNP (no déficit motor, no alteración sensibilidad vibratoria/ artrocinética/táctil /RMP, no alteración ENG) .

- **2009**: POSIBLE (1), PROBABLE (1+ ENG n.sural NORMAL), DEFINIDA (1+2+biopsia cutánea).

PRIMERA CONCLUSIÓN:

- En la AhTTR es frecuente el debut con afectación de FF en sus formas de inicio precoz >tardía.
    - RECORDAR:
        - NEUROPATÍA AUTONÓMICA.
        - NEUROPATÍA DE FIBRAS FINA (A+TermoAlgésica).
- PARA EL DIAGNÓSTICO PRECOZ y SEGUIMIENTO DE PORTADORES:
    - ¿QUÉ PRUEBAS NOS RECOMIENDAN HACER?

SEGUIMIENTO DE PORTADORES VAL30MET

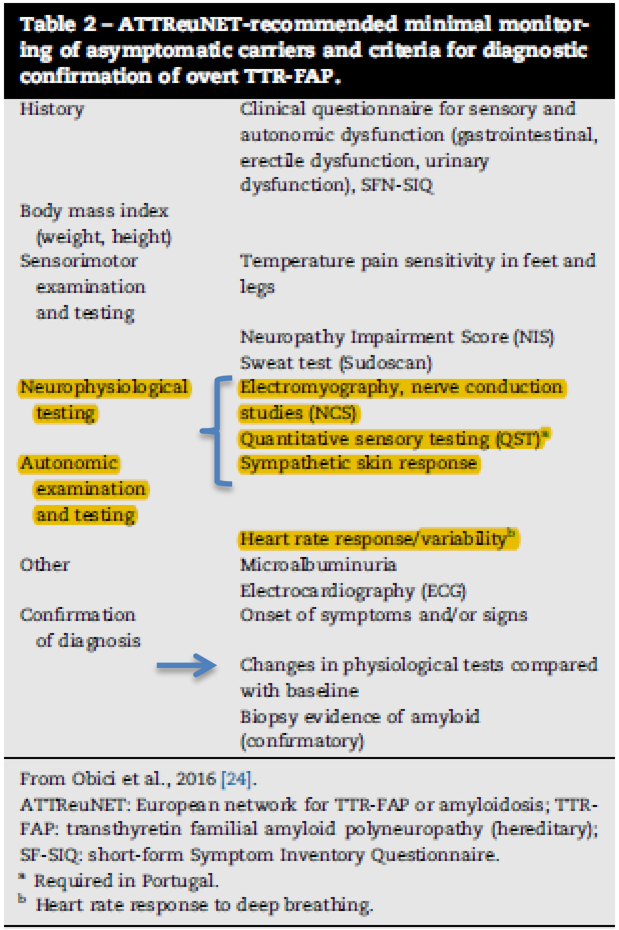


Table 2 – ATTReuNET-recommended minimal monitoring of asymptomatic carriers and criteria for diagnostic confirmation of overt TTR-FAP.

History	Clinical questionnaire for sensory and autonomic dysfunction (gastrointestinal, erectile dysfunction, urinary dysfunction), SFN-SIQ
Body mass index (weight, height)	
Sensorimotor examination and testing	Temperature pain sensitivity in feet and legs
	Neuropathy Impairment Score (NIS)
	Sweat test (Sudoscan)
Neurophysiological testing	Electromyography, nerve conduction studies (NCS)
	Quantitative sensory testing (QST)[a]
Autonomic examination and testing	Sympathetic skin response
	Heart rate response/variability[b]
Other	Microalbuminuria
	Electrocardiography (ECG)
Confirmation of diagnosis	Onset of symptoms and/or signs
	Changes in physiological tests compared with baseline
	Biopsy evidence of amyloid (confirmatory)

From Obici et al., 2016 [24].
ATTReuNET: European network for TTR-FAP or amyloidosis; TTR-FAP: transthyretin familial amyloid polyneuropathy (hereditary); SF-SIQ: short-form Symptom Inventory Questionnaire.

[a] Required in Portugal.

[b] Heart rate response to deep breathing.

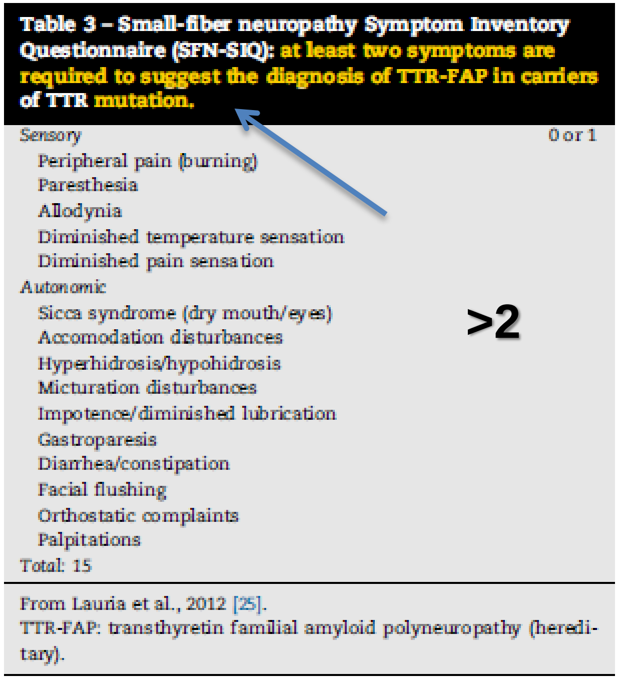
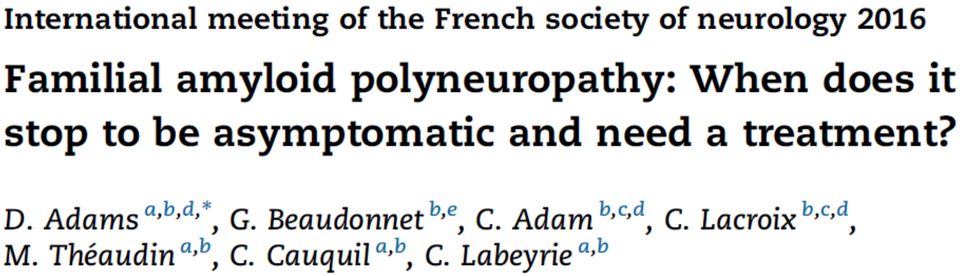


Table 3 – Small-fiber neuropathy Symptom Inventory Questionnaire (SFN-SIQ): at least two symptoms are required to suggest the diagnosis of TTR-FAP in carriers of TTR mutation.

Sensory	0 or 1
Peripheral pain (burning)	
Paresthesia	
Allodynia	
Diminished temperature sensation	
Diminished pain sensation	
Autonomic	
Sicca syndrome (dry mouth/eyes)	
Accomodation disturbances	
Hyperhidrosis/hypohidrosis	
Micturation disturbances	
Impotence/diminished lubrication	
Gastroparesis	
Diarrhea/constipation	
Facial flushing	
Orthostatic complaints	
Palpitations	
Total: 15	

From Lauria et al., 2012 [25].
TTR-FAP: transthyretin familial amyloid polyneuropathy (hereditary).

>2



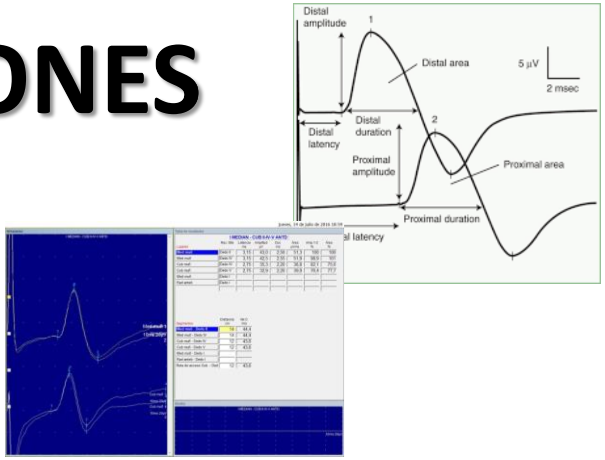
International meeting of the French society of neurology 2016

Familial amyloid polyneuropathy: When does it stop to be asymptomatic and need a treatment?

D. Adams [a,b,d,*], G. Beaudonnet [b,e], C. Adam [b,c,d], C. Lacroix [b,c,d], M. Théaudin [a,b], C. Cauquil [a,b], C. Labeyrie [a,b]

- PROTOCOLO DE ESTUDIO ANTE UNA SOSPECHA DE TTR-PNP.
- SEGUIMIENTO PORTADORES.

PRINCIPALES EXPLORACIONES NEUROFISIOLOGICAS .


Distal amplitude
1
Distal area
5 µV
2 msec
2
Distal latency
Distal duration
Proximal amplitude
Proximal area
Proximal duration
l latency

EXPLORACION NEUROFISIOLOGICA

- **EMG**: ENG /VCN ⇨ exploramos fibra gruesa (M/S) (**Aα/Aß**).
- **Valoración de FIBRA FINA termo-algésica (Aδ y C)**.
    1. **QST (TEST SENSORIAL CUANTITATIVO).**
    2. LEPs (PE por laser).
    3. CHEPs (PE por calor).
    4. PREMPs. (PE por estímulo eléctrico doloroso) .
- **Valoración de FIBRA FINA autonómica (C)**.
    1. **RESPUESTA SIMPATICO CUTANEA** (SN simpático): **RSC.**
    2. **INTERVALO R-R** (SN parasimpático): **HrVRR.**
- MICRONEUROGRAFÍA **(Aδ y C)** .

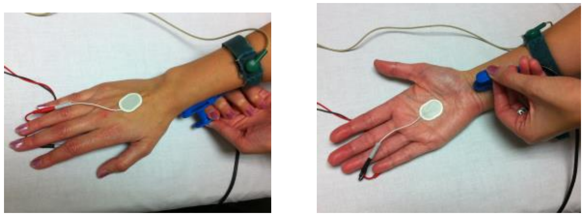
1.ELECTROMIOGRAFÍA

- Ante la sospecha de neuropatía de fibra fina:
  - ENG debe ser NORMAL + soporte de test específicos.
- Ante la sospecha de inicio síntomas PNP en paciente portador :
  - VALORAR CAMBIOS SIGNIFICATIVOS EN ENG BASAL

  (seguimiento evolutivo): caída de amplitud del SNAP/CMAP.
- Ante una sospecha de PNP HEREDITARIA POR TTR esperaremos encontrar:
  - POLINEUROPATIA SENSITIVA>MOTORA DE PREDOMINIO AXONAL (amplitudes bajas) de inicio DISTAL EN EEII +STC.

2.VALORACIÓN NEUROFISIOLÓGICA DE FIBRA FINA: RESPUESTA SIMPÁTICO CUTÁNEA.

- Es el potencial registrado ante el cambio de resistencia cutánea provocado por la sudoración tras un estímulo.
  - ESTÍMULO SOMESTÉSICO, ACÚSTICO O MAGNÉTICO.
  - Información indirecta sobre la función sudomotora colinérgica simpática.



