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Cause of acquired onset of diplopia due to isolated third, fourth, and sixth cranial nerve palsies in patients aged 20 to 50 years in Korea: A high resolution magnetic resonance imaging study

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ABSTRACT

Aims: This study aimed to describe the etiologies of acquired onset of diplopia due to isolated third, fourth, and sixth cranial nerve palsies in young adults in Korea.
Methods: This retrospective study included 127 patients aged 20 to 50 years with acquired onset isolated third, fourth, and sixth cranial nerve palsies who received care at the Strabismus and Neuro-ophthalmology Department of Samsung Medical Center from 2013 to 2017. The etiologies of the palsies determined by clinical assessment, high-resolution magnetic resonance imaging (MRI) with three-dimensional constructive interference in steady state, and laboratory testing were analyzed.
Results: Fifty-nine patients manifested sixth cranial nerve palsy. Forty-six patients had fourth cranial nerve palsy and 22 patients had third cranial nerve palsy. The most common etiologies of the ocular motor nerve palsies were presumed inflammatory lesions (21.3%), followed by presumed microvascular causes (17.3%), and neoplasms involving the central nervous system (15.7%). Neoplasms were the most common cause of sixth cranial nerve palsy (25.4%). The most common cause of fourth cranial nerve palsy was presumed microvascular ischemia (28.3%), and presumed inflammatory lesions was the most common cause of third cranial nerve palsy (36.4%). Other non-traumatic causes included vascular lesions, ischemic brainstem stroke, intracranial hemorrhage, non-aneurysmal neuro-vascular contact, multiple sclerosis, and infection.
Conclusion: A substantial proportion of young adult patients with ocular motor nerve palsies manifested pathologies other than presumed microvascular ischemia or idiopathic causes. Neuroimaging and laboratory tests have important roles in the evaluation of patients aged 20–50 years with acquired ocular motor nerve palsies.

1. Introduction

Neurologically isolated ocular motor (third, fourth, and sixth) nerve palsies are common entities observed in neuro-ophthalmology practices. However, ocular motor nerve palsies in young adults below 50 years of age are uncommon. Two retrospective studies have addressed the causes of sixth nerve palsy in patients younger than 50 years old. One was reported in 1984 [1] and another was reported in 2002 [2]. Both studies reported that acquired sixth nerve palsy was the initial manifestation of a serious condition, such as a brain tumor, in a substantial proportion of the patients. The prevalence of neoplasms was 16% [1] or 33% [2]. The former study was carried out before the use of neuroimaging techniques, which allow each cranial nerve to be viewed [1]. The latter study included substantial numbers of non-isolated cranial nerve palsies accompanied by concomitant neurologic signs and symptoms [2]. For example, among 15 patients with mass lesions associated with the central nervous system in their study, only three exhibited isolated nerve palsy. The possible causes of cranial nerve palsies might vary between patients with isolated and non-isolated cranial nerve palsy. Regarding third and fourth nerve palsies, few studies have reported the prevalence of different causes in young adults.

Thus, in this study, the authors investigated the etiologies of acquired onset of diplopia due to ocular motor nerve palsies using clinical assessments, high-resolution MRI, and laboratory testing in young Korean adults aged 50 years or less.

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2. Methods

A retrospective review was performed on patients aged 20 to 50 years with acquired onset isolated third, fourth, and sixth cranial nerve palsies who received care at the Strabismus and Neuro-ophthalmology Department of Samsung Medical Center from March 2013 to August 2017. The Institutional Review Board of Samsung Medical Center approved the study and waived informed consent. The study was conducted according to the tenets of the Declaration of Helsinki. The study included patients 20 to 50 years old who presented with acquired onset of diplopia due to isolated third, fourth, or sixth cranial nerve palsy. Patients with restrictive strabismus, previous extraocular muscle surgery, or other previous neurological disorders that might affect ocular alignment were excluded from the study. Patients with bilateral nerve palsy, combined palsies involving two or more ocular motor nerves, or papilledema were also excluded.

The methods of clinical assessment, blood work, chest radiography, and the MRI protocols used in this study were described in detail in the authors' previous studies [3,4]. Different MRI protocols were used for the children in the former study [3] and the adults in the current study.

