



Original Article

Acquired paralytic strabismus in Southern Taiwan

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Abstract

Background: Third, fourth, and sixth cranial nerve (CN3, CN4, and CN6) palsies are not uncommon in neuro-ophthalmology. The time and quality of recovery depend on the causes of the cranial nerve palsy. The purpose of our study was to evaluate the causes and outcome of acquired paralytic strabismus (PS) in a southern Taiwan population.

Methods: This study involved a retrospective chart review of patients at Kaohsiung Veterans General Hospital from January 2006 through July 2009. A total of 196 patients were enrolled. Outcomes and recovery times were recorded for the patients who exhibited C3, C4, and C6 palsies. The patients were categorized into four etiologic groups: vascular, idiopathic, traumatic, and neoplastic. The onset of PS, its continuing medical management, recovery, and other outcomes were followed up in these patients over a period of up to 10 years.

Results: The mean age of the 196 patients enrolled was 58.35 ± 17.60 years (range 11–90 years), and the mean follow-up time was 13.6 months. Seventy-seven patients (39.29%) had CN3 palsy, 38 patients (19.39%) had CN4 palsy, and 81 patients (41.33%) had CN6 palsy. The most common causes were vascular diseases (35.20%), followed by trauma (33.67%), and idiopathic causes (21.94%). About 50% of the patients recovered within 6 months. Among the four etiologic groups of patients, the vascular group showed the best recovery: about half of the patients recovered within 3 months. Longer recovery periods were necessary for patients in the neoplastic group than for those in the traumatic, vascular, and idiopathic groups ($p = 0.01$; $p < 0.001$; $p < 0.001$, respectively).

Conclusion: The prognosis for patients with PS depended mostly on the cause of their disease. Patients with PS attributable to a vascular cause had a better prognosis than the other patients, and those in the neoplastic group required the longest time to recover.

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1. Introduction

Third, fourth, and sixth cranial nerve (CN3, CN4, and CN6) palsies are not uncommon in neuro-ophthalmology. Paralytic strabismus (PS) typically results in intractable diplopia and an unacceptable head or face posture. The causes of these cranial nerve palsies include trauma, tumor, vasculopathy, elevated intracranial pressure, inflammation, and idiopathy.^{1–4} The time and quality of recovery depend on the cause of the cranial nerve palsy. Generally speaking, complete recovery may be

expected in most cases within several months. We performed this study to better understand the incidence, etiologies, and clinical characteristics of acquired PS and evaluate their prognosis in Southern Taiwan.

2. Methods

We retrospectively reviewed the charts of all patients diagnosed with CN3, CN4, and CN6 palsies at Kaohsiung Veterans General Hospital from January 2006 to July 2009. All patients underwent ophthalmologic evaluation including assessment of global alignment, extraocular muscle movement, pupil size, pupillary reaction, biomicroscopy, fundus examination, intraocular pressure, and visual acuity. The age of onset, sex, and previous medical history, especially the

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presence of vasculopathic factors such as diabetic mellitus, hypertension, hypercholesterolemia, cigarette smoking, aneurysm, and history of trauma or intracranial lesions, were recorded. The intracranial lesions included skull base tumor (e.g., nasopharyngeal carcinoma), intracranial tumor (e.g., astrocytoma or meningioma), and meningitis. The ocular examinations were recorded at each follow-up. Institutional Review Board Ethic Committee approval was obtained for this study (VGHKS 98-CT8-09).

All cases of congenital cranial nerve palsies, strabismus secondary to myasthenia gravis, thyroid orbitopathy, multiple acquired cranial nerve palsies, and birth injury were excluded. Patients with incomplete records were also excluded. Complete recovery of nerve palsies was defined as the patient being subjectively free of diplopia in all gaze positions with full recovery of ocular ductions. The patients were categorized into four etiologic groups: vascular, idiopathic, traumatic, and neoplastic. The vascular group consisted of those who had one or more vascular risk factors such as diabetic mellitus, hypertension, hypercholesterolemia, or cigarette smoking, with no history of trauma or evidence of neoplasm on imaging studies. Patients with vascular risk factors and obvious recent trauma or intracranial tumor further complicating the picture they were assigned to the trauma or neoplasm group, respectively.

