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Original Article NEUROLOGY

Isolated abducens nerve palsy: Comparison of microvascular and other causes

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ABSTRACT

OBJECTIVE: Abducens nerve paralysis is the most common ocular motor neuropathy. In this article, we aimed to compare the causes of isolated abducens nerve palsy in terms of demographic, clinical features, and prognosis.

METHODS: Thirty-six isolated abducens nerve palsy patients were prospectively enrolled in the study. The demographic, clinical features, and prognosis compared in two etiological groups as microvascular and other causes.

RESULTS: The most common etiology was microvascular, which was seen in 16/36 (44.4%) patients. Mean clinical recovery time was 2.5±1.3 months (range, 10 days–6 months). When etiological groups were compared as microvascular and other causes, the mean age of the microvascular group was significantly higher (62.8±13.3 vs. 44.5±16.4, p=0.001). Diabetes mellitus was seen significantly higher in the microvascular group than other causes group (p=0.001), but no significant difference was observed in terms of other atherosclerotic risk factors (p>0.05). The fasting blood glucose and hemoglobin A1c value were significantly higher in the microvascular group (p=0.02 and p=0.02, respectively). There was no significant difference in terms of clinical improvement and clinical recovery times between groups (p>0.05).

CONCLUSION: There is no difference between microvascular group and other causes in terms of clinical outcome, while the mean age and presence of diabetes were higher in the microvascular group. The presence of diabetes should be questioned in cases with isolated abducens nerve palsy.

Keywords: Abducens nerve; cranial neuropathy; isolated; palsy.

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The abducens nerve (sixth cranial nerve, CNVI) innervates the lateral rectus muscle. The nucleus of the abducens nerve is located in the dorsal pons, comes out of the pontomedullary junction, passes through the tip of the petrous part of the temporal bone at an angle, and then enters the cavernous sinus through the Dorello's canal. In the sinus cavity, just below the internal carotid artery enters the orbit through the superior orbital fissure and finally innervates the lateral rectus muscle [1, 2]. It is referred to as 6th cranial nerve palsy when the abducens nerve dysfunction occurs along its course anywhere from the pons to the lateral rectus muscle. Abducens nerve dysfunction results in unilateral abduction disability and binocular horizontal diplopia [3, 4].

The abducens nerve palsy is seen at a rate of 11.3/100,000. The abducens motor nerve palsy is the most common cranial neuropathy in adults, mostly seen in 60–70 ages [3]. Besides diplopia, headache, or pain around the eyes may be accompanied. Oculomotor, trochlear, and trigeminal nerve palsy or other neurological find-

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ings may see at the same time [5, 6]. The most common underlying pathology is microvascular causes, especially in advanced age. Trauma, demyelinating or inflammatory diseases (such as Tolosa-Hunt syndrome), infections, tumors, aneurysm, and the increased intracranial pressure are the other major causes of abducens nerve palsy [3, 4].

Studies on this area have generally considered ocular motor paralysis as a whole, the number of studies evaluating isolated abducens paralysis is limited and they are mostly retrospective. We aimed to compare the microvascular and other causes of isolated abducens nerve palsy in terms of demographic, clinical features, and prognosis.

MATERIALS AND METHODS

Forty-four patients were enrolled in this study prospectively between January 2017 and January 2020. The patients over 17 years old and diagnosed as isolated partial or complete abducens nerve palsy with no other neurologic signs other than periorbital pain were included in the study. Eight of the patients were excluded from the study because of additional neurological findings emerged in clinical follow-up (e.g., ocular nerve palsy other than abducens in six patients and weakness in non-ocular muscles in two patients) and the study was continued with 36 patients. The study was approved by the Istanbul Training and Research Hospital Ethics Committee; the informed consent was obtained from all patients and controls (ethical number: 1141, December 15, 2017).

Medical history, laboratory, and radiological studies analyzed in terms of microvascular and non-vascular risk factors. Laboratory and radiological data were enrolled as the following:

1. Complete blood cell count with differential, hemoglobin A1c (Hba1c), sedimentation rate, and C-reactive protein,
2. Cerebrospinal fluid (CSF) for protein, glucose, cell count, and herpes simplex virus titters,
3. Magnetic resonance imaging (MRI) of the brain and orbits (with and without gadolinium) and computerized tomographic angiogram of the brain.

Furthermore, the fundus and vision examinations of the patients were performed by a neuro-ophthalmologist. Hypertension, diabetes, hypercholesterolemia, coronary artery disease, or tobacco were accepted as vascular risk factors for acute-onset abducens nerve palsy. Finally, we grouped the patients with acute-onset abducens nerve palsy into the microvascular (microvascular group; Group I) and other causes (non-vascular group; Group II). The patients who diagnosed as Wernicke encephalopathy, intracranial hypotension, Behçet disease, headache associated with neurological deficits, and CSF lymphocytosis (HaNDL) syndrome were grouped as other.

