Causes and Treatment Outcomes of Third, Fourth and Sixth Cranial Nerve Palsy

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Objective: *To evaluate the causes and the treatment outcomes of third, fourth and sixth cranial nerve palsy.*
Material and Method: *Medical records of 157 cases with extra-ocular muscle palsy from third, fourth or sixth cranial nerve palsy between January 1995 and December 2009 were reviewed. Demographic data, age, causes of extra-ocular muscle palsy and treatment outcomes were record and analyzed. The patients who were followed-up less than 6 months, myasthenia gravis and extra-ocular muscles fibrosis were excluded from the present study.*
Results: *One hundred and fifty-seven cases from 600 cases were included in the present study. The most common cranial nerve palsy was the sixth cranial nerve with 63 cases (40.1%). Of 157 cases, the causes were trauma 41 cases (26.1%), microvascular occlusion cause 34 cases (21.7%) and congenital cause 21 cases (13.4%). Cranial nerve palsy patients from microvascular occlusion cause spontaneously improved 25 of 34 cases (73.5%) in 6 months. All patients (21 cases) from congenital cranial nerve palsy had extra-ocular muscle surgery and 17 patients (80.9%) were successful.*
Conclusion: *Sixth cranial nerve palsy was the most common cranial nerve palsy. Most patients with cranial nerve palsy from vascular cause spontaneously improved in 6 months. Congenital cranial nerve palsy patients need extra-ocular muscle surgery and most cases were successful*

Keywords: *Cranial nerve, Palsy, Diplopia, Strabismus, Extra-ocular muscle*

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Extra-ocular muscles are supplied by third, fourth, and sixth cranial nerves. Cranial nerve palsies can lead to ocular motility problems that cause diplopia or amblyopia in children, although there were several reports of cranial nerve palsies in etiology, affected cranial nerves, and recovery rates[1-5]. Currently, advanced technology and medical knowledge help us in accurate diagnosis and proper treatment. Some patients with unresolved cranial nerve palsies need extra-ocular muscle surgery to reduce diplopia and maintain fusion. The objective of the present study was to examine the causes and treatment outcomes of third, fourth, and sixth cranial nerve palsies which will be useful for ophthalmologists in guiding diagnosis and treatment evaluation.

Material and Method

The charts of the patients with third, fourth, or sixth cranial nerve palsies at Department of ophthalmology, Siriraj Hospital, Mahidol University, Bangkok, Thailand from January 1995 to December 2009 were reviewed. The authors included all the patients who had extra-ocular muscle palsy from third, fourth, or sixth cranial nerve palsy and excluded the patients who could not be followed-up until complete treatment or at least 6 months after muscle surgery, diagnosed myasthenia gravis and the patients with extra-ocular muscle fibrosis.

The collected data were type of cranial nerve palsies, age of onset, sex, laterality, etiology and treatment outcomes. The present study defined the success of extra-ocular muscle surgery with the angle of deviation after surgery less than or equal to 10 prism diopters.

The study was approved by Siriraj Institutional Review Board. (SI 692/2008). The program SPSS version 15.0 was used for descriptive statistical analysis in the present study.

Results

Of 600 patients diagnosed with third, fourth or sixth cranial nerve palsy, 443 patients were excluded from the present study. One hundred and fifty-seven

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patients met the criteria. Eighty-one patients were female and 76 patients were male. Age of onset was 1 day to 82 years old. Mean age was 45.6 years old. Congenital causes were 21 cases (13.4%) and acquired causes 136 cases (86.6%). Lateral cases were right eye in 82 patients (52.2%), left eye in 70 patients (44.6%) and bilateral in 5 patients (3.2%). In bilateral cases, the authors found that 3 patients were congenital fourth cranial nerve palsies, 1 patient was pachymeningitis with combined third and sixth cranial nerve palsy and the last one with idiopathic cause sixth cranial nerve palsy. This patient had a history of seizures before sixth cranial nerve palsy and after 1 year, the sixth cranial nerve palsy was spontaneously resolved.

