

Nontraumatic Focal Neuropathies: Distribution and Retrospective Analysis of the Cases

Nontravmatik Fokal Nöropatiler: Olguların Dağılımı ve Retrospektif Analizi

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Summary

Objective: Focal neuropathies are the most frequently encountered disorders in the electroneuromyography (ENMG) practice. In this study, in order to obtain useful data on the epidemiology and classification of nontraumatic focal neuropathies, we retrospectively evaluated the etiology of the nontraumatic focal neuropathies as well as their distribution according to the nerves involved in patients who presented to our electrophysiology laboratory.

Materials and Methods: The patient records were retrospectively analyzed to perform the study. A total of 4759 patients [3843 (80.8%) females and 916 (19.2%) males], who presented with the referral diagnosis of focal neuropathy between 1996 and 2009, were included.

Results: The ENMG study was normal in 2136 (44.9%) patients. The referral diagnosis was concordant with the final diagnosis in 2502 (52.6%) patients, and focal neuropathy was evident. Polyneuropathy was diagnosed in 63 (1.3%) patients while 58 (1.2%) had other diagnoses (radiculopathy, motor neuron disease). Two thousand and seven (80.2%) patients with focal neuropathy were females and 495 (19.8%) were males. The mean age of the subjects was 48.33±13.32 years. The median nerve was the most frequently affected nerve and carpal tunnel syndrome (CTS) (74.6%) was the most frequently encountered focal neuropathy. Facial nerve (16.8%) and ulnar nerve (4.7%) neuropathies followed them.

Conclusion: The proportion of the normal cases was high in our study and the concordance between referral and final diagnosis was not satisfactory. This result indicates that ENMG must be performed after a detailed history and physical examination. In contrast to traumatic focal neuropathies, females predominated among the patients with nontraumatic focal neuropathies and the mean age was higher than that of men. Unlike traumatic focal neuropathies (ulnar and sciatic nerves), the median nerve was the most frequently affected nerve and CTS was the most frequently encountered focal neuropathy, as mentioned in the literature. *Türk J Phys Med Rehab 2012;58:114-20.*

Key Words: Focal neuropathy, nontraumatic

Özet

Amaç: Fokal nöropatiler, klinik elektronöromiyografi (ENMG) pratiğinde en sık rastlanan bozukluklardır. Bu çalışmada, elektrofizyoloji laboratuvarımıza başvuran nontravmatik fokal nöropatilerin sinirlere göre dağılımlarını ve etiyojilerini retrospektif olarak değerlendirek, nontravmatik fokal nöropatilerin epidemiyolojisi ve klasifikasyonunda yararlı olabilecek veriler elde etmek hedeflenmiştir.

Gereç ve Yöntem: Çalışma, arşiv defterlerindeki hasta kayıtlarının retrospektif incelenmesiyle gerçekleştirildi. Çalışma kapsamına, 1996-2009 döneminde nontravmatik fokal nöropati ön tanısı ile başvuran 3843 (%80.8) kadın, 916 (%19,2) erkek olmak üzere toplam 4759 hasta alındı.

Bulgular: 2136 (% 44,9) hastada ENMG çalışması normal bulundu. Ön tanıtani 2502 (%52,6) hastada uyumlu idi ve fokal nöropati saptandı. Altmış üç (%1,3) hastaya polinöropati, 58 hastaya ise diğer tanılar (radikülöpato, motor nöron hastalığı) konuldu. Nontravmatik fokal nöropatili hastaların, 2007'si (%80,2) kadın ve 495'i (%19,8) erkek idi ve yaş ortalaması 48,33±13,32 bulundu. En sık etkilenen sinir median sinir ve en sık rastlanan fokal nöropati türü karpal tünel sendromu (KTS, %74,6) idi. Bunu fasiyal sinir (%16,8) ve ulnar sinir (%4,7) nöropatileri izlemekte idi.