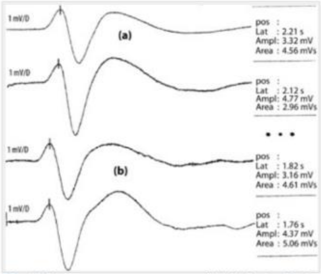


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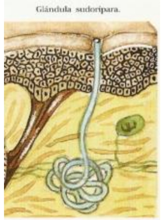
Fig1: A typical sympathetic skin response recording. Typical SSR recordings taken from the right palm (upper trace) and left palm (lower trace) (a) following electrical stimulus of left median nerve and (b) magnetic stimulation of cervical cord

- **FISIOLOGÍA:**
  - Reflejo polisináptico.
  - Múltiples aferencias: estímulo emocional, acústico, eléctrico-sensitivo.
  - SNC: hipotálamo, formación reticular, médula espinal (columna lateral) ipsilateral.
  - Vía eferente: fibras simpáticas sudomotoras pre y postganglionares (fibra amielínica C).
  - Activación glándulas sudoríparas. Está presente en pacientes con ausencia congénita de gl.sudoríparas.



2.VALORACIÓN NEUROFISIOLÓGICA DE FIBRA FINA: RESPUESTA SIMPÁTICO CUTÁNEA.

ESPECIFICACIONES TÉCNICAS:

a) Estímulo eléctrico

- N.mediano, n.tibial, n.trigémino.
- Dur 0.1-0.2ms.
- Int 10-30mA (x3 umbral sens).
- No doloroso.
- Frecuencia irregular (>30sg)
  - Evitar habituación.

b) Estímulo acústico

c) Estímulo magnético, estímulo láser.

Registro

- Mano: palma-dorso mano.
- Pie: planta-dorso pie.
- Tiempo: 5-10s.
- Filtros: LFF 0,1-2Hz, HFF 100Hz.
- Sens: 0.2-2mV/div

Ventajas:

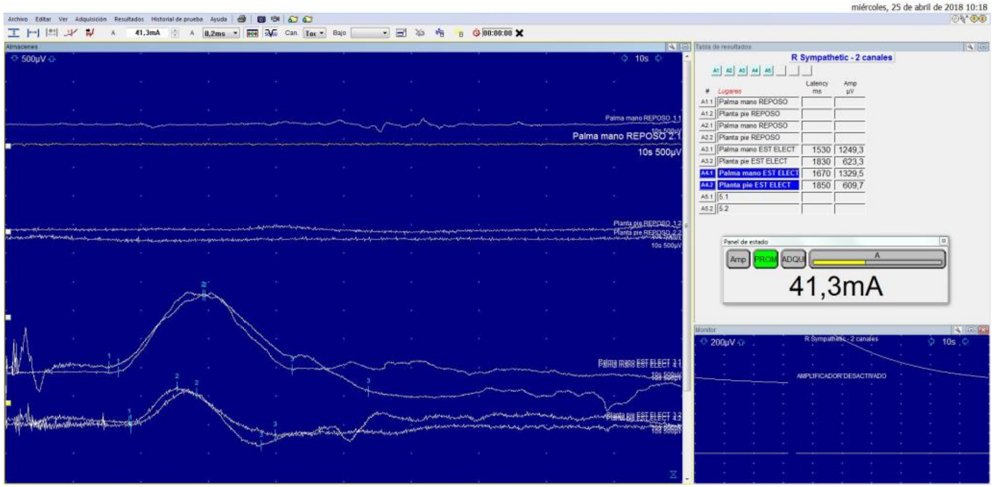
* Fácil realización.
* Método cribaje, screening.
* ALTA ESPECIFICIDAD.

Desventajas:

* Gran variabilidad.
* Tendencia habituación.
* No claros criterios definidos de anormalidad.
  *ausencia
  *↓amplitud >50% D-E
* BAJA SENSIBILIDAD.

Mayor utilidad en la valorar la funcionalidad de fibras fina (C) más que en patología autonómica.

2.VALORACIÓN NEUROFISIOLÓGICA DE FIBRA FINA: RESPUESTA SIMPÁTICO CUTÁNEA.


Archivo Editar Ver Adquisición Resultados Historial de prueba Ayuda
41,3mA
0,2ms
00:00:00
Almacenes
500µV
10s
Palma mano REPOSO 1.1
Palma mano REPOSO 2.1
10s 500µV
Planta pie REPOSO 1.2
Planta pie REPOSO 2.2
10s 500µV
Palma mano EST ELECT 3.1
Planta pie EST ELECT 3.2
Panel de estado
Amp
PROM
ADQU
A
Monitor
200µV
R Sympathetic - 2 canales
AMPLIFICADOR DESACTIVADO

miércoles, 25 de abril de 2018 10:18

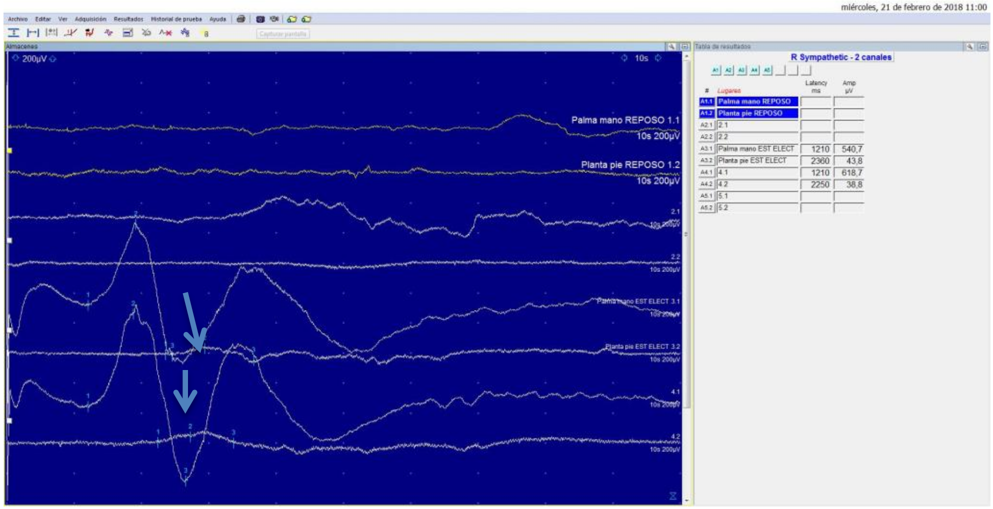
Tabla de resultados

R Sympathetic - 2 canales

#	Lugares	Latency ms	Amp µV
A1.1	Palma mano REPOSO		
A1.2	Planta pie REPOSO		
A2.1	Palma mano REPOSO		
A2.2	Planta pie REPOSO		
A3.1	Palma mano EST ELECT	1530	1249,3
A3.2	Planta pie EST ELECT	1830	623,3
A4.1	Palma mano EST ELECT	1670	1329,5
A4.2	Planta pie EST ELECT	1850	609,7
A5.1	5.1		
A5.2	5.2		

41,3mA

NORMAL


Archivo Editar Ver Adquisición Resultados Historial de prueba Ayuda
Capturar pantalla
Almacenes
200µV
10s
Palma mano REPOSO 1.1
10s 200µV
Planta pie REPOSO 1.2
10s 200µV
2.1
2.2
Palma mano EST ELECT 3.1
Planta pie EST ELECT 3.2
4.1
4.2
10s 200µV

miércoles, 21 de febrero de 2018 11:00

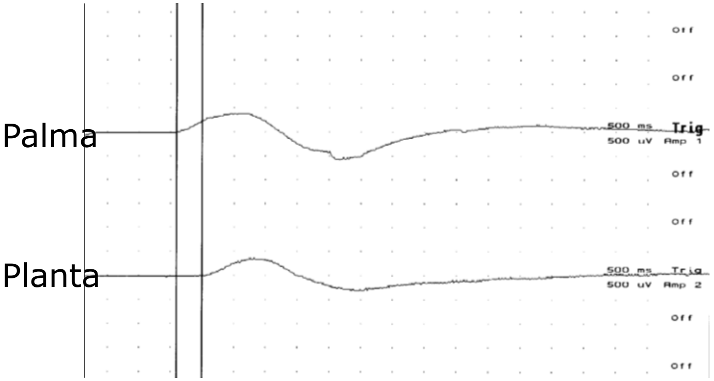
Tabla de resultados

R Sympathetic - 2 canales

#	Lugares	Latency ms	Amp µV
A1.1	Palma mano REPOSO		
A1.2	Planta pie REPOSO		
A2.1	2.1		
A2.2	2.2		
A3.1	Palma mano EST ELECT	1210	540,7
A3.2	Planta pie EST ELECT	2360	43,8
A4.1	4.1	1210	618,7
A4.2	4.2	2250	38,8
A5.1	5.1		
A5.2	5.2		

RSC PATOLOGICA PARA PIE

2.VALORACIÓN NEUROFISIOLÓGICA DE FIBRA FINA: RESPUESTA SIMPÁTICO CUTÁNEA.

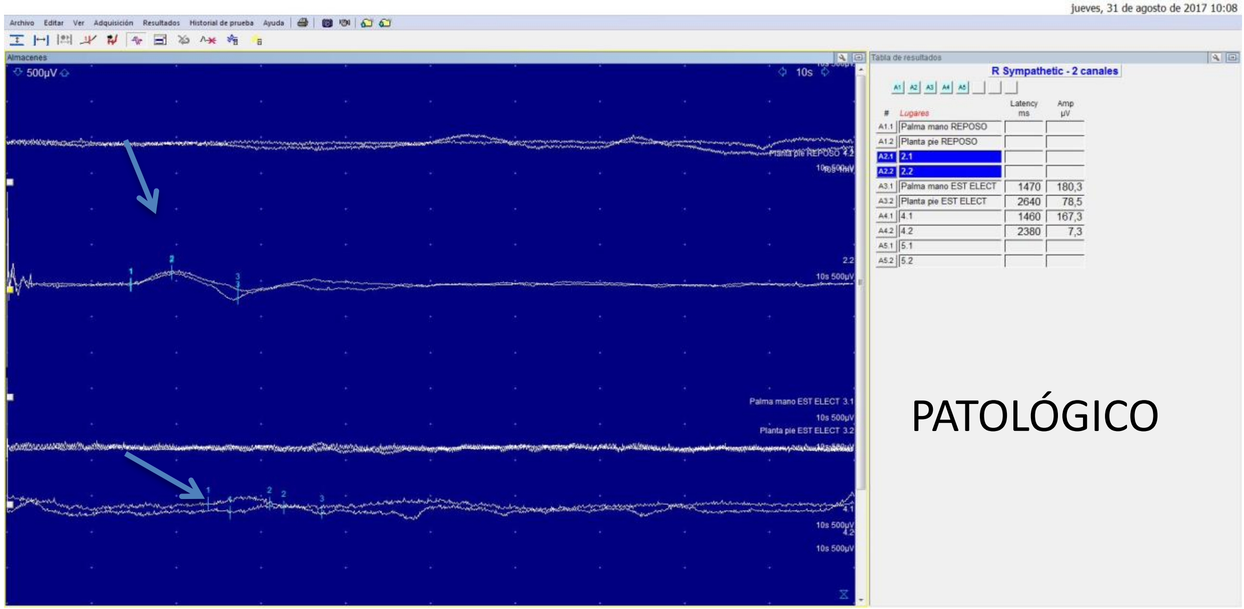

Palma
Planta
off
500 ms Trig
500 uV Amp 1
500 ms Trig
500 uV Amp 2

conduction along unmyelinated fibers, and latenc
measurement is not useful. Initially regarded as a
all-or-none phenomenon, now as techniques are r
fined, amplitude criteria are defined. According t
Hoeldtke,[37] latency in hands is 1.6 ± 0.1 s, amplitud
in hands is 1.3 ± 0.2 mV, latency in feet is 2.1 ± 0.1
and amplitude in feet is 0.8 ± 0.1 mV. According t
Knezevic,[45] latency in hands is 1.5 ± 0.1 s, amplitud
in hands is 0.5 ± 0.1 mV, latency in feet is 2.1 ± 0.2
and amplitude in feet 0.1 ± 0.04 mV. According t
Drory,[19] mean latency in hands is 1.5 s, mean ampl
tude in hands is 0.450 mV, mean latency in feet is 1.
s, and mean amplitude in feet is 0.15 mV.