The present study found that sixth cranial nerve was the most common cranial nerve palsy with 63 patients (40.1%) followed by the third cranial nerve palsy 49 patients (31.2%), fourth cranial nerve palsy 36 patients (22.9%), combined third and sixth cranial nerves 6 patients (3.8%) and combined third, fourth and sixth cranial nerves 3 patients (1.9%). Table 1 shows the type and laterality of cranial nerves palsies of the 157 patients.

Isolated third cranial nerve palsy

Forty-nine patients had isolated third cranial nerve palsy and etiologies were identified in Table 2.

The most common cause was trauma 20 patients (40.8%), followed by microvascular occlusion 11 patients (22.4%), tumor 6 patients (12.2%). The other causes were idiopathic 3 patients, congenital 2 patients, aneurysm 2 patients, sphenoiditis 2 patients, Tolosa-Hunt syndrome 1 patient, orbital pseudotumor 1 patient and postviral infection 1 patient.

The most common tumor that caused third cranial nerve palsy was meningioma 3 patients (50%), pituitary adenoma 1 patient, hypothalamic harmatoma 1 patient and intrasellar tumor 1 patient (Table 5).

The third cranial nerve supplies medial rectus muscle (MR), inferior rectus muscle (IR), inferior oblique muscle (IO), superior rectus muscle (SR) and levator superioris muscle. All muscles affected were categorized as incompleted third cranial nerve palsy and some muscles affected were categorized as incompleted third cranial nerve palsy. The authors found completed third cranial nerve palsy in 37 of 49 patients (75.5%) and incomplete third cranial nerve palsy 12 of 49 patients (24.5%). The etiologies of completed third cranial nerve palsy were trauma 14 patients and microvascular occlusion 11 patients and incompleted third cranial nerve palsy were trauma 6 patients and tumor 3 patients.

Isolated fourth cranial nerve palsy

Thirty six patients were diagnosed as isolated fourth cranial nerve palsy. The most common cause was congenital 16 patients (44.4%), followed by trauma 10 patients (27.7%) and microvascular occlusion 6 patients (19.4%). The other causes were idiopathic 3 patients and Noonan syndrome 1 patient. Table 3 shows the etiologies of isolated fourth nerve cranial palsy.

Isolated sixth cranial nerve palsy

Sixty three patients were diagnosed isolated sixth cranial nerve palsy. The common causes were microvascular occlusion 17 patients (27%), trauma 11 patients (17.5%), idiopathic 10 patients (15.9%) and tumor 8 patients (12.7%).

The other causes were congenital 3 patients, post-viral infection 3 patients, traumatic carotid-carvernous (C-C) fistula 2 patients, spontaneous C-C fistula 2 patients, vasculitis 1 patient, pseudotumor cerebri 1 patient, congenital hydrocephalus 1 patient, aneurysm 1 patient and arteriovenous malformation 1

Table 1. Distribution of affected cranial nerves and laterality

Cranial nerve	Laterality			Total	Mean age (years)
	OD	OS	OU		
III	24	25	0	49	43
IV	22	11	3	36	39
VI	31	31	1	63	38
III, VI	4	1	1	6	56
III, IV, VI	1	2	0	3	52
Total	82	70	5	157	45.6

III = third cranial nerve, IV = fourth cranial nerve, VI = sixth cranial nerve, OD = right eye, OS = left eye, OU = both eyes

Table 2. Etiology of isolated third cranial nerve palsy

Etiology	Number of patients (%)
Trauma	20 (40.8)
Microvascular occlusion	11 (22.4)
Tumor	6 (12.2)
Others	12 (24.6)
Total	49 (100)

Table 3. Etiology of fourth cranial nerve palsy

Etiology	Number of patients (%)
Congenital	16 (44.4)
Trauma	10 (27.7)
Microvascular occlusion	6 (19.4)
Idiopathic	3 (5.5)
Noonan syndrome	1 (2.7)
Total	36 (100)

Table 4. Etiology of isolated sixth cranial nerve palsy

Etiology	Number of patients (%)
Congenital	3 (4.8)
Microvascular occlusion	17 (27)
Duane retraction syndrome	2 (3.1)
CNS aneurysm	1 (1.6)
Tumor	8 (12.7)
Idiopathic	10 (15.9)
Trauma	11 (17.5)
CNS vasculitis	1 (1.6)
Pseudotumor cerebri	1 (1.6)
Traumatic C-C fistula	2 (3.1)
Postviral infection	3 (4.8)
Congenital hydrocephalus	1 (1.6)
AVM	1 (1.6)
Spontaneous C-C fistula	2 (3.1)
Total	63 (100)

CNS = central nervous system, AVM = arteriovenous malformation, C-C fistula = carotid-carvernous fistula

patient (Table 4).