Sonuç: Araştırmamızda, normal olgu oranı yüksek bulundu ve ön tanı - tanı uyumu yeterli değildi. Bu da ENMG'nin ayrıntılı bir öykü ve fizik muayene sonrası yapılması gerektiğini işaret eden bir sonuçtur. Nontravmatik fokal nöropatilerde, travmatik fokal nöropatilerin aksine kadın hakimiyeti vardı ve yaş ortalaması daha yüksek idi. Travmatik fokal nöropatilerden (ulnar ve siyatik sinir) farklı olarak en sık median sinir etkilenmiş idi ve en sık görülen fokal nöropati literatüre benzer şekilde KTS olarak belirlendi. *Türk Fiz Tıp Rehab Derg 2012;58:114-20.*

Anahtar Kelimeler: Fokal nöropati, nontravmatik

Introduction

Focal neuropathies are the most frequently encountered disorders in the electroneuromyography (ENMG) practice. Focal neuropathies are divided into two groups as traumatic and nontraumatic, according to their etiology. Nontraumatic causes are shown in Table 1 (1). The most common nontraumatic causes are the compression neuropathies (Table 2) (1). Early in their course, they may be misdiagnosed for more proximal lesions of the plexus or nerve roots, orthopedic disorders, and for occasionally central nervous system disorders. Certain clinical clues in the history and examination, however, often will suggest the correct diagnosis, aided by appropriate electrodiagnostic (EDX) and imaging studies when indicated (1). In this study, in order to obtain useful data on the epidemiology and classification of nontraumatic focal neuropathies, we retrospectively evaluated the etiology of the nontraumatic focal neuropathies as well as their distribution according to the nerves involved in patients who presented to our electrophysiology laboratory.

Methods

Between 1996 and 2009, 4759 patients presented to our ENMG laboratory with the referral diagnosis of nontraumatic focal neuropathy. Our ENMG laboratory is a referral clinic for ENMG studies for both outpatients and inpatients attending the physical medicine and rehabilitation, orthopedics, plastic and reconstructive surgery and the otorhinolaryngology clinics in our hospital. The patients are coming from all over Turkey since our hospital is a major referral center affiliated with the Ministry of Health, and is located in the capital city of Turkey, in Central Anatolia.

The patient records were retrospectively analyzed to perform the study. The results of the electrophysiological studies were considered for the analysis. The collected data included demographic variables, the affected nerve and the cause of neuropathy. All patients had a detailed neurological examination. Motor and sensory conduction studies and needle examination were performed by standard techniques using Neuropack 2-MEB 7102-K 2 channels EMG-EP machine (Nihon Kohden Corp. Tokyo, Japan) and after 2008 Neuropack S1 EMG/EP Measuring System MEB-9400 (Nihon Kohden Corp. Tokyo, Japan). For the diagnosis, the American Association of Neuromuscular and Electrodiagnostic Medicine guidelines were used (1). Normal values and criteria of abnormality which we used are summarized in Table 3 (2).

Descriptive statistics used included means and frequencies.

Results

The EMG results of 4759 patients who applied to ENMG laboratory with the referral diagnosis of nontraumatic focal neuropathy were investigated. 3843 (80.8%) patients were female and 916 (19.2%) were male. The mean age was 45.74±13.02 years. 2502 (52.6%) patients had nontraumatic

focal neuropathies, 63 (1.3%) patients had polyneuropathies and 58 (1.2%) patients had other disorders (radiculopathy, motor neuron disease). The ENMG study was normal in 2136 (44.9%) patients. Of the patients with normal EMG, 1774 (83%) were female, and 362 patients were (17%) male and the mean age was 42.51±11.67 years.

There were 2007 (80.2%) females and 495 (19.8%) males among 2502 patients with nontraumatic focal neuropathies, and their mean age was 48.33±13.32 years (Figure 1).

The distribution of 2502 patients who were diagnosed as having nontraumatic focal neuropathy is presented in Table 4. The most commonly affected nerve was the median nerve. Median nerve neuropathy was detected in 1878 (75.1%) patients. 1707 (90.8%) of these patients were female and 171 (9.2%) were male, and the mean age was 49.52±11.10 years.

The most commonly encountered type of nontraumatic focal neuropathy was carpal tunnel syndrome (CTS). 3491 patients have been applied with the referral diagnosis of CTS, however, CTS was determined in 1807 (51.7%) of them. The distribution of the referral diagnosis of the patients with CTS is shown in Table 5. 1701 (91.3 %) patients who had the diagnosis of CTS were female, 163 were male, and the mean age was 49.59±10.90 years. The characteristics of the patients with CTS are summarized in Table 6.

The second most commonly affected peripheral nerve in nontraumatic focal neuropathies was the ulnar nerve. Ulnar neuropathy was detected in 118 (4.7%) patients. 50.4% of patients were female and 49.9% were male, and the mean age was 47.43±16.52 years. Entrapment was evident at the elbow (77.1%) and the wrist (13.5%) (Table 4).

Radial nerve neuropathy was present in 26 (1%) patients. The radial nerve was affected in only one patient with vasculitic focal neuropathy who applied with dropped finger.