In this study, high-resolution pre- and post-cranial nerve MRI was performed with three-dimensional sequences (3D). The MRIs were performed for all patients using a 3-T system (Magnetom Skyra; Siemens Healthineers, Erlangen, Germany) with a 32-channel phased-array head coil. Two-dimensional axial turbo spin-echo T2-weighted imaging was performed to visualize the entire brain with the following parameters: repetition time, 4620 ms; echo time, 97 ms; field of view, 240 × 188 mm; matrix, 512 × 410; and section thickness, 5 mm. Proton density (PD)-weighted images were obtained using 3D sampling perfection with application-optimized contrasts and different flip angle evolution (SPACE) sequences to visualize the cisternal segment of the cranial nerves. The slab thickness (6.4 cm) of the 3D-SPACE sequence was measured from the anterior commissure to the cervico-medullary junction. The detailed parameters of the 3D-SPACE sequence were as follows: repetition time, 1000 ms; echo time, 32 ms; flip angle, 120°; field of view 170 × 170 mm; matrix, 320 × 320; section thickness, 0.5 mm; and acquisition time, 6 min and 57 s. An additional 3D constructive interference steady state (3D-CISS) sequence was performed to visualize the cisternal segment of the fourth cranial nerve with the following parameters: repetition time, 8.30 ms; echo time, 3.62 ms; flip angle, 50°; field of view, 150 × 150 mm; matrix, 512 × 512; section thickness, 0.25 mm; and acquisition time, 7 min and 56 s. The slab thickness (1.5 cm) of the 3D-CISS sequence was measured from the lower midbrain to the upper pons, including the inferior margin of the inferior colliculus. Following an intravenous injection of 0.1 mmol/kg gadobutrol (Gadovist; Bayer Pharma AG, Leverkusen, Germany), 3D magnetization-prepared rapid acquisition with gradient-echo (MPRAGE) sequence with fat saturation was obtained to visualize the nerve surrounded by a venous plexus using the following parameters: repetition time, 1900 ms; echo time, 3.19 ms; flip angle, 10°; field of view, 170 × 170 mm; matrix, 256 × 256; section thickness, 0.5 mm; and acquisition time, 5 min and 50 s. The slab thickness (8 cm) of the 3D-MPRAGE sequence was measured from the body of the lateral ventricle to the cervico-medullary junction. The axial source images of the 3D-SPACE, 3D-CISS, and 3D-MPRAGE sequences were mainly used to evaluate the cranial nerves. The reconstructed coronal images of 3D sequences were used simultaneously.

Presumed microvascular ischemia was assigned as the cause of ocular motor nerve palsy in patients for whom the MRI scan and laboratory testing did not reveal an alternative cause, other neurological signs remained absent, and the ocular motor nerve palsy resolved spontaneously [5]. Presumed inflammation was assigned as the cause of ocular motor nerve palsy in patients for whom the MRI scan showed enhancing lesions involving the corresponding ocular motor nerves or definite enhancement confined to the cranial nerves with or without related pain, and the MRI scan and laboratory testing did not reveal alternative causes such as tumorous conditions, infarctions, or vascular abnormalities. Tolosa-Hunt syndrome was defined by the criteria from the present International Classification of Headache Disorders (ICHD)-3 beta [6]. The detailed definition of presumed inflammation confined to the cranial nerves was described in a previous report [4].

3. Results

This study included 127 patients with a mean age of 38 ± 9 years (range, 20–50 years). Eighty-four (66%) patients were males and 43 (34%) were females. All patients, except one African American and one European American, were Asians. The patients had 57 right-sided palsies and 70 left-sided palsies. This study included 59 patients with sixth cranial nerve palsy, 46 patients with fourth cranial nerve palsy, and 22 patients with third cranial nerve palsy (13 were partial and nine were complete). Forty-one (32%) patients had symptoms of headaches or ocular pain at their initial presentation.

The most common causes of third, fourth, and sixth cranial nerve palsies were presumed inflammations (21.3%), followed by presumed microvascular causes (17.3%) and neoplasms involving the central nervous system (15.7%). Among the 27 patients with presumed inflammations causing ocular motor nerve palsy, the clinical and radiologic features of 11 patients met the diagnostic criteria of Tolosa-Hunt syndrome from ICHD-3 beta [6]. In six other patients, the MRIs revealed enhancing lesions involving the nerve without corresponding pain. The clinical and radiologic findings in these patients resolved after steroid treatment. In the remaining 10 patients, the MRIs showed enhancement confined to the third or sixth cranial nerves without any other brain or orbital lesions.

Table 1 presents the number of patients in each etiologic category of acquired isolated 3rd, 4th, and 6th cranial nerve palsies.

Table 1
Characteristics and underlying etiologies of patients with isolated third, fourth, and sixth cranial nerve palsies.

