Samsun Sağlık Bilimleri Dergisi,
Journal of Samsun Health Sciences
e-ISSN: 2791-9722, JSHS August 2022, 7(2): 407-418

Coexistence of Migraine and Carpal Tunnel Syndrome

Migren ile Karpal Tünel Sendromu Birlikteliği

Güner Koyuncu[1]

[1]Konya Şehir Hastanesi, Konya

• **koyuncuguner@hotmail.com** • ORCID > 0000-0001-8772-472X

Makale Bilgisi / Article Information

Makale Türü / Article Types: Araştırma / Research
Geliş Tarihi / Received: 20 Aralık / December 2021
Kabul Tarihi / Accepted: 29 Haziran / June 2022
Yıl / Year: 2022 | **Cilt – Volume:** 7 | **Sayı – Issue:** 2 |**Sayfa / Pages:** 407-418

Atıf/Cite as: Koyuncu, G. "Coexistence of Migraine and Carpal Tunnel Syndrome " Journal of Samsun Health Sciences 7(2), August 2022: 407-418.

Sorumlu Yazar / Corresponding Author: Güner KOYUNCU

Yazar Notu / Author Note: Bu çalışma 29-31 Ekim 2021 tarihleri arasında online olarak yapılan 2.Ulusal Klinik Nörofizyoloji EEG-EMG Sanal Kongresi'sinde sözel bildiri olarak sunulmuştur.

https://doi.org/10.47115/jshs.1039119

COEXISTENCE OF MIGRAINE AND CARPAL TUNNEL SYNDROME

ABSTRACT:

Aim: Migraine and carpal tunnel syndrome (CTS) are two common health problems that have some common features and are frequently encountered in society. Is it possible for these two tables, which have so much in common, to coexist? If so, is this association meaningful? The study was designed in order to find answers to these questions.

Method: This study was performed with a total of 345 subject as 178 patients having carpal tunnel syndrome (CTS) and 167 migraine patients. The first group was composed of those diagnosed with CTS based on the nerve conduction measurements in the electrophysiology laboratory. These patients were classified according to the international headache classification criteria and those with and without migraine were determined in the light of the data in the questionnaire. The second group, called as migraine group, comprised of those admitted to the neurology outpatient clinic and diagnosed with migraine. The study was designed as a cross-sectional and comparative study.

Results: Of the 345 patients who remained in the study after exclusion criteria, 178 were in the CTS group and 167 were in the migraine group. Although approximately 80,3% of those with CTS had migraine, only 12,6% of those diagnosed with migraine had CTS.

Conclusion and Suggestions: We consider that migraine headaches may create a predisposition to contract CTS in the future. Additional studies are needed to support this view.

Keywords: *Carpal Tunnel Syndrome; Comorbidity; Migraine; Physiopathogenesis; Frequency.*

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MİGREN İLE KARPAL TÜNEL SENDROMU BİRLİKTELİĞİ

ÖZ:

Amaç: Migren ve karpal tünel sendromu (KTS), toplumda sık rastlanılan iki ayrı hastalık tablosudur. Birbirinden tamamen farklı olan bu iki tablonun bazı ortak özelliklere sahip olduğu dikkatimizi çekmiştir. Bu yüzden bu iki tablonun birlikteliği var mıdır? Var ise bu birliktelik anlamlı mıdır? Sorularına cevap bulmak amacı ile bu çalışma planlanmıştır.

Yöntem: Bu çalışma 178 KTS ve 167 migren olmak üzere toplam 345 hasta ile yürütüldü. Çalışmada iki grup oluşturuldu. Birinci grup, elektrofizyoloji laboratuvarında KTS tanısı konulan hastalardan oluştu. Bu hastalara uluslararası baş ağrısı sınıflama kriterlerine göre hazırlanan migren tarama anketi yapıldı. Bu ankete göre hastalarda migreni olanlar ve olmayanlar belirlendi. İkinci grup ise nöroloji polikliniğine başvuran ve migren tanısı konulan hastalardan oluşturuldu. Bu grup ise migren grubu olarak adlandırıldı. Bu çalışma kesitsel ve karşılaştırmalı olarak dizayn edildi.