Table 1. Nontraumatic focal neuropathies.

Compression neuropathies	Acute Chronic
Infectious neuropathies	Hereditary Herpes zoster Lyme disease
	Acquired immunodeficiency syndrome (AIDS)
	Leprosy mononeuropathy
	Bell's palsy Brachial plexus neuropathy (neuralgic amyotrophy)
Inflammatory neuropathies	
Acute lumbar plexus neuropathy	
Vasculitic neuropathy	
Radiation neuropathy	
Tumor	Neurofibroma Carcinomatous neuropathy

Nontraumatic brachial plexus neuropathy was determined in 4 (0.16%) patients. It was idiopathic in one patient, related to radiation in one patient, and it was related to tumor (mediastinum and lung apex tumor) in two patients. Thoracic outlet syndrome (TOS) was diagnosed in 11 (0.44%) of 259 patients who had the referral diagnosis of TOS. Long thoracic nerve, suprascapular nerve, sciatic and femoral nerve entrapment neuropathies, tarsal tunnel syndrome, Morton's neuroma, Meralgia paresthetica, and peroneal nerve neuropathy were the least common focal neuropathies (less than 1%) (Table 4).

Tourniquet paralysis was seen in 13 patients. The distribution of the patients with tourniquet paralysis was summarized in Table 7.

Hereditary neuropathy with liability to pressure palsies (HNPP) was detected in 2 (0.08%) patients. A 34-year-old male patient presented with the pre-diagnosis of CTS and ulnar entrapment neuropathy, and a 63-year-old female patient applied with the referral diagnosis of bilateral peroneal entrapment neuropathy.

Nontraumatic peripheral facial paralysis was detected in 420 (16.8%) patients; in 49.7% of them was right-sided, in 49.7% was left-sided, and in 0.6% was bilateral. It was partial in 395 patients and total in 25 patients. 48.3% of patients were male and 51.7% were female and their mean age was 44.23 ± 18.70 years. The patients were admitted mostly in spring (132 patients, 31.4%) and autumn followed it.

Table 2. Compression neuropathies.

Acute	Tourniquet paralysis Saturday night palsy (radial nerve palsy) Crossed-leg palsy (peroneal nerve palsy) Perioperative ulnar nerve palsy
Chronic	a. Compression in a fibroosseous tunnel Carpal tunnel syndrome Cubital tunnel syndrome Tarsal tunnel syndrome b. Angulation and stretching Tardy ulnar nerve palsy Thoracic outlet syndrome c. Recurrent compression by external forces Some ulnar compression neuropathy at elbow Deep branch neuropathy of the ulnar nerve Meralgia paresthetica Hereditary

Discussion

Many articles on EDX emphasize the following: EDX studies are the extension of clinical examination and careful history, and they cannot replace clinical examination (3). The causes for

Table 3. Normal nerve conduction data (2).

Anatomical Site	Terminal Latency (msec) and NCV (m/sec)		Amplitude
	Mean \pm SD	Normal Limit	
Upper Extremities			
Median nerve	-	-	-
<i>Sensory conduction</i>			
Palm-wrist	41.85 \pm 3.90	34.05	10 μ V
Finger-wrist	49.54 \pm 4.14	41.26	10 μ V
<i>Motor conduction</i>			
Terminal latency	2.78 \pm 0.41	3.60	5 mV
Wrist-elbow	58.78 \pm 4.41	49.96	-
Elbow-axilla	65.76 \pm 4.90	55.96	-
F-wave latency	25.32 \pm 2.19	29.70	-
Ulnar nerve			
<i>Sensory conduction</i>			
Finger-wrist	47.48 \pm 4.11	39.26	8 μ V
<i>Motor conduction</i>			
Terminal latency	2.03 \pm 0.24	2.51	5 μ V
Wrist-elbow	61.15 \pm 5.27	50.61	-
Across elbow	51.31 \pm 4.25	42.81	-
Elbow-axilla	63.33 \pm 5.47	52.69	-
Erb's point-axilla	68.36 \pm 5.07	58.22	-
F-wave latency	25.68 \pm 2.29	30.26	-
Radial nerve			
<i>Sensory conduction (distal)</i>	50.87 \pm 3.28	44.31	10 μ V
Lower Extremities			
Peroneal nerve (motor)			
Terminal latency	3.72 \pm 0.53	4.78	4 mV
Knee-ankle	49.51 \pm 3.93	41.85	-
Knee-popliteal fossa	53.93 \pm 7.11	39.11	-
F-wave latency	46.88 \pm 4.25	55.38	-
Posterior tibial nerve (motor)			
Terminal latency	3.85 \pm 0.63	5.11	5 mV
Knee-ankle	49.83 \pm 4.60	40.63	-
F-wave latency	48.89 \pm 4.19	57.27	-
Sural nerve (sensory)			
Mid-calf-lateral malleolus	43.26 \pm 4.26	34.68	6 μ V