	Isolated third, fourth, and sixth cranial nerve palsies			
	Sixth (n = 59)	Fourth (n = 46)	Third (n = 22)	Total (n = 127)
Age (mean ± SD) (years)	37 ± 9	39 ± 8	38 ± 9	38 ± 9
Gender (male/female)	32/27	27/19	17/5	76/51
Underlying etiologies				
Presumed inflammatory	12 (20.3%)	7 (15.2%)	**8 (36.4%)**	27 (21.3%)
Presumed microvascular	8 (13.6%)	**13 (28.3%)**	1 (4.5%)	22 (17.3%)
Neoplastic	**15 (25.4%)**	2 (4.3%)	3 (13.6%)	20 (15.7%)
Meningioma	7	0	1	8
Other primary	8	2	2	12
Idiopathic	9 (15.3%)	8 (17.4%)	1 (4.5%)	18 (14.2%)
Traumatic	4 (6.8%)	9 (19.6%)	3 (13.6%)	16 (12.6%)
Vascular lesion	6 (10.2%)	2 (4.3%)	2 (9.1%)	10 (7.9%)
Ischemic brain stem stroke		1 (2.2%)		1 (0.8%)
Intracranial hemorrhage	1 (1.7%)			1 (0.8%)
Non-aneurysmal vascular contact			1 (4.5%)	1 (0.8%)
Multiple sclerosis	3 (5.1%)			3 (2.4%)
Congenital[a]		3 (6.5%)		3 (2.4%)
Viral infection			1 (4.5%)	1 (0.8%)
Others	1 (1.7%)	1 (2.2%)	2 (9.1%)	4 (3.1%)

SD: standard deviation.
The proportions of most common causes of third, fourth, and sixth cranial nerve palsies are marked in bold.
[a] These patients had acquired onset diplopia caused by fourth cranial nerve palsy. However, the etiology was concluded to be congenital based on the absence or atrophy of the fourth nerve with or without atrophy of the superior oblique muscle in the paretic eye.

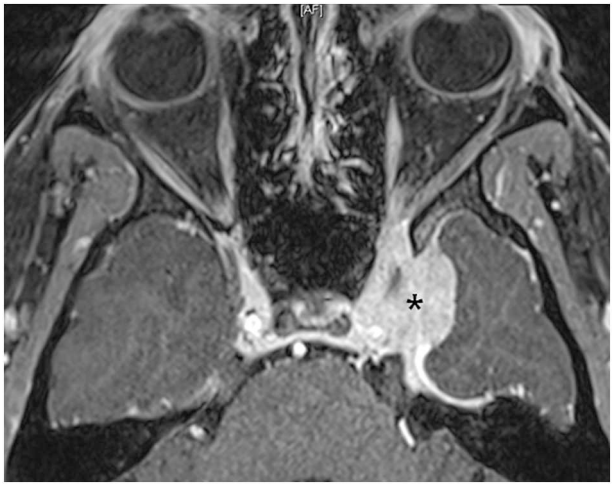

Fig. 1. A 41-year-old female patient with left sixth nerve palsy. On axial 3D MPRAGE image, a well-enhanced soft-tissue mass lesion involving the left cavernous sinus (asterisk), suggestive of meningioma, is observed.

3.1. Sixth cranial nerve palsy

Among the 59 subjects with sixth cranial nerve palsy, neuroimaging and other studies identified neoplasms involving the central nervous system in 15 (25.4%) patients; presumed inflammation in 12 (20.3%) patients; presumed microvascular causes in eight (13.6%) patients; vascular lesions, such as varix, aneurysm, venous anomaly, and moyamoya disease in six (10.2%) patients; and multiple sclerosis in three (5.1%) patients. In nine (15.3%) patients, the cause was indeterminate and the etiology was classified as idiopathic.

Among the 15 patients with primary brain tumors, seven had meningiomas involving the cavernous sinuses (Fig. 1). Brain tumors in the other patients included gliomas, benign and malignant peripheral nerve sheath tumors, meningoendothelioma, and ruptured dermoid cyst.

Among the 12 patients with presumed inflammations, the clinical and radiologic features in five patients met the diagnostic criteria of Tolosa-Hunt syndrome according to the ICHD-3 beta [6]. The MRIs revealed enhancing lesions involving the nerve in two patients without corresponding pain. The clinical and radiologic findings in these patients resolved after steroid treatment. In five patients, the MRIs showed enhancement confined to the sixth cranial nerve without other brain or orbital lesions.

Eight patients with presumed microvascular causes displayed various vasculopathic risk factors including hypertension, smoking, cholesterolemia, and diabetes mellitus. In three of these patients, high cholesterol was first diagnosed during the workup for sixth nerve palsy and was treated with lipid-lowering medication.

One of nine patients with undefined causes reported an episode of unilateral sixth cranial nerve palsy one year after first sixth cranial nerve palsy. Both episodes spontaneously resolved within several months. Flu symptoms preceded sixth nerve palsy in another patient with an undefined cause. Another three patients with undefined causes developed sixth nerve palsy during antibiotic treatment for sinusitis or otomastoiditis. The other patient developed sixth nerve palsy after heavy alcohol intake a day before. He did not have other neurologic symptoms or signs such as confusion, ataxia, or memory disturbance.