Bulgular: Dışlama kriterleri sonrası çalışmada kalan toplam 345 hastanın 178'i KTS grubunda, 167'si migren grubunda idi. KTS hastalarının %80,3'ünde migren saptanırken, migren olanların %12,6'sında KTS saptandı.

Sonuç ve Öneriler: Bulduğumuz KTS grubunda yüksek oranda migren, migren grubunda ise düşük oranda KTS saptanmış olması, migren baş ağrılarının gelecekte KTS olmaya yatkınlık oluşturabileceği yargısını doğurdu. Bu görüşümüzü desteklemek için ek çalışmalara ihtiyaç olduğu kanaatindeyiz.

Anahtar Kelimeler: *Karpal Tünel Sendromu; Migren; Patofizyoloji; Sıklık, Komorbidite.*

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INTRODUCTION

Carpal Tunnel Syndrome (CTS) is the most frequent entrapment neuropathy affecting nearly 3% of the normal population. In contrast to symptomatic CTS, idiopathic or primary CTS is considered a nonspecific inflammation of unknown etiopathogenesis. Radiological and preoperative findings showed that connective tissue proliferation causes CTS (Festen-Schrier and et al., 2018; Bland, 2007). In various histological studies investigating CTS, while edema and fibrosis were shown to be effective in tenosynovia (Scelsi and et al., 1989) , the microvascular damage was also proposed to have effects on the condition (Faithfull and et al., 1986 Fuchs and et al., 1991, Lluch and et al., 1992, Menke and et al., 1994, Nakamichi andet al., 1998). Migraine, on the other hand, ranks third among the most common diseases in society, with a prevalence of approximately 10-18% (Steiner and et al., 2013, Rasmussen and et al., 1991, Vos and et al., 2012). There are some common points in both migraine and CTS, such as the presence of be unilateral or bilateral, higher prevalence among women, the effect of genetic and environmental factors and its etiopathogenesis is not fully known. The fact that the two disorders have common features so much so that they lead to such questions as whether migraine and CTS develop together coincidentally, whether there is a common physiopathological or genetic mechanism causing the two to develop, or whether

one of the disorders constitutes a ground for the other are noteworthy, and therefore such questions urged us to seek answers to such questions in the present study. Thus, the present study aims at seeking answers to such questions.

METHODS

Ethical approval for this study was obtained from The Karatay University in 2020, (Number: 05/11/2020-E.3827). The study was designed as a cross-sectional and comparative study. The present study was carried out in Konya City Hospital between April-May in 2021.The patients included in this study diagnosed with CTS in the electrophysiology laboratory and those diagnosed with migraine under the classification criteria of International Headache Society (IHS) (Headache Classification Committee of the International Headache Society, 2013). Male and female patients between the ages of 18-80 who applied to the neurology outpatient clinic of our hospital were included in the study. Those diagnosed with headaches other than migraine and the patients with secondary CTS were excluded in the study.

The patients were recruited in as two separate groups. The first group, called as CTS group, was composed of the patients diagnosed with CTS based on the nerve conduction measurements in the electrophysiology laboratory. These patients were questioned according to the migraine screening questionnaire prepared by the researcher under the international headache classification criteria, and those having migraine were detected in light of the data obtained from the questionnaires. However, the second group, also called migraine group, consisted of those admitted to the neurology out-patient clinic and diagnosed with migraine. CTS protocol was performed in the electrophysiology laboratory, regardless of the presence of any clinical complaint among migraineurs. CTS was electrodiagnostically diagnosed under the criteria released by the American Academy of Neurology (AAN)/American Association of Neuromuscular and Electrodiagnostic Medicine (AANEM) (Jablecki and et al., 1993).

