Clinical Neurophysiology Practice 3 (2018) 40–44

Contents lists available at ScienceDirect

Clinical Neurophysiology Practice

journal homepage: www.elsevier.com/locate/cnp

Case report

Evidence of neurophysiological improvement of early manifestations of small-fiber dysfunction after liver transplantation in a patient with familial amyloid neuropathy

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ARTICLE INFO

Article history:
Received 2 November 2017
Received in revised form 13 January 2018
Accepted 23 January 2018
Available online 17 February 2018

Keywords:
Small fiber polyneuropathy
Familial amyloidosis
Quantitative sensory testing
Nociceptive evoked potentials
Psychophysical testing
Liver transplantation

ABSTRACT

Introduction: Small fiber polyneuropathy (SFP) is a common heralding clinical manifestation of damage to the nervous system in patients with familial amyloidosis. The diagnosis of SFP is a significant factor in the decision to treat a previously asymptomatic gene carrier, as treatment would prevent irreversible nerve damage. This requires detection of the earliest but unequivocal signs of peripheral nerve involvement.

Case report: We present the case of a young female who was diagnosed of SFP, supported by data from quantitative sensory testing. She had preserved sensory nerve action potentials in the distalmost nerves of her feet and recordable nociceptive evoked potentials. She was successfully transplanted the liver from a previously healthy donor, and recovered fully of her symptoms and signs. Improvement was documented with repeated psychophysical and electrodiagnostic testing in the course of 4 years after transplantation.

Significance: This case illustrates the utility of psychophysical testing to support the diagnosis of SFP.

1. Introduction

Transthyretin familial amyloid polyneuropathy (TTR-FAP) is a rare hereditary neuropathy of adult onset, with autosomal transmission, caused by endoneural accumulation of amyloid deposits. Val30Met is the most prevalent mutation, but many other gene mutations have been reported (Planté-Bordeneuve and Said, 2011). Onset of symptoms is usually insidious and, therefore, the diagnosis can be delayed for years in cases with unknown family history (Conceição and De Carvalho, 2007). Axonal damage in small myelinated and unmyelinated nerve fibers may cause the first symptoms, such as distal lower-limb paresthesia, ‘lightning’ or ‘burning’ pain and defective thermoalgesic sensation (Wang et al., 2008). Erectile, urinary and gastrointestinal dysfunctions are also common and can indicate autonomic nervous system involvement (Chao et al., 2015). The initial small fiber neuropathy progresses to the involvement of larger fibers, leading to fatal outcome within 7–12 years of onset. The most commonly available treatment is liver transplantation (Bergethon et al., 1996), to suppress the main source of systemic production of mutant TTR. A TTR tetramer stabilizer drug (tafamidis), which inhibits the release of highly amyloidogenic monomers and oligomers, has been only recently introduced (Coelho et al., 2012, Coelho et al., 2016, Waddington Cruz and Benson, 2015).

Periodic neurophysiological tests, including those useful for the assessment of small fibers (Montagna et al., 1996, Devigili et al., 2008), are advisable on carriers at risk of developing the disease for early diagnosis of polyneuropathy in time to devise the appropriate therapy (Chao et al., 2015, Conceição et al., 2008, Adams et al., 2016). This procedure is recommended as a routine examination test by the European Network for TTR-FAP, since the involvement of peripheral nervous system is considered a major criterion in the selection of candidates for liver transplantation (Conceição et al., 2014). Once established, though, the neuropathic lesion may be irreversible or reinnervation may take too long for any meaningful clinical changes to be observed (De Carvalho et al., 2009, Adams et al., 2000).

We report a case in which the use of psychophysical methods and thermoalgesic evoked potentials helped early detection of onset of polyneuropathy. The patient had successful liver transplantation after just a few months of disease progression, and

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https://doi.org/10.1016/j.cnp.2018.01.002
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clinical and neurophysiological signs of improvement were documented with the same neurophysiological and psychophysical methods in a follow-up examination up to 4 years after transplantation.