Clinical Comments. The main advantages of th
SSR are that it is sensitive, reproducible, semiqua
titative, simple, fast, and readily obtained on mo

>1.1 mV mano
>0.7 mV pie

>0.4 mV mano
>0,15 mV pie


Archivo
Editar
Ver
Adquisición
Resultados
Historial de prueba
Ayuda
Almacenes
500µV
10s
Tabla de resultados
A1
A2
A3
A4
A5
Planta pie REPOSO 4.2
2.2
10s 500µV
Palma mano EST ELECT 3.1
10s 500µV
Planta pie EST ELECT 3.2
4.1
4.2

jueves, 31 de agosto de 2017 10:08

R Sympathetic - 2 canales

#	Lugares	Latency ms	Amp µV
A1.1	Palma mano REPOSO		
A1.2	Planta pie REPOSO		
A2.1	2.1		
A2.2	2.2		
A3.1	Palma mano EST ELECT	1470	180,3
A3.2	Planta pie EST ELECT	2640	78,5
A4.1	4.1	1460	167,3
A4.2	4.2	2380	7,3
A5.1	5.1		
A5.2	5.2		

PATOLÓGICO

2.VALORACIÓN NEUROFISIOLÓGICA DE FIBRA FINA: INTERVALO R-R

- Registro de la variabilidad de la frecuencia cardiaca (R-R) en reposo.
  - Arritmia fisiológica sinusal (n.vago).

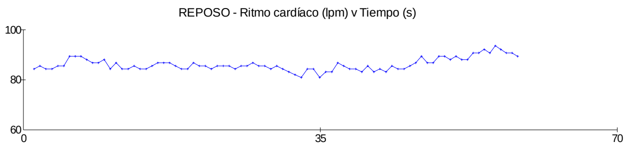
- Registro de la variabilidad de la frecuencia cardiaca (R-R) tras activaciones (HV, Valsalva).

- Programa automático (cálculo): media de 5 ciclos.

2.VALORACIÓN NEUROFISIOLÓGICA DE FIBRA FINA: INTERVALO R-R

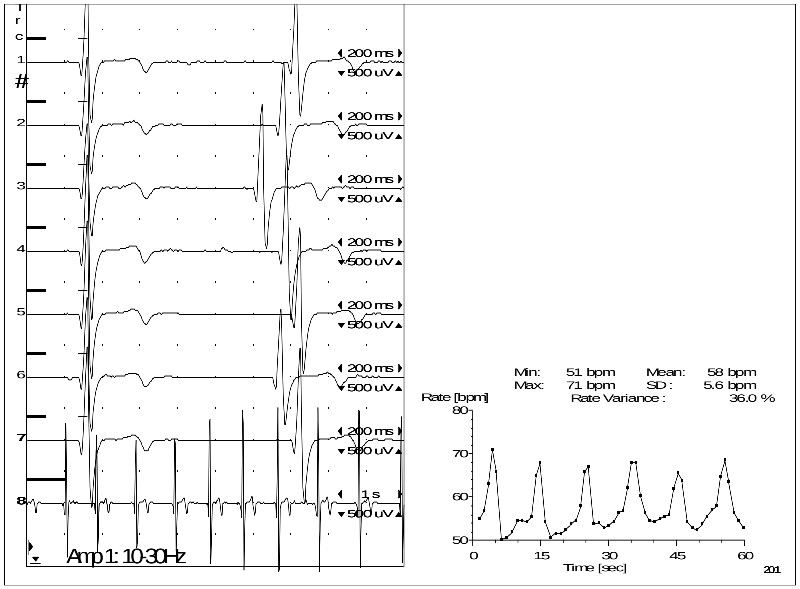
a)R-R Intérvalo.
Condiciones basales.

- ❖Registro durante 1 min.
- ❖Promedio 5 min.
- ❖Arritmia sinusal normal:
  - inspiración ↓ RR
  - espiración ↑RR
- ❖Variabilidad >10% RR



b)R-R Intérvalo .
Respiración profunda 6 rpm.

- ❖ Registro durante 1 min a 6 rpm (5’’I /5’’E).
- ❖ Inspiración ↓ RR - Espiración ↑RR
- ❖ Diferencias entre FC min y FC max >10 lpm


1
2
3
4
5
6
7
8
200 ms
500 uV
1 s
Amp1: 10-30Hz
Min: 51 bpm
Max: 71 bpm
Mean: 58 bpm
SD: 5.6 bpm
Rate Variance: 36.0 %
Rate [bpm]
80
70
60
50
0
15
30
45
60
Time [sec]

2.VALORACIÓN NEUROFISIOLÓGICA DE FIBRA FINA: INTERVALO R-R

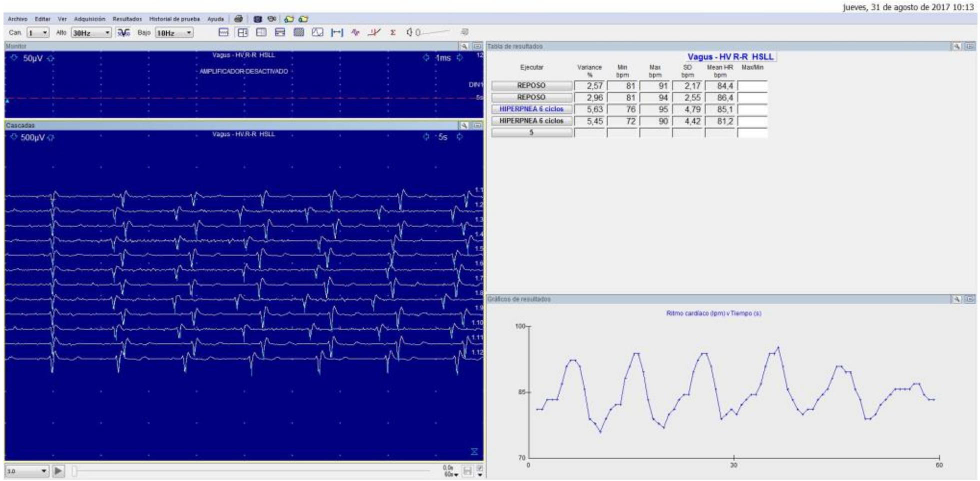

jueves, 31 de agosto de 2017 10:13

Tabla de resultados

Vagus - HV R-R HSLL

Ejecutar	Variance %	Min bpm	Max bpm	SD bpm	Mean HR bpm	Max/Min
REPOSO	2,57	81	91	2,17	84,4	
REPOSO	2,96	81	94	2,55	86,4	
HIPERPNEA 6 ciclos	5,63	76	95	4,79	85,1	
HIPERPNEA 6 ciclos	5,45	72	90	4,42	81,2	
5						

Monitor
Vagus - HV R-R HSLL
AMPLIFICADOR DESACTIVADO
50µV
1ms
Cascadas
500µV
5s
Gráficos de resultados
Ritmo cardiaco (bpm) v Tiempo (s)
100
85
70
0
30
60

NORMAL

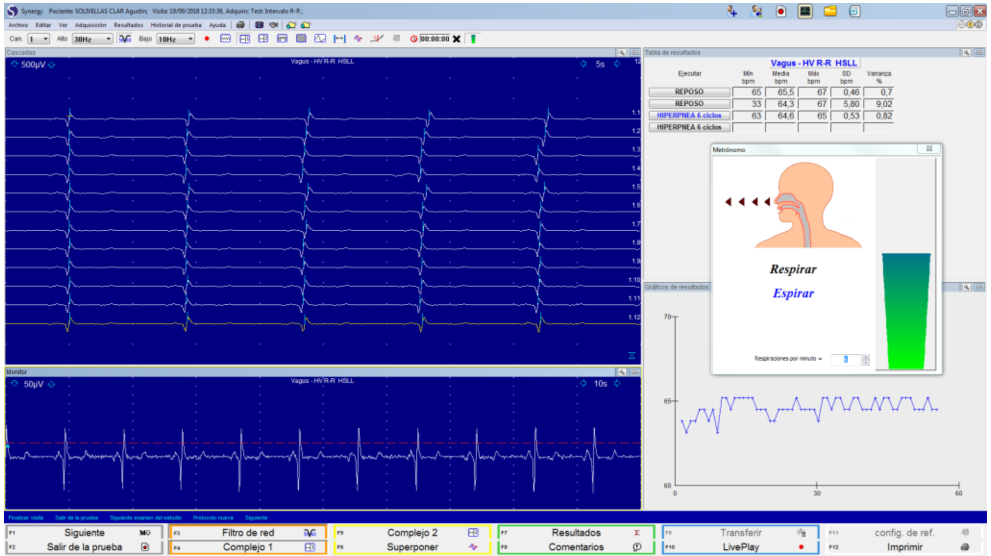

Synergy Paciente: SOLIVELLAS CLAR Agustin; Visita: 19/09/2018 12:33:39, Adquirir; Test: Intervalo R-R ;

Tabla de resultados

Vagus - HV R-R HSLL

Ejecutar	Min bpm	Media bpm	Máx bpm	SD bpm	Varianza %
REPOSO	65	65,5	67	0,46	0,7
REPOSO	33	64,3	67	5,80	9,02
HIPERPNEA 6 ciclos	63	64,6	65	0,53	0,82
HIPERPNEA 6 ciclos					

Archivo Editar Ver Adquisición Resultados Historial de prueba Ayuda
Can. 1 Alto 30Hz Bajo 10Hz
Cascadas
500µV
Vagus - HV R-R HSLL
5s
Metrónomo
Respirar
Espirar
Respiraciones por minuto =
Gráficos de resultados
70
65
60
0
30
60
Monitor
50µV
10s
Siguiente
Salir de la prueba
Filtro de red
Complejo 1
Complejo 2
Superponer
Resultados
Comentarios
Transferir
LivePlay
config. de ref.
Imprimir

PATOLÓGICO

3.VALORACIÓN NEUROFISIOLÓGICA DE FIBRA FINA: QST (TEST CUANTITATIVO SENSORIAL).

