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Observational multicentric survey on carpal tunnel syndrome: demographic and clinical data from 34 Italian centers

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Abstract. – OBJECTIVE: To evaluate the current management of carpal tunnel syndrome (CTS) at a national level.

PATIENTS AND METHODS: A multicentric observational study was conducted in 34 Italian centers by specialists participating in the Management of Peripheral Neuropathies Study Group on 377 patients (age, mean±SD 56±14.4 years, 73.2% females) with CTS. The characteristics of the disease and its management were recorded at baseline and during a 2-month follow-up using a standardized clinical record and assessed with validated clinical tests.

RESULTS: A wide variability in the interventions prescribed and classified according to three categories (physical, pharmacological and neurotrophic therapies) was evident. A subgroup of 303 patients was treated with a combination of neurotrophic agents containing alpha-lipoic acid (ALA). At the end of the follow-up, a general improvement in symptoms and functional impairment was observed, with a significant reduction in BCTQ (Boston Carpal Tunnel Questionnaire) ($p<0.001$) and in NRS (Pain Numeric Rating Scale, $p<0.001$ for both nocturnal and diurnal pain).

CONCLUSIONS: An appropriate approach to CTS implies a multimodal and multidisciplinary management, involving several specialists and using a variety of conservative interventions. Conservative (physical and pharmacological) interventions can provide a clinical improvement in patients with CTS.

Key Words:
(Mesh terms) Carpal tunnel syndrome, Neuropathy, Neuropathic pain, Pain management, Alpha-lipoic acid.

Introduction

Carpal Tunnel Syndrome (CTS) is an entrapment neuropathy of the median nerve at the wrist. Symptoms include neuropathic pain, paraesthesia, dysaesthesia and functional motor impairment. The initial stage of the disease is characterized by positive sensory symptoms (pain, worsening paraesthesia with radiation to the forearm), the advanced stage of a rather unpredictable evolution of motor weakness and sensory loss, sometimes leading to paralysis.

CTS is considered a quite common condition, with an estimated prevalence of 3.8% in the general population, higher in females (9.2%). The estimated yearly incidence is approximately 0.3%. The typical onset is described in the fifth or sixth decade of life. In women, two incident peaks during pregnancy and perimenopause are reported. It may occur as a work-related disorder, with a five-fold higher incidence in workers exposed to repetitive motion or vibrating tools[1,2].

Moreover, a genetic predisposition has been hypothesized, while endocrine or metabolic risk factors such as obesity, diabetes mellitus, thyroid disorders, and other pathological or physiological changes in hormonal balance (pregnancy and menopause) have been implicated[1-3].

The pathogenesis of CTS is quite complex. The functional and anatomic damage have to be ascribed to two major mechanisms: the increased pressure on the median nerve in the carpal tun-

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nel at the wrist and the ischemic damage to local microcirculation. Mechanical compression of the median nerve, both at rest and during wrist extension or flexion disrupts local blood flow[4], causing nerve fiber irritation and the discharge of autonomous action potentials, which are responsible for paraesthesia and pain, typical of the early phase of the condition. This series of events, if protracted in time, together with the sustained mechanical compression during hand movements, support the transition from a functional irritation to structural damage, with axonal demyelination. Moreover, the increased perineural compression is associated with a reduction in nerve perfusion, which spreads from the external to the internal fibers. This marks the moment of irreversibility in the axonal degeneration, since endoneural oedema cannot be reverted in the absence of a local lymphatic system. Thus, the neuropathy is worsened by external compression and ischemia of *vasa nervorum,* that results in an increased oxidative stress and a vicious circle leading, again, to a degenerative status[4,5].

CTS may be classified according to symptoms and signs into three stages: early, intermediate and advanced. In the early phase patients complain of nocturnal pain and paraesthesia. In the intermediate stage, with the progression of median nerve degeneration, symptoms persist, thus, pain and paraesthesia are present also during the day. Moreover, irritative symptoms may be accompanied by functional impairment and a mild hypotrophy of thenar eminence. The advanced phase is characterized by the persistence of sensory symptoms and the progression in functional impairment[6].

The burden of the disease is relevant, particularly in the elderly, regarding severity and duration of symptoms, disability and impact on the quality of life[1,2,6].

In spite of the public health importance of CTS, there are no universally accepted indications about its optimal management, which remains a matter of debate. Currently, guidelines have not reached consensus on certain recommendations and evidence is not strong enough to draw straightforward indications for management[2,6-11].

A large panel of therapeutic options is available, and in clinical practice, there is considerable variation in how treatments are selected or sequenced without any definition of first line intervention or of a shared therapeutic algorithm.

