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Etiology, clinical characteristics, and treatment outcome in patients with isolated sixth cranial nerve palsy

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Abstract

Background & Objective: Isolated sixth cranial nerve palsy was the most common isolated cranial nerve palsy causing extraocular muscle dysfunction. As magnetic resonance imaging (MRI) quality had improved and knowledge had grown in recent years, the etiology previously classified as idiopathic might be re-classified to be another in the current era, and some require specific treatments. We therefore studied the etiology, clinical characteristics, and treatment outcome in patients with isolated sixth cranial palsy in recent years. *Methods:* The medical records of 88 patients with isolated sixth cranial nerve palsy visited at the Neurological Institute of Thailand from January 2013 to December 2020 were reviewed. Clinical and demographical data included age, gender, laterality, headache location, vascular risk factors, etiology, treatment, and prognosis were collected and analyzed. *Results:* The most common etiology was microvascular ischemia (29.5%), followed by inflammation (25.0%), and vascular disorders (20.5%). Neoplasm, abducens palsy mimics and false localizing sign, and idiopathic were less common (13.6%, 6.8% and 4.5%, respectively). Compared to patient with sixth cranial nerve palsy from microvascular ischemia, those with inflammatory cause were younger ($p<0.001$), were more likely to have headache ($p=0.004$), and had better prognosis at 3 months ($p=0.018$).
Conclusion: Microvascular ischemia was the most common etiology of isolated sixth cranial nerve palsy. Age at onset and presence of headache were the important clues for distinguishing sixth cranial nerve palsy due to microvascular ischemia from inflammation. Prognosis was more favorable in inflammation than microvascular ischemia group. We suggest MRI scan to exclude other causes before making a diagnosis of microvascular ischemia or idiopathic.

Keywords: Abducens nerve palsy, sixth cranial nerve palsy, lateral rectus palsy

INTRODUCTION

Sixth cranial nerve palsy, also known as abducens nerve palsy, was the most common isolated cranial nerve palsy causing extraocular muscle dysfunction with an annual incidence around 11 cases per 100,000 people.[1] Previous studies found that ischemia, trauma, neoplasm, and idiopathic were the common causes of isolated sixth cranial nerve palsy.[2-12] Additional common etiologies were multiple sclerosis, infection and subarachnoid hemorrhage.[13-17] In term of prognosis, abducens nerve palsy caused by ischemia, trauma, inflammation, and idiopathic had a better prognosis than neoplasm.[5-9,11,15-17] In Thailand, a study on the etiologies of isolated sixth cranial nerve palsy that included the patients presented during 1995 to 2009 demonstrated that ischemia, neoplasm, trauma, and idiopathic were the common causes and ischemia had the best prognosis without any treatment.18 However, the mentioned study did not include the MRI findings.

As magnetic resonance imaging (MRI) quality has improved and knowledge has grown in recent years, the etiology previously classified as idiopathic may be re-classified to be another in the current era, which may have impact on treatments and outcomes. We therefore studied the etiology, clinical characteristics, treatment, and prognosis of patients with isolated sixth cranial nerve palsy, which provide additional information to previous

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studies that focus on etiology.[2-4,10,13,14]

METHODS

We reviewed the medical records of patients who were more than 15 years of age, and were diagnosed with ICD-10 code H492 (sixth [abducent] nerve palsy) at Neurological Institute of Thailand (NIT) during January 2013 - December 2020. Exclusion criteria were: 1. Combined other neurological deficits, such as multiple cranial nerves palsy, weakness, sensory impairment, abnormal cerebellar sign, Horner's syndrome, gait abnormality, dysarthria, and seizure; 2. Symptoms and signs suggesting increased intracranial pressure, which abducens nerve palsy may be a false localizing sign[19]; 3. Inadequate neuroimaging picture in our database; 4. Inadequate clinical data in medical records.

A total of 329 cases were identified by searching the database. Two hundred and forty-one patients were excluded because of inadequate clinical data, or combined other neurological deficits. The remaining 88 cases were included in our study. All negative MRI were reviewed again by the experienced neuroradiologist. Clinical and demographical data included age, gender, laterality, headache location, vascular risk factors, etiology, treatment, and prognosis were collected.