With tumor caused isolated sixth cranial nerve palsy, the authors found that carcinoma of nasopharynx was the most common cause 4 patients, followed by meningioma 2 patients, plasmacytoma 1 patient and olfactory ethisioblastoma 1 patient (Table 5) .

Combined third and sixth cranial nerve palsy

Six patients had combined third and sixth cranial nerves palsy. The etiologies were tumor 2 patients (33%), idiopathic pachymeningitis 2 patients, aneurysm 1 patient and vasculitis 1 patient.

Combined third, fourth, and sixth cranial nerve palsy

Three patients had combined third, fourth, and sixth cranial nerve palsy and all of them were diagnosed as Tolosa-Hunt syndrome.

Of 157 patients, the authors found that 66 patients (42%) were observed, 65 patients (41.4%) underwent extra-ocular muscle surgery, 10 patients (6.4%) received medication for treatment of the causes, 4 patients (2.5%) received chemotherapy, 4 patients (2.5%) had radiologic intervention and the others got other treatments (vessel clipping, tumor surgery, embolization and ventriculo-peritoneal shunt) as shown in Table 6.

Forty-six of 66 patients (69.7%) were resolved from cranial nerve palsy in 6 months and 59 patients (89.4%) were resolved in 1 year. The last patient had been observed until 36 months. Forty six of 65 patients (70.8%) were successful with extra-ocular muscle surgery. Table 6 shows the treatment modalities.

Congenital patients

Twenty one patients had congenital cranial nerve palsy and all of them underwent extraoculr muscle surgery. Seventeen of 21 patients (80.9%) were success with the angle of deviation after surgery less than or equal to 10 prism diopters (PD).

Microvascular occlusion patients

Thirty-two of 34 patients (87.2%) from microvascular occlusion group improved with observation. Twenty-six of 34 patients in this group had systemic diseases such as diabetes mellitus, essential hypertension, dyslipidemia or cardiovascular disease. Eleven patients didn't take any medication for cranial nerve palsy and 11 patients were given aspirin (two patients had already taken aspirin before having cranial nerve palsy). Twelve patients were given vitamin B. Twenty seven patients of 34 patients (79.4%) achieved complete recovery in 6 months. In 27 patients who were resolved, 11 patients were in the no medication group, 9 patients were in the aspirin group, and 7 patients were in the vitamin B group. Two patients of 34 patients had undergone muscle surgery with alignment success in both patients.

In the observation group, the authors analysed the recovery period compared between aspirin-receiving group (9 of 11 patients) and the group

Table 5. Tumor and cranial nerves palsy

Tumor	Affected cranial nerves			Total
	CN III	CN VI	CN III,VI	
CA nasopharynx	0	4	0	4
Meningioma	3	2	1	6
Pituitary adenoma	1	0	0	1
Plasmacytoma	0	1	0	1
Hypothalamic hamartoma	1	0	0	1
Olfactory ethisioblastoma	0	1	0	1
Optic nerve sheath neurilemmoma	0	0	1	1
Intrasellar tumor	1	0	0	1
Total	6	8	2	16

CN III = third cranial nerve, CN VI = sixth cranial nerve, CA = carcinoma

Table 6. Treatment modality

Cranial nerve	Observation (cases)		Muscle surgery (cases)		Other (cases)
	≤ 6 mo	> 6 mo	≤ 10PD	> 10 PD	
III	16	9	9	7	8
IV	6	1	24	5	0
VI	24	10	13	7	9
III, VI	0	0	0	0	6
III, IV, VI	0	0	0	0	3
Total	46	20	46	19	26

III = third cranial nerve, IV = fourth cranial nerve, VI = sixth cranial nerve
≤6 mo = resolve within 6 months, > 6mo = resolve more than 6 months
Other = chemotherapy, medication, radiointervention, vascular clipping, tumor removal, embolization, ventriculo-peritoneal shunt

not receiving aspirin group (11 of 11 patients). The authors found that the time of cranial nerve palsy recovery was not different between the groups with 95% confidential interval.