Conservative treatments include splints, pharmacological therapies, and physical therapies: rehabilitation, ultrasounds, TECAR (Capacitive and Resistive Energy Transfer), laser therapy, iontophoresis, and TENS (Transcutaneous Electrical Nerve Stimulation). The level of supporting evidence for these options is limited and their indication controversial[5-7,9].

As far as pharmacological therapies are concerned, the most robust evidence is in favor of local-injection steroids, even if they provide short-term benefits, while the effectiveness of NSAIDs (Non-Steroidal Anti-inflammatory Drugs) or diuretics is controversial[5-9].

Antioxidant and neurotrophic agents may be helpful in CTS. Alpha-lipoic acid (ALA), an antioxidant able to positively influence the course of neuropathic pain[12,13], has been proven effective in improving symptoms and nerve fiber conduction in CTS in a randomized-controlled trial in 180 patients[14] and in a controlled trial in 112 patients, where it was combined with gamma-linolenic acid (GLA)[15], a neurotrophic agent improving neural functions[16]. L-Acetyl-carnitine (LAC) has been shown to have analgesic effects in a series of 109 patients affected by CTS[17]. At the moment, there is no convincing evidence about pyridoxine (B6 vitamin)[5,18].

Surgical treatment with median nerve decompression is widely preferred over nonsurgical or conservative interventions, in the majority of CTS. In a systematic Cochrane Review on surgical interventions in CTS, the reviewers concluded that surgical treatment is more effective than conservative therapies in preserving mid- to long-term improvement[10]. There is clear indication for surgical treatment for overtly symptomatic patients (intermediate or advanced stage or with a heavy interference in daily life[2,5,10].

This study has been designed to verify the actual management of CTS at a national level of all patients with different conditions characterized by the predominance of neuropathic pain. Thus, the management of peripheral neuropathies study group, which included specialists in different fields, has conducted an observational study to provide an updated and realistic representation of CTS and to collect information about the effects of the available interventions routinely used in clinical practice in real life setting. They have been analyzed following a classification into three main categories: physical therapy, pharmacological therapy (analgesics and anti-inflammatory drugs) and antioxidant and neurotrophic agents. The study group selected the parameters to be evaluated and the tests to be performed according to the international literature.

Patients and Methods

Patients

This observational study has been conducted from May 2012 to March 2013 in 34 Italian centers specialized in Orthopaedics, Physical Medicine and Rehabilitation, Neurology, Neurosurgery, and Rheumatology and participating in the *Management of Peripheral Neuropathies Study Group*. It enrolled 377 consecutive patients with no indication for surgical intervention or in waiting list/in whom the surgical had been deferred.

The study was aimed at providing a deeper knowledge of clinical presentation, diagnosis, and treatment of CTS and addressing the most relevant issues related to the management of patients.

A model of dedicated clinical record was developed to collect clinical and instrumental data in addition to parameters routinely used in clinical practice, and to adopt homogeneous criteria for diagnosis, monitoring, and outcomes.

Patients' evaluation was performed at baseline and 2 months after conservative treatment.

The study was conducted in accordance with current guidelines of good clinical practice (GCP) regulations relating to clinical trials and the Declaration of Helsinki and was approved by the local Ethics Committees.

Informed consent was obtained from all patients after exhaustively explaining the aim of the study.

Characteristics of Patients

We enrolled adult female or male patients (older than 18 years) with a CTS diagnosis without any indication to surgical intervention or for whom the surgical intervention had not been planned for two months. At the study enrolment demographic and anthropometric data, work activity information and any occupational exposure possibly related to CTS, referral from general practitioners or specialists, comorbidities, duration and characteristics of CTS, physical examination including semiotic maneuvers, previous instrumental diagnostic procedures, previous and ongoing treatments (physical therapy, pharmacological therapy or pathogenetic treatments with antioxidant or neurotrophic agents) were collected.

Diagnostic Semiotic Maneuvers and Instrumental Examinations

As far as clinical semiotic tests, we assessed and collected the results of Tinel's sign and Phalen's test (both provocative tests specific for CTS) and evaluated their agreement.

Tinel's sign[19] is performed by lightly percussing median nerve at the wrist. It is positive when eliciting tingling in the thumb, index, and middle fingers, partially in the ring finger, which are innervated by the median nerve.

Phalen's test[20] is performed by asking the patient to hold his/her wrist in complete and forced flexion for 60 seconds. It is positive when eliciting paresthesia of the thumb, index, middle and ring finger.

Considering instrumental examinations, patients underwent electromyography and were assigned to the grades of Padua severity scale[21] according to the neurophysiological parameters recorded.