The investigations were carried out through the Neuro-Mep (Verison 3) electromyography (EMG) device with the use of standard techniques based on the AANEM practice parameters (Jablecki and et al., 1993). In addition, the procedures were implemented at standard room temperature, and the orthodromic records of the median sensory nerve action potential (SNAP) was obtained after stimulating the index finger with ring electrodes. Such features as the onset latency, peak amplitude and sensory conduction velocity (SCV) were also evaluated. The median nerve compound muscle action potentials (CMAPs) were recorded from the abductor pollicis brevis after stimulating the nerve at the wrist. The distal motor latency (DML) and peak amplitude of CMAPs were also measured. In addition, the ulnar nerve was stimulated at the fifth digit through the records obtained at the wrist. In terms of motor assessments, the nerve was stimulated at the wrist,

and the motor potential was recorded from abductor digit minimi. In performing the differential sensory investigations, the laboratory references were detected as median SCV >50 m/s and median nerve DML <4.0 m/s (Jablecki and et al., 1996). Given the assessments of headache patients in terms of CTS, the patients were divided into three groups as those without headache, migraine group and tension-type headache (TTH) group. While those with TTH and without headaches constituted the group without migraine within the analysis period, the participants diagnosed with migraine constituted the migraine group. A total of 370 patients, including 190 with CTS and 180 with migraine patients, were included into the study.

STATISTICAL ANALYSIS

To determine whether two or more variables are independent of each other, the crosstab analysis was performed to show the relationship between categorical variables, and the chi-square test was utilized to indicate the significance. In the comparison of the averages of continuous variables for the assumptions between two independent groups, the t-test was performed for significant differences after assessing the normality. More than two groups were compared with one-way ANOVA. In the crosstab analyses, the frequencies and percentages were given in tables related to the mean values in median tests and the standard deviation (SD) values. The Standard Package for Social Sciences for Windows soft-ware, version 15.0 (SPSS Inc, Chicago, IL, USA) was used to calculate the statistical values in the tests.

RESULTS

One hundred ninety patients with CTS and 180 migraine patients were included into the study. After excluding those not fully meeting the study criteria, 178 of the remaining patients were put into the CTS group, and 167 participated in the migraine group. Statistical analysis was performed with patients in both groups.

In the first analysis, the incidence of migraine and other headaches in the CTS group (Table 1) and the incidence of CTS in migraine were evaluated (Table 2)

Table 1. Headache and its rates in the CTS group

			NH	Migraine	TTH	Total
Group	**CTS**	Count	22	143	13	178
		% within Group	12.4%	80.3%	7.3%	100.0%
	Migraine	Count	0	167	0	167
		% within Group	.0%	100.0%	.0%	100.0%

*Carpal tunnel syndrome NH*No headache TTH*Tension-type headache
Chi-square=36.544, p<0,001CTS

Table 2. CTS rates in the migraine group

			NON-CTS	CTS	
Group	**CTS**	Count	0	178	178
		% within Group	.0%	100.0%	100.0%
	Migraine	Count	146	21	167
		% within Group	87.4%	12.6%	100.0%

Chi-square=259.383, p<0,001 CTS*Carpal tunnel syndrome

Headache could not be detected in 22 (12.4%) of 178 patients in the remaining CTS patients after exclusion, while 143 had migraine headache (80.3%), 13 had tension-type headache (TTH, 7.3%) detected (Table 1).

While CTS was not detected in 146 (87.4%) of a total of 167 migraine patients, CTS was present in 21 (12.6%). This situation was statistically significant (Table 2).

While the youngest, highest and average age rates were measured as 25.81 and 47 in CTS group respectively, the age rates were found to be 23.77 and 45 in the migraine group, respectively. Outcomes of this analysis demonstrate that there was not significant difference between the CTS and migraine groups in terms of the patients' mean age rates (p=0.051).