Highlight key points

- Microvascular and other groups have similar clinical outcome.
- Microvascular causes are the most common etiology of isolated abducens nerve palsy.
- Diabetes mellitus is an important reason for microvascular etiology.

Statistical Methods

The findings were expressed as mean values, standard deviation, median values, lowest and highest values, frequency, and ratio values. The normality of variable distributions was measured with the Kolmogorov–Smirnov test. The groups were compared in terms of continuous variables using the independent sample t-test or the Mann–Whitney U-test. The categorical variables were analyzed using Chi-square or Fisher's exact test. The statistical analyses were made with SPSS 22.0 program.

RESULTS

The mean age of all patients was 52.6±17.5 years (ranges 24–90 years) and 15 (41.7%) subjects were female and 21 (58.3%) subjects were male. The clinical distributions were 18 (50%) subjects with the right abducens palsy, 12 (33.3%) subjects with the left abducens, palsy and 6 (16.7%) subjects bilaterally. Isolated abducens paralysis was presented with diplopia in 28 (77.8%) patients and with headache in 8 (22.2%) patients. Besides, in 20 (55.6%) patients, abducens nerve paralysis was accompanied by ipsilateral periorbital pain (Table 1).

The most common underlying etiological pathology was microvascular causes, which was seen in 16 (44.4%) patients. Other etiological causes were intracranial hypertension 3 (8.3%) patients, inflammatory disease 3 (8.3%) such as Tolosa–Hunt syndrome, unknown etiology 3 (8.3%), demyelination disease 2 (5.6%), tumors in 2 (5.6%), congenital 2 (5.6%), trauma 1 (2.8%), and other reasons 4 (11.1%). Isolated abducens paralysis was associated with a vascular risk factor such as diabetes in 16 (44.4%) patients, hypertension in 12 (33.3%), coronary artery disease in 5 (13.9%), smoking in 5 (13.9%), and hyperlipidemia in 3 (8.3%) patients (Table 1).

Table 1. Demographic, etiological, clinical features, and prognosis in patients with isolated abducens palsy

	Min.	Max.	Mean±SD
Age	24.0	90.0	52.6±17.5
Gender			
Male			21±58.3
Female			15±41.7
Diabetes			16±44.4
Hypertension			12±33.3
Coronary artery disease			5±13.9
Smoking			5±13.9
Hypercholesterolemia			3±8.3
Blood sugar level	67.0	273.0	135.5±58.1
HbA1c 3.1	53.9	9.5±10.5	
LDL 47.6	172.0	121.2±36.0	
Triglyceride level	42.0	454.0	167.4±88.8
Vitamin B12	8.9	1500	267.4±251.7
WBC 4.3	18.7	8.2±3.4	
CRP 0.1	127.0	6,4±23.3	
Sedimentation	4.0	116.0	25.1±28.0
Orbital pain			20±55.6
CSF pressure	130.0	350.0	208.3±61.3
CSF glucose	53.0	118.0	80.4±20.7
CSF protein	27.5	97.0	50.7±22.5
Abducens palsy			
Right			18±50.0
Left		12±33.3	
Bilaterally			6±16.7
Presentation			
Horizontal diplopia			28±77.8
Headache			8±22.2
Etiology			
Microvascular			16±44.4
Intracranial pressure			3±8.3
Inflammatory			3±8.3
Unknown			3±8.3
Demyelination			2±5.6
Malignity			2±5.6
Congenital			2±5.6
Trauma			1±2.8
Others			4±11.1
Recovery			
Yes			27±75.0
No			5±13.9
Could not be reached			4±11.1
Recovery time (month)	0.3	6.0	2.5±1.3
Treatment			
Glucose regulation			11±30.6
Steroid			11±30.6
No treatment			7±19.4
Acetazolamide			2±5.6
Others			5±13.9

Min: Minimum; Max: Maximum; SD: Standard deviation

The treatment protocols were blood glucose regulation in 11 (30.6%), steroid therapy in 11 (30.6%), diazoxide in 2 (5.6%), and other treatment options (such as surgery) in 5 (13.9%) of all patients. Seven patients were followed without treatment. Mean clinical recovery time was 2.5±1.3 months (range, 10 days–6 months). Clinical improvement occurred in 27 (75%) patients, but 5 (13.9%) patients did not improve, and 4 (11.1%) patients could not be further evaluated (Table 1).