Padua severity scale classifies the severity of CTS according to electrophysiological data, as follows:

0: negative for CTS (normal electrophysiological results)
1: very mild/minimal CTS (an alteration among segments or in comparative nerve conduction study)
2: mild CTS (reduction in sensory median nerve conduction velocity with normal terminal motor latency)
3: moderate CTS (impairment in sensory potential and terminal motor latency)
4: severe CTS (absence of sensory potentials and impairment in terminal motor latency)
5: extreme/extremely severe CTS (absence of sensory and motor potentials).

The severity of pain and functional disability was assessed using two internationally standardized questionnaires whose Italian translations have been previously validated.

The NRS (Numeric Rating Scale)[22] is a verbally administered, segmented numerical horizontal bar on which patients have to select a whole number (from 0 "no pain" to 10 "worst possible pain") that best reflects the intensity of their pain. It has become a widely used instrument for pain assessment in many health care environments and has been adopted by Pain in Europe (http://www.paineurope.com), the European survey on chronic pain.

The BCTQ (Boston Carpal Tunnel Questionnaire)[23] is a disease-specific measure of self-reported symptom severity and functional status. The scale for severity of symptoms ranges from 11 ("no symptoms") to 55 ("worst possible symptoms"), the scale for functional status from 8 ("normal") to 40 ("complete impairment").

Statistical Analysis

Quantitative variables were reported as mean±-standard deviation (SD) and range, qualitative variables as absolute and relative frequencies.

Demographic and clinical data, symptoms scores, prescribed treatments were summarized in frequency tables or central tendency and dispersion tables, using the most appropriate indicators to represent the distribution of each variable (mean, standard deviation, minimum and maximum observations). Data were presented by means tables and figures as appropriate and were analyzed by standard descriptive statistics.

The intragroup differences in semiotic tests and in pain assessment tests (baseline *vs.* end of follow-up) were evaluated using paired *t*-test. The *t*-test was used to assess whether there is a significant variation of parameters (NRS, BCTQ) (baseline *vs.* end of follow-up) and corrections for multiple comparisons were applied to the *p*-values. Differences have been considered significant where $p<0.05$.

To evaluate the variations of pre-post treatment parameters (NRS, BCTQ) in the different grades of CTS, data were stratified according to the severity degree of CTS based on Padua severity scale. We decided to stratify data according with 3 severity grades: minimal-mild (grade 1 and 2 on Padua's scale), moderate (grade 3 on Padua's scale) and severe-extremely severe (grade 4 and 5 on Padua's scale), in order to have a sufficient number of patients for each group and analyze the effects of conservative treatment in different severity grades of CTS.

The ANOVA test was used to assess the variation of NRS scores in every severity group (baseline *vs.* end of follow-up).

The Bonferroni test was performed to verify whether there were significant variations in pre-post treatment parameters between the different severity groups.

The Wilcoxon test was used to assess whether there was a significant variation of BCTQ scores in every severity group (baseline *vs.* end of follow-up).

The Kruskal-Wallis test was used to verify whether there were significant variations in pre-post treatment parameters in the different severity groups.

In the case of significant results, the Mann-Whitney U test was performed to explore significant differences between groups.

The agreement between Tinel's sign and Phalen's test was assessed with *k* index.

No direct comparison between treatments was performed.

No missing data have been replaced, and no replacement policy has been implemented; as a matter of fact, the analysis fully reflects the observed values.

The statistical analysis has been performed using the software SPSS Statistical Package, version 16.0 (SPSS Inc. Chicago, IL, USA).

Results

Patients

Baseline characteristics of the 377 patients (age, mean±SD 56±14.4 years, 73.2% females) with CTS enrolled in the study are reported in Table I. Among all patients, 12.4% were menopausal and 2% pregnant women.

Patients had bilateral involvement in 38% of cases, right involvement in 41% of cases, left involvement in 21% of cases.

Table I. Demographic and clinical characteristics of patients at baseline.