3.2. Fourth cranial nerve palsy

Among 46 subjects with fourth cranial nerve palsy, neuroimaging and other studies identified neoplasms of the central nervous system in two (4.3%) patients; presumed inflammation in seven (15.2%) patients; presumed microvascular causes in 13 (28.3%) patients; vascular lesions, such as arteriovenous anomalies and moyamoya disease in two (4.3%) patients; and ischemic brainstem stroke in one (2.2%) patient. In eight (17.4%) patients, the cause was not determined and it was classified as idiopathic.

One of the two patients with brain tumors had a schwannoma of the fourth nerve. The results of a conventional MRI in this patient were negative. When high-resolution MRI was performed in this patient, the neoplasm was found (Fig. 2).

In the seven patients with presumed inflammations, the clinical and radiologic features of three patients met the diagnostic criteria of Tolosa-Hunt syndrome. In four patients, the MRI showed enhancing lesions involving the nerve without corresponding pain. The clinical and radiologic findings in these patients resolved after steroid treatment.

Thirteen patients with presumed microvascular causes had various vasculopathic risk factors, including hypertension, smoking, high cholesterol, diabetes mellitus, and heart valve disease. Cholesterolemia was first diagnosed during the workup for fourth nerve palsy in two patients and diabetes mellitus was first diagnosed during the workup for fourth nerve palsy in one patient. These patients were treated with medication.

All eight patients with undefined causes denied any preceding symptoms related to the flu or sinus infections.

The onset time of symptom of fourth cranial nerve palsy was determined according to the patients' reports regarding the onset of diplopia or head tilting. This was further supported by family reports or

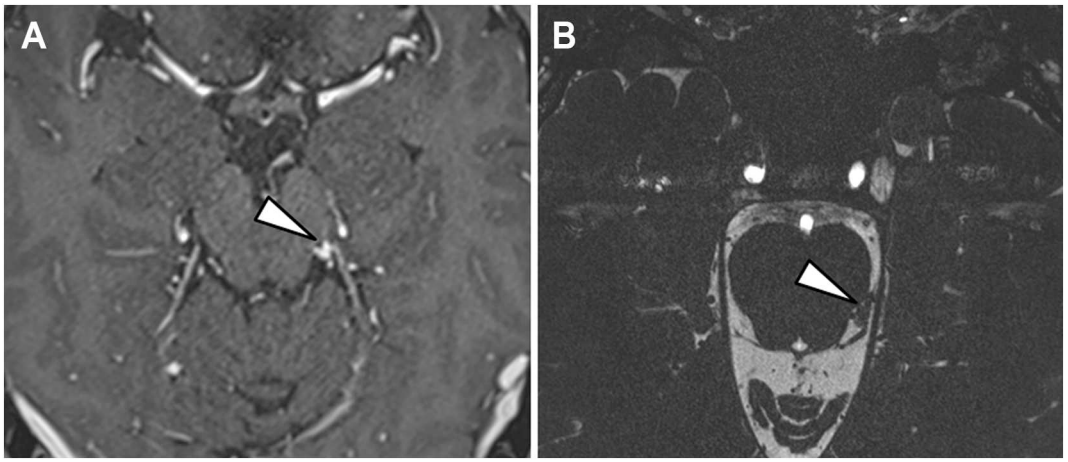

Fig. 2. A 50-year-old male patient with left fourth nerve palsy. Axial 3D-MPRAGE image (A) and 3D-CISS image (B) demonstrate nodular enhancement, suggestive of schwannoma (arrowheads). The size of the enhancing mass did not change on repeated magnetic resonance imaging during two years of follow-up.

old photos showing the patients' normal head positions. However, after a detailed investigation, the etiology was concluded as congenital in three patients based on the absence or atrophy of the fourth cranial nerves with or without atrophy of the superior oblique muscle in the paretic eye in MRI examinations.

3.3. Third cranial nerve palsy

Neuroimaging and other studies identified neoplasms involving the central nervous system in three (13.6%) of 22 patients with third cranial nerve palsy. One patient had meningioma and the other two patients had pituitary tumors. Both patients with pituitary tumors had partial third nerve palsy with pupillary involvement and very mild ipsilateral ptosis. Neither patient showed any limitations in ocular movement.

Presumed inflammation was detected in eight (36.4%) patients. The clinical and radiologic features of three patients met the diagnostic criteria of Tolosa-Hunt syndrome. In five patients, the MRIs showed enhancement confined to the third cranial nerve without any other brain or orbital lesion.

Two patients presented with aneurysms of the posterior communicating artery. They had initially presented with isolated third cranial nerve palsy. Of these two patients, one patient showed complete, while the other patient had incomplete, third nerve palsy with pupillary involvement. Both patients underwent surgical treatment for their aneurysms.

