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BRIEF COMMUNICATION

Can we identify hereditary TTR amyloidosis by the screening of carpal tunnel syndrome patients?

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Abstract
Hereditary TTR amyloidosis (ATTRv) is a progressive e disabling disease, leading to a gradual loss of ambulation and death. In the last decade, new treatments have drastically revolutionized natural history of disease, and they are more efficacious if precociously administered. However, diagnostic delay still represents an important challenge to resolve. We reported a case of two asymptomatic brothers that received a very precocious diagnosis of ATTRv thanks to the diagnosis of carpal tunnel syndrome. We proposed screening of the well-defined carpal tunnel syndrome to detect patients with ATTRv in a pre-symptomatic stage.

Keywords TTR · Amyloidosis · Carpal tunnel syndrome · Early diagnosis

Introduction

Hereditary transthyretin amyloidosis (ATTRv) is a rare, dominant, progressive, disabling, and life-threatening disease, due to deposition of amyloid fibrils of mutated transthyretin (TTR). Amyloid deposits occur prevalently in the peripheral nervous system (PNS) and heart, though they may also involve kidneys, eyes, leptomeningeal vessels, and ligaments [1]. PNS involvement is responsible for axonal, length-dependent, sensory-motor neuropathy with autonomic symptoms [2]. Some manifestations, such as carpal tunnel syndrome (CTS) or lumbar spinal stenosis, may precede by many years the onset of neuropathy [3]. PNS involvement is progressive and ATTRv gets worse over time and patient become wheelchair bound after 4–7 years from disease onset. In non-endemic area, diagnosis can be delayed by 3–4 years because of sporadic, late-onset, highly variable clinical presentation patterns due to several TTR variants [4].

In the last years, tetramer stabilizers as Tafamidis and more recently gene-silencers molecules, as short interfering RNAs (Patisiran) and antisense oligonucleotides (Inotersen) drastically changed ATTRv natural history. However, these therapies can be prescribed only at the early stages of disease. In this scenario, ATTRv diagnosis should not be delayed, considering that treatments are more efficacious if they are precociously administered [5]. Consequently, the ideal condition might be the identification of TTR variants in pre-symptomatic patients and routinely monitor them to detect as soon as possible signs of disease [6].

We reported a case of two asymptomatic brothers that received a very precocious diagnosis of ATTRv thanks to the diagnosis of carpal tunnel syndrome.

Patients

The proband is a 54-year-old man that complained about 3 years numbness and tingling at the first three fingers of right hand, and more recently also at the left hand. Medical history was unremarkable, and no CTS risk factors were present. Family history was positive for CTS since his elder brother underwent carpal transverse ligament release many years before.

Neurologic examination showed severe muscle weakness at the right abductor pollicis brevis, bilateral reduction of light touch and pinprick sensibility in the first three fingers, positive Tinél and Phalen signs in both hands. The nerve conduction study (NCS) showed findings compatible with a

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bilateral extreme degree CTS [7], and surgical decompression of median nerve was proposed.

At age of 56 years old, the patient referred no clear improvement from surgery, and recently developed occasional tingling and numbness at both feet. Neurological examination showed normal findings except for reduced sensibility of first three fingers at both hands. NCS showed a bilateral medium degree CTS and electrophysiological findings at lower limbs were normal.

Considering the positive family history and no clear-risk factors for CTS, a genetic testing for ATTRv was proposed to the proband and showed the Phe64Leu variant in *TTR* gene, confirming also in the elder and asymptomatic brother.

Both siblings underwent an extensive multidisciplinary evaluation [6]: (1) standard NCS protocol to detect large fiber damage; (2) sympathetic skin response (SSR) to detect sudomotor function; (3) tactile and thermal quantitative sensory testing (QST) to detect somatic small nerve fibers function [8, 9]; (4) N-terminal pro-brain natriuretic peptide (NT-pro-BNP) plasma dosage to detect cardiac involvement; (5) color-Doppler-echocardiography to detect restrictive cardiomyopathy; (6) ^{99m}Tc-DPD bone scintigraphy to detect cardiac TTR amyloid deposits [10].