	Patients (No.=377)
Gender, No. (%)	
- females	276 (73.2%)
- males	101 (26.8%)
Age (years)	
mean±SD (range)	56±14.4
(21-89)	
Body weight (kg)	
mean±SD (range)	72.1±14.2
(42-151)	
Height (cm)	
meand±SD (range)	166.2±8
(148-190)	
Smoking habit, No. (%)	
1. No	227 (60.2%)
2. Yes	100 (26.5%)
- ND	50 (13.3%)
Work activity, No. (%)	
1. Blue collar	59 (15.6%)
2. White collar	87 (23.1%)
3. Homeworker	102 (27.1%)
4. Retirees	89 (23.6%)
5. Others	31 (8.2%)
- ND	9 (2.4%)
Work-related STC, No. (%)	
1. No	175 (46.5%)
2. Yes	85 (26.5%)
3. Uncertain	88 (23.3%)
- ND	29 (7.7%)

ND: Not determined

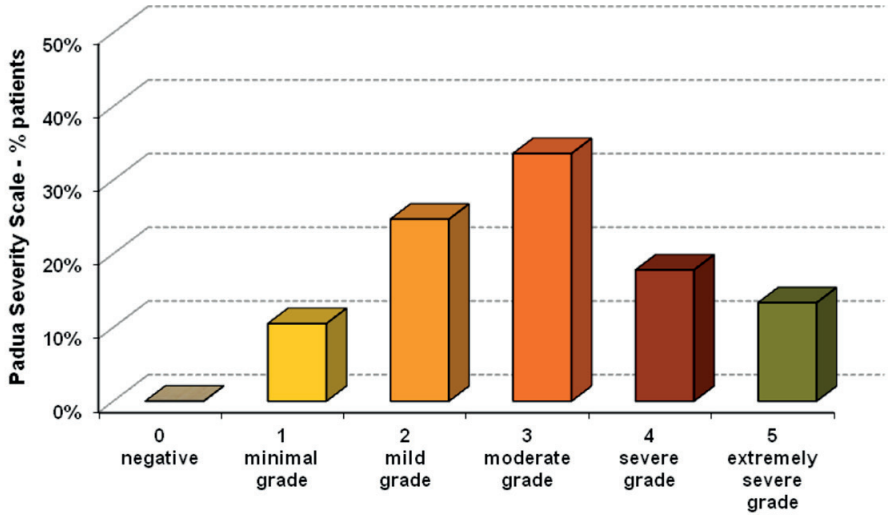

Figure 1. Distribution of patients according to Padua severity scale (n=247).

For 41.3% of patients' time since the initial diagnosis ranged from 1 to 12 months.

The most common comorbidities were osteoarthritis (24.1%), diabetes mellitus (18.6%), thyroid disorders (9.6%), and rheumatoid arthritis (4.0%).

Instrumental Diagnostic Procedures

Electromyography was performed in 247 (65.5%) patients. Figure 1 shows the distribution of the 247 patients according to the Padua severity scale. Among these patients, 87 (35.2%) were classified as minimum-mild grade, 83 (33.6%) as moderate grade and 77 (31.2%) as a severe-extremely severe grade.

Clinical Tests

Tinel's sign was positive in all cases (n=302) it has been assessed, with the following localization: right 45.4%, left 20.2%, and bilateral 34.4%.

Phalen's test was positive in all cases (n=299) it has been assessed, with the following localization: right 45.2%, left 19.7%, and bilateral 35.1%.

The agreement between Tinel's sign and Phanel's test was excellent (k =0.94, p<0.001).

The vast majority of patients reported the simultaneous presence of nocturnal (right 67.9%, left 45.9%) and diurnal (right 42.2%, left 28.4%) paresthesia. Similarly, a large number of patients reported both nocturnal (right 57.6%, left 35.8%) and diurnal (right 31.8%, left 23.1%) pain.

Hypotrophy of thenar eminence was observed in 44 right hands and 43 left hands.

Treatments Prescribed Before Enrolment

Previous treatments before enrolment had been prescribed by the GPs in 43.2% of patients, by a specialist in 35.5% of patients. The response to previous treatments according to patient's judgment, classified in the three main categories (physical therapy, pharmacological therapy, and neurotrophic therapy), is reported in Table II.

Physical therapy interventions were associated with suboptimal response rates (in general less than a third of patients) with the exclusion of corset (41.4% of responders), TENS (38.5%), and ultrasounds (31.6%).

Response rates to pharmacological therapy showed a wide variability, ranging between 21.1% with NSAIDs and 71.4% with opioids. Satisfactory response rates (65.2%) were obtained with combinations containing ALA, as well as with carnitine (62.1%) or B complex vitamins (40.6%).

Treatments Prescribed at the Study Entry

A wide variability in the interventions prescribed at the study entry and classified according to the same three main categories is apparent (Table II).

As regards pharmacological therapy administered with analgesic intent, NSAIDs and paracetamol (14.6% and 17%, respectively) were more frequently used than corticosteroids (oral 6.1% and infiltration 4%). Opioids were prescribed in 6.4% of cases.

Among neurotrophic agents, the most prescribed (59.2%) was an association of ALA, GLA, ho-

Table II. Treatments prescribed before enrolment and at the study entry.