Trauma

Twenty-six of 41 patients (63.4%) with cranial nerves palsy from trauma had undergone muscle surgery and success rate was 61.5% while 15 patients were only observed. Eight patients in the observation group were resolved. So, overall the spontaneously improved rate in traumatic group was 19.5% (8 of 41 patients).

Tumor

Sixth and third cranial nerve palsy were common in central nervous system tumors, as shown in Table 5. Many treatments were applied for 16 patients with cranial nerve palsy from central nervous system tumors and carcinoma of nasopharynx. The treatments of choice depended on the location and types of the tumors. The treatments were chemotherapy, radiation, tumor surgery, and observation.

Discussion

Of 157 patients, the most common cranial nerve palsy was sixth cranial nerve. The authors found that 63 patients (40.1%) had sixth cranial nerve palsy. Richards BW et al[1] studied in 4,278 patients and found that sixth cranial nerve was the most common cranial nerve palsy. Because of its longest subarachnoid course, it is prone to injury. The present study showed that trauma 41 patients (26.1%), microvascular occlusion 34 patients (21.7%) and congenital 21 patients (13.4%), could be the common causes of cranial nerve palsies.

In third cranial nerve palsy, trauma 20 patients (40.8%) was the most common cause and the second was microvascular occlusion 11 patients (22.4%) in the present study. Keane J R's study[6] showed that of 1,400 patients with third cranial nerve palsy, trauma was the most common cause (26%) and microvascular occlusion was the common cause in 234 patients with diabetes mellitus.

In isolated fourth cranial nerve palsy, congenital and trauma were the leading causes. These results were the same as in the study of Von Noorden et al[7]. The authors found that congenital was common in the pediatric group and trauma in the adult group.

In isolated sixth cranial nerve palsy, microvascular occlusion was the most common cause. Patients with sixth cranial nerve palsy combined with third cranial nerves palsy, usually had pathology in the central nervous system such as tumors or pachymeningitis. These might suggest that if patients presented with multiple cranial nerve palsies, aggressive investigation should be performed.

Previous studies showed that recovery rates of cranial nerve palsy were 38 - 80%[1-5]. In the present study, 46 patients (29.3 %) were complete recovery within 6 months with observation. In this group, the authors found that microvascular occlusion was the leading cause, 26 of 46 patients (56.5%). If the authors analyzed in each etiology, patients with congenital cranial nerve palsy rarely recovered and all of them underwent muscle surgey. The authors did early extra-ocular muscle surgery in congenital cranial nerve palsy if they didn't improve to maintain binocular function and prevent visual suppression. Seventeen of 21 patients' extra-ocular muscle surgeries were successful.

In the present study, twenty-six of 32 patients (81.3%) in microvascular occlusion group showed spontaneous improvement in 6 months, comparing with 71% in the study of Rush J A, Younge B R[2]. The patients of the present study had underlying medical diseases of arteriosclerosis such as diabetes mellitus, dyslipidemia, and hypertension. With subgroup analysis for aspirin consumption, there was no significant difference of the recovery period between the patients receiving aspirin group and those who did not receive aspirin. The authors thought that aspirin might prevent further microvascular occlusion not promote nerve regeneration, therefore recovery time was not different in each group. However, the present study had not have so many patients as to conclude this finding and it needs further study to confirm this result.

In trauma cause, only 8 of 41 patients (19.5 %) had spontaneous recovery in 6 months and 26 patients had to undergo extra-ocular muscle surgery to reduce diplopia and 16 of 26 patients were successful in surgery. This spontaneous recovery might depend on the severity of head injury. In minor injury, cranial nerves should have more potential of nerve regeneration than that in the severe injury cases. In previous studies[2,8,9], the recovery rate at 6 months was 39-73%. Holmes J M et al[9] showed that unilateral palsy had better recovery rate than bilateral palsy.