In one patient, non-aneurysmal vascular contact was the presumed cause of third cranial nerve palsy (Fig. 3). The patient had partial left third nerve palsy and MRI revealed third nerve compression by the basilar artery and the posterior communicating artery. The third nerve palsy recovered spontaneously in this patient. In one patient with third cranial nerve palsy, a herpes zoster viral infection was the cause. The cause was not determined in only one patient and it was classified as idiopathic.

4. Discussion

4.1. Neoplasms involving the central nervous system

Our results showed that tumors affecting the central nervous system were the most common etiology of sixth nerve palsies and the second most common etiology of third nerve palsies in young adult patients below 50 years of age. Overall, 15.7% of the patients with acute isolated ocular motor nerve palsies exhibited neoplasms. The proportion of neoplasms in patients with sixth nerve palsy was 25.4% in this study and ranged from 16% in the study of Moster et al. [1] to 33% in the study of Peters et al. [2], although direct comparison was difficult because the former study was carried out before the routine use of MRI, while the latter study included non-isolated cases. Twelve out of 15 patients found to have neoplasms in the latter study were non-isolated cases. A meningioma involving the cavernous sinus was the most common neoplasm in the present study. Eight patients had meningiomas involving the cavernous sinus. Other primary neoplasms included gliomas, benign and malignant peripheral nerve sheath tumors, meningoendothelioma, pituitary tumors, and ruptured dermoid cyst. Oculomotor nerve palsy is a relatively rare symptom of pituitary tumors [7–9]. Neither patient in this study showed apoplectic features in MRI and both had mild partial third nerve palsy. Notably, there was one patient who had a normal conventional MRI result and manifested a neoplasm under repeated 3D-CISS MRI. High-resolution MRI with contrast enhancement and repeated imaging might have important roles in suspected cases.

4.2. Presumed inflammation

Presumed inflammation was the most common etiology of third nerve palsy and the second most common etiology of sixth nerve palsy. Overall, presumed inflammation was identified as the etiology in 21.3% of the patients with acute isolated ocular motor nerve palsy. Among the 27 patients with presumed inflammation, the clinical and radiologic features of 11 patients met the diagnostic criteria of Tolosa-Hunt syndrome. In the six other patients, the MRIs revealed enhancing lesions involving the nerve without corresponding pain. Their clinical and radiologic findings resolved after steroid treatment. In the remaining 10 patients, the MRIs showed enhancement confined to the third or sixth cranial nerve without any other brain or orbital lesions. Granulomatous processes, such as Tolosa-Hunt syndrome, are well-known causes of ocular motor nerve palsy [10]. However, non-granulomatous inflammation, such as idiopathic inflammation or bacterial and fungal sphenoid sinusitis, could also cause ocular motor nerve palsy [11–13]. When the inflammation is confined to the cranial nerves, inflammatory neuropathy may be difficult to distinguish from ischemic optic neuropathy [14] and both of them could have benign clinical courses [4,15–18]. Therefore, it is possible that a certain proportion of patients were assigned to the wrong ischemia and inflammation categories or had ischemia and inflammation of a complex nature.

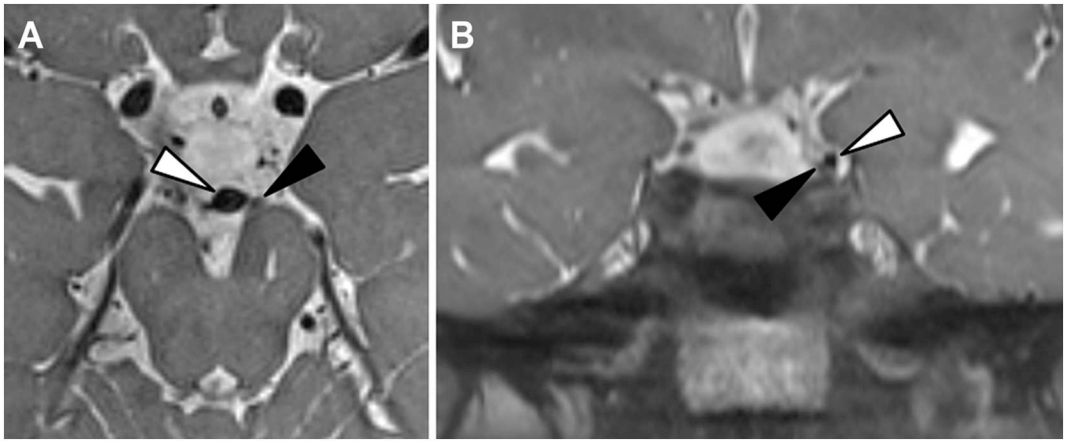

Fig. 3. A 39-year-old male patient with partial left third nerve palsy due to non-aneurysmal neurovascular contact. (A) The axial 3D-CISS image demonstrates mild left third nerve (black arrowhead) compression and mild inferior displacement by the basilar artery (white arrowhead) in the interpeduncular cistern region. (B) The coronal 3D-CISS image demonstrates compression of the third nerve (black arrowhead) by the posterior communicating artery (white arrowhead) in the neural sleeve region. The patient spontaneously recovered completely one day after symptom onset.