	Treatments prescribed before enrolment				Treatments prescribed at the study entry
	Patients treated, No. (%)	Clinical response			Patients treated, No. (%)
		No.	Yes	ND	
Physical therapy, No. (%)					
Splint	58 (15.4%)	24 (41.4%)	24 (41.4%)	10 (17.2%)	59 (15.6%)
Carbon dioxide laser	37 (9.8%)	25 (67.6%)	10 (27%)	2 (5.4%)	50 (13.3%)
Ionophoresis	31 (8.2%)	18 (58.1%)	7 (22.6%)	6 (19.4%)	24 (6.4%)
Ultrasounds	57 (15.1%)	29 (50.9%)	18 (31.6%)	10 (17.5%)	59 (15.6%)
TENS	26 (6.9%)	14 (53.8%)	10 (38.5%)	2 (7.7%)	15 (4%)
Others	7 (1.9%)	2 (28.6%)	4 (57.1%)	1 (14.3%)	5 (1.3%)
Pharmacological therapy, No. (%)					
NSAIDs	123 (32.6%)	66 (53.7%)	26 (21.1%)	31 (25.2%)	55 (14.6%)
Corticosteroids (oral)	25 (6.6%)	13 (52%)	8 (32%)	4 (16%)	23 (6.1%)
Corticosteroids (infiltration)	31 (8.2%)	16 (51.6%)	14 (45.2%)	1 (3.2%)	15 (4%)
Paracetamol	47 (12.5%)	23 (48.9%)	15 (31.9%)	9 (19.1%)	64 (17%)
Opioids	14 (3.7%)	3 (21.4%)	10 (71.4%)	1 (7.1%)	24 (6.4%)
Others	2 (0.5%)	1 (50%)	-	1 (50%)	1 (0.3%)
Neurotrophic therapy, No. (%)					
ALA	69 (18.3%)	9 (13%)	45 (65.2%)	15 (21.7%)	234 (62.1%)
Carnitine	29 (7.7%)	10 (34.5%)	18 (62.1%)	1 (3.4%)	69 (18.3%)
B complex vitamins	32 (8.5%)	14 (43.8%)	13 (40.6%)	5 (15.6%)	26 (6.9%)
Others	12 (15.4%)	3 (25%)	5 (41.7%)	4 (33.3%)	26 (6.9%)
1. No	175 (46.5%)				
2. Yes	85 (26.5%)				
3. Uncertain	88 (23.3%)				
- ND	29 (7.7%)				

ND: Not determined; TENS: Transcutaneous Electrical Nerve Stimulation; NSAIDs: Non-Steroidal Anti-Inflammatory Drugs; ALA: Alpha-Lipoic Acid.

nokiol, and B complex vitamins. The use of carnitine or B complex vitamins was relatively limited, accounting for approximately 13%.

The comparison between pharmacological therapies prescribed before enrolment and at the study entry showed a trend towards a reduction in NSAIDs use (from 32.6% to 14.6%), together with a relative increase in paracetamol (from 12.5% to 17%) and opioids (from 3.7% to 6.4%) use. Also, the prescription of combinations containing ALA and other neurotrophic agents increased (from 18.3% to 62.1%).

At the final evaluation, the compliance to treatments and the need for dose changing were recorded.

Physical therapy was completed as planned in 42.7% of patients. Considering pharmacological therapy, daily administration schedule of conventional medications was unchanged in 53.1% of patients and withdrawn in 1.5%. Considering neurotrophic therapy, daily administration schedule was unchanged in 62.9% of patients and withdrawn in 2.4%.

Surgical intervention was recommended in 46.9% of patients. In particular, surgery was recommended in 19.5% of patients with minimum-mild grade CTS, 51.8% of patients with moderate grade CTS and 70.1% of patients with severe-extremely severe grade CTS.

Pain and Disability Evaluation

At the end of the study, after a 2-month follow-up, a general improvement in both perceived pain and functional disabilities was observed.

Specifically, NRS significantly improved in both nocturnal pains (baseline *vs.* end of follow-up, mean±SD: right 6.4±2.8 *vs.* 3.3±2.8; left 6.1±3 *vs.* 3.2±2.7; $p<0.001$ for both) and diurnal pain (right 5.2±2.8 *vs.* 2.4±2.5; left 4.6±3 *vs.* 2.7±2.7; $p<0.001$ for both).