The patients in the migraine group were about four years younger than those in the CTS group (Table 3).

Table 3. Age analysis according to the diagnosis

Group	N	Mean	Min	Max	Std. Deviation	t-test	Sig
CTS	178	46.8427	25	81	9.86737	1.954	0.051
Migraine	167	44.5988	23	77	11.34777		

CTS*Carpal tunnel syndrome

The gender distribution of the patients in the CTS and migraine groups was also observed to be different. While the presence of both diseases was more common among women in both groups (82.6% in the CTS group and 94.6% in the migraine group), the rates of the diseases among men were detected as 17.4% in the CTS group and 5.4% in the migraine group. Based on these findings, it is possible to point out that the rate of male was approximately three fold higher in the CTS patients than that of migraineurs, while the rate of female was about 10% higher among those in the migraine group, compared with the CTS patients (Table 4).

Table 4. Gender distribution according to the diagnosis of the patients

			Gender		Total
			Female	Male	Female
Group	CTS	Count	147	31	178
		% within Group	82.6%	17.4%	100.0%
	Migraine	Count	158	9	167
		% within Group	94.6%	5.4%	100.0%
Total		Count	305	40	345
		% within Group	88.4%	11.6%	100.0%

Chi-square=12.158, p<0.001

When the mean age of patients with and without CTS was analyzed in a total of 167 migraine patients, the mean age of those with CTS was 53, while the mean age of those without CTS was 43, which was statistically significant (p< 0.001) (Table 5). It was found that those with CTS in the migraine group were approximately 10 years older than those without CTS. As a result of evaluating the headaches in 178 patients admitted to the department with the complaint of CTS, the patients were divided into three groups for the analysis and compared in terms of the mean age levels. In the light of these comparisons, the mean age levels among the patients withouth headache, those with migraine and those with TTH were found to be 49.7, 46.2 and 48.3 years of age, respectively. As a result, those with migraine constituted the group having the lowest average age (Table 5).

Table 5. Age analysis in migraine and CTS patients

MIGRAINE	N	Mean	Std. Deviation	t-test	Sig.
Without CTS	146	43.3973	10.86816	-3.747	<0.001
With CTS	21	52.9524	11.34229		
CTS	**N**	**Mean**	**Std.Dev.**	**F-test**	**Sig.**
MIGRAINE	143	46.2587	9.23993	1.355	0.261
NH	22	49.7273	12.75476		
TTH	13	48.3846	10.92046		

F-test: One-way ANOVA CTS*Carpal tunnel syndrome NH*No headache TTH *Tension-type headache

DISCUSSION

In our study, while approximately 80.3% of the patients with CTS had migraine, 12.6% of those with migraine were found to have CTS. In a study investigating the same entity, where completely different materials and methods were used by Huay-zong et al., while the migraine prevalence was 34% in the patients with CTS, the prevalence of CTS was found as 8% among those with migraine (Law and et al., 2015). Although the design, and the materials and methods in our study and in the study by Huay-zong et al. were different, the findings in both studies were similar and corroborative each other. Our hypothesis is that based on such findings, migraine headaches may create a predisposition to contract CTS in the future, rather than the genetic coexistence of these two conditions. There were also two additional results of our study supporting our hypothesis: First, the average age in the CTS group was about 4 years higher than that of the migraine group; second, the average age of those with CTS in the migraine group was 10 years higher than that of those without CTS. The number of the reports suggesting that central nervous system (CNS) contributes to peripheral neuropathy is gradually increasing (Tecchio and et al., 2002; Woolf, 2011), and in the study investigating the effects of CNS on peripheral neuropathy, Huay-zong concluded that migraine headaches have effects on the peripheral nerves (Law et al., 2015).

