The Canadian Journal of Neurological Sciences (2023), 1–5
doi:10.1017/cjn.2023.268

Canadian Journal of Neurological Sciences
Journal Canadien des Sciences Neurologiques

Original Article

Characteristics of Carpal Tunnel Syndrome in Wild-Type Transthyretin Amyloidosis

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ABSTRACT: ***Background:*** Carpal tunnel syndrome (CTS) is one of the most common extra-cardiac manifestations of wild-type transthyretin amyloidosis (wtATTR); however, the characteristics of CTS in this population remain poorly understood. ***Methods:*** This retrospective cohort study reports findings from a single-centre experience of comprehensive neurological screening at the time of wtATTR diagnosis by nerve conduction studies (NCS) and neurologist assessment. ***Results:*** Seventy-nine patients underwent neurological screening, 73 (92%) males, mean age 79.2 ± 7.5 years. Seventy-four (94%) had electrodiagnostic findings of median neuropathy at the wrist (MNW), 37 (50%) of which had a prior diagnosis of CTS and 37 (50%) had a new diagnosis of MNW. Over half of wtATTR patients (42, 53%) had bilateral MNW on screening. Most with pre-existing CTS had bilateral disease (28, 76%) and underwent bilateral carpal tunnel release (CTR) (23, 62%) prior to screening. Twenty-one (19%) wrists had mild MNW, 43 (38%) moderate and 49 (43%) severe. Twenty-one (28%) wtATTR patients with MNW were asymptomatic, 10 of which (48%) had moderate disease. Nineteen (36%) wtATTR patients with symptomatic MNW had recurrent disease despite previous CTR. As a result of screening, 36 (68%) patients with symptomatic MNW were referred for CTR. ***Conclusions:*** MNW is exceptionally common at the time of wtATTR diagnosis, affecting 94% of our patients. Most had severe, bilateral MNW on NCS. Some were asymptomatic, despite having moderate disease. The rate of recurrence following CTR was observed to be higher in wtATTR patients than the general population.

RÉSUMÉ : Caractéristiques du syndrome du canal carpien dans le cas de l'amylose provoquée par transthyrétine (forme sauvage). ***Contexte :*** Le syndrome du canal carpien (SCC) est l'une des manifestations extracardiaques les plus courantes de l'amylose provoquée par la transthyrétine (forme sauvage) (ATTS). Cela dit, les caractéristiques du SCC au sein de ce groupe de patients restent mal comprises. ***Méthodes :*** Cette étude de cohorte rétrospective entend rapporter au sein d'un seul établissement de santé les résultats d'une expérience de dépistage neurologique complet au moment du diagnostic de l'ATTS au moyen d'études de la conduction nerveuse (ECN) et de l'évaluation d'un neurologue. ***Résultats :*** Au total, 79 patients, dont 73 (92 %) étaient des hommes, ont subi un dépistage neurologique. Leur âge moyen était de 79,2 ± 7,5 ans. Précisons que 74 d'entre eux (94 %) présentaient des signes électro-diagnostiques de neuropathie médiane du poignet (NMP), dont 37 (50 %) avaient déjà reçu un diagnostic de SCC et 37 autres (50 %) un nouveau diagnostic de NMP. Plus de la moitié des patients atteints d'ATTS (42, 53 %) présentaient une neuropathie médiane bilatérale du poignet (NMBP) lors du dépistage. La plupart des patients souffrant d'un SCC préexistant donnaient à voir une maladie bilatérale (28,76 %) et avaient subi une libération bilatérale du canal carpien (LBCC) (23,62 %) avant le dépistage. Ce sont ainsi 21 poignets (19 %) qui présentaient une NMP légère, 43 (38 %) une NMP modérée et 49 (43 %) une NMP sévère. Ajoutons que 21 patients (28 %) atteints d'ATTS avec NMP étaient asymptomatiques tandis que 10 d'entre eux (48 %) avaient une maladie modérée. 19 patients (36 %) patients atteints d'ATTS avec NMP symptomatique donnaient à voir une maladie récurrente malgré une LBCC antérieure. À la suite d'un dépistage, 36 patients (68 %) présentant une NMP symptomatique ont été orientés en vue d'une LBCC. ***Conclusions :*** La NMP est exceptionnellement fréquente au moment du diagnostic de l'ATTS. Elle a en effet affecté 94 % de nos patients. La plupart d'entre eux présentaient une NMP sévère et bilatérale lors d'une ECN. Certains d'entre eux étaient asymptomatiques malgré une maladie modérée. Le taux de récidive après une LBCC s'est avéré plus élevé chez les patients atteints d'ATTS qu'au sein de la population générale.