4.3. Presumed microvascular cause

Microvascular ocular motor palsies are thought to occur most often in adults 50 years of age or older with existing vasculopathic risk factors, such as hypertension, hyperlipidemia, diabetes, or smoking [5,18,19]. Several pathology studies investigating ocular motor nerve palsies with presumed microvascular causes have revealed demyelination [20–22], damage to the nerve sheath [21], and arterial hyalinization [20–22]. However, the classification of cranial nerve palsies based on pathology is impossible in a clinical setting. The diagnosis of ischemic cranial nerve palsies is speculative and based on the presence of vasculopathy or risk factors in isolated palsies [23]. In this study, patients with vasculopathic risk factors, including smoking, diabetes mellitus, arterial hypertension, hypercholesterolemia, or heart valve disease, previously or newly-diagnosed during the work up without any other definite lesion causing cranial nerve palsies, were classified as presumed microvascular causes. Therefore, all patients in this category had one or more vasculopathic risk factors. Although it is possible that certain cases with other hidden causes were misclassified as presumed microvascular nerve palsies, presumed microvascular causes might include a substantial proportion of cranial nerve palsies in patients in their 20s to 50s. Thus, presumed microvascular causes should be considered if the patient has one or more vasculopathic risk factors, even for young adults in their 20s.

4.4. Idiopathic

High-resolution MRIs were performed in all idiopathic patients and no corresponding lesions were found. Moreover, all serologic tests and blood work that included antibody tests for Graves' disease, myasthenia gravis, and Miller Fisher syndrome, were normal. Our report was comparable to a previous study that reported idiopathic cases in up to 18% of patients aged 20–50 with non-traumatic isolated sixth nerve palsies [2].

4.5. Vascular lesions

Ten patients with isolated ocular motor nerve palsies showed vascular lesions that included varix, moyamoya disease, arterial aneurysms, and large venous anomalies. Two patients with third nerve palsy harbored a posterior communicating arterial aneurysm. Of these two patients, one patient had complete and the other patient had incomplete, third nerve palsy with pupillary involvement.

4.6. Multiple sclerosis

Multiple sclerosis was the etiology of isolated sixth nerve palsy in three patients in the study. Rucker et al. reported that multiple sclerosis generally affected the sixth nerve [24] and rarely affected the third and fourth nerve [24]. The proportion of multiple sclerosis patients in this study was lower than in previous studies that reported a 24% prevalence of sixth nerve palsy [2]. The discrepancy may be attributed to the much lower incidence of multiple sclerosis in Asia than in Western countries [25].

4.7. Congenital

Three cases in this study were diagnosed with late decompensation of congenital fourth cranial nerve palsy. Previous reports have described cases of congenital fourth nerve agenesis in which the symptoms developed later in life [26]. That study included congenital fourth nerve palsy due to agenesis manifesting diplopia after age 50. Thus, congenital fourth nerve palsy might be a final diagnosis in patients who acquired diplopia at any age.

4.8. Others

A single patient was diagnosed with third cranial nerve palsy caused by a herpes zoster viral infection. Intracranial hemorrhage was found in one patient with sixth nerve palsy. Acute brainstem infarction was discovered in one patient with fourth nerve palsy. In one patient, the presumed etiology of the third nerve palsy was non-aneurysmal vascular contact. Because neurovascular compression in ocular motor nerve palsies could have high sensitivity but low specificity for nerve palsy [27,28], the true causative association is debatable. There have only been sparse reports of third nerve palsy presumed to result from neurovascular compression [29–33]. Among them, one study reported a patient with a transient third nerve palsy who was found to have neurovascular compression of the cisternal oculomotor nerve as it curved over a duplicated superior cerebellar artery [29]. Our case might also support the previously reported occurrence of transient third nerve palsy due to non-aneurysmal neurovascular compression [29]. 3D-CISS MRI might be beneficial in the evaluation of this type of cranial nerve palsy.