2. Case report

A 29 years old woman recently diagnosed of TTR-FAP secondary to Val-30-Met mutation was derived in June 2012 to the Neurophysiology Department of our Institution for evaluation of polyneuropathy. She had been known as an asymptomatic carrier since 2008. Her symptoms were limited to a few episodes of diarrhea alternating with constipation and occasional orthostatic hypotension without syncope. Echocardiogram, cardiac MRI, EKG holter monitoring and effort tests performed were normal, but cardiac MIBG scintigraphy demonstrated minimal signs of sympathetic denervation. A biopsy of nasal turbinate showed the presence of amyloid deposit, leading to the diagnosis of FAP (Munar-Ques et al., 2008). No ocular or renal involvement was detected.

In March 2012, she started to complain of mild paresthesias and hyperalgesia at the distal region of both lower limbs. Liver transplantation was already considered the best therapeutical option (Munar-Qués et al., 2011), and the patient entered in the waiting list for a suitable donor. When she was first seen in our clinic, three months after onset of neurological symptoms, her conventional physical examination showed normal strength, tendon jerks and sensation to touch and position. However, thermal sensation was reduced in her feet to warm and cold probes. We performed conventional electrodiagnostic tests and quantitative sensory testing and recorded thermoalgesic contact heat evoked potentials (CHEPs) and sympathetic skin responses (SSR) to feet and hands stimuli. Neurophysiological and psychophysical tests were repeated three months later, just before the patient underwent liver transplantation, only 7 months after onset of her neurological symptoms. After transplantation, she experienced a gradual improvement of her neurological condition until significant remission of her sensory disturbances and recovery of thermal sensation. Follow-up neurophysiological and psychophysical examinations were performed 2 and 4 years after transplantation.

3. Methods

All neurophysiological tests were done using a KeyPoint Net electromyograph (Natus, U.S.A.) in the same room and by the same person. We used conventional methods for routine electrodiagnostic (EDX) testing, and established methods for the assessment of small fibers (Medici et al., 2013, Granovsky et al., 2016).

3.1. Conventional EDX testing

We performed sensory nerve conduction studies in conventional nerves (sural, superficial peroneal, ulnar, median) as well as in distal nerves of the feet (dorsal sural and medial plantar nerves). Motor nerve conduction studies were also done in peroneal and median nerves. The F wave was recorded from the flexor hallucis brevis muscle to tibial nerve stimulation.

3.2. Nociceptive evoked potentials

Contact heat evoked potentials were applied to the left forearm and leg using Pathway (Medoc, Israel). The temperature of the thermode was made to rise from 32 °C to 52 °C at a speed of 70 °C/s. Stimuli were applied 10–12 times in each region and the expected contact heat evoked potentials (CHEPs) were recorded from Cz with reference to the bridge of the nose. Care was taken to keep the patient's attention throughout the study, avoiding blinking and facial movements during recording.

3.3. Sympathetic skin response

The sympathetic skin response (SSR) was recorded from the palm of the right hand, with reference to hand dorsum, simultaneously with the nociceptive evoked potentials. Recording time was 5 s.

3.4. Psychophysical testing

Quantitative thermal thresholds were assessed on the left forearm and leg. We used the method of limits to determine heat detection threshold (HDT), heat pain threshold (HPT), cold detection threshold (CDT) and cold pain threshold (CPT). Cutoff temperatures were 10 °C and 50 °C. The rate of temperature change was 1 °C/s. Four stimuli were applied in each region and the patient asked to press a button when perceiving the sensation requested as per instruction.

We also examined dynamic thermal testing using the protocol described by Medici et al. (2013). The patient was instructed to express the sensation felt and how it changed throughout time during the application of slowly increasing temperature stimuli (0.5 °C/s). Stimuli were again applied to the same sites (forearm and leg). Data were collected from a linear potentiometer that the patient moved along a visual analog scale, which had a neutral midpoint and two continuous scales: one toward warm and heat pain sensations and the other, toward cold and cold pain sensation.