ordering EDX are as follows: diagnosis, description of the disease (old/new, static/dynamic, pathophysiology), longitudinal monitoring of the disease, and to have an advise on the management and prognosis (3,4). Appropriate EDX studies are essential for existing diagnosis of focal neuropathies and imaging studies can be performed whenever indicated (5, 6). In our series, the diagnosis of nontraumatic focal neuropathy was confirmed in only 52.6% of patients who were referred with the referral diagnosis of nontraumatic focal neuropathy. However, other diagnoses were detected in 2.5% and EDX studies were normal in 2136 (44.9%) patients and EDX enlightened the diagnosis. The referral diagnosis-diagnosis concordance was not satisfactory in our study. In previous studies; Kul-Panza et al. (7) found the referral diagnosis-diagnosis concordance to be 42.3% while Adam et al. (8) found it as 46.4%. Discordance of referral

diagnosis and diagnosis suggested that ENMG was performed unnecessarily in a number of patients. Establishing the correct indication for the test through a detailed history and physical examination would enable more efficient use of ENMG laboratories (8).

The most commonly seen of nontraumatic focal neuropathies are entrapment and compressive neuropathies and they are frequently encountered disorders for an EDX medicine consultant. Focal compromise of peripheral nerves is secondary to entrapment within a compartment of relatively fixed size, compression by an internal or external source, repetitive trauma and overuse, or some other etiology (5, 6). We found that the most common cause was entrapment compression. CTS constituted 74.6% of nontraumatic focal neuropathies. CTS symptoms are usually prominent in the dominant hand,

Table 4. Distribution of nontraumatic focal neuropathies.

	N	%
CTS	1864	74.6
Anterior interosseous syndrome	5	0.2
Pronator syndrome	3	0.12
CTS + ulnar entrapment neuropathy in the wrist	3	0.12
Ulnar entrapment neuropathy in elbow (tardy ulnar / cubital tunnel syndrome)	91	3.64
Ulnar entrapment neuropathy in the wrist	13	0.52
Tourniquet paralysis (ACN) (median, ulnar, radial nerves)	13	0.52
Perioperative ulnar paralysis (ACN)	1	0.04
Posterior interosseous syndrome (radial)	6	0.24
Saturday night paralysis (radial) (ACN)	3	0.12
Entrapment neuropathy in the spiral groove (radial)	3	0.12
Vasculitic neuropathy (radial)	1	0.04
TOS	11	0.44
Long thoracic nerve entrapment neuropathy	3	0.12
Suprascapular nerve entrapment neuropathy	2	0.08
Idiopathic acute brachial plexopathy	1	0.04
Brachial plexopathy related to tumor invasion (mediastinum and lung apex tumor)	2	0.08
Brachial plexopathy related to radiation	1	0.04
Femoral nerve entrapment neuropathy (in inguinal region)	3	0.12
Sciatic nerve entrapment neuropathy (in piriformis muscle)	4	0.16
TTS	27	1.08
Peroneal nerve Şbula compression entrapment neuropathy	7	0.28
Peroneal nerve crossed leg syndrome (ACN)	8	0.32
Meralgia paresthetica	3	0.12
Morton neuroma	1	0.04
Acute lumbar plexus neuropathy	1	0.04
HNPP	2	0.08
Facial nerve paralysis	420	16.78

CTS: Carpal tunnel syndrome; ACN: Acute compressive neuropathy; TOS: Thoracic outlet syndrome; TTS: Tarsal tunnel syndrome;

HNPP: Hereditary neuropathy with liability to pressure palsies.

however, it is usually bilateral. 67% of our cases were bilateral. The prevalence of CTS in the general population is roughly 3-6 %, and it usually affects middle-aged women (9,10). Similarly, in our CTS series of 1864 patients, women predominated (90.8%). Female/male ratio was 10.4 in our study. The incidence and prevalence studies in the general population indicated that CTS affected females at variable ratios such as 5.7 and 1.4, and gender was reported to be an independent risk factor. Female/male ratio was reported as 379/33 (11.48 %) in a study by Kurt et al. (11). In one of our previous studies, we found this ratio as 297/36 (88.25%) (12).