4.9. Limitations

Several limitations exist in this study. First, it was a retrospective study. All patients were tested for acetylcholine receptor antibodies. However, no patient underwent further tests for myasthenia gravis such as repetitive nerve stimulation tests, because of the absence of clinically suspected symptoms or signs. Second, a possible selection bias might exist. Patients referred to a tertiary hospital might have a greater prevalence of serious underlying pathologies compared to those referred to primary or secondary hospitals. Third, even with high-resolution MRI and blood work, the palsy etiologies were concluded to be idiopathic or presumed ischemia in a substantial proportion of the patients. We hope that the future development of imaging technology and a deeper understanding of the mechanism of cranial nerve palsy can facilitate the clarification of etiologies in this proportion of patients. Fourth, the majority of data were associated with a single ethnicity. As mentioned earlier, the incidence of multiple sclerosis can vary according to ethnicity [25]. Therefore, the proportion of this disease entity is not directly applicable to other ethnicities. Fifth, patients with papilledema were excluded in this study to remove patients with optic nerve involvement, however, non-ophthalmic specialists may have difficulty with fundus examination and this restriction may make it harder to directly apply our study results to their practice.

5. Conclusions

A substantial proportion of young adult patients with ocular motor nerve palsies in Korea had pathologies other than presumed microvascular ischemia or idiopathic cause. Prompt neuroimaging and laboratory testing have important roles in the evaluation of patients in this age group. Further studies including different ethnicities are needed to generalize our study results.

Author contributions

Kyung-Ah Park wrote the main manuscript text and prepared the tables and figures. Kyung-Ah Park, Sei Yeul Oh, Ju-Hong Min, and Byoung Joon Kim, prepared and analyzed the dataset. Kyung-Ah Park, Sei Yeul Oh, and Yikyung Kim conceived of the idea and supervised the findings of this work.

Declaration of Competing Interests

The authors have no financial or non-financial competing interests.

Meeting presentation

None.