The contributions of vascular endothelial signals to migraine are quite strong, and the dysregulation in any part of vascular signal processes is considered to lead to migraine. As a result of activation of CNS, such substances as acetylcholine (AC), vasoactive intestinal polypeptide (VIP), pituitary adenylate cyclase activatingpol-

ypeptide (PACAP) and nitric oxide (NO) are secreted from the parasympathetic postganglionic fibers in the sphenopalatine ganglion. These substances activate the alternative vasodilation path signals of the vessels. VIP receptors are expressed in the body from different cells, also including endothelial cells, and this mechanism leads to the expression and secretion of vascular endothelial growth factor (VEGF) from the endothelial cell, which also brings about an increase in the angiogenesis. VEGF causes the production of different inflammatory cytokines that are also considered to be involved in pain pathology during the angiogenesis. In addition, VEGF also causes the accumulation of such immune cells as macrophages and neutrophils into the injured tissue, and thus the inflammation occurs. Under inflammatory conditions, endothelial nitric oxide synthase (eNOS) and VEGF are increased even more (Jacobs and Dussor, 2016). Neurogenic inflammation appears first in the dura mater and leads to the secretion of harmful substances, including neuropeptide Y-like immunoreactivity (NPY-LI), calcitonine gene-related peptide (CGRP-LI), substance P-like immunoreactivity (SP-LI) neurokinin A (NKA-LI) and VIP (Messlinger and et al., 2011; Li ans et al., 2017). Thus, neurogenic inflammation stimulates and activates the central trigeminal neurons, and then also leads to an increase in primary nociceptive afferent activation. During migraine attacks, CGRP was shown to increase in jugular venous plasma (Goadsby and et al., 1990). A large number of inflammatory mediators, such as interleukin-6 (IL-6), tumour necrosis factor-alpha (TNF-alpha), NO and prostoglandin E2 (PGE2), are released into blood stream during the headache attacks, and an increase is observed in cyclooxygenase-2 (COX-2). It is considered that migraine headache is associated with inflammation occuring through proinflammatory cytokines and neuropeptides secreted during the attacks (Di Renzo and et al., 2018). The secretion of these neuropeptides leads to the arterial vasodilation and the plasma extravasation from the postcapillary venules, called neurogenic inflammation (Holzer, 1998)23. Idiopathic CTS, however, is considered to be a nonspecific inflammation, the etiopategenesis of which still remains unknown, and various studies showed that connective tissue proliferation is caused by idiopathic CTS (Festen-Schrier and et al., 2018; Bland, 2007). Edema and fibrosis in tenosynovia (Scelsi and et al, 1989), thickening in the vessel wall and intimal hyperplasia (Neal et al., 1987), and thrombosis and microvascular damage (Fuchs and et al., 1991; Neal and et al., 1987; Shum and et al., 2002) were shown in CTS with various histological studies. Endothelial damage leads to edema in the carpal tunnel by increasing vascular permeability. Increased interstitial fluid pressure also leads to the compression in the carpal tunnel, especially in the median nerve. Therefore, this situation results in poor blood circulation in the flexor synovial cells and the median nevre (Fuchs and et al., 1991; Kerr and Sybert., 1992). In various studies, it was demonstrated that there is a relationship between CTS and the risk factors of atherosclerosis in young adults. In a review performed by Simon Sacco et al., migraine especially accompanied by aura was found to be associated with increased cardiovascular risks