Ulnar nerve involvement was only 4.7% in nontraumatic focal neuropathies, and it had the second rank in the upper extremity. Entrapment was most commonly determined at the level of elbow (3.64%). In the literature, similar to our findings, ulnar neuropathy across the elbow is reported to be the second most common entrapment neuropathy of the upper extremity (6).

The mean age of the patients diagnosed with nontraumatic

Table 5. The distribution of the referral diagnosis of the patients who had the diagnosis of carpal tunnel syndrome.

The referral diagnosis	The number of the patients who had the diagnosis of CTS n (%)
CTS (n=3491)	1807 (51.7%)
Ulnar entrapment neuropathy (n=343)	25 (7.3%)
TOS (n=259)	26 (10%)
Brachial plexus neuropathy (n=35)	6 (17.1%)
Total	1864

CTS: Carpal tunnel syndrome; TOS: Thoracic outlet syndrome

Table 6. The characteristics of the patients with carpal tunnel syndrome.

Female / male ratio	10.4
Mean age	49.59±10.90
Bilateral CTS	67%
Right CTS	21.8%
Left CTS	11.2%
Previous CTS surgery	3.7%
Abnormal electrophysiological findings in surgically treated hand	70%

CTS: Carpal tunnel syndrome

Table 7. The distribution of the patients with tourniquet paralysis.

	n
Radial nerve	3
Radial+ulnar nerves	7
Radial+ulnar+median nerves	3

focal neuropathy was 48.33±13.32 years, however, in our traumatic nerve injury series we observed that a younger age group was more commonly affected (mean age 31.86±17.44) (13). Nontraumatic focal neuropathies were mostly seen in women (80.2%), however, traumatic nerve injuries most commonly occurred in men (%71) (13). The most frequently encountered nontraumatic focal neuropathy was CTS, however, in traumatic neuropathies, the ulnar nerve (27%) in the upper limb and the sciatic nerve (11.1%) in the lower limb were the most commonly injured nerves (13). In the literature, CTS is the most common, whereas cubital syndrome is the second most common compressive neuropathy. The other most common entrapment sites may include the ulnar nerve at the wrist (Guyon’s canal), the superficial radial nerve in the distal forearm, the peroneal nerve entrapment at the fibular neck, and the lateral femoral cutaneous nerve at the inguinal ligament (meralgia paresthetica) (10). Similar with the literature, in our series, the most common neuropathy in the upper extremity was CTS, however, tarsal tunnel syndrome (TTS) was the most common neuropathy in lower extremity. TTS is the most common form of entrapment neuropathy of the tibial nerve (1). In our series, entrapment of the peroneal nerve at the caput fibulae was the second most common neuropathy after TTS. These dissimilarities may be due to anatomical differences of the Turkish population. In this study the referrals from the departments of neurology and neurosurgery were performed in the EDX laboratory of neurology department. Therefore, the profile of diseases and referral diagnosis are different from those of our laboratory. This may also be another cause of the dissimilarities. For example, patients with drop foot may firstly present to neurology or neurosurgery department rather than our laboratory.

Tourniquet paralysis is a well known but rare acute compression neuropathy that develops after the use of a pneumatic tourniquet during surgery to obtain a bloodless surgical field. Clinically, it is characterized by motor and sensory deficits distal to the location of the pneumatic tourniquet. The radial, median and ulnar nerves are involved most frequently,

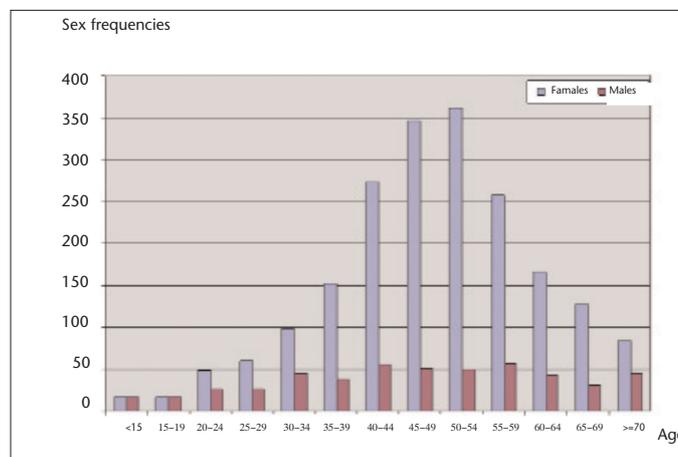


Figure 1. Age and sex distribution of nontraumatic focal neuropathy patients.