In tumor cause, the present study showed that meningioma was common in third cranial nerve palsy and carcinoma of nasopharynx was common in sixth cranial nerve palsy. These tumors may directly invade the cranial nerves. Robertson et al[8] reported that their sixth cranial nerve palsy patients with intracranial neoplasia had other neurological signs such as decreased corneal sensation, papilledema, or nystagmus but Harley's[10] study didn't show other neurological findings in sixth cranial nerve palsy with intracranial neoplasia patients.

Conclusion

Sixth cranial nerve palsy was the most common cause of extra-ocular muscle palsy. Microvascular occlusion was the common etiology in sixth cranial nerve palsy whereas trauma was in third cranial nerve palsy and congenital was in fourth cranial nerve palsy. Patients with microvascular occlusion cranial nerve palsy could spontaneously recover but with congenital etiology patients having ungergone extra-ocular muscle surgery. Patients with multiple cranial nerve palsies need more investigation to find the cause.

Potential conflicts of interest

None.

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สาเหตุและผลการรักษาภาวะอัมพาตประสาทสมองเส้นที่ 3, 4 และ 6

ธรรมนูญ สุรชาติกำธรกุล เพ็ญนภา สุนทราภา สุชาดา กัมปนาทแสนยากร ไธวดี ดุลยจินดา

วัตถุประสงค์*: เพื่อประเมินสาเหตุและผลการรักษาของภาวะอัมพาตประสาทสมองเส้นที่ 3, 4 และ 6*

วัสดุและวิธีการ*:ทำการศึกษาย้อนหลังจากเวชระเบียนของผู้ป่วย 157 ราย ที่มีภาวะอัมพาตของกล้ามเนื้อตาจากประสาทสมอง เส้นที่ 3, 4 หรือ 6 ตั้งแต่เดือน มกราคม พ.ศ. 2538 ถึง เดือน ธันวาคม พ.ศ. 2552 ข้อมูลพื้นฐาน,อายุ, สาเหตุ และวิธีการรักษาของภาวะกล้ามเนื้อตาอัมพาตได้ถูกบันทึกและนำมาวิเคราะห์ ผู้ป่วยที่มาติดตามผลการรักษาน้อยกว่า 6 เดือน, มีภาวะ myasthenia gravis และภาวะกล้ามเนื้อตาเป็นพังผืด ถูกตัดออกจากการศึกษานี้*

ผลการศึกษา*: ผู้ป่วย 157 ราย จากข้อมูลทั้งหมด 600 ราย ได้ถูกรวบรวมนำมาศึกษา ภาวะอัมพาตของประสาทสมองที่พบบ่อยสุด คือ ประสาทสมองเส้นที่ 6 พบได้ 63 ราย (ร้อยละ 40.1) ในผู้ป่วย 157 ราย มีสาเหตุจากอุบัติเหตุ 41 ราย (ร้อยละ 26.1), สาเหตุจากหลอดเลือดขนาดเล็กอุดตัน 34 ราย (ร้อยละ 21.7) และภาวะเป็นตั้งแต่กำเนิด 21 ราย (ร้อยละ 13.4) ผู้ป่วยที่มีภาวะอัมพาตของประสาทสมองที่มีสาเหตุจากหลอดเลือดขนาดเล็กอุดตันสามารถหายได้เอง 25 รายใน 34 ราย (ร้อยละ 73.5) ภายใน 6 เดือน ผู้ป่วยทุกราย (21 ราย) ที่มีภาวะอัมพาตประสาทสมองที่เป็นตั้งแต่กำเนิด ต้องได้รับการผ่าตัดกล้ามเนื้อตา และผู้ป่วย 17 ราย (ร้อยละ 80.9) หลังผ่าตัดกล้ามเนื้อตาได้ผลสำเร็จดี*

สรุป*: ภาวะอัมพาตของประสาทสมองเส้นที่ 6 เป็นภาวะอัมพาตที่พบบ่อยที่สุด ภาวะอัมพาตของประสาทสมองที่มีสาเหตุจากหลอดเลือดขนาดเล็กอุดตันมักจะหายได้เองภายใน 6 เดือน ผู้ป่วยที่มีภาวะอัมพาตของประสาทสมองตั้งแต่กำเนิด ส่วนใหญ่ต้องได้รับการผ่าตัดและผลการผ่าตัดเป็นที่น่าพอใจ*