Keywords: Carpal tunnel syndrome; electrodiagnostic studies; peripheral neuropathy; wild-type transthyretin amyloidosis

(Received 24 April 2023; final revisions submitted 28 July 2023; date of acceptance 31 July 2023)

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Cite this article: Russell A, Khayambashi S, Fine NM, Chhibber S, and Hahn C. Characteristics of Carpal Tunnel Syndrome in Wild-Type Transthyretin Amyloidosis. *The Canadian Journal of Neurological Sciences*, https://doi.org/10.1017/cjn.2023.268

Background

Wild-type transthyretin amyloidosis (wtATTR) is an important cause of infiltrative cardiomyopathy in older adults, especially males.[1,2] It results from the deposition of misfolded native (non-mutated) transthyretin (TTR) proteins in organs and tissues.[1,2] Carpal tunnel syndrome (CTS) is one of the most common extra-cardiac manifestations of wtATTR and can predate cardiac symptoms by 5–10 years.[3,4] Wild-type ATTR protein deposition commonly causes median nerve entrapment at the wrist, resulting in CTS.[5] Bilateral CTS is more common in wtATTR than hereditary ATTR,[6] and the prevalence of CTS in wtATTR is thought to be higher than in light chain (AL) amyloidosis.[7] The association between CTS and wtATTR has been described in several case series;[3–6] however, the characteristics of CTS in this population remain poorly understood.

At our centre, all patients with a new diagnosis of wtATTR are referred for comprehensive neurological screening by way of nerve conduction studies (NCS) and neurologist assessment. The purpose of our study was to evaluate the prevalence, clinical features, severity and disease course of CTS in wtATTR patients, as well as the risk of recurrence following carpal tunnel release (CTR).

Methods

Study Population

This retrospective cohort study reports findings from a single-centre experience of comprehensive neurological screening at the time of wtATTR diagnosis. Consecutive wtATTR patients followed at the University of Calgary Cardiac Amyloidosis Clinic (Calgary, Alberta, Canada) between February 2014 and December 2021 were included. A diagnosis of wtATTR was confirmed using the following criteria: [1] exclusion of AL amyloidosis by the absence of serum and urine monoclonal protein, [2] evidence of cardiac amyloidosis by either right ventricular endomyocardial biopsy or positive technetium-99 m-pyrophosphate nuclear scintigraphy, defined as a grade 2–3 myocardial uptake or heart-to-contralateral lung ratio >1.5[8] and [3] absence of an ATTR gene mutation using genetic testing or proteomic analysis by mass spectrometry performed on biopsy tissue sample.[9] This study was approved by the University of Calgary Research Ethics Board, and the requirement of informed patient consent was waived.

Electrodiagnostics

Neurological screening included NCS, performed in a dedicated and accredited laboratory, along with a complete history and physical examination by a neurologist at the time of electrophysiologic testing. Standard of practice at our laboratory is in keeping with the 2011 American Association of Neuromuscular and Electrodiagnostic Medicine (AANEM) monograph on electrodiagnostic evaluation of CTS.[10] All patients had bilateral ulnar and median sensory nerve action potentials (SNAPs) and compound muscle action potentials (CMAPs) assessed, along with median versus ulnar digit 4 comparison studies. Additional median to other nerve comparison studies were done when needed, as outlined in the monograph. Recording sites, inter-electrode distance and temperature were all standardised per laboratory protocol. Testing was performed using either a Cadwell Sierra Wave machine running version 3.1.32 of Cadlink or a Natus Ultrapro S100 machine running version 22.3.0.21 of Synergy.