When etiological causes were compared as microvascular and other causes, the mean age in the microvascular group was significantly higher than other causes (62.8±13.3 vs. 44.5±16.4, respectively p=0.001). There was no gender difference between the groups (F/M: 6/14 vs. 9/7, p>0.05). When we evaluated the vascular atherosclerotic risk factors, diabetes was significantly higher in the microvascular group (p=0.001), but no significant difference was observed in terms of other atherosclerotic risk factors than other causes groups (p>0.05). The fasting blood glucose and Hba1C value were significantly higher in the microvascular group (p=0.02 and p=0.02, respectively) when no significant difference was observed between other blood parameters (p>0.05). There was no significant difference regarding the amount of clinical improvement and the clinical recovery times between groups (p>0.05) (Table 2).

DISCUSSION

The clinical features and final outcomes of the patient presenting with isolated abducens nerve paralysis were evaluated. Considering the age of the patients admitted to neurology clinics with isolated abducens nerve palsy, microvascular causes were the most common etiologic causes, unlike pediatric and neurosurgical clinics. We revealed the similar and different aspects of clinical and prognostic factors between microvascular and other causes in this study. As far as we know, although few studies are comparing these two groups with different aspects [7], our study is the first study to compare clinical features and prognoses.

Abducens nerve palsy is a common condition in neurology practice. The diagnosis may seem easy in isolated cases without other neurological findings, considering the anatomical course and etiological factors, but the presentation of many various etiological causes with similar clinical findings may cause difficulties in the differential diagnosis [4]. In a retrospective study which continued almost 15 years, the underlying causes were hypertension and less commonly diabetes in 35% of the cases; idio-

Table 2. Comparison of microvascular and other groups in terms of demographic characteristics, clinical features, and prognoses

	Other causes (n=20) Mean±SD	Microvascular group (n=16) Mean±SD	p
Age	44.5±16.4	62.8±13.3	0.001[t]
Gender female/male	6±30.0	9±56.3%	0.112[X²]
Hypertension	5±25.0	7±43.8%	0.236[X²]
Diabetes	2±10.0	14±87.5%	0.001[X²]
Hyperlipidemia	1±5.0	2±12.5%	0.574[X²]
Smoking	17±85.0	14±87.5%	0.829[X²]
Coronary artery disease	3±15.0	2±12.5%	0.829[X²]
Orbital pain	12±60.0	8±50,0%	0.549[X²]
Blood glucose level	117.7±47.7	159.2±63.8	0.022[m]
HbA1c	6.1±1.2	12.5±14.0	0.024[m]
LDL level	122.5±34.5	119.5±39.1	0.970[m]
Triglyceride	147.0±65.7	193.7±108.7	0.210[m]
B12	301.9±325.5	225.6±111.2	0.620[m]
WBC	9.0±4.0	7.0±2.0	0.243[m]
CRP	3.1±6.6	10.1±33.7	0.835[m]
Sedimentation	23.5±30.7	27.3±25.4	0.207[m]
CSF pressure	218.8±69.8	180.3±10.5	0.474[m]
CSF glucose	78.7±19.8	86.3±27.6	0.483[m]
CSF protein	54.1±22.8	31.8±6.0	0.093[m]
Abducens palsy			
Right	10±50.0	8±50.0	0.245[X²]
Left	5±25.0	7±43.8	
Bilaterally	5±25.0	1±6.3	
Presentation			
Diplopia	15±75.0	13±81.3	0.698[X²]
Headache	5±25.0	3±18.8	0.058[X²]
Recovery			
Yes	15±78.9	12±92.3	0.598[X²]
No	4±21.1	1±7.7	
Could not be reached	1	3	
Recovery time (month)	2.2±1.6	2.8±0.7	0.087[m]

SD: Standard deviation; LDL: Low-density lipoprotein; WBC: White blood cell; CRP: C-reactive protein; CSF: Cerebrospinal fluid; m: Mann–Whitney U-test; t: t-test; X^2: Ki-kare test (Fisher's test).

pathic causes in 26%, multiple sclerosis in 7%, neoplasm in 5%, and aneurysm in 2% [3]. In another study, hypertension was the most common microvascular cause at 71%, and diabetes 54%, hypercholesterolemia 48%, and hyperlipidemia in 53% [5]. In our patient group, the most common etiological reasons were microvascular causes, as concluded in the literature. In contrast to the previous studies concluding that hypertension is the most common etiological risk factor, diabetes was the most common vascular risk factor in our results. This finding may be associated with long-term blood sugar dysregulation, considering the difference in HbA1c level. Other vascular causes had a similar distribution. Furthermore, some rare cases not reported in the literature were included in our study. Such as, a 57-year-old male patient who did not have vascular risk factors developed unilateral abducens paralysis and diagnosis as HaNDL. Contrast-enhanced cranial and orbital MRI was within normal limits in this patient. Lymphocytosis was dominant in the lumbar puncture analysis when performed at the time the patient had migraine-like pain episodes. Then, his gaze restriction improved within weeks under lamotrigine treatment. Furthermore, a 24-year-old male patient with isolated abducens paralysis was diagnosed as Behçet's disease.