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References

[1] M.L. Moster, P.J. Savino, R.C. Sergott, T.M. Bosley, N.J. Schatz, Isolated sixth-nerve palsies in younger adults, Arch. Ophthalmol. 102 (1984) 1328–1330.
[2] G.B. Peters 3rd, S.J. Bakri, G.B. Krohel, Cause and prognosis of nontraumatic sixth nerve palsies in young adults, Ophthalmology 109 (2002) 1925–1928.
[3] K.A. Park, S.Y. Oh, J.H. Min, B.J. Kim, Y. Kim, Acquired onset of third, fourth, and sixth cranial nerve palsies in children and adolescents, Eye (Lond.) 33 (2019) 965–973.
[4] K.A. Park, J.H. Min, S.Y. Oh, B.J. Kim, Idiopathic third and sixth cranial nerve neuritis, Jpn. J. Ophthalmol. 63 (2019) 337–343.
[5] D.M. Jacobson, T.D. McCanna, P.M. Layde, Risk factors for ischemic ocular motor nerve palsies, Arch. Ophthalmol. (Chicago, Ill.: 1960) 112 (1994) 961–966.
[6] Classification Committee of the International Headache Society, The international classification of headache disorders, 3rd edition (beta version), Cephalalgia 33 (2013) 629–808.
[7] A.R. Cohen, P.R. Cooper, M.J. Kupersmith, E.S. Flamm, J. Ransohoff, Visual recovery after transsphenoidal removal of pituitary adenomas, Neurosurgery 17 (1985) 446–452.
[8] A. Poon, P. McNeill, A. Harper, J. O'Day, Patterns of visual loss associated with pituitary macroadenomas, Aust. N. Z. J. Ophthalmol. 23 (1995) 107–115.
[9] L.J. Sullivan, J. O'Day, P. McNeill, Visual outcomes of pituitary adenoma surgery. St. Vincent's hospital 1968-1987, J. Clin. Neuro-Ophthalmol. 11 (1991) 262–267.
[10] L.B. Kline, W.F. Hoyt, The Tolosa-Hunt syndrome, J. Neurol. Neurosurg. Psychiatry 71 (2001) 577–582.
[11] D.A. Nelson, W.J. Holloway, S.C. Kara-Eneff, H.I. Goldenberg, Neurological syndromes produced by sphenoid sinus abscess, Neurology 17 (1967) 981–987.
[12] M.M. Fanous, C.E. Margo, L.M. Hamed, Chronic idiopathic inflammation of the retropharyngeal space presenting with sequential abducens palsies, J. Clin. Neuroophthalmol. 12 (1992) 154–157.
[13] E. Tay, A. Gibson, N. Chaudhary, J. Olver, Idiopathic orbital inflammation with extensive intra- and extracranial extension presenting as 6th nerve palsy—a case report and literature review, Orbit 27 (2008) 458–461.
[14] O.O. Adesina, J. Scott, K.L. McNally, B.J. Salzman, J.E.A. Katz, M.M. Warner, et al., Diffusion-weighted imaging and post-contrast enhancement in differentiating optic neuritis and non-arteritic anterior optic neuropathy, Neuro-Ophthalmol. (Aeolus Press) 42 (2018) 90–98.
[15] R.W. Miller, A.G. Lee, J.S. Schiffman, T.C. Prager, R. Garza, P.F. Jenkins, et al., A practice pathway for the initial diagnostic evaluation of isolated sixth cranial nerve palsies, Med. Decis. Mak. 19 (1999) 42–48.
[16] T. Akagi, K. Miyamoto, S. Kashii, N. Yoshimura, Cause and prognosis of neurologically isolated third, fourth, or sixth cranial nerve dysfunction in cases of oculomotor palsy, Jpn. J. Ophthalmol. 52 (2008) 32–35.
[17] U.C. Park, S.J. Kim, J.M. Hwang, Y.S. Yu, Clinical features and natural history of acquired third, fourth, and sixth cranial nerve palsy, Eye (London, England) 22 (2008) 691–696.
[18] S.K. Sanders, A. Kawasaki, V.A. Purvin, Long-term prognosis in patients with vasculopathic sixth nerve palsy, Am J. Ophthalmol. 134 (2002) 81–84.
[19] S.V. Patel, S. Mutyala, D.A. Leske, D.O. Hodge, J.M. Holmes, Incidence, associations, and evaluation of sixth nerve palsy using a population-based method, Ophthalmology 111 (2004) 369–375.
[20] A.K. Asbury, H. Aldredge, R. Hershberg, C.M. Fisher, Oculomotor palsy in diabetes mellitus: a clinico-pathological study, Brain 93 (1970) 555–566.
[21] P.M. Dreyfus, S. Hakim, R.D. Adams, Diabetic ophthalmoplegia; report of case, with postmortem study and comments on vascular supply of human oculomotor nerve, AMA Arch. Neurol. Psychiatry 77 (1957) 337–349.
[22] R.B. Weber, R.B. Daroff, E.A. Mackey, Pathology of oculomotor nerve palsy in diabetics, Neurology 20 (1970) 835–838.
[23] P.A. Tiffin, C.J. MacEwen, E.A. Craig, G. Clayton, Acquired palsy of the oculomotor, trochlear and abducens nerves, Eye (Lond.) 10 (Pt 3) (1996) 377–384.
[24] C.W. Rucker, Paralysis of the third, fourth and sixth cranial nerves, Am J. Ophthalmol. 46 (1958) 787–794.
[25] M. Alter, J. Good, M. Okihiro, Optic neuritis in Orientals and Caucasians, Neurology 23 (1973) 631–639.
[26] S. Lee, S.H. Kim, H.K. Yang, J.M. Hwang, J.H. Kim, J.S. Kim, et al., Imaging demonstration of trochlear nerve agenesis in superior oblique palsy emerging during the later life, Clin. Neurol. Neurosurg. 139 (2015) 269–271.
[27] H.G. Boecher-Schwarz, K. Bruehl, G. Kessel, M. Guenthner, A. Perneczky, P. Stoeter, Sensitivity and specificity of MRA in the diagnosis of neurovascular compression in patients with trigeminal neuralgia. A correlation of MRA and surgical findings, Neuroradiology 40 (1998) 88–95.
[28] C. Du, Y. Korogi, S. Nagahiro, Y. Sakamoto, A. Takada, Y. Ushio, et al., Hemifacial spasm: three-dimensional MR images in the evaluation of neurovascular compression, Radiology 197 (1995) 227–231.
[29] S. Joshi, W.W.H. Tee, C. Franconi, D. Prentice, Transient oculomotor nerve palsy due to non-aneurysmal neurovascular compression, J. Clin. Neurosci 45 (2017) 136–137.
[30] T.H. Tsai, J.L. Demer, Nonaneurysmal cranial nerve compression as cause of neuropathic strabismus: evidence from high-resolution magnetic resonance imaging, Am. J. Ophthalmol. 152 (2011) 1067–1073 e1062.
[31] M. Hashimoto, K. Ohtsuka, H. Akiba, K. Harada, Vascular compression of the oculomotor nerve disclosed by thin-slice magnetic resonance imaging, Am J. Ophthalmol. 125 (1998) 881–882.
[32] C. Liang, Y. Du, X. Lin, L. Wu, D. Wu, X. Wang, Anatomical features of the cisternal segment of the oculomotor nerve: neurovascular relationships and abnormal compression on magnetic resonance imaging, J. Neurosurg. 111 (2009) 1193–1200.
[33] H. Nakagawa, S. Nakajima, Y. Nakajima, Y. Furuta, O. Nishi, K. Nishi, Bilateral oculomotor nerve palsies due to posterior cerebral arterial compression relieved by microvascular decompression—case report, Neurol. Med. Chir. 31 (1991) 45–48.