Data Collection and Analysis

Medical records of wtATTR patients were reviewed for a prior history of CTS and CTR; the presence of prior unilateral or bilateral disease was noted where available. This information was supplemented by patient history, taken at the time of neurologic evaluation, as prior CTS and CTR were often remote. Comorbidities commonly associated with CTS were collected, including diabetes, hypothyroidism, monoclonal gammopathy of undetermined significance, multiple myeloma, haematologic malignancy, rheumatoid arthritis, osteoarthritis, pregnancy and inherited neuropathy. The presence of CTS symptoms, including numbness, tingling, pain and weakness in the median nerve distribution, were also collected, along with abductor pollicis brevis (APB) atrophy and weakness. The presence and characteristics of bilateral disease were noted, as was New York Heart Association (NYHA) functional class for all patients. Diagnosis of CTS was based on neurologist interpretation of patient history, physical examination and electrodiagnostic data. Electrodiagnostic criteria for median neuropathy at the wrist (MNW) and electrodiagnostic severity were derived from the AANEM practice parameters.[10] Mild CTS was defined as prolonged sensory latencies with normal motor studies, without evidence of axon loss.[10] Abnormal median sensory latencies and prolongation of median motor distal latency without evidence of axon loss defined moderate CTS.[10] Severe CTS was defined by any of the aforementioned abnormalities with evidence of axon loss, as defined by either: [1] an absent or low-amplitude SNAP, [2] a low-amplitude or absent thenar CMAP or [3] needle electromyography with fibrillation potentials or motor unit potential changes.[10] Data pertaining to interventions offered were obtained, including wrist splinting, steroid injection and CTR. Recurrence after CTR was also recorded. Descriptive statistics were performed.

Results

Patient Population and Characteristics

A total of 124 wtATTR patients were eligible for inclusion. Seventy-nine underwent neurological screening. The remaining 45 patients either declined screening or were awaiting screening at the time of data collection. Patient demographics, NYHA functional class, comorbidities commonly associated with CTS, presence of pre-existing CTS and prior CTR are presented in Table 1.

Neurologic Evaluation

Prevalence and characteristics of MNW at the time of neurological screening are outlined in Table 2. The presence of CTS symptoms and physical examination findings in patients with MNW at the time of screening are also shown, along with electrodiagnostic severity and rate of recurrence following CTR.

Seventy-four (94%) wtATTR patients had electrodiagnostic findings of MNW, 37 (50%) of which had a prior diagnosis of CTS and 37 (50%) had a new diagnosis of MNW on testing. Three (4%) wtATTR patients with MNW had CTR prior to screening, resulting in complete resolution of CTS symptoms at the time of screening. Over half of wtATTR patients (42, 53%) were found to have bilateral MNW on electrophysiologic testing. The majority of wtATTR patients with pre-existing CTS had bilateral disease (28, 76%) and underwent bilateral CTR (23, 62%) prior to screening. Most wtATTR patients that met electrodiagnostic criteria for MNW were symptomatic (53, 72%) at the time of screening. Thirty-two (43%) wtATTR patients with MNW had APB weakness

https://doi.org/10.1017/cjn.2023.268 Published online by Cambridge University Press

Table 1: Baseline patient characteristics

	wtATTR ($n = 79$)
Clinical characteristics	
Age (years)	79.2 ± 7.5 (IQR = 10)
Male	73 (92%)
NYHA functional class	
I	9 (11%)
II	30 (38%)
III	39 (49%)
IV	1 (1%)
Comorbidities	
Diabetes	14 (18%)
Hypothyroidism	15 (19%)
MGUS/MM/Heme malignancy	4 (5%)
Rheumatoid arthritis	1 (1%)
Osteoarthritis	18 (23%)
Pregnancy	0
Inherited neuropathy	0
Pre-existing CTS	37 (47%)
Bilateral	28 (35%)
Previous release	31 (39%)
Previous bilateral release	23 (29%)

CTS, carpal tunnel syndrome; IQR, interquartile range; MGUS, monoclonal gammopathy of undetermined significance; MM, multiple myeloma; NYHA, New York Heart Association; wtATTR, wild-type transthyretin amyloidosis.