4. Results

The patient had normal sensory nerve action potentials (SNAP) in all 4 examination periods. Specifically, no deficit was observed in sural or medial plantar nerves SNAPs (Fig. 1) in the pre-transplantation exams, nor any change in the post-transplantation exams. The sural nerve SNAP amplitude ranged between 12 μV and 15 μV, and conduction velocity between 49 m/s and 54 m/sin all 4 recordings. In the medial plantar nerve, the SNAP amplitude ranged between 3 μV and 4 μV, and conduction velocity ranged between 43 and 45 m/s, in all 4 recordings. Similarly, there were no changes in the characteristics of the SNAPs recorded from sensory nerves of the upper limbs, nor on data from motor nerve conduction studies and the F wave (not reported), which were within limits for healthy subjects in our department. CHEPs and SSRs to thermal stimulation were also present in all 4 examination sessions but there were slight differences between the two exams pre-transplantation and the two exams post-transplantation. Noticeably, CHEPs amplitude to leg stimulation showed a tendency to decrease in the second with respect to the first pre-transplantation exams (Fig. 2). They also showed a clear increase in amplitude in the two post-transplantation exams. Each thermoalgesic stimulus elicited also a SSR of normal latency and amplitude in the hands, except for delayed and reduced responses to foot stimulation in the second pre-transplantation exam (see Fig. 2). No changes were seen along the course of the 4 exams in the CHEPs or the SSR elicited to upper limbs stimulation, where data were within normal limits for the patient's gender, age and height (Granovsky et al., 2016).

Thermal thresholds were clearly abnormal in the first, and more so in the second, pre-transplantation examinations (Table 1). The results of dynamic thermotest are shown in Fig. 3. Again, there was a clear difference between the first and the second pre-transplantation exams, with delayed detection of temperature

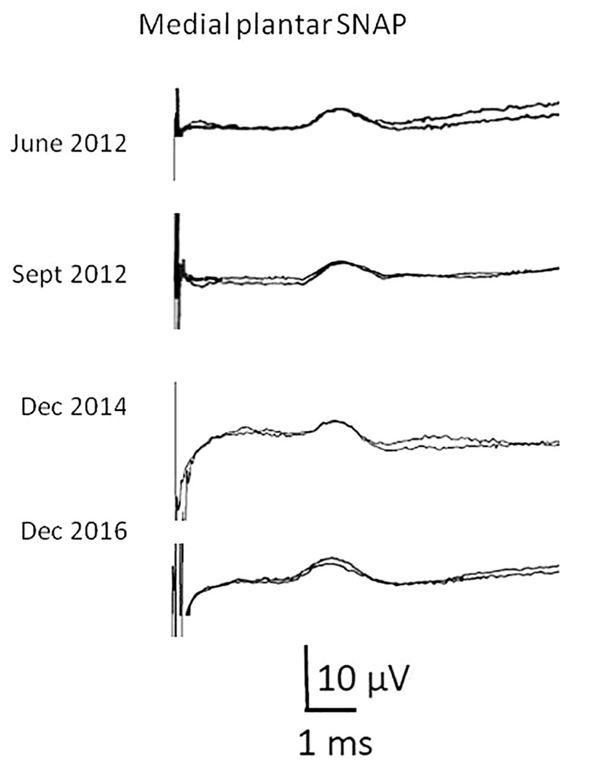

Fig. 1. Sensory nerve action potentials of the medial plantar nerve in all four examinations. Stimuli were applied to the sole of the foot and recordings were obtained from the medial retromalleolar site. Note the integrity of large sensory nerve fibers in the distalmost nerve segments. *SNAP: Sensory Nerve Action Potential.*

and decreased level of sensation in the second with respect to the first exam. There was the opposite change after transplantation, when temperature detection occurred earlier, and the level of sensation increased to match or even improve the values of the first exam. The patient continued asymptomatic except for the occasional episodes of incontinence and orthostatic hypotension when she was last examined 4 years after transplantation.