- TEST PSICOFÍSICO (no invasivo) de evaluación de **UMBRALES SENSITIVOS** a estímulos sensoriales cuantificados en las diferentes vertientes sensitivas.
    - Exploración más generalizada para la detección de disfunción fibras finas.
    - Batería de pruebas.
- Permite evaluar de forma objetiva la SENSIBILIDAD y cuantificar la TERMOALGESIA.
- Permitirá evaluar tanto la HIPOESTESIA COMO LA HIPERALGESIA.
    - Distintas modalidades sensibilidad:
        - **térmica: Aδ, C (thermotest) –método de los límites-niveles-**
        - vibratoria: Aβ (estímulo vibratorio-vibrometro-).
        - táctil: Aβ (monofilamentos).

- Estudio funcionalidad totalidad del circuito nervioso sensitivo : central y periférico.
- Pobre efecto localizador.
- Depende colaboración del paciente.
- “Time consuming”…

3.VALORACIÓN NEUROFISIOLÓGICA DE FIBRA FINA: QST (TEST CUANTITATIVO SENSORIAL).

CASE IV System

CASE IV

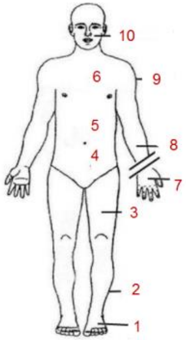
TSA II

Q SENSE

Q Sense
Medoc
Conditioned Pain Modulation
Medoc

3.VALORACIÓN NEUROFISIOLÓGICA DE FIBRA FINA: QST (TEST CUANTITATIVO SENSORIAL).

BATERIA DE TEST en el QST :

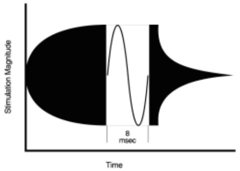


1. **UMBRALES SENSIBILIDAD TACTIL SUPERFICIAL:**
   - Monofilamento Semmes-Weinstein
   - Filamentos de von Frey

- Distintos algoritmos
- PJ Dyck (WR Medical Electronics):
  - el test se inicia en la zona 2 y luego en la 8; según resultados obtenidos se utilizan distintos grosores de filamentos, y el test sigue distalmente, o bien proximalmente.
  - puntuación según resultados en cada punto anatómico.escala cuantitativa de deterioro neuropático.

2. **UMBRALES SENSIBILIDAD VIBRATORIA**:
   - Estímulo vibratorio onda sinusoidal
     - Variación frecuencia vibración.
     - Variación intensidad (amplitud) vibración (125 Hz): 0-30g + frec.

CASE IV System



Vibration Stimulation Waveform

Fibras Aβ

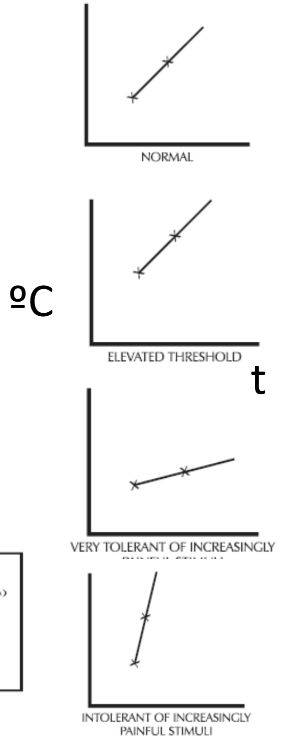
3.VALORACIÓN NEUROFISIOLÓGICA DE FIBRA FINA: QST (TEST CUANTITATIVO SENSORIAL).

3. **UMBRALES TERMO-ALGESICOS (THERMOTEST):**
   - **Termodo**: aplicación sobre la piel.
     - **Principio de Peltier**: el paso de corriente eléctrica a través de dos semiconductores genera calor o frío dependiendo de la dirección de la corriente.
     - Temperatura adaptación: 32ºC.
     - Rango temperaturas: 0ºC – 50ºC.
   - **SE VALORAN UMBRALES AL:**
   - **Frío:** fibras Aδ.
   - **Calor:** fibras C.
   - **Dolor por frío:** fibras Aδ y C.
   - **Dolor por calor:** fibras C.
   - **ÚTIL**: CUANTIFICA TANTO HIPOESTESIA COMO HIPERALGESIA.
   - Variabilidad explorador/colaboración paciente.

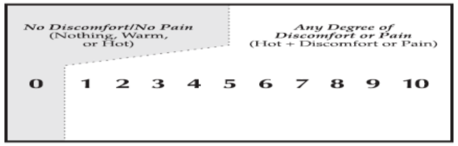
Fibras Aδ y C

3.VALORACIÓN NEUROFISIOLÓGICA DE FIBRA FINA: QST (TEST CUANTITATIVO SENSORIAL).

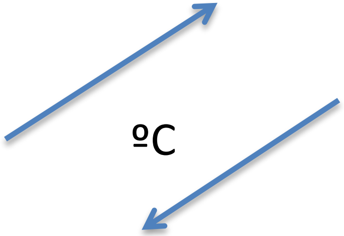
- UMBRALES: TÉCNICA:
  - Estímulo dinámico. MÉTODO DE LOS LÍMITES.
    - **Estímulo contínuo** de intensidad creciente o descendente.
    - El paciente señala cuando el estímulo es percibido.
    - Umbral, tiempo de reacción incluído.
  - Estímulo estático . MÉTODO DE LOS NIVELES.
    - Varias **series de estímulos** estáticos de distinta magnitud .
    - Cambio de la intensidad del estímulo.
    - Estímulos nulos.
    - Algoritmo 4,2,1: 15-20 estímulos
    - Umbral: promedio.



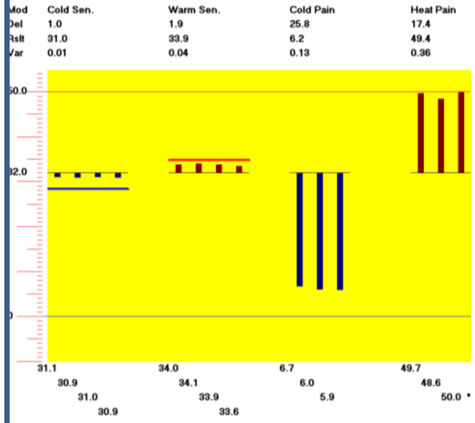
- CUANTIFICACIÓN DEL DOLOR AL CALOR:
  - Estudio perfil percepción dolor. Estímulo estático.
  - Respuesta en base a una escala visual analógica (VAS):
  - Cálculo: **Umbral HP:0.5** → inicio dolor. **Umbral HP:5.0** → nivel intermedio de dolor.
    - La diferencia entre los umbrales HP:0.5 y HP:5.0 umbral muestra la tolerancia del sujeto a los estímulos dolorosos crecientes


No Discomfort/No Pain
(Nothing, Warm, or Hot)
Any Degree of Discomfort or Pain
(Hot + Discomfort or Pain)
0
1
2
3
4
5
6
7
8
9
10

MÉTODO DE LOS LIMITES: THERMOTEST

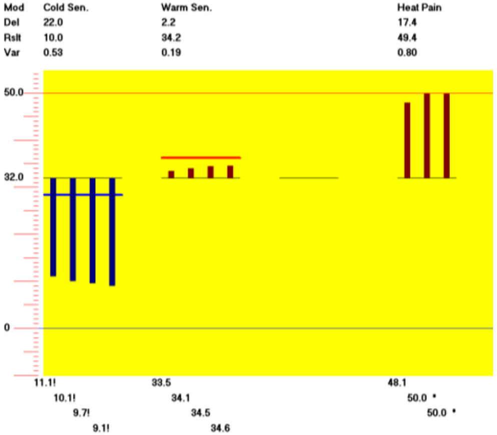


Normal

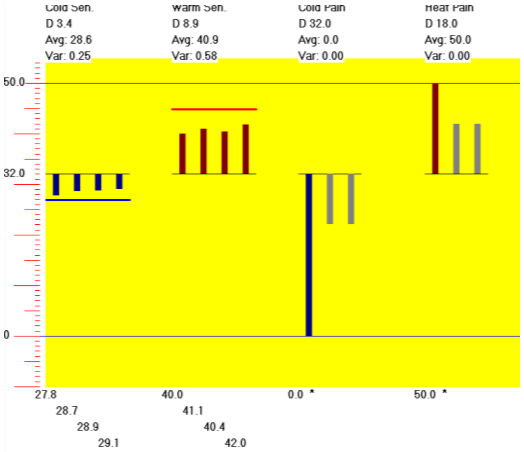


Mod	Cold Sen.	Warm Sen.	Cold Pain	Heat Pain
Del	1.0	1.9	25.8	17.4
Rslt	31.0	33.9	6.2	49.4
Var	0.01	0.04	0.13	0.36

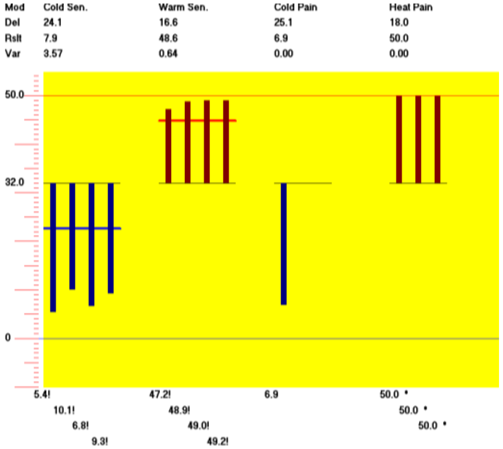
Patológico



Mod	Cold Sen.	Warm Sen.	Heat Pain
Del	22.0	2.2	17.4
Rslt	10.0	34.2	49.4
Var	0.53	0.19	0.80



Cold Sen.	Warm Sen.	Cold Pain	Heat Pain
D 3.4	D 8.9	D 32.0	D 18.0
Avg: 28.6	Avg: 40.9	Avg: 0.0	Avg: 50.0
Var: 0.25	Var: 0.58	Var: 0.00	Var: 0.00



Mod	Cold Sen.	Warm Sen.	Cold Pain	Heat Pain
Del	24.1	16.6	25.1	18.0
Rslt	7.9	48.6	6.9	50.0
Var	3.57	0.64	0.00	0.00

Test de Función SUDOMOTORA

- SUDOSCAN:
  - Cuantifica la conductancia del Cl- (microsiemens, µS) tras un estímulo eléctrico (placa acero) a 4v (desencadena respuesta electroquímica ⌦ secreción de Cl- por las glándulas sudoríparas).
    - Sirve como biomarcador de la función de las gl.sudoríparas.
    - Localizar pacientes que tengan "riesgo de disfunción autonómica".

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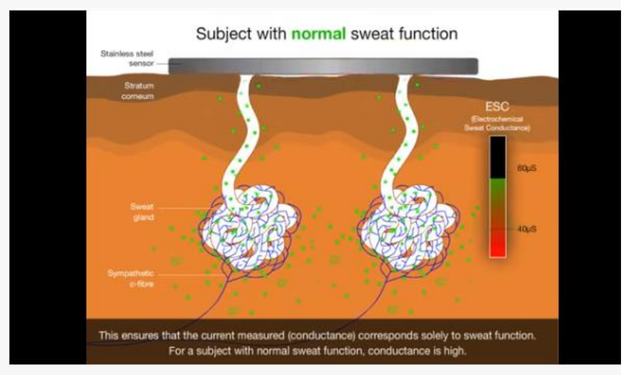
The Advantage of
Early Detection

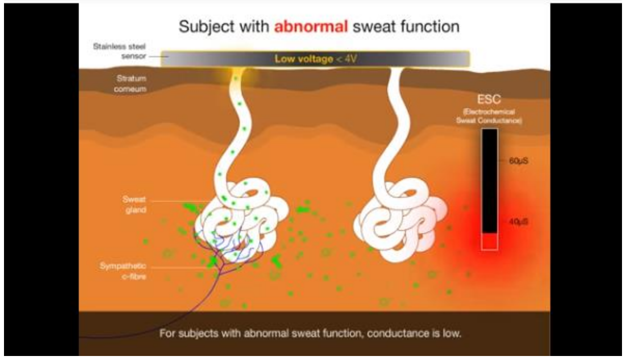
SUDOSCAN®: An innovative device for early detection and follow-up of Autonomic and Small Fiber Neuropathy.