Loss of blood supply to small vessel of the nerve is thoughted to be the cause of microvascular ischemia. We defined CN VI palsy from microvascular ischemia in patients with normal MRI or unrelated findings, ESR less than 30 mm/hour, and normal CRP level, as defined in previous study[1,20], together with at least one of these risk factors: hypertension, diabetes mellitus, dyslipidemia and active smoking. Whereas neuritis was defined by contrast enhancement of abducens nerve on MRI, vascular disorders causing abducens nerve palsy included abnormal blood vessels or vascular loop compression. Patients with normal MRI or unrelated findings, normal investigational results and without any vascular risk factors were classified in idiopathic group.

Headache location was classified as periorbital, temporal, frontal, and occipital. Some patients had more than one headache location. Patients who had headache location other than aforementioned or bilateral headache were classified as others. The missing data we classified as undetermined.

Full recovery was defined by complete resolution of limitation of lateral rectus muscle movement and no diplopia. In microvascular ischemia group, time to recovery was counted from onset of symptom. In inflammation group, time to recovery was counted from the date when corticosteroid was started.

Culprit lesion location in hypertrophic pachymeningitis was defined by the location of the lesions along the course of abducens nerve. Some patients had more than one culprit locations.

Kruskal-Wallis test was used to test the age difference between six groups and Mann-Whitney test was used between two groups. Fisher's exact test was used to test the difference of gender, laterality, headache, and full recovery among six groups. P-value less than 0.05 was considered statistically significant for all analyses. SPSS 16.0 was used. The study was approved by the medical ethics review committee of the Neurological Institute of Thailand, no. 64-041.

RESULTS

Eighty-eight patients were eligible for analysis. The most common etiology was microvascular ischemia (29.5%), followed by inflammation (25.0%), and vascular disorders (20.5%). Neoplasm, abducens palsy mimics and false localizing sign, and idiopathic were less common (13.6%, 6.8% and 4.5%, respectively). Median age was 53.5 years old (range 17-86 years old). Forty-six patients (52.3%) were male. Forty-four patients had left lateral rectus palsy, while 39 patients had problem on the right. Unfortunately, 5 patients (5.7%) had bilateral involvement (Table 1).

CN VI palsy caused by microvascular ischemia

Twenty-six patients (29.5%) were in this group. They were 43-86 years old (median 62.5 years old). Twenty-four patients (92.3%) were older than 50 years old. Their gender and laterality of abducens nerve palsy were described in Table 1. Among 9 patients (34.6%) with headache, the most common location was periorbital (55.6%) (Table 2). The common risk factors were dyslipidemia, hypertension, and diabetes mellitus (N=19 (73.1%), 18 (69.2%), and 18 (69.2%), respectively). Only 5 patients (19.2%) were active smoker. Antiplatelet was prescribed in some patients. Three patients received corticosteroid treatment. Among 18 patients who did not loss to follow-up, three of them (16.7%) fully recovered within 1 month, while 6 and 13 patients fully recovered within 3 and 6 months (33.3%, and 72.2% respectively). Only 5 patients (27.8%) partially recovered at 6 months after onset. (Table 3).

Table 1: Characteristics of patients in each etiology group

Parameters		Etiology						P-value	Total
		Microisc	Inflm	Vasc dis	Neopl	Idio	Mimics		
Number (%)		26 (29.5%)	22 (25.0%)	18 (20.5%)	12 (13.6%)	4 (4.5%)	6 (6.8%)	-	88 (100%)
Age Median (IQR)		62.5 (57.0-70.0)	47.0 (39.5-55.5)	52.5 (38.5-62.0)	45.0 (38.75-57.0)	35.5 (29.0-54.0)	28.5 (17.0-36.25)	<0.001†	53.5 (40.0-61.0)
Gender	M	16 (61.5%)	10 (45.5%)	12 (66.7%)	4 (33.3%)	2 (50.0%)	2 (33.3%)	0.371*	46 (52.3%)
	F	10 (38.5%)	12 (54.5%)	6 (33.3%)	8 (66.7%)	2 (50.0%)	4 (66.7%)		42 (47.7%)
Laterality	L	15 (57.7%)	10 (45.5%)	11 (61.1%)	4 (33.3%)	2 (50.0%)	2 (33.3%)		44 (50.0%)
	R	10 (38.5%)	12 (54.5%)	7 (38.9%)	7 (58.3%)	1 (25.0%)	2 (33.3%)	0.147*	39 (44.3%)
	B	1 (3.8%)	0	0	1 (8.3%)	1 (25.0%)	2 (33.3%)		5 (5.7%)