Table 2: Characteristics of MNW in wtATTR patients on neurological screening

	wtATTR ($n = 79$)
EDX diagnosis of MNW	74 (94%)
Pre-existing CTS	37 (47%)
Resolved post CTR (remote)	3 (4%)
New diagnosis on screening	37 (47%)
Bilateral	42 (53%)
History and physical exam	
Symptomatic	53 (67%)
Asymptomatic	21 (27%)
APB atrophy	27 (34%)
APB weakness	32 (41%)
EDX severity	
Mild	21 (19%) wrists
Moderate	43 (38%) wrists
Severe	49 (43%) wrists
Recurrence after CTR	19 (24%)

APB, abductor pollicis brevis; CTR, carpal tunnel release; CTS, carpal tunnel syndrome; EDX, electrodiagnostic; MNW, median neuropathy at the wrist; wtATTR, wild-type transthyretin amyloidosis.

on examination, and 27 (36%) had APB atrophy. Twenty-one (19%) wrists had mild MNW, 43 (38%) moderate and 49 (43%) severe on electrophysiologic testing. Twenty-one (28%) wtATTR patients with MNW were asymptomatic, 10 of which (48%) had moderate disease and 11 (52%) had mild disease. Nineteen (36%) wtATTR patients with symptomatic MNW on screening had recurrent disease despite previous CTR.

The prevalence of MNW and recurrent MNW following CTR according to NYHA functional class in wtATTR patients is presented in Figure 1.

Regarding NYHA functional class, 39 (49%) wtATTR patients had class III heart failure symptoms, 30 (38%) class II, 9 (11%) class I and 1 (1%) class IV. MNW in wtATTR patients was severe in the majority (49, 43%) of wrists examined, compared to moderate (43, 38%) and mild (21, 19%) disease. The rate of severe MNW was similar across NYHA functional classes.

Interventions

As a result of screening, a total of 19 (36%) wtATTR patients with symptomatic MNW were prescribed wrist splinting, 3 (6%) steroid injection and 36 (68%) were referred for CTR following screening (Figure 2). Some wtATTR patients were prescribed more than one intervention. Those wtATTR patients with MNW that did not receive treatment recommendations (27, 36%) were either asymptomatic (18, 67%) or minimally symptomatic (9, 33%).

Discussion

This study shows that CTS is very common in patients with newly diagnosed wtATTR. We observed that MNW was seen in the vast majority of wtATTR patients at the time of electrophysiologic testing; half had a pre-existing history of CTS and half had a new diagnosis of MNW on screening. Many with pre-existing CTS had bilateral disease and prior CTR. At the time of electrophysiologic testing, most wtATTR patients with MNW were symptomatic and over half had bilateral involvement. APB weakness and atrophy were seen in some patients. MNW was severe in the majority of wrists examined, compared to mild and moderate disease. Recurrence after CTR was common. Nearly half of wtATTR patients had NYHA class III heart failure at the time of screening. The prevalence of MNW and recurrent disease following CTR was similar across wtATTR patients with NYHA class I, II and III heart failure. Nearly half of asymptomatic patients with MNW on screening had moderate disease.

At our centre, routine comprehensive neurological screening by way of NCS and neurologist assessment led to the diagnosis of mild and moderate MNW in many wtATTR patients. This included a proportion of wtATTR patients with MNW that were asymptomatic at the time of electrodiagnostic evaluation. Diagnosis of MNW at mild and moderate stages facilitated early intervention for symptomatic patients. The majority (64%) of wtATTR patients were prescribed a therapeutic intervention; most were referred for CTR surgery. Early decompression of the median nerve results in a more timely and complete improvement in pain, sensory abnormalities and hand function compared to delayed CTR.[11]

In our study of 79 patients, 94% had MNW on electrophysiologic testing, an exceptionally high proportion which has not been reported previously. We observed that CTS affected 67%

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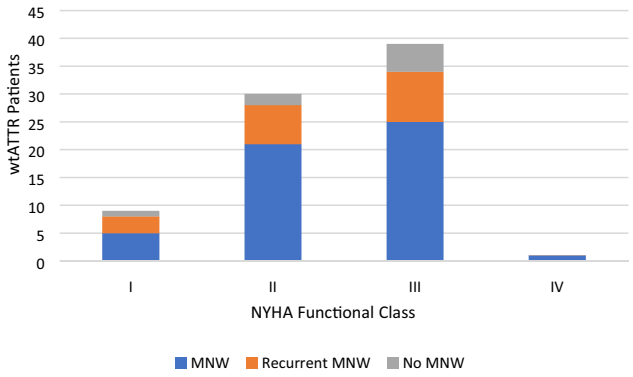

Figure 1: Frequency of median neuropathy at the wrist (MNW) diagnosed on neuropathy screening among patients with wild-type transthyretin amyloidosis (wtATTR) according to New York Heart Association (NYHA) functional class. The proportion of patients with recurrent MNW on neuropathy screening, following carpal tunnel release, is also shown.