Subject with **normal** sweat function

Stainless steel sensor
Stratum corneum
Sweat gland
Sympathetic c-fibre
ESC
(Electrochemical Sweat Conductance)
60µS
40µS

This ensures that the current measured (conductance) corresponds solely to sweat function.
For a subject with normal sweat function, conductance is high.



Subject with **abnormal** sweat function

Stainless steel sensor
Low voltage < 4V
Stratum corneum
Sweat gland
Sympathetic c-fibre
ESC
(Electrochemical Sweat Conductance)
60µS
40µS

For subjects with abnormal sweat function, conductance is low.

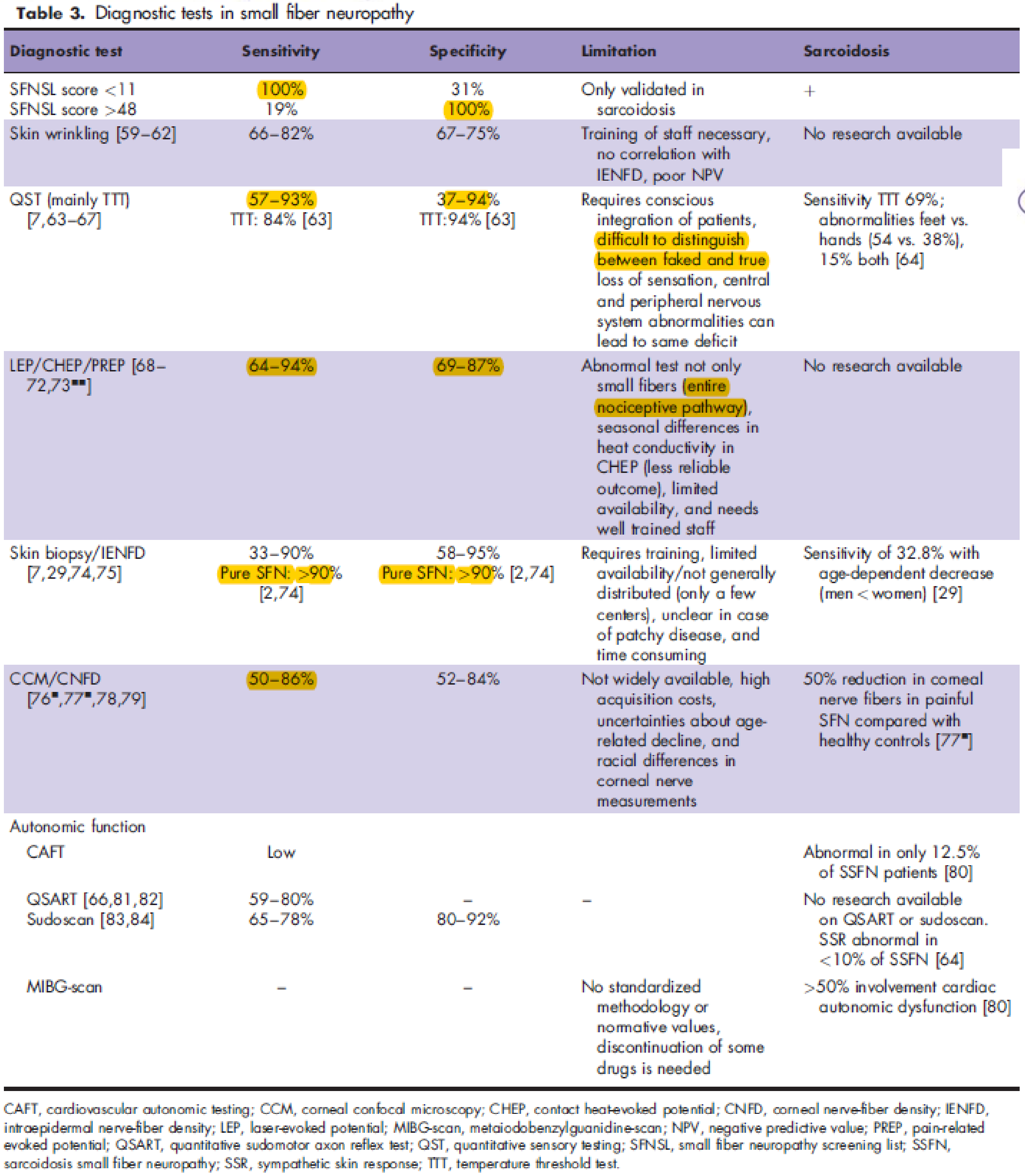
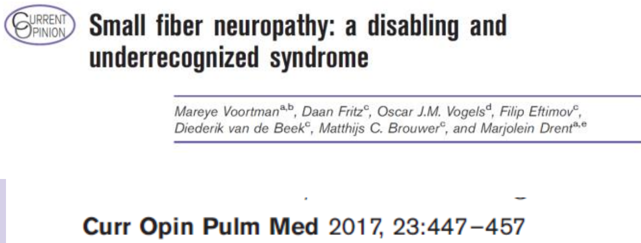


Table 3. Diagnostic tests in small fiber neuropathy

Diagnostic test	Sensitivity	Specificity	Limitation	Sarcoidosis
SFNSL score <11 SFNSL score >48	100% 19%	31% 100%	Only validated in sarcoidosis	+
Skin wrinkling [59–62]	66–82%	67–75%	Training of staff necessary, no correlation with IENFD, poor NPV	No research available
QST (mainly TTT) [7,63–67]	57–93% TTT: 84% [63]	37–94% TTT:94% [63]	Requires conscious integration of patients, difficult to distinguish between faked and true loss of sensation, central and peripheral nervous system abnormalities can lead to same deficit	Sensitivity TTT 69%; abnormalities feet vs. hands (54 vs. 38%), 15% both [64]
LEP/CHEP/PREP [68–72,73■■]	64–94%	69–87%	Abnormal test not only small fibers (entire nociceptive pathway), seasonal differences in heat conductivity in CHEP (less reliable outcome), limited availability, and needs well trained staff	No research available
Skin biopsy/IENFD [7,29,74,75]	33–90% Pure SFN: >90% [2,74]	58–95% Pure SFN: >90% [2,74]	Requires training, limited availability/not generally distributed (only a few centers), unclear in case of patchy disease, and time consuming	Sensitivity of 32.8% with age-dependent decrease (men < women) [29]
CCM/CNFD [76■,77■,78,79]	50–86%	52–84%	Not widely available, high acquisition costs, uncertainties about age-related decline, and racial differences in corneal nerve measurements	50% reduction in corneal nerve fibers in painful SFN compared with healthy controls [77■]
Autonomic function				
CAFT	Low			Abnormal in only 12.5% of SSFN patients [80]
QSART [66,81,82] Sudoscan [83,84]	59–80% 65–78%	– 80–92%	–	No research available on QSART or sudoscan. SSR abnormal in <10% of SSFN [64]
MIBG-scan	–	–	No standardized methodology or normative values, discontinuation of some drugs is needed	>50% involvement cardiac autonomic dysfunction [80]

CAFT, cardiovascular autonomic testing; CCM, corneal confocal microscopy; CHEP, contact heat-evoked potential; CNFD, corneal nerve-fiber density; IENFD, intraepidermal nerve-fiber density; LEP, laser-evoked potential; MIBG-scan, metaiodobenzylguanidine-scan; NPV, negative predictive value; PREP, pain-related evoked potential; QSART, quantitative sudomotor axon reflex test; QST, quantitative sensory testing; SFNSL, small fiber neuropathy screening list; SSFN, sarcoidosis small fiber neuropathy; SSR, sympathetic skin response; TTT, temperature threshold test.



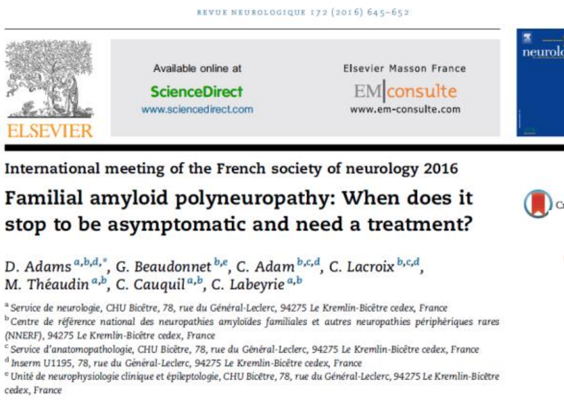
CURRENT OPINION

Small fiber neuropathy: a disabling and underrecognized syndrome

Mareye Voortman[a,b], Daan Fritz[c], Oscar J.M. Vogels[d], Filip Eftimov[c], Diederik van de Beek[c], Matthijs C. Brouwer[c], and Marjolein Drent[a,e]

Curr Opin Pulm Med 2017, 23:447–457

II JORNADAS
AMILOIDOSIS HEREDITARIA


REVUE NEUROLOGIQUE 172 (2016) 645–652

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Revue neurologique

International meeting of the French society of neurology 2016

Familial amyloid polyneuropathy: When does it stop to be asymptomatic and need a treatment?