Etiology: Microisc = Microvascular ischemia, Inflm = Inflammation, Vascdis = Vascular disorders, Neopl = Neoplasm, Idio = Idiopathic, Mimics = Abducens palsy mimics and false localizing sign
Abbreviation: M = male, F = female, L = left, R = right, B = bilateral
†Kruskal-Wallis test, *Fisher's exact test

CN VI palsy caused by inflammation

Twenty-two patients (25.0%) had abducens nerve palsy due to neuritis or hypertrophic pachymeningitis. Idiopathic hypertrophic pachymeningitis was the most common cause in this group (68.18%), followed by neuritis (18.18%), IgG4-related hypertrophic

Table 2: Headache location in each etiology

Etiology	Headache N (%)	Headache location (same side to lateral rectus palsy)					
		Periorbital N (%)	Temporal N (%)	Frontal N (%)	Occipital N (%)	Others N (%)	Undetermined N (%)
1. Microvascular	9/26 (34.6%)	5/9 (55.6%)	2/9 (22.2%)	1/9 (11.1%)	1/9 (11.1%)	1/9 (11.1%)	2/9 (22.2%)
2. Inflammation	17/22 (77.3%)	8/17 (47.1%)	7/17 (41.2%)	2/17 (11.8%)	0	2/17 (11.8%)	3/17 (17.6%)
3. Vascular	10/18 (55.6%)	3/10 (30.0%)	3/10 (30.0%)	0	1/10 (10.0%)	1/10 (10.0%)	4/10 (40.0%)
4. Neoplasm	5/12 (41.7%)	1/5 (20.0%)	0	0	0	1/5 (20.0%)	3/5 (60.0%)
5. Idiopathic	2/4 (50.0%)	0	0	0	0	1/2 (50.0%)	1/2 (50.0%)
6. Abducens palsy mimics and false localizing sign	2/6 (33.3%)	0	0	0	0	1/2 (50.0%)	1/2 (50.0%)

Table 3: Comparison of age, presence of headache, and recovery between microvascular ischemia and inflammation group

Factors		Microvascular ischemia	Inflammation	P-value
Age Median (IQR)		62.5 (57.0-70.0)	47.0 (39.5-55.5)	<0.001†
Headache Number (%)		9/26 (34.6%)	17/22 (77.3%)	0.004*
Recovery N (%)	Full recovery within 1 month	3/18 (16.7%)	5/18 (27.8%)	0.691*
	Full recovery within 3 months	6/18 (33.3%)	14/18 (77.8%)	0.018*
	Full recovery within 6 months	13/18 (72.2%)	16/18 (88.9%)	0.402*
	Not fully recovered within 6 months	5/18 (27.8%)	2/18 (11.1%)	

†Mann-Whitney test, *Fisher's exact test

pachymeningitis (9%), and ANCA-associated hypertrophic pachymeningitis (4.5%) (Table 4). Median age of patients in this group was 47.0 years old (range 27-79 years old), which is significantly younger than the ones in microvascular ischemia group (62.5 VS 47.0 years old, p<0.001) (Table 3). Proportion of male and female, and the laterality were similar (Table 1). Compared to microvascular ischemia group, more proportion of patient in this group had headache (77.3% VS 34.6%, p=0.004) (Table 3). Most common location was periorbital (47.1%) and temporal (41.2%) (Table 2). The headache location related to the location of inflammation. Among patients with hypertrophic pachymeningitis of any causes (N=18), most common culprit location was cavernous sinus (72.2%). Other locations were Dorello's canal (22.2%), superior orbital fissure (16.7%), and orbital apex (5.6%). Two patients did not have well defined lesion along the course of sixth cranial nerve but in other location. Corticosteroids were prescribed in 90.9% of the patients. Most of them got IV methylprednisolone followed by oral prednisolone (Table 5). Two patients (10.0%) lost to follow-up. Five patients fully recovered within 1 month (27.8%), while 14 (77.8%) and 16 patients (88.9%) fully recovered within 3 and 6 months respectively. Compared to CN VI palsy caused by microvascular ischemia, this group of patients had better prognosis at 3 months (77.8% VS 33.3%, p=0.018), however the differences of outcome at 6 months did not reach statistical significance (88.9% VS 72.2%, p=0.402) (Table 3). Among 2 patients who did not receive corticosteroid or immunomodulator, one, who was diagnosed with idiopathic hypertrophic pachymeningitis, had disease progression and developed optic neuropathy. The other patient, who was diagnosed with IgG4-related hypertrophic pachymeningitis fully recovered within 3 months without any treatment.