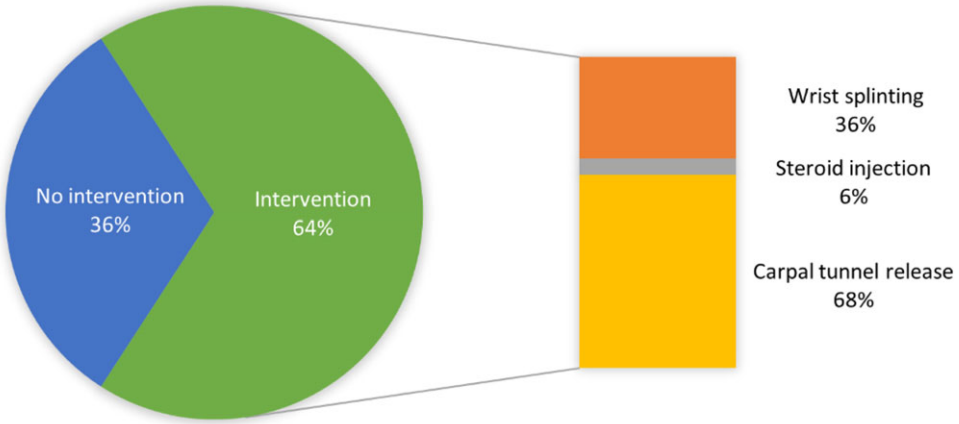

Figure 2: Proportion of wild-type transthyretin amyloidosis (wtATTR) patients prescribed interventions for median neuropathy at the wrist (MNW). Patients that did not receive treatment recommendations were either asymptomatic or minimally symptomatic. Type and frequency of interventions prescribed are also represented. Some patients were prescribed more than one intervention.

of our patients with newly diagnosed wtATTR, which is in keeping with the prevalence reported in prior studies, ranging from 41 to 68%.[4,6,7,12] Half of our wtATTR patients with MNW on screening had a prior history of CTS, and many had bilateral disease and prior CTR. This supports the understanding that CTS is often an early clinical manifestation of wtATTR that predates cardiac symptoms.[3,4] Our study also supports the notion that CTS is relatively aggressive in patients with wtATTR, as it is often bilateral and rapidly progressive with a higher rate of recurrence compared to patients without wtATTR.[13] At the time of wtATTR diagnosis, most of our patients had severe MNW and over half had bilateral disease. In comparison, patients with diabetes often have mild to moderate CTS at the time of diagnosis.[14] Recurrence after CTR was seen in 36% of our wtATTR patients with symptomatic MNW at the time of screening, which is higher than the rate of recurrence in the general population, estimated at 3–20%.[15] For this reason, it has been suggested that a history of bilateral recurrent CTS should prompt consideration of tissue biopsy at the time of repeat CTR.[13] Tenosynovium and transverse carpal ligament biopsies should also be considered in men with bilateral CTS and concurrent left ventricular hypertrophy, as the rate of wtATTR is 33% in this population, according to one study.[13] Lastly, we found that wtATTR patients with NYHA class I, II and III heart failure had similar rates of MNW and recurrence following CTR on electrophysiologic testing. Severe MNW was more common than mild or moderate disease across these NYHA functional classes. Collectively, these are novel observations.

Limitations

Limitations of this study include the retrospective single-centre cohort design and small sample size; therefore, the presence of bias cannot be excluded. Neurologists were not blinded to clinical data. Information collected pertaining to pre-existing CTS was largely based on history, as detailed neurologic data prior to their wtATTR diagnosis were not available in most patients. Histopathological confirmation of amyloid neuropathy was not collected as tenosynovial biopsy was not routinely pursued at our centre. The prevalence of comorbidities commonly associated with CTS in some wtATTR patients included in this study confounds the ability to determine causality for the findings reported. Our sample size precludes controlling for these comorbidities.