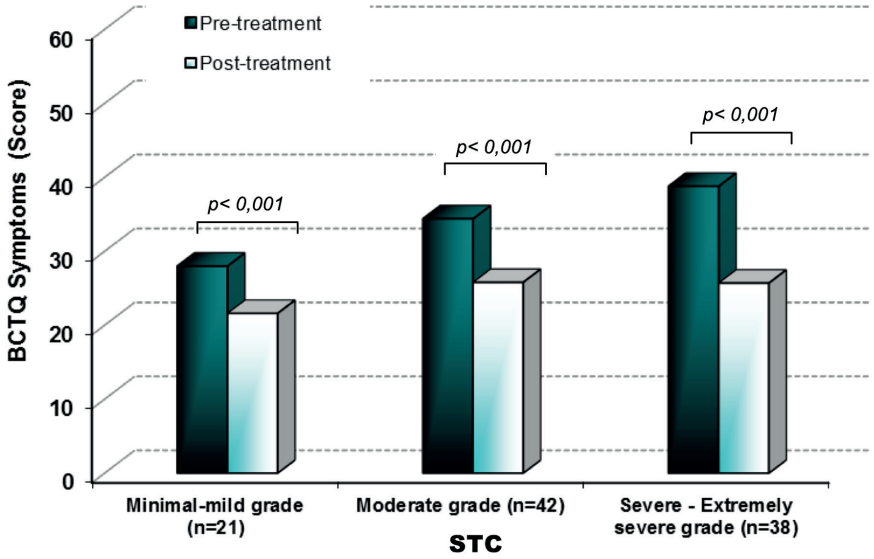

Figure 2. BCTQ (Boston Carpal Tunnel Questionnaire) symptoms before and after treatment (n=101). Data are stratified by the severity of CTS.

III reports the variation of NRS between baseline and end of follow-up in the different degrees of severity of CTS. Pain decreases more consistently after conservative treatment in the heaviest forms of CTS than in the milder ones ($p<0.05$).

BCTQ score (case assessed baseline *vs.* end of follow-up 244 *vs.* 170) significantly improved regarding both symptoms (baseline *vs.* end of follow-up, mean±SD: 32.7±9.2 *vs.* 24.1±9.3; $p<0.001$) and functional disabilities (19.5±8.1 *vs.* 16.7±7; $p<0.001$).

Data stratified according to the severity of CTS are reported in Figure 2 and Figure 3. The improvement in BCTQ scores for both symptoms and disability was significantly higher in the severe-extremely severe group than in the moderate group ($p<0.01$) and in the minimal-mild severity group ($p<0.005$).

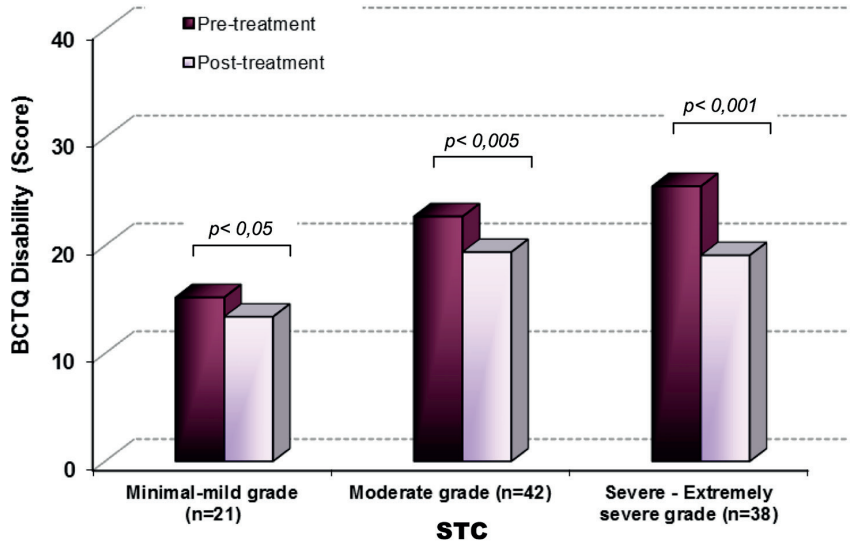

Figure 3. BCTQ (Boston Carpal Tunnel Questionnaire) disability before and after treatment (n=101). Data are stratified by the severity of CTS.

Table III. Numeric Pain Intensity Scale (NRS): variation between end of follow-up and baseline. Data are stratified by the severity of CTS.

	CTS			
	Minimal-mild grade Variation	Moderate grade Variation	Severe-extremely severe grade Variation	p[(2)]
NRS – Nocturnal pain (0-10)				
Right	-2.4±1.9	-2.9±2.8	-3.5±2.2	ns
Left	-2.0±1.9	-2.7±2.5	-3.5±2.4[a]	< 0.05
NRS – Diurnal pain (0-10)				
Right	-2.1±2.1	-2.5±2.3	-3.1±1.9[a]	< 0.05
Left	-1.3±1.5	-1.9±2.1	-2.8±2.1[a]	< 0.03

(2) ANOVA. [a]Bonferroni test: "severe-extremely severe grade" *vs*. "minimal-mild grade" $p < 0.05$.