CN VI palsy caused by vascular disorders

Eighteen patients had vascular disorders (20.5%). Among these, dural arteriovenous fistulas was found in ten patients (at cavernous sinus in 9 patients and inferior petrosal sinus in 1 patient). Four patients had aneurysm (vertebral artery aneurysm in 3 patients and internal carotid artery aneurysm in a patient). Vertebrobasilar dolichoectasia, AICA vascular loop compression, and bleeding cavernoma at brainstem were also found (1,2,1 patients, respectively) (Table 4). The median age was 52.5 years old (range 17-78 years old). Gender of the patients and the affected sided were shown in Table 1. Ten (55.6%) of patients had headache, which location was undetermined in majority of the patients (40%). Among the rest, most common location was periorbital and temporal (30.0% both) (Table 2). The headache location also correlated with location of vascular disorders. Management and prognosis were variable according to individual etiology.

CN VI palsy caused by neoplasm

Twelve patients (13.6%) had neoplasm, which were meningioma in 7 cases, chordoma in 4 cases,

Table 4: Detailed etiology in each group

Etiology	Number (%)
1. Microvascular ischemia	**26 (29.5%)**
2. Inflammation	**22 (25.0%)**
- Idiopathic hypertrophic pachymeningitis	15 (17.0%)
- Neuritis	4 (4.6%)
- IgG4-related hypertrophic pachymeningitis	2 (2.3%)
- ANCA-associated hypertrophic pachymeningitis	1 (1.1%)
3. Vascular disorders	**18 (20.5%)**
- Dural arteriovenous fistulas	10 (11.4%)
- Aneurysm	4 (4.6%)
- Vertebrobasilar dolichoectasia	1 (1.1%)
- AICA vascular loop compression	2 (2.3%)
- Cavernoma	1 (1.1%)
4. Neoplasm	**12 (13.6%)**
- Meningioma	7 (8.0%)
- Chordoma	4 (4.6%)
- Pituitary macroprolactinoma	1 (1.1%)
5. Idiopathic	**4 (4.5%)**
6. Abducens palsy mimics and false localizing sign	**6 (6.8%)**
- Strabismus	2 (2.3%)
- Ocular myasthenia gravis	1 (1.1%)
- Graves' orbitopathy	1 (1.1%)
- Idiopathic intracranial hypertension	2 (2.3%)
Total	**88 (100%)**

and pituitary macroprolactinoma in one patient. Three out of seven meningiomas and 3 out of 4 chordoma were proven by pathological findings (Table 4). The median age was 45.0 years old (range 22-69 years old). Patient's gender and sided of involvement were shown in Table 1. One patient had bilateral abducens nerve palsy, and clival chordoma was diagnosis in this patient. Five patients (41.7%) had headache and the location was undetermined in majority of the patients (60%) (Table 2). Management was variable. No spontaneous recovery was found in this group.

Idiopathic CN VI palsy

Four patients (4.5%) were categorized to have idiopathic abducens nerve palsy (Table 2). First patient was a 39-year-old man with bilateral CN VI palsy, his MRI showed arachnoid cyst at right paramedullary cistern. Second patient was 32 years old man with left abducens nerve palsy, his MRI demonstrated empty sella turcica. The other two patients were 28 and 59 years old whose MRI showed no abnormality. The latter one was presumed to be microvascular ischemia because of his age, but he had none of

Table 5: Treatment prescribed in the patients in inflammation group

Regimens	Number (%)
IV methylprednisolone then oral prednisolone	12 (54.6%)
IV dexamethasone then oral prednisolone	5 (22.7%)
Oral prednisolone	3 (13.6%)
No corticosteroid	2 (9.1%)

risk factors. Fortunately, all patients in this group fully recovered within 6 months spontaneously.