CrossMark

D. Adams[a,b,d,*], G. Beaudonnet[b,e], C. Adam[b,c,d], C. Lacroix[b,c,d], M. Théaudin[a,b], C. Cauquil[a,b], C. Labeyrie[a,b]

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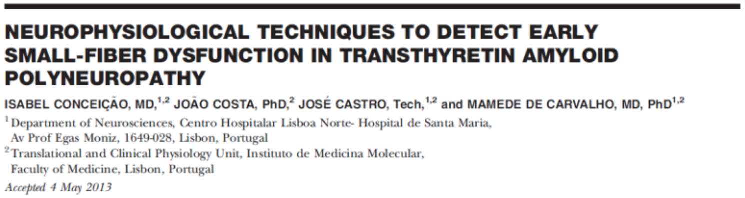
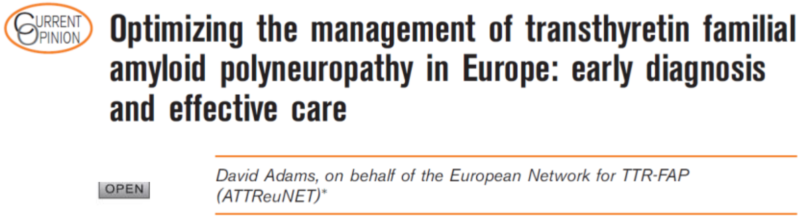

NEUROPHYSIOLOGICAL TECHNIQUES TO DETECT EARLY SMALL-FIBER DYSFUNCTION IN TRANSTHYRETIN AMYLOID POLYNEUROPATHY

ISABEL CONCEIÇÃO, MD,[1,2] JOÃO COSTA, PhD,[2] JOSÉ CASTRO, Tech,[1,2] and MAMEDE DE CARVALHO, MD, PhD[1,2]

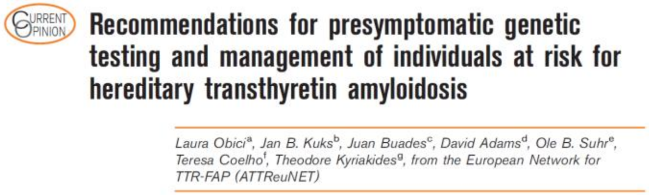
[1] Department of Neurosciences, Centro Hospitalar Lisboa Norte- Hospital de Santa Maria, Av Prof Egas Moniz, 1649-028, Lisbon, Portugal
[2] Translational and Clinical Physiology Unit, Instituto de Medicina Molecular, Faculty of Medicine, Lisbon, Portugal

Accepted 4 May 2013


CURRENT OPINION

Optimizing the management of transthyretin familial amyloid polyneuropathy in Europe: early diagnosis and effective care

*David Adams, on behalf of the European Network for TTR-FAP (ATTReuNET)**

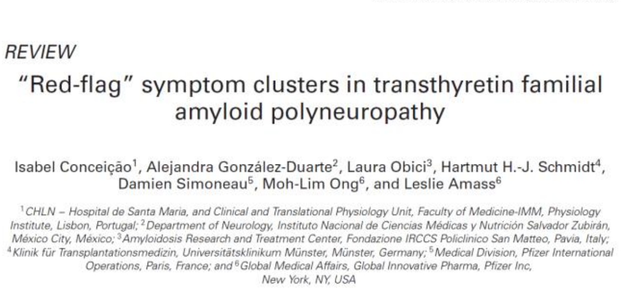

OPEN

CURRENT OPINION

Recommendations for presymptomatic genetic testing and management of individuals at risk for hereditary transthyretin amyloidosis

Laura Obici[a], Jan B. Kuks[b], Juan Buades[c], David Adams[d], Ole B. Suhr[e], Teresa Coelho[f], Theodore Kyriakides[g], from the European Network for TTR-FAP (ATTReuNET)

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


REVIEW

"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]

[1] CHLN – Hospital de Santa Maria, and Clinical and Translational Physiology Unit, Faculty of Medicine-IMM, Physiology Institute, Lisbon, Portugal; [2] Department of Neurology, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, México City, México; [3] Amyloidosis Research and Treatment Center, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy; [4] Klinik für Transplantationsmedizin, Universitätsklinikum Münster, Münster, Germany; [5] Medical Division, Pfizer International Operations, Paris, France; and [6] Global Medical Affairs, Global Innovative Pharma, Pfizer Inc, New York, NY, USA

SEGUIMIENTO PORTADORES VAL30MET HSLL

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Oftalmología
Dr. Carles Montalà
Neurología
Dra. Inés Losada
Medicina Interna
Sra. María José Jaume
Gestión

RESEARCH REPORT

Transthyretin familial amyloid polyneuropathy (TTR-FAP) in Mallorca: a comparison between late- and early-onset disease

Juan Buades-Reinés[1], Manuel Raya-Cruz[1], Cristina Gallego-Lezaún[1], Tomás Ripoll-Vera[2], Mercedes Usón-Martín[3], Hernán Andreu-Serra[4], and Eugenia Cisneros-Barroso[5]

[1] Department of Internal Medicine, Son Llàtzer Hospital, Carretera de Manacor; [2] Department of Cardiology, Son Llàtzer Hospital, Carretera de Manacor; [3] Department of Neurology, Son Llàtzer Hospital, Carretera de Manacor; [4] Department of Digestive Medicine, Son Llàtzer Hospital, Carretera de Manacor; and [5] Clinical Research Coordinator A-TTR Group, Son Llàtzer Hospital, Carretera de Manacor, Palma, Spain

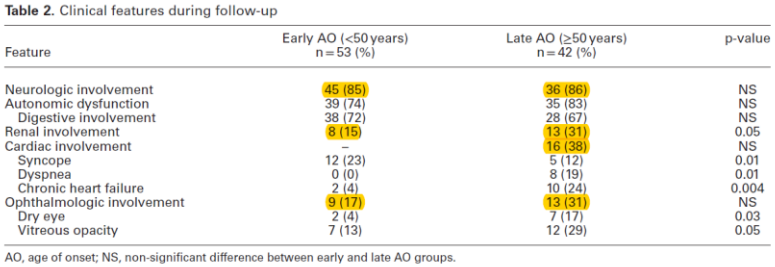


Table 2. Clinical features during follow-up

Feature	Early AO (<50 years) n = 53 (%)	Late AO (≥50 years) n = 42 (%)	p-value
Neurologic involvement	45 (85)	36 (86)	NS
Autonomic dysfunction	39 (74)	35 (83)	NS
Digestive involvement	38 (72)	28 (67)	NS
Renal involvement	8 (15)	13 (31)	0.05
Cardiac involvement	–	16 (38)	NS
Syncope	12 (23)	5 (12)	0.01
Dyspnea	0 (0)	8 (19)	0.01
Chronic heart failure	2 (4)	10 (24)	0.004
Ophthalmologic involvement	9 (17)	13 (31)	NS
Dry eye	2 (4)	7 (17)	0.03
Vitreous opacity	7 (13)	12 (29)	0.05

AO, age of onset; NS, non-significant difference between early and late AO groups.

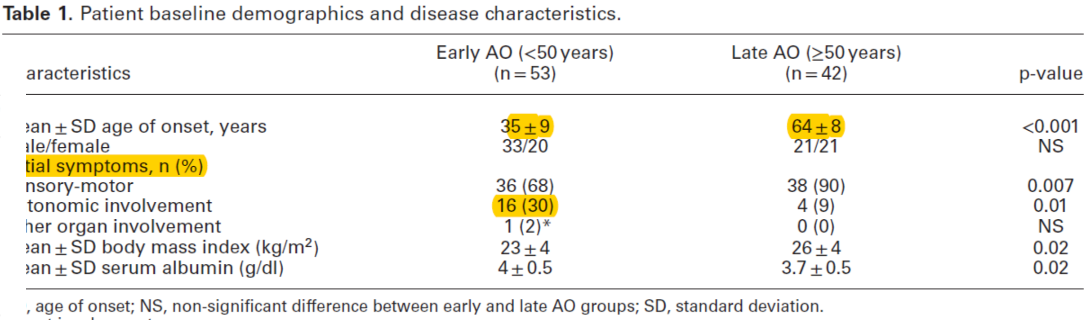


Table 1. Patient baseline demographics and disease characteristics.

aracteristics	Early AO (<50 years) (n = 53)	Late AO (≥50 years) (n = 42)	p-value
ean ± SD age of onset, years	35 ± 9	64 ± 8	<0.001
ale/female	33/20	21/21	NS
tial symptoms, n (%)			
nsory-motor	36 (68)	38 (90)	0.007
tonomic involvement	16 (30)	4 (9)	0.01
her organ involvement	1 (2)*	0 (0)	NS
ean ± SD body mass index (kg/m^2)	23 ± 4	26 ± 4	0.02
ean ± SD serum albumin (g/dl)	4 ± 0.5	3.7 ± 0.5	0.02

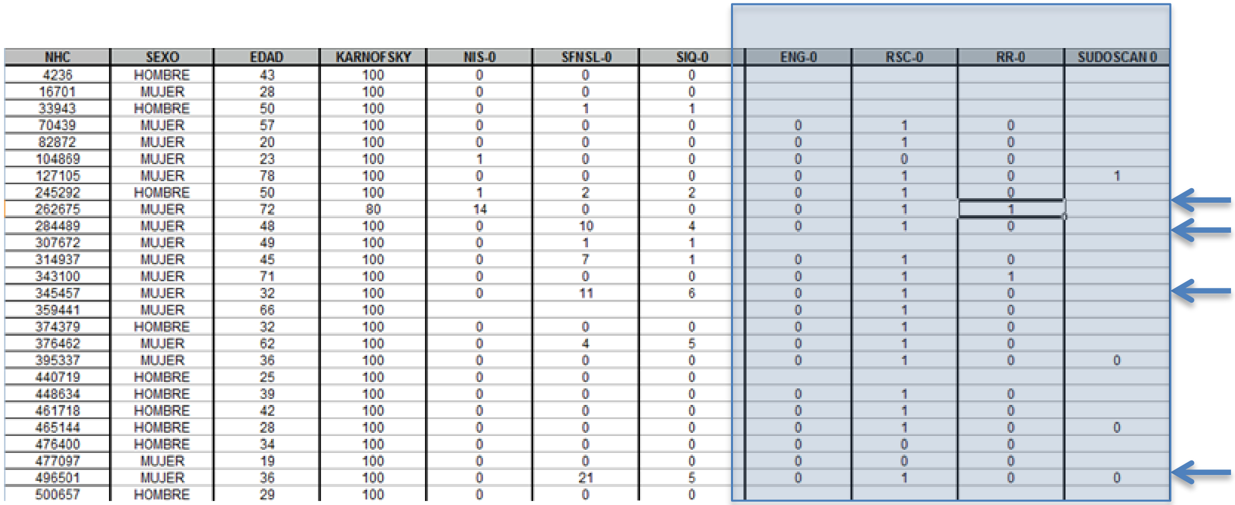
, age of onset; NS, non-significant difference between early and late AO groups; SD, standard deviation.