Conclusions

Our study shows that CTS affects the majority of wtATTR patients and often predates wtATTR diagnosis, which is in keeping with prior studies. We observed that MNW is very common in patients at the time of wtATTR diagnosis, affecting 94% of our patients on screening. Twenty-eight percent of our patients were asymptomatic despite more than half of those having moderate severity MNW on NCS. We also observed that most wtATTR patients had severe MNW and bilateral MNW on electrophysiologic testing, with a rate of recurrence after CTR that was higher than the general population. This supports that CTS is relatively aggressive in wtATTR. Our results demonstrate

https://doi.org/10.1017/cjn.2023.268 Published online by Cambridge University Press

the importance of routine comprehensive neurological screening by way of NCS and neurologist assessment at the time of wtATTR diagnosis. This facilitated early diagnosis of MNW in our wtATTR patients and early intervention in symptomatic patients.

Acknowledgements. This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Statement of authorship. AR participated in study design, data collection and analysis, and manuscript preparation. CH, NMF, SC, and SK participated in study design, data analysis and manuscript preparation.

Competing interests. Dr. Chhibber has received honoraria from Alexion. Dr. Fine has received consulting fees and research support from Pfizer, Akcea and Alnylam. Dr. Hahn has received consulting fees from Pfizer, Akcea and Alnylam. Dr. Khayambashi has received honoraria from Alnylam. Dr. Russell has no conflicts of interest to declare.

References

1. Nativi-Nicolau J, Maurer MS. Amyloidosis cardiomyopathy: update in the diagnosis and treatment of the most common types. Curr Opin Cardiol. 2018;33:571–9.
2. Ruberg FL, Grogan M, Hanna M, Kelly JW, Maurer MS. Transthyretin amyloid cardiomyopathy: JACC state-of-the-art review. J Am Coll Cardiol. 2019;73:2872–91.
3. Milandri A, Farioli A, Gagliardi C, et al. Carpal tunnel syndrome in cardiac amyloidosis: implications for early diagnosis and prognostic role across the spectrum of aetiologies. Eur J Heart Fail. 2020;22:507–15.
4. Nakagawa M, Sekijima Y, Yazaki M, et al. Carpal tunnel syndrome: a common initial symptom of systemic wild-type ATTR (ATTRwt) amyloidosis. Amyloid. 2016;23:58–63.
5. Boyle RP, Sharan J, Schwartz G. Carpal tunnel syndrome in transthyretin cardiac amyloidosis: implications and protocol for diagnosis and treatment. Cureus. 2021;13:e14546.
6. Trimarchi G, Perna A, Zampieri M, et al. Prevalence of carpal tunnel syndrome in patients with transthyretin cardiac amyloidosis. Eur Heart J Suppl. 2021;23:suab142.056.
7. Ng B, Connors LH, Davidoff R, Skinner M, Falk RH. Senile systemic amyloidosis presenting with heart failure: a comparison with light-chain-associated amyloidosis. Arch Intern Med. 2005;165:1425–9.
8. Gillmore JD, Maurer MS, Falk RH, et al. Nonbiopsy diagnosis of cardiac transthyretin amyloidosis. Circulation. 2016;133:2404–12.
9. JA Vrana, Gamez JD, Madden BJ, Theis JD, Bergen HR, Dogan A. Classification of amyloidosis by laser microdissection and mass spectrometry-based proteomic analysis in clinical biopsy specimens. Blood. 2009;114:4957–9.
10. Werner RA, Andary M. Electrodiagnostic evaluation of carpal tunnel syndrome. Muscle Nerve. 2011;44:597–607.
11. Musad M, Rashid M, Malik SA, Khan MI, Sarwar S. Does the duration and severity of symptoms have an impact on relief of symptoms after carpal tunnel release? J Brachial Plex Peripher Nerve Inj. 2019;14:e1–8.
12. Russell A, Hahn C, Chhibber S, Korngut L, Fine NM. Utility of neuropathy screening for wild-type transthyretin amyloidosis patients. Can J Neurol Sci. 2021;00:1–9.
13. Elzinga K, Khayambashi S, Hahn C, Mahe E, Fine NM. Amyloidosis and carpal tunnel syndrome: surgical technique for extended carpal tunnel release with tenosynovium and transverse carpal ligament biopsies. Plast Reconstr Surg – Glob Open. 2023;11:e4757.
14. Yurdakul FG, Bodur H, Cakmak OO, et al. On the severity of carpal tunnel syndrome: diabetes or metabolic syndrome. J Clin Neurol. 2015;11:234–40.
15. Osiak K, Elnazir P, Walocha JA, Pasternak A. Carpal tunnel syndrome: state-of-the-art review. Folia Morphol. 2022;81:851–62.

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