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Brief report

# Early diagnosis in patients with transthyretin familial amyloid polyneuropathy: A comparative study

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ABSTRACT

*Introduction and objective:* Transthyretin-associated familial amyloid polyneuropathy (TTR-FAP) is a disease caused by the deposit of abnormal transthyretin on tissues, mainly nerves. Small nerve fibers are altered earlier during the course of the disease; hence, detection of their involvement may have serious consequences on the natural history of disease.
*Methods:* A cross-sectional, observational study, was carried out on symptomatic patients, involving the conduct of several tests for small nerve fibers: Vibration, Touch Pressure (TP) and Heat Pain (HP). Results were compared with those obtained during a conventional neurological examination carried out on a group of healthy individuals.
*Results:* Fifteen symptomatic patients were recruited at an early stage of the disease (60% stage 1), along with 13 healthy individuals, with both patient groups having similar epidemiological characteristics in terms of gender, age, weight, height or BMI. A comparison carried out between the neuropsychological tests performed revealed statistically significant differences: Vibration ($P < .05$), TP ($P < .05$) and HP ($P < .05$, except volar forearm).
*Conclusions:* The neurophysiological tests performed revealed significant differences between both groups, allowing for an earlier detection of neurological injuries compared to conventional neurological examinations.



## Diagnóstico precoz en pacientes con polineuropatía amiloidótica familiar asociada a transtirretina. Estudio comparativo

*Palabras clave:*
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RESUMEN

*Introducción y objetivo:* La polineuropatía amiloidótica familiar causada por transtirretina) está caracterizada por la afectación del sistema nervioso. Las fibras nerviosas pequeñas se alteran de manera más precoz, por lo que la detección de su afectación tiene implicaciones serias en la historia natural de la enfermedad.
*Métodos:* Estudio transversal, en el que se realizaron pruebas de detección de afectación de fibras nerviosas pequeñas en pacientes sintomáticos con TTR-PAF: *Vibration, Touch Pressure* (TP) y *Heat Pain* (HP). Los resultados se compararon con la exploración neurológica convencional y con un grupo de individuos sanos.

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*Resultados:* Se seleccionaron 15 pacientes con TTR-PAF en una fase precoz de la enfermedad (60% en estadio 1) y 13 individuos sanos. En la comparación entre ambos grupos no existían diferencias en cuanto a sexo, edad, peso, talla o IMC; sin embargo, en los test neurofisiológicos realizados se evidenciaron diferencias estadísticamente significativas: *Vibration* ($p < 0{,}05$), TP ($p < 0{,}05$) y HP ($p < 0{,}05$, excepto en la localización de antebrazo).

*Conclusiones:* Los test neurofisiológicos realizados describen diferencias significativas entre ambos grupos, lo que podría permitir la detección del daño neurológico de forma más precoz que cuando se realiza una exploración neurológica convencional.



## Introduction

Transthyretin familial amyloid polyneuropathy (TTR-FAP) is a hereditary disease characterized by the involvement of the sensory nervous system, motor and autonomic.[1] In our country, the largest endemic focus is on the Balearic Islands, which has published a series of 107 cases.[2]

The diagnosis may be obtained by the presence of mutated TTR, identification of amyloid deposits in tissues (adipose tissue, salivary glands, nerve or intestine) and the existence of polyneuropathic involvement confirmed by neurological test.[1]

Conventional neurophysiological studies (electroneurography) are limited to determining the effect of large myelinated fibers, showing motor impairment and impaired pain sensitivity; however, the use of other tools to quantify the involvement of the smaller nerve fibers and determine early damage on the thermal-pain and postganglionic sympathetic nerve endings is necessary.[3]

The aim of this study was to compare a group of symptomatic patients with a group of healthy individuals using a diagnostic tool to assess the involvement of the small nerve fibers. Furthermore, a comparison between conventional neurological examination and the Touch Pressure (TP) test was performed.

## Methods

Cross-sectional single-center study in the TTR-FAP multidisciplinary unit of the Internal Medicine Service of Hospital Son Llàtzer during 2015.

### *Patients*

*Cases:* fifteen symptomatic patients with positive Val30Met mutation obtained by TTR/DNA genetic testing, which also had peripheral neuropathy confirmed by electroneurography.

*Controls:* healthy individuals in whom any neurological diseases or other conditions such as diabetes mellitus, hypothyroidism, neoplasia, thrombocytosis, HIV infection or hypoproteinaemia had been ruled out, including being under the influence of alcohol or other drugs.

*Collected variables:* age, sex, weight, height, body mass index (BMI), clinical manifestations, PND classification and FAP stage.

### *Neurological studies*

A neurological examination aimed to explore the sensitivity and motor system of the middle third of the volar forearm, central dorsal part of the hand, anterior middle third of the tibia and dorsum of the foot was performed. It was considered unchanged (0 points) when the force/sensitivity was greater than 75% of that expected in a healthy individual, decreased (1 point) when there was a reduction of 50%, and suppressed (2 points) when less than 25% of expected was obtained.

Neurophysiological studies were performed in these locations using *Computer Aided Sensory Evaluator IV*, which allows to detect and characterize sensory thresholds of the nerve fibers expressed according to age, sex and BMI.

The tests performed were:

*Vibration:* vibratory stimulation in the first toe, which is increased exponentially. It has 25 levels of intensity, according to the *just noticeable difference* by means of the 4,2,1 rule described by PJ Dyck. The *software* determines the percentile of the patient, considered normal when it is less than or equal to the 95th percentile.[4]

*TP:* modified Semmes–Weinstein monofilament test, in which 19 touch-pressure magnitudes are evaluated with a 2:1 algorithm. When the individual did not perceive the correct stimulus on 3 out of 5 occasions, it was considered as suppressed sensitivity (2 points), decreased (1 point) when $\leq$2 stimuli were not perceived, and normal when all stimuli (0 points) were perceived.

*Heat pain (HP):* exponential heating (according to PJ Dyck) from 34 to 49 °C with a duration of 10 s. The following variables are obtained; HP 5.0: painless heat detection threshold and HP 0.5: intermediate painless heat response. Normal values in healthy subjects[5] of HP 5.0 are between 21 and 23, and the HP 0.5, between 18 and 21.

A descriptive study was performed by means of calculating the frequencies for qualitative variables, as well as mean and standard deviation, or median and interquartile range for quantitative variables. In addition, a comparative analysis between the two groups was conducted; the chi-square test was used for qualitative variables and the Student's *t* test for quantitative variables. The level of statistical significance was set at 0.05. SPSS® 15.0 for Windows was used.

## Results

The clinical characteristics of both groups are described in Table 1.

### *Comparison between the two groups as per the neurological studies conducted*

In the *Vibration* test, the case group had an average percentile of 98.47 (0.85), while the control group had 48.6 (38.2). Statistically significant differences were found ($p < 0.05$; 29.47–70.14). Only 2 (13.3%) cases had a normal test (percentile 88 and 94).

In the TP test, all controls were found to have a normal examination (0 points); however, in the case group, all examined areas were compromised, with statistically significant differences, as described in Table 2.

The HP test showed that for the HP 5.0, no case was normal in the tibial area, only one (6.7%) was normal in the foot, 3 (20%) were normal in the forearm and one (6.7%) in the hand. Regarding the HP 0.5 test, 3 (20%) cases had normal results in the tibial area, one (6.7%) in the foot, 10 (66.7%) in the forearm and 4 (26.7%) in the hand.

Statistically significant differences were found in the comparison between the two groups, described in Table 2.