Since the development of MRI, the etiological causes of acute ocular cranial neuropathies including intracranial neoplasms, aneurysms, inflammation, infection, and brainstem infarction have become easier to identify and to give curable treatments [8]. On the other hand, some researchers suggest as "neuroimaging is not required in the early period in cases with isolated sixth nerve palsy accompanied by vascular risk factors, only may perform when clinic of the patient does not improve within 3 months" [9–11]. In a previous study which compared the underlying pathologies of isolated acute ocular motor nerve paralysis between vascular and non-vascular groups, 61% of the patients in the non-vascular group were found to have some vascular causes in further investigation on this results, they suggest to perform MRI in the early course of the disease, regardless of major vascular risk factors [7]. One of our patient with major vascular risk factors later revealed abducens paralysis due to clivus chordoma in cranial MRI. Therefore, early stage neuroimaging is important in differential diagnosis and treatment.

In addition to the vascular risk factors for diagnosis, the history of systemic malignancy, giant cell arteritis, head trauma, alcohol use, spinal surgery or procedure, oral and genital aphthae, and head trauma should be questioned. Causes of Wernicke's encephalopathy such as intracranial hypotension and Behçet's disease should be excluded. The accompanying pain in the restricted gaze typically indicates an inflammatory or vascular etiology [12, 13]. In our results, 55.6% of the patients with abducens nerve paralysis accompanied ipsilateral periorbital pain. However, when microvascular and other causes were compared,

periorbital pain was similar in both groups. Abducens nerve paralysis due to microvascular causes generally has a good prognosis and almost complete recovery is expected in an average of 3 months [5, 14]. As a result of a 6-year follow-up, it has been shown that 86% of the patients with microvascular-related sixth nerve palsy recover fully, and this recovery takes between 3 months and 1 year [5]. After our follow-up for about 3 years, complete recovery was observed in 12 (92.3%) of 13 patients with abducens paralysis due to microvascular causes. There was no significant difference between the vascular and non-vascular groups in terms of the complete clinical recovery. This situation may be attributed to the importance of advances in imaging methods in the early detection of non-vascular causes.

Therapeutic modalities ranged from conservative treatment, botulinum toxin injections, and surgical treatment in cases of abducens nerve palsy. Treatment should be directed toward the etiology in cases of abducens nerve palsy. The basis of treatment for microvascular causes is to control risk factors such as diabetes mellitus and blood pressure, smoking, hyperlipidemia. Surgery for neoplasms, surgical and endovascular treatments for aneurysms is available. Steroid therapy is given for abducens nerve paralysis due to inflammatory and demyelinating diseases. Parenteral thiamine therapy is used in Wernicke's encephalopathy due to vitamin deficiency. Abducens nerve palsy may resolve spontaneously without the need for additional treatment in some cases such as post-viral infections [6]. Diabetes was the most common etiology in our study, so the most common treatment option was blood sugar regulation. Steroid therapy, acetazolamide, and surgical procedures were the main treatment options in our study.

The main limitation of our study is the small number of patients. The reason for this is that patients with abducens nerve paralysis with additional neurological findings were excluded from the study. Furthermore, abducens nerve palsy due to trauma and malignancy applies to neurosurgery clinics, and pediatric age patients did not apply to our clinic that problems prevent a homogeneous distribution among etiological causes. Therefore, a wide variety of clinical studies that abducens nerve paralysis cases can apply will provide more objective data.

Our results revealed that vascular risk factors can be seen in both groups, but diabetes is an important reason for microvascular etiology. Both groups have similar features in terms of clinical outcome. Considering the various etiological reasons, it is necessary to use auxiliary diagnostic methods for early diagnosis and treatment even in the presence of microvascular risk factors.

Ethics Committee Approval: The Istanbul Training and Research Hospital Clinical Research Ethics Committee granted approval for this study (date: 15.12.2017, number: 1141).

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Authorship Contributions: Concept – YE, UE; Design – YE; Supervision – TG, UE; Materials – YE; Data collection and/or processing – YE; Analysis and/or interpretation – YE, TG, UE; Literature review – YE, TG; Writing – YE; Critical review – UE.

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