since tourniquet is most commonly used in the upper extremity. In rank order, the radial, ulnar and median nerves were involved in our series. The prognosis for tourniquet paralysis is good. Clinical and electrophysiological improvements by a few months have been reported. This disorder, with a good prognosis, must be kept in mind in a paralysis that develops after application of tourniquet (1). In our series, similar to the literature, tourniquet paralysis was rarely seen, in 0.52% of the cases, however, it was the most common etiological factor for acute compressive neuropathies. This may be due to the high number of patients referred from the departments of orthopedics, hand surgery and plastic surgery that commonly use tourniquet during surgical intervention.

We detected HNPP in 2 patients (0.08 %) in our series. HNPP is a rare disorder, characterized by susceptibility to pressure palsies (1).

Although presence of minor disagreements on clinic, EDX and treatment of frequent entrapment neuropathies such as CTS, ulnar neuropathy in the elbow and peroneal neuropathy in the knee, there are no major disagreements. On the other hand, there are major disagreements about some entrapment syndromes, including even whether or not they exist (14). The most controversial entity among these is TOS. The diagnosis of neurogenic TOS is more challenging because; its nerve compression symptoms are not unique. To date, there are still no reliable objective tests to confirm the diagnosis; however measurements of the antebrachial cutaneous nerve appear promising. The EDX abnormalities in true neurogenic TOS include an absent or decreased amplitude of the medial antebrachial cutaneous (MABC) sensory nerve action potential, less frequently, an absent or decreased amplitude of median nerve compound muscle action potential (CMAP), ulnar sensory nerve action potential and ulnar CMAP. It was previously proposed that the MABC nerve conduction study abnormalities show close relationship with the median CMAP alterations (15). Disputed TOS is a sensory syndrome without definitive objective signs. The clinical tools have poor sensitivity and specificity, and nerve conduction studies are normal (14,16,17). Neurogenic TOS often comes into mind in evaluation of the patients with acroparesthesia but in fact, "true neurogenic TOS" is extremely rare and its prevalence is reported to be one in a million (18). Some physicians even doubt the existence of TOS. Because there is no objective confirmatory test for TOS, there is also much disagreement among clinicians with regard to its true incidence, with reported incidences ranging from 3 to 80 cases per 1000 in the population (16). Gilliat et al. (19) reported that the number of real neurogenic TOS cases encountered in their 25 years of practice was less than 20. Our experience is also similar. We have encountered only 11 true neurogenic TOS cases in our laboratory in which approximately 1200 ENMG are performed annually in 13 years. In our patients with CTS, TOS was the third rank between referral diagnosis after CTS and ulnar entrapment. This data shows that although TOS is rarely seen as mentioned in the

literature, it is frequently considered as a referral diagnosis. Furthermore, physicians and especially surgeons frequently diagnose TOS and plan surgery. The most basic principle is doing no harm to the patient. Surgery may result in objective deficits in a significant percentage of patients who do not have a deficit before surgery. A careful patient selection is critical for a successful surgical outcome, and it must be kept in mind that true neurogenic TOS is an extremely rare clinical entity (14,16,17).

The mononeuropathy in the second rank order in our patients was facial nerve palsy. Facial nerve compromise is likely to be the most commonly encountered cranial neuropathy. The etiology is not known in most patients, and it is called as Bell's palsy (Idiopathic Facial Paralysis) (20). It is usually unilateral, however, bilateral cases have been rarely reported (21). Only 0.6% of our cases were bilateral. Illiczyk et al. (22) investigated 110 peripheral facial paralyses. Of the 110 patients, 106 were diagnosed with idiopathic Bell's palsy. Similar to our results, they reported that the proportion of males and females was equal. There was no considerable difference between the sexes regarding age distribution. In their material, peripheral facial palsy was significantly more frequent in the cold period of late autumn, winter, and early spring. In our series, the peak admission was in the spring (March) (% 31.4) and autumn followed it.

Conclusions

As a result, we found that the most common cause of focal neuropathies was entrapment and the most commonly involved nerve was the median nerve. These studies help in precise localization of the lesion and also in assessing its severity, thus, facilitating the treatment options. The data of this study may be useful for epidemiology and classification of nontraumatic focal neuropathies.

Conflict of Interest:

Authors reported no conflicts of interest.

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