Abducens palsy mimics and false localizing sign

In our study, 6.8% of the patients were initially thought to have CN VI nerve lesions, but were later found to be diagnosed with decompensated strabismus, ocular myasthenia gravis, Graves' orbitopathy, and idiopathic intracranial hypertension (Table 4). In 2 patients with idiopathic intracranial hypertension, both had headache but did not have clear clinical features of increased intracranial pressure and no papilledema on physical examination. CSF pressure was more than 30 cm H_2O in both cases.

DISCUSSION

This retrospective study focusing on the cause of CN VI palsy in patients presented at Neurological Institute of Thailand during 2013 - 2020 demonstrated that the most common etiology was microvascular ischemia, followed by inflammation, vascular disorders, and neoplasm. Similar to previous studies[5,7,8,11,15,17,18], the most common cause was microvascular ischemia. Interestingly, idiopathic abducens nerve palsy was infrequently found in our study, which is different from previous studies.[2-13,15-18] Hypertrophic pachymeningitis, mostly idiopathic cause, was more prevalent, compared to other studies.[2-18] These might be due to development of high-resolution 3T MRI in recent years. As Neurological Institute of Thailand was the neurological super tertiary center, neither infection nor trauma was found in our study.

Median age in microvascular ischemia group was significantly higher than in other groups. Among patients in this group, proportion of patients older than 50 years of age was similar to a previous study (92% and 93% respectively[21]). Aging was one of the microvascular risk factors, and there was a suggestion that microvascular non-arteritic oculomotor nerve palsy should be diagnosed in a patient over 50 years of age.[20] Microvascular ischemia was a rare cause of bilateral abducens nerve palsy[14], and only 1 case was found in our study. Headache was less frequent in patients with microvascular ischemia compared to patients with the other causes. Ipsilateral periorbital was the headache location in about half of patients who had headache, similar to the previous study.[22] Antiplatelet was prescribed in some patients although a study showed that aspirin did not reduce rate of microvascular ischemic abducens nerve palsy.[23] Rate of spontaneous recovery was variable depending on follow-up period, roughly range from 60% to 90%.[5-8,15,21,24,25] In our study, full recovery within 6 months was observed in 72.2% of the patients, and the remaining patients partially improved at time of follow up.

Median age in inflammation group was significantly lower than in microvascular ischemia group, and headache was more frequently observed in inflammation group. The most common culprit location was cavernous sinus, where lesion in this area is known to be a cause of isolated sixth nerve palsy.[26] Cranial nerve neuritis and hypertrophic pachymeningitis were corticosteroid responsive.[27,28] Most the patients in this group received corticosteroid, and their prognosis was significantly better than microvascular ischemia at 3 months ($p = 0.018$) and slightly better at 6 months. Differentiating between these two conditions was very important. Age and headache may be important clues for distinguishing them from each other.

In patients presented with isolated CN VI palsy and microvascular ischemia was the most likely diagnosis (clinical clues were older age, vascular risk factors, and normal lab investigation), there was a controversy whether to proceed to neuroimaging to exclude other diseases.[1,20] Based on our findings that combined prevalence of inflammation, vascular disorders, and neoplasm was more than that of microvascular ischemia (59.1% VS 29.5%), we suggested initial CT or CTA brain. If the results were negative, an MRI should be performed, especially in patients under the age of 50 and with headache, to rule out inflammation, some vascular disorders, or neoplasms that were not detectable on brain CT. In addition, MRI was more sensitive in detecting abnormalities of cranial nerves[29] and detecting hypertrophic pachymeningitis.[27] Furthermore, the patients in inflammation group, which mostly needed MRI for diagnosis and required steroid treatment, had a more favorable prognosis than the patients in microvascular ischemia group, which did not require specific treatment. Finally, in a patient with no abnormalities found in MRI, microvascular ischemia (if there were any risk factors), or abducens palsy mimics should also be think of, and idiopathic sixth cranial nerve palsy could be diagnosed after excluding other causes.

There were some limitations of this study. As it was retrospective study, some data such as severity of lateral rectus palsy, which may influence the prognosis, was not available.

In conclusion, Microvascular ischemia was the most common etiology of isolated sixth cranial nerve palsy. Age at onset and presence of headache are the important clues for distinguishing CN VI palsy due to microvascular ischemia from inflammation. Prognosis was more favorable in inflammation than microvascular ischemia group. We suggest further MRI to exclude other causes before making a diagnosis of microvascular ischemia or an idiopathic.

DISCLOSURE

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