5. Discussion

Early diagnosis of neurological dysfunction in carriers of TTR-FAP is crucial to initiate therapy. This is the only way to prevent persistent neurological damage. Several published reports provide compelling evidence that liver transplantation canslow or stop disease progression, especially at early stages due to lower risk of death (Ericzon et al., 2015). Consensus criteria should be implemented in every case (Adams et al., 2016). Insidious onset of symptoms may be unperceived by patients and, therefore, neurophysiological tests performed periodically help to detect the initial signs of neurological impairment.

The disorder affects mostly small fibers at onset and, therefore, tests for the assessment of small fibers function are the most appropriate. Typically, in early-onset cases, autonomic dysfunction may prevail over organ damage and neuropathic pain (Conceição and De Carvalho, 2007). This is in fact what occurred in our patient, who remained with subtle signs of autonomic dysfunction, such as orthostatic hypotension and diarrhea episodes, even after transplantation. Conceição et al. (2014) stressed the importance of recording the SSR in the sole of the feet as one of the earliest signs of abnormality in small fiber function in patients with amyloidosis. This could have certainly been appropriate in our case. However, we did not perform such recording in the pre-transplantation tests, done before Conciençao et al.'s publication, and, therefore, we did not consider it for the post-transplantation follow-up. Instead, we based our assessment of small fibers function in psychophysical testing. This included not only the more conventional QST, but also the so-called dynamic thermotest. The latter helps with the objective assessment of thermoalgesic sensation as subjects have to engage their attention to the continuously changing afferent input, with more information points and less possibilities for mistakes and errors (Medici et al., 2013). Our patient showed full remission of neurological symptoms after transplantation. Improvement in the sensory domain was documented by repeating the same

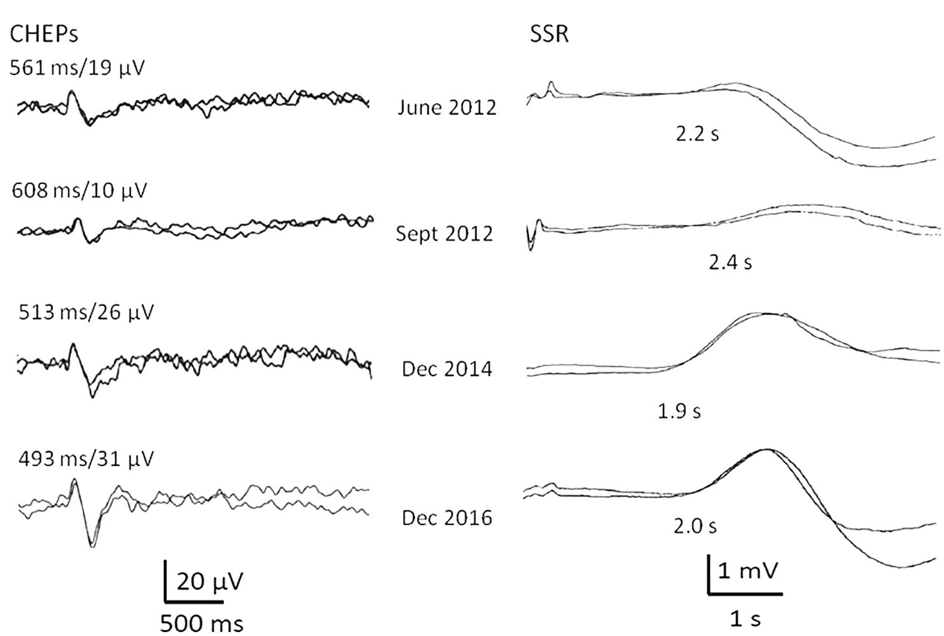

Fig. 2. Contact heat evoked potentials (CHEPs) recorded from Cz, and sudomotor skin response (SSR) recorded from the right hand, to leg stimulation. Note the relative reduction in amplitude of CHEPs and SSR in the second with respect to the first pre-transplantation exams, and their relative increase in the two post-transplantation exams.