Discussion

This observational study provides a real life representation of clinical presentation and management of carpal tunnel syndrome (CTS) in Italy, in terms of patients' characteristics, diagnostic procedures and therapeutic interventions.

The group of patients selected is likely representative of the whole population suffering from this condition: predominance of female patients, sixth decade of life, onset of signs and symptoms generally occurring in the last 12 months with pain and paraesthesia, mostly occurring at night, signs of nerve degeneration.

The indication for surgical treatment with median nerve decompression, which represents the elective intervention and often obtains the complete resolution[2,5,10], was planned in less than 50% of cases.

Patients had been previously treated with several available conservative treatments. Notably, analyzing the trend in the prescription of the various pharmacological therapies, the participation in a study focused on peripheral neuropathies and managed by specialists resulted in a reduction in NSAIDs associated with an increase in neurotrophic agents. Among the latter, combinations containing ALA were prescribed at the dose of 600 mg daily, as appropriate[13-15].

Surprisingly conservative treatment, mostly based on neurotrophic agents, had significantly higher effects in the more severe CTS in terms of pain relief (NRS), CTS symptoms (BCTQ-symptoms) and functional impairment (BCTQ-disability).

A plausible explanation for this phenomenon may relate to the increase in prescription of neurotrophic agents, in particular, ALA. Considering the mechanisms underlying the neuropathy, the combination of ALA with other specific neurotrophic agents, e.g. GL ≥ GLA[15,16], honokiol[24], and B complex vitamins[18], used in the majority of the patients included in the present study, may be of benefit.

Among pathogenetic therapies, the best evidence is accruing about the clinical effectiveness of ALA for the treatment of chronic neuropathic pain[12]. In fact, it has been recommended as a first line choice in neuropathic pain[13].

ALA is endowed with three main mechanisms of action: it acts as an antioxidant, as an anti-inflammatory (inhibition of IL-1, IL-6, and TNF-α biosynthesis; decreased NF-kB activation) and as a coenzyme in cellular energy metabolism (increased ATP biosynthesis)[25,26].

In a study of patients with CTS, the combination of ALA, GLA, and B complex vitamins was proven effective regarding improvement in symptoms scores and functional impairment together with an increase in nerve conduction velocity[15]. According to experimental data, pre-surgical and post-surgical expositions to a combination of ALA and neurotrophic agents provide an advantage regarding faster recovery, compared to pre-surgical exposition alone[14].

Neurotrophic therapies represent a promising option, since they act on the main pathophysiological mechanisms, which support the neuropathy, preventing the progression of median nerve degeneration. They exert synergic effects with analgesic medications and rehabilitation, since they can have an impact on the course of the disease and the mechanisms leading to its chronicity and can favor a reduction in the use of anti-in-

flammatory and analgesic medications, with a beneficial improvement in risk/benefit ratio of the whole therapeutic strategy[3].

Conclusions

According to the results of the study, neurotrophic agents may be recommended for the conservative management of CTS, in patients waiting for or with no indication to the surgical intervention.

All interventions have to be included in a multimodal and multidisciplinary approach, considering the multifaceted pathophysiology and the various clinical issues of CTS, encompassing the most accurate diagnostic procedures, in terms of pain assessment, functional disability, or quality of life, and combining all available treatments able to obtain the best management of the condition.

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Conflict of interest

The authors declare no conflicts of interest.

References

1) Ibrahim I, Khan WS, Goddard N, Smitham P. Carpal tunnel syndrome: a review of the recent literature. Op Orthop J 2012; 6: 69-76.
2) Keith MW, Masear V, Chung KC, Amadio PC, Andary M, Barth RW, Maupin K, Graham B, Watters WC 3rd, Turkelson CM, Haralson RH 3rd, Wies JL, McGowan R; American Academy of Orthopaedic Surgeons. American academy of orthopaedic surgeons clinical practice guideline on the treatment of carpal tunnel syndrome. J Bone Joint Surg Am 2010; 92: 218-219.
3) Sud V, Freeland AE. Biochemistry of carpal tunnel syndrome. Microsurgery 2005; 25: 44-46.
4) Corwin HM. Compression neuropathies of the upper extremity. Clin Occup Env Med 2005; 5: 333-352.
5) Alfonso C, Jann S, Massa R, Torreggiani A. Diagnosis, treatment and follow-up of the carpal tunnel syndrome: a review. Neurol Sci 2010; 31: 243-252.
6) Ogur T, Yakut ZI, Teber MA, Alp F, Turan A, Tural A, Gelisen O. Ultrasound elastographic evaluation ofthe median nerve in pregnant women with car-

pal tunnel syndrome. Eur Rev Med Pharmacol Sci 2015; 19: 23-30.