(Sacco and et al., 2013). The reason for such an association is considered to be the peripheral vascular dysfunction caused by endothelial dysfunction, which is also assumed to contribute to the migraine pathophysiology. However, the association considered to be present between migraine and increased cardiovascular risk was reported to be varied by the duration of migraine, severity of the attacks and whether migraine is active or inactive (MacClellan and at al., 2007; Etminan and et al., 2005). On the other hand, when the synovial tissue biopsies obtained from syptomatic CTS patients to undergo surgery were investigated, the expression of PGE2 and VEGF was shown to be increased. (Aboonq, 2015; Hirata and et al., 2004), and this condition can trigger the vascular proliferation and subsequent fibrosis. VEGF has a strong effect on vascular permeability, which may be the cause of the edema seen in CTS (Hirata and et al., 2004). VEGF triggers the endothelial cell, vascular smooth muscle cells and pericyte proliferation, and thereby contributing to synovial thickening. It was found that there is a close association between the expression levels of PGE2 and VEGF, and that PGE2 may regulate the release of VEGF in tenosynovium (Hirata and et al., 2004). In the biochemical study performed with the samples obtained from the tenosynovium of CTS patients by Freeland et al., PGE2 and IL-6 were reported to increase significantly (Freeland and et al., 2002). A very important emphasis put by Hitashi is that PGE2 is temporarily produced in the tenosynovium (Zanette and et al., 2010). Previous studies investigating the images of the carpal tunnel content showed that the median nerve in the carpal tunnel is enlarged. The enlargement of median nerve is also considered to cause an increase in the pressure in the carpal tunnel without any primary structural change in idiopathic CTS (Bland, 2007; Faithfull and et al., 1986; Fuchs and et al.,1991; Menke and et al.,1994; Nakamichi and et al., 1998).

Some specific serum cytokines significantly increased were detected in blood samples drawn from the patients with CTS and neuropathic pain, compared to healthy controls. Following the intraneural ischemia in CTS, the edema formation, demyelination with human Schwan cells (reactive type), subsequent ectopic impulse production and central sensitization were demonstrated (Schmid and et al., 2013). In addition, neuroinflammation has recently been reported to have a strong contribution to the pathogenesis of CTS (Schmid and et al., 2013). In the rats with trapped neuropathy having mild peripheral nerve compression, macrophage and chronic neuroinflammation with T cell invasion were demonstrated locally in nerve compression area and related dorsal root ganglia (Costigan and et al., 2009). In the evaluation of multiple cytokines and chemokines, the profile pattern of neuropathy-specific cytokines was observed to be dysregulated in CTS.

In our study, both migraine and CTS were more common in women, and the rate was higher in the migraine group (94.6%). In the group with CTS, the rate of being female was 82.6%. This makes us think that if a woman has migraine, the probability of having CTS in the future may be higher in women than in men.

As in migraine, the sex hormones were shown to have effects on CTS in some studies. In studies investigating the gender difference in CTS, the prominence of female gender was reported as approximately 2:1 or 3:1. Epidemiological studies also demonstrated that the risk of CTS was higher among women than that in men.
As the limitations of our study, no comparisons and provocative tests were performed in order to diagnose CTS, and the cases indicating slight symptoms of CTS were not included into the criteria. The patients with clinically positive EMG negativity were also excluded from the study. In conclusion, it was found in our study that migraine headaches may create a predisposition to the future development of CTS. However, further studies are needed to demonstrate that migraine headaches lead to the basis for the future formation of CTS. Future studies should be planned to prove this situation, and such entities over whether migraine and CTS develop on the same side, and whether there is an association between the severity, duration and frequency of migraine headaches, and the severity and development of CTS should be investigated.

Our study has various limitations. Since the sensitive nerve measurement tests were not included in our study protocol, the cases with very mild CTS were not included in the study. In addition, the fact that the migraine-induced headaches decrease or completely disappear as the age advances, or the elderly do not remember such previous events as headaches clearly has led us to evaluate this age segment as those with no migraine due to misleading information in terms of the diagnosis of migraine.

Conflict of Interest

There is no conflict of interest in this study.

Authorship Contribution Rates

Çalışmanın Tasarlanması (Design of Study): GK (%100),

Veri Toplanması (Data Acquisition): GK (%100),

Veri Analizi (Data Analysis): GK (%100),

Makalenin Yazımı (Writing Up): GK (%100),

Makale Gönderimi ve Revizyonu (Submission and Revision): GK (%100)

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