Results from proband showed abnormalities in a length-dependent fashion of thermal QST, whereas the other instrumental findings were normal (Table 1). The elder brother did not complain neurological symptoms and had an unremarkable neurological examination. NCS revealed normal findings with exception of reduction of amplitude of SAP in both superficial peroneal nerves. SSR was absent at lower limbs. Both tactile and thermal QST revealed severe abnormalities. Cardiac findings disclosed a mild increase of interventricular septum thickness (13 mm) at color-Doppler-echocardiography and an increase of NT-pro-BNP (352 pg/ml). ^{99m}Tc-DPD bone scintigraphy showed a grade I cardiac uptake according to Perugini grading scale (Table 1), as expected since the low sensitivity of bone scintigraphy in detecting Phe64Leu mutation-related TTR cardiac amyloidosis [11].

The proband was maintained at 6-month follow-up, while the elder brother, although still asymptomatic, was considered as a symptomatic subject and start pharmacological therapy, according to international consensus [6].

Both patients signed informed consent to participate in the study, which was approved by the local ethical committee of University of Naples "Federico II" (Naples, Italy).

Discussion

Our case showed how it is possible identify ATTRv patients in an extremely early stage through diagnosing of CTS. As many studies showed, amyloid fibrils can deposit in transverse carpal ligament, preceding by many years polyneuropathy and cardiomyopathy onset [3]. However, CTS in ATTRv is not a simply compression of median nerve at carpal tunnel by amyloid fibrils. Recent studies on nerve ultrasound in ATTRv patients demonstrated a morpho-functional dissociation of median nerve in CTS, characterized by a nerve enlargement that did not correlate with neurophysiological severity, as instead occurs in idiopathic CTS [12, 13]. Altogether, we can suppose that the entrapment injury of the median nerve can occur in pre-symptomatic stage through the deposition of amyloid in the carpal ligament [14], but contextually there is already a systemic damage of nerves that starts proximally [15].

In this view, patients with CTS may be considered a target group to ATTRv screening. Nevertheless, offering TTR genetic test to any patient with CTS diagnosis is inconceivable because CTS is the most common entrapment neuropathy in general population. However, CTS patients could be screened for TTR variant if we select CTS with definite demographic and electrophysiological features. In general population, many risk factors take role in CTS development: hand-working activities; metabolic and hormonal disease such as diabetes mellitus, overweight, and obesity; thyroid dysfunction; rheumatologic diseases such as rheumatoid or

Table 1 Summary of multidisciplinary examination

	Elder brother (65 y.o.)	Proband (56 y.o.)
Nerve conduction study	Reduced SAP from both superficial peroneal nerves	Normal
Sympathetic skin response	No response at lower limbs	Normal
Tactile QST	Altered at foot	Normal
Thermal QST	Altered at foot, leg, thigh, hand	Altered at foot, leg, thigh, hand
Doppler-echocardiography (IVS)*	13 mm	12 mm
NT-pro-BNP**	352 pg/ml	108 pg/ml
99mTc-DPD bone scintigraphy	Negative (grade I)	Negative (grade I)

SAP, sensory action potential; *QST*, quantitative sensory test; *IVS*, interventricular septum

Normal value: * < 12 mm; ** < 125 pg/ml

Table 2 Demographic ed electrophysiological features of CTS patients deserving TTR genetic analysis

Demographic features	Electrophysiological features
Young age (< 60)	Bilateral
Males > females	Severe/extreme degree
White collar workers	Progressive CTS
No comorbidity	
Positive family history for CTS	

CTS, carpal tunnel syndrome

psoriatic arthritis; and lastly advanced age and female gender are independent risk factors for CTS. Furthermore, electrophysiological findings point out that CTS usually involves the dominant hand, 80% of cases are minimum-moderate degree; it is stable or even improves over time [16].

Considering these features, we can identify red flags that may raise the suspicion for TTR-related CTS (Table 2). A subject with an early age of onset (< 60 years) and positive family history, without risk factors predisposing for CTS (such as hand-working activities or comorbidities) and with bilateral, severe-extreme degree, and progressive CTS can represent the patient deserving further investigation through TTR genetic analysis.

We suggested that the selection of patients with CTS with all abovementioned features can help clinician (from general practitioner, neurologist, neurophysiologist to orthopedic) to raise up the suspicion of TTR-related CTS and to propose the genetic analysis.

Declarations

Ethics approval and informed consent Ethical approval was waived by the local Ethics Committee of University of Naples "Federico II" in view of the retrospective nature of the study and all the procedures being performed were part of the routine care.

Consent to publish The participant has consented to the submission of the case report to the journal.

Competing interests The authors declare no competing interests.

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