7) Lundborg G. Nerve injury and repair: regeneration, reconstruction and cortical remodeling. Elsevier, 2004.
8) Piazzini DB, Aprile I, Ferrara PE, Bertolini C, Tonali P, Maggi L, Rabini A, Piantelli S, Padua L. A systematic review of conservative treatment in carpal tunnel syndrome. Clin Rehabil 2007; 21: 299-314.
9) O'Connor D, Marshall S, Massy-Westropp N. Non-surgical treatment (other than steroid injection) for carpal tunnel syndrome. Cochrane Database Syst Rev 2003; 1: CD003219.
10) Verdugo RJ, Salinas RS, Castillo J, Cea JG. Surgical versus non-surgical treatment for carpal tunnel syndrome. Cochrane Database Syst Rev 2003; 3: CD001552.
11) Ranieri M, Sciuscio M, Cortese AM, Santamato A, Di Teo L, Ianieri G, Bellomo RG, Stasi M, Megna M. The use of alpha-lipoic acid (ALA), gamma linolenic acid (GLA) and rehabilitation in the treatment of back pain: effect on health-related quality of life. Int J Immunopathol Pharmacol 2009; 22: 45-50.
12) Lee FH, Raja SN. Complementary and alternative medicine in chronic pain. Pain 2011; 152: 28-30.
13) Watson JC, Dyck PJ. Peripheral neuropathy: a practical approach to diagnosis and symptom management. Mayo Clin Proc 2015; 90: 940-951.
14) Pajardi G, Bortot P, Ponti V, Novelli C. Clinical usefulness of oral supplementation with alpha-lipoic acid, curcumin phytosome, and B-group vitamins in patients with carpal tunnel syndrome undergoing surgical treatment. Evid Based Complement Alternat Med 2014; 2014: 891310.
15) Di Geronimo G, Caccese AF, Caruso L, Soldati A, Passaretti U. Treatment of carpal tunnel syndrome with alpha-lipoic acid. Eur Rev Med Pharmacol Sci 2009; 13: 133-139.
16) Jamal GA. The use of gamma linolenic acid in the prevention and treatment of diabetic neuropathy. Diabet Med 1994; 11: 145-149.
17) De Grandis D. Tolerability and efficacy of L-acetylcarnitine in patients with peripheral neuropathies. A short-term open multicentre study. Drug Invest 1998; 15: 73-79.
18) Aufiero E, Stitik TP, Foye PM, Chen B. Pyridoxine hydrochloride treatment of carpal tunnel syndrome: a review. Nutr Rev 2004; 62: 96-104.
19) Tinel J. Le signe du fourmillement dans les lésions des nerfs périphériques. Presse Médicale 1915; 47: 388-389.
20) Phalen GS. The carpal-tunnel syndrome: clinical evaluation of 598 hands. Clin Orthop 1972; 83: 29-40.
21) Padua L, Lo Monaco M, Padua R, Gregori B, Tonali P. Neurophysiological classification of carpal tunnel syndrome assessment of 600 symptomatic hands. Ital J Neurol Sci 1997; 18: 145-150.
22) Farrar JT, Young JP Jr, LaMoreaux L, Werth JL, Poole RM. Clinical importance of changes in chronic pain intensity measured on an 11-point numerical pain rating scale. Pain 2001; 94: 149-158.
23) Levine DW, Simmons BP, Koris MJ, Koris MJ, Daltroy LH, Hohl GG, Fossel AH, Katz JN. A self-administered questionnaire for the assessment of severity of symptoms and functional status in carpal tunnel syndrome. J Bone Joint Surg Am 1993; 75: 1585-1592.
24) Fukuyama Y, Nakade K, Minoshima Y, Yokoyama R, Zhai H, Mitsumoto Y. Neurotrophic activity of honokiol on the cultures of fetal rat cortical neurons. Bioorg Med Chem Lett 2002; 12: 1163-1166.
25) Ying Z, Kampfrath T, Sun Q, Parthasarathy S, Rajagopalan S. Evidence that α-lipoic acid inhibits NF-κB activation independent of its antioxidant function. Inflamm Res 2011; 60: 219-225.
26) Packer L, Witt EH, Tritschler HJ. α-lipoic acid as a biological antioxidant. Free Radic Biol Med 1995; 19: 227-250.