II JORNADAS
AMILOIDOSIS HEREDITARIA
por TRANSTIRRETINA (AhTTR)

Asociación Española
Enfermedad de Andrade
(Amiloidosis Hereditaria por Transtirretina)

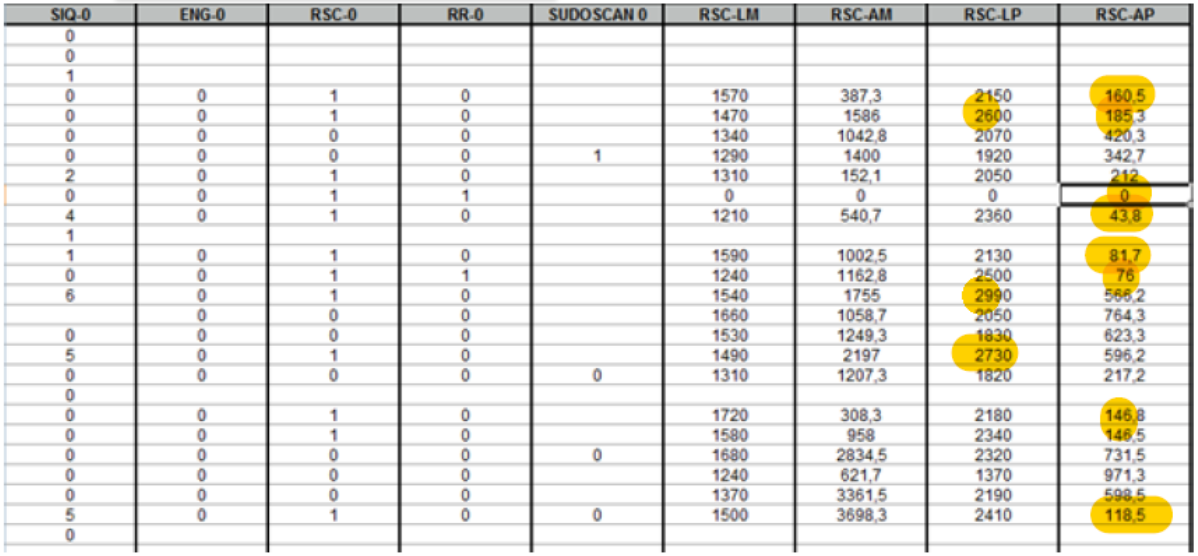
ESTUDIO HSLL

SEGUIMIENTO PORTADORES VAL30MET



NHC	SEXO	EDAD	KARNOFSKY	NIS-0	SFNSL-0	SIQ-0	ENG-0	RSC-0	RR-0	SUDOSCAN 0
4236	HOMBRE	43	100	0	0	0				
16701	MUJER	28	100	0	0	0				
33943	HOMBRE	50	100	0	1	1				
70439	MUJER	57	100	0	0	0	0	1	0	
82872	MUJER	20	100	0	0	0	0	1	0	
104869	MUJER	23	100	1	0	0	0	0	0	
127105	MUJER	78	100	0	0	0	0	1	0	1
245292	HOMBRE	50	100	1	2	2	0	1	0	
262675	MUJER	72	80	14	0	0	0	1	1	
284489	MUJER	48	100	0	10	4	0	1	0	
307672	MUJER	49	100	0	1	1				
314937	MUJER	45	100	0	7	1	0	1	0	
343100	MUJER	71	100	0	0	0	0	1	1	
345457	MUJER	32	100	0	11	6	0	1	0	
359441	MUJER	66	100				0	1	0	
374379	HOMBRE	32	100	0	0	0	0	1	0	
376462	MUJER	62	100	0	4	5	0	1	0	
395337	MUJER	36	100	0	0	0	0	1	0	0
440719	HOMBRE	25	100	0	0	0				
448634	HOMBRE	39	100	0	0	0	0	1	0	
461718	HOMBRE	42	100	0	0	0	0	1	0	
465144	HOMBRE	28	100	0	0	0	0	1	0	0
476400	HOMBRE	34	100	0	0	0	0	0	0	
477097	MUJER	19	100	0	0	0	0	0	0	
496501	MUJER	36	100	0	21	5	0	1	0	0
500657	HOMBRE	29	100	0	0	0				

ESTUDIO RSC y RR



SIQ-0	ENG-0	RSC-0	RR-0	SUDOSCAN 0	RSC-LM	RSC-AM	RSC-LP	RSC-AP
0								
0								
1								
0	0	1	0		1570	387,3	2150	160,5
0	0	1	0		1470	1586	2600	185,3
0	0	0	0		1340	1042,8	2070	420,3
0	0	0	0	1	1290	1400	1920	342,7
2	0	1	0		1310	152,1	2050	212
0	0	1	1		0	0	0	0
4	0	1	0		1210	540,7	2360	43,8
1								
1	0	1	0		1590	1002,5	2130	81,7
0	0	1	1		1240	1162,8	2500	76
6	0	1	0		1540	1755	2990	566,2
	0	0	0		1660	1058,7	2050	764,3
0	0	0	0		1530	1249,3	1830	623,3
5	0	1	0		1490	2197	2730	596,2
0	0	0	0	0	1310	1207,3	1820	217,2
0								
0	0	1	0		1720	308,3	2180	146,8
0	0	1	0		1580	958	2340	146,5
0	0	0	0	0	1680	2834,5	2320	731,5
0	0	0	0		1240	621,7	1370	971,3
0	0	0	0		1370	3361,5	2190	598,5
5	0	1	0	0	1500	3698,3	2410	118,5
0								

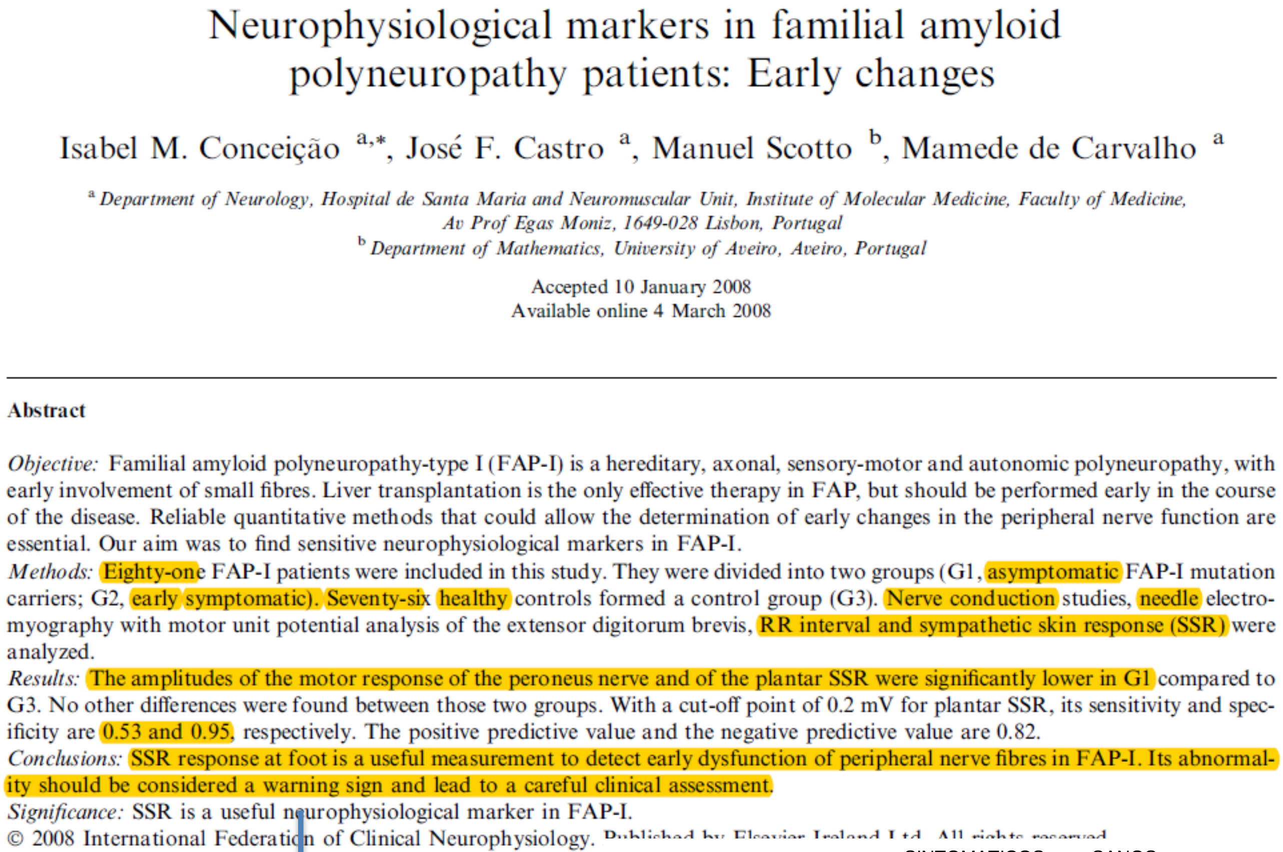
26 portadores estudiados

(38 a 3/10/2018)

10 H:16 M

20 EMG + FF (32 a 3/10/2018)

- Disfunción FF para EEII:
  9/20.
  (6<50 a.)



Neurophysiological markers in familial amyloid polyneuropathy patients: Early changes

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Abstract

Objective: Familial amyloid polyneuropathy-type I (FAP-I) is a hereditary, axonal, sensory-motor and autonomic polyneuropathy, with early involvement of small fibres. Liver transplantation is the only effective therapy in FAP, but should be performed early in the course of the disease. Reliable quantitative methods that could allow the determination of early changes in the peripheral nerve function are essential. Our aim was to find sensitive neurophysiological markers in FAP-I.

Methods: Eighty-one FAP-I patients were included in this study. They were divided into two groups (G1, asymptomatic FAP-I mutation carriers; G2, early symptomatic). Seventy-six healthy controls formed a control group (G3). Nerve conduction studies, needle electromyography with motor unit potential analysis of the extensor digitorum brevis, RR interval and sympathetic skin response (SSR) were analyzed.

Results: The amplitudes of the motor response of the peroneus nerve and of the plantar SSR were significantly lower in G1 compared to G3. No other differences were found between those two groups. With a cut-off point of 0.2 mV for plantar SSR, its sensitivity and specificity are 0.53 and 0.95, respectively. The positive predictive value and the negative predictive value are 0.82.

Conclusions: SSR response at foot is a useful measurement to detect early dysfunction of peripheral nerve fibres in FAP-I. Its abnormality should be considered a warning sign and lead to a careful clinical assessment.

Significance: SSR is a useful neurophysiological marker in FAP-I.

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1.ENG
2.EMG
3.RR
4.RSC

VALORES MENORES DE 0.2 mV
de la RSC en pie deben ser
considerados un
SIGNO DE ALARMA.

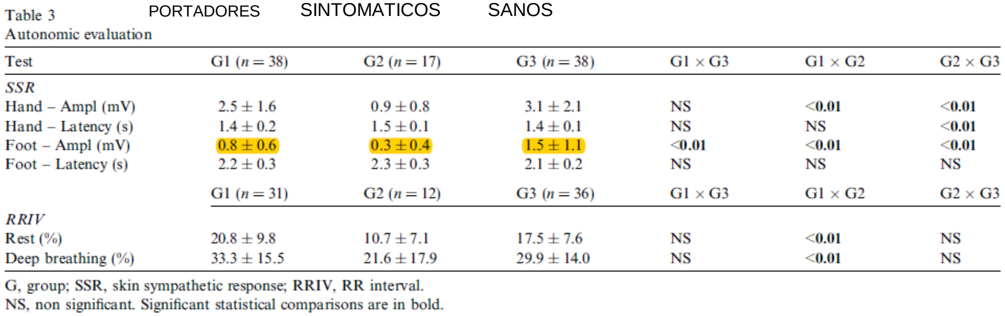
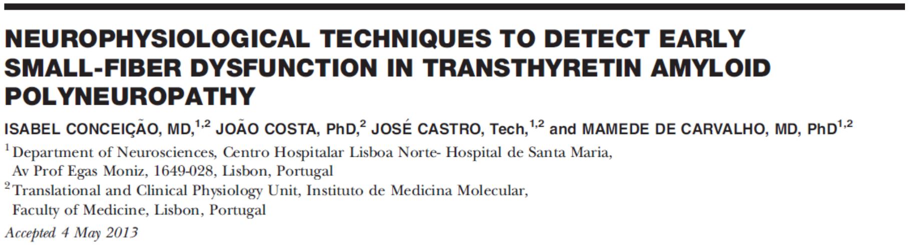


Table 3
Autonomic evaluation

	PORTADORES	SINTOMATICOS	SANOS			
Test	G1 (*n* = 38)	G2 (*n* = 17)	G3 (*n* = 38)	G1 × G3	G1 × G2	G2 × G3
SSR						
Hand – Ampl (mV)	2.5 ± 1.6	0.9 ± 0.8	3.1 ± 2.1	NS	**<0.01**	**<0.01**
Hand – Latency (s)	1.4 ± 0.2	1.5 ± 0.1	1.4 ± 0.1	NS	NS	**<0.01**
Foot – Ampl (mV)	0.8 ± 0.6	0.3 ± 0.4	1.5 ± 1.1	**<0.01**	**<0.01**	**<0.01**
Foot – Latency (s)	2.2 ± 0.3	2.3 ± 0.3	2.1 ± 0.2	NS	NS	NS
	G1 (*n* = 31)	G2 (*n* = 12)	G3 (*n* = 36)	G1 × G3	G1 × G2	G2 × G3
RRIV						
Rest (%)	20.8 ± 9.8	10.7 ± 7.1	17.5 ± 7.6	NS	**<0.01**	NS
Deep breathing (%)	33.3 ± 15.5	21.6 ± 17.9	29.9 ± 14.0	NS	**<0.01**	NS

G, group; SSR, skin sympathetic response; RRIV, RR interval.
NS, non significant. Significant statistical comparisons are in bold.