Table 1
Data in °C on quantitative thermal threshold obtained in the two pre-transplantation and the two post-transplantation examinations. Note the clear improvement in the post-transplantation evaluations in all domains and regions explored.

Stimulation site		June 2012	Sept 2012	Dec 2014	Dec 2016
Ventral forearm	HDT	36.2	36.7	34.9	33.8
	HPT	41.2	41.6	41.8	42.3
	CDT	29.7	29.2	30.1	30.3
	CPT	–	–	–	14.6
Medial distal leg	HDT	42.1	43.5	38.7	37.7
	HPT	48.1	48.6	41.5	42.7
	CDT	25.2	24.8	29.4	29.7
	CPT	23.4	23.7	–	–

HDT: Heat Detection Threshold; HPT: Heat Pain Threshold; CDT: Cold Detection Threshold; CPT: Cold Pain Threshold.

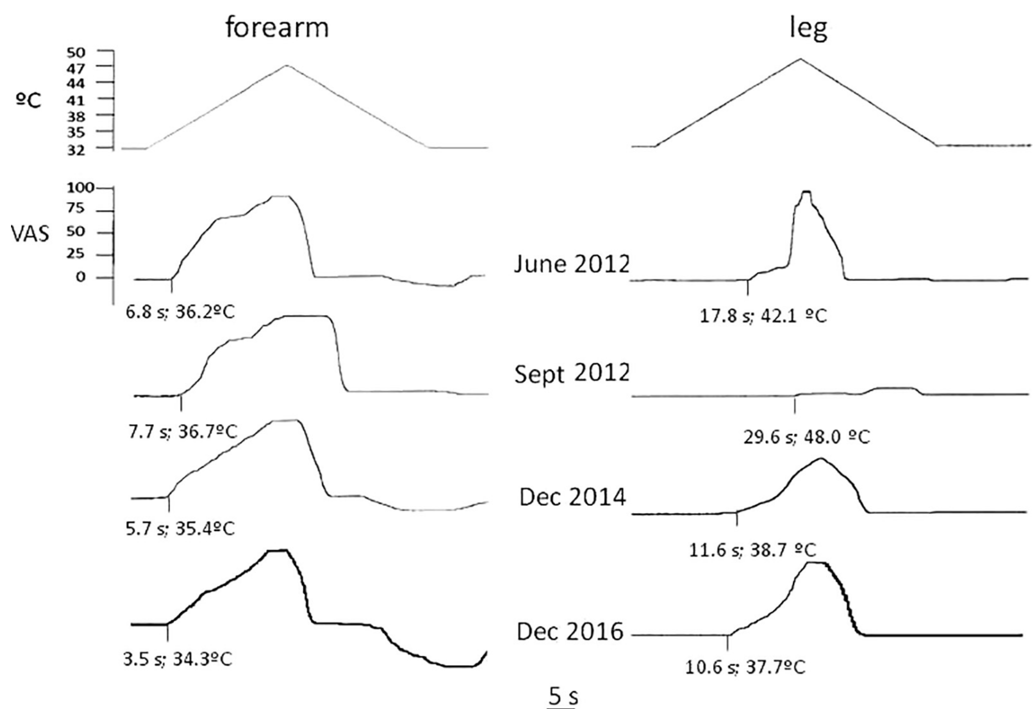

Fig. 3. Dynamic thermal testing in the forearm (left side) and leg (right side). The upper graph shows the temperature stimulus: a slow increase and decrease slopes at 0.5 °C/s, together with the scale of temperature. The subsequent 4 recordings in each column show the responses given by the patient to the stimulus, using an electronic visual analogic scale, represented to the left of the first recording and applicable to all recordings. Labels show the mean value of temperature and time at detection threshold.

neurophysiological and psychophysical testing in follow up repeated examinations 2 and 4 years after liver transplantation, providing more evidence in favor of the importance of early diagnosis and the potential for recovery if neurological damage remains within limits.

Conflict of interest statement

The authors declare no conflict of interest.

Acknowledgment

The authors thank Andalucia Vila SanJuan for her kind collaboration.

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