NEUROPHYSIOLOGICAL TECHNIQUES TO DETECT EARLY SMALL-FIBER DYSFUNCTION IN TRANSTHYRETIN AMYLOID POLYNEUROPATHY

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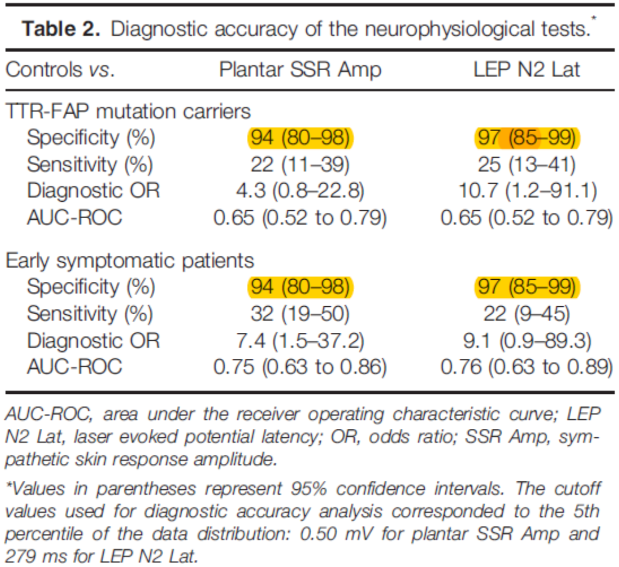
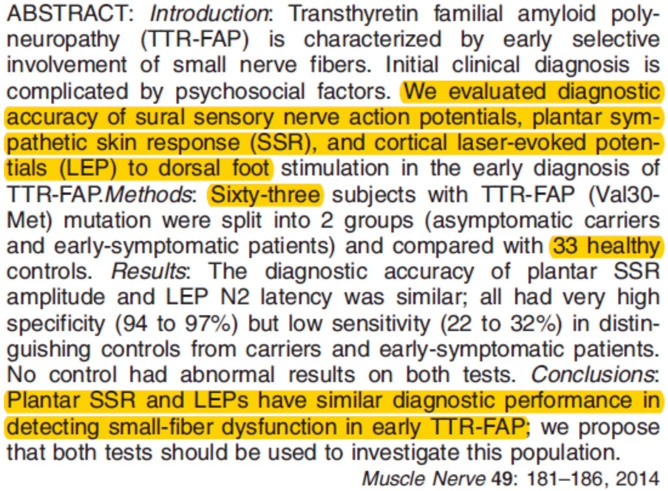


Table 2. Diagnostic accuracy of the neurophysiological tests.*

Controls *vs*.	Plantar SSR Amp	LEP N2 Lat
TTR-FAP mutation carriers		
Specificity (%)	94 (80–98)	97 (85–99)
Sensitivity (%)	22 (11–39)	25 (13–41)
Diagnostic OR	4.3 (0.8–22.8)	10.7 (1.2–91.1)
AUC-ROC	0.65 (0.52 to 0.79)	0.65 (0.52 to 0.79)
Early symptomatic patients		
Specificity (%)	94 (80–98)	97 (85–99)
Sensitivity (%)	32 (19–50)	22 (9–45)
Diagnostic OR	7.4 (1.5–37.2)	9.1 (0.9–89.3)
AUC-ROC	0.75 (0.63 to 0.86)	0.76 (0.63 to 0.89)

AUC-ROC, area under the receiver operating characteristic curve; LEP N2 Lat, laser evoked potential latency; OR, odds ratio; SSR Amp, sympathetic skin response amplitude.

**Values in parentheses represent 95% confidence intervals. The cutoff values used for diagnostic accuracy analysis corresponded to the 5th percentile of the data distribution: 0.50 mV for plantar SSR Amp and 279 ms for LEP N2 Lat.*



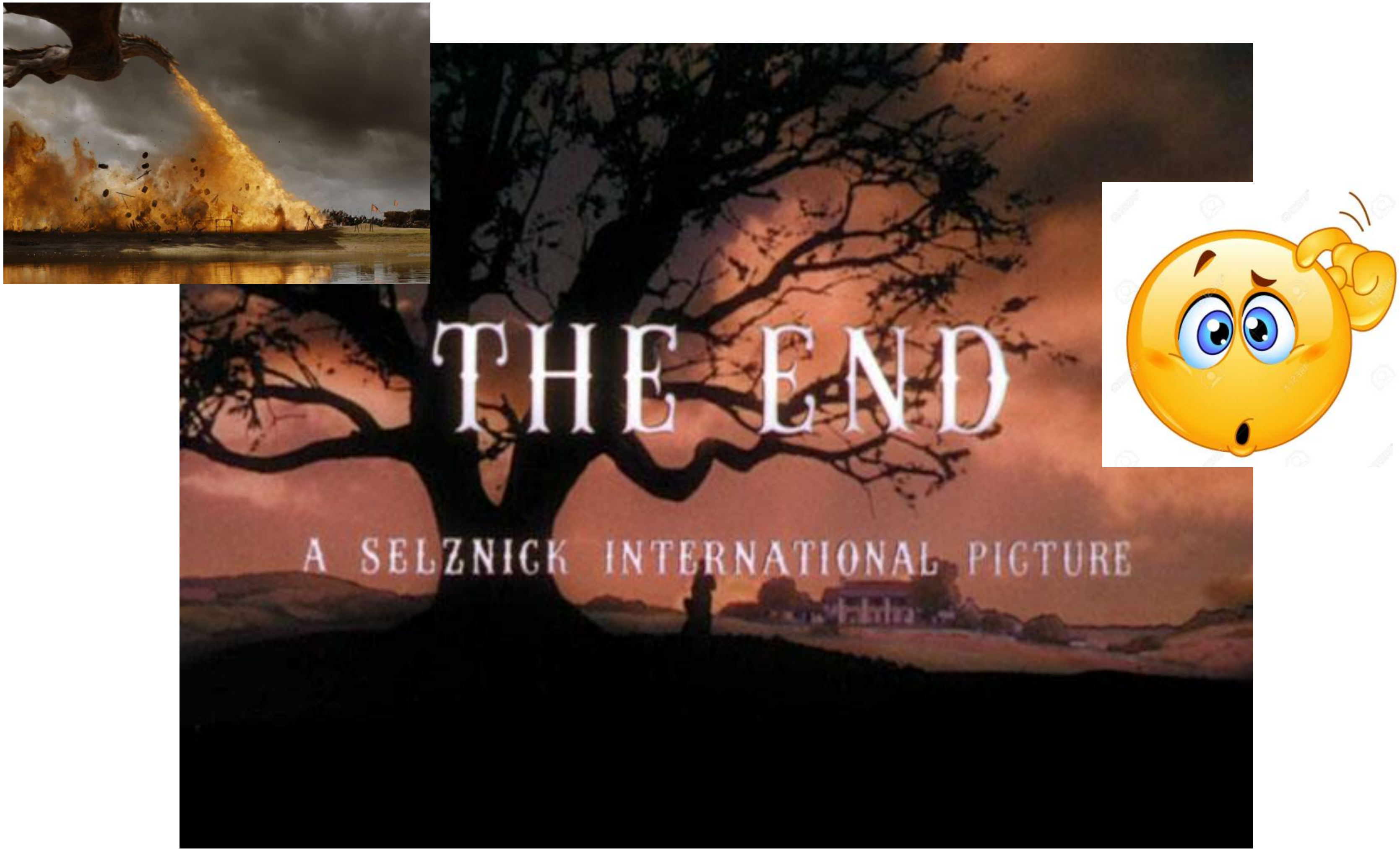
ABSTRACT: *Introduction*: Transthyretin familial amyloid polyneuropathy (TTR-FAP) is characterized by early selective involvement of small nerve fibers. Initial clinical diagnosis is complicated by psychosocial factors. We evaluated diagnostic accuracy of sural sensory nerve action potentials, plantar sympathetic skin response (SSR), and cortical laser-evoked potentials (LEP) to dorsal foot stimulation in the early diagnosis of TTR-FAP.*Methods*: Sixty-three subjects with TTR-FAP (Val30-Met) mutation were split into 2 groups (asymptomatic carriers and early-symptomatic patients) and compared with 33 healthy controls. *Results*: The diagnostic accuracy of plantar SSR amplitude and LEP N2 latency was similar; all had very high specificity (94 to 97%) but low sensitivity (22 to 32%) in distinguishing controls from carriers and early-symptomatic patients. No control had abnormal results on both tests. *Conclusions*: Plantar SSR and LEPs have similar diagnostic performance in detecting small-fiber dysfunction in early TTR-FAP; we propose that both tests should be used to investigate this population.

Muscle Nerve 49: 181–186, 2014

1. RSC
2. LEP
3. ENG

RESTO DE CONCLUSIONES:

- La NEUROPATÍA DE FIBRA FINA SE DIAGNOSTICA POR LA CLINICA + TEST DIAGNOSTICO que valore la FIBRA FINA NERVIOSA.
  - ALODINIA y/o HIPERESTESIA y/o ALTERACION PERCEPCION TERMICA.
  - QST patológico.
  - Biopsia cutánea.
- Para el seguimiento de portadores y diagnóstico precoz de la NEUROPATIA DE FIBRA FINA y PNP nos recomiendan realizar una batería de test neurofisiológicos que incluyen: EMG, RSC, RR, QST.
- HAY QUE "PERSEGUIR" SÍNTOMAS AUTONÓMICOS Y/O DE FIBRA FINA TERMOALGÉSICA que a pesar de ser en ocasiones INESPECIFICOS Y VARIABLES pueden ser estudiados por diferentes TEST QUE EXPLORAN DIFERENTES VERTIENTES DEL SNA y FF y QUE entre ellos SE COMPLEMENTAN (buscar > 2 test alterados : SNA o S.Termo-Algésica).
- ESTUDIO EMG/ENG ES NORMAL en la NEUROPATIA DE FIBRA FINA : un EMG normal no implica que no haya afectación de fibras nerviosas.


THE END
A SELZNICK INTERNATIONAL PICTURE

GRACIAS