2.1. Statistical analysis

Statistical analyses were conducted using Statistical Package for the Social Sciences version 17.0 for Windows (SPSS Inc., Chicago, IL, USA). Descriptive statistics such as mean, standard deviation, range, and frequency distribution were used to describe the characteristic data of the patients in each group with different cranial nerve palsies. A Chi-square test or independent samples one-way analysis of variance was used to test the differences in characteristic profiles among the groups with different disease causes. The Kaplan–Meier method was used to estimate the unrecovery time of groups with different disease causes, and the log-rank test was used to compare

survival distributions for the different categories of disease cause. Cox proportional hazard regression was used to explore the association between patients' cause of disease and recovery and the hazard rate (recovery rate) at any certain point in time. A p value <0.05 was regarded as statistically significant.

3. Result

There were 196 patients enrolled in this study; 122 were male (62.24%) and 74 were female (37.76%). The mean age was 58.35 ± 17.60 years old (range 11–90 years), and the mean follow-up time was 13.6 months. Seventy-seven patients (39.29%) had CN3 palsy, 38 patients (19.39%) had CN4 palsy, and 81 patients (41.33%) had CN6 palsy. The total number, age, and etiology of the patients in each group are shown in Table 1.

Vascular diseases such as diabetes mellitus and hypertension were the most common causes of PS in 69 patients (35.20%), followed by trauma in 66 patients (33.67%) and idiopathic causes in 43 patients (21.94%). In addition, there were 18 patients (9.18%) with PS caused by intracranial lesions or skull base tumors (Table 1).

The most common cause of each cranial nerve palsy was different. For patients with CN6 palsy, the most common cause was vascular (37.04%), whereas trauma was most common for CN4 palsy (36.84%) and CN3 palsy (49.35%) (Table 1). During the follow-up period, 116 (59.18%) patients showed complete recovery, and the median time necessary for recovery was 6.0 months. The unrecovery time of patients with acquired PS and the cumulative proportion surviving (unrecovering) at a particular point in time are shown in Table 2.

Kaplan–Meier analysis revealed that half of the trauma patients needed more than 10 months to recover, half of vascular patients needed more than 3 months to recover, and half of idiopathic patients needed more than 4 months to recover. Overall, about half the patients needed more than 6 months to recover (Table 3).

The results of applying the log-rank test showed that the distribution of unrecovery curves for the different levels of

Table 1
Demographic characters of 196 patients with paralytic strabismus.

	Cranial nerve 3 palsy	Cranial nerve 4 palsy	Cranial nerve 6 palsy	p	Total
n	77	38	81		196
Sex, M/F	37/40	30/8	55/26	0.002 ^{b,*}	122/74
Age (y), mean \pm SD	54.53 \pm 15.84	61.63 \pm 17.61	60.43 \pm 18.70	0.047 ^{a,*}	58.35 \pm 17.60
Vascular factors					
Diabetes mellitus	21	6	28	0.086 ^b	55
Hypertension	26	10	26	0.708 ^b	62
Cause					
Vasculopathy	29	10	30		69
Trauma	38	14	14		66
Idiopathic cause	8	13	22		43
Neoplasm	2	1	15		18

* $p < 0.05$.

SD = standard deviation.

^a Analysis of variance.

^b Chi-square test.

Table 2
Survival table for patients with acquired paralytic strabismus.

Time (months)	<i>p</i>	Time (months)	<i>p</i>	Time (months)	<i>p</i>
0.5	0.98	7	0.46	16	0.32
1	0.93	8	0.43	20	0.30
2	0.78	9	0.41	23	0.29
3	0.69	10	0.39	39	0.27
4	0.60	12	0.36	48	0.24
5	0.52	13	0.35		
6	0.49	15	0.34		

p = survival rate.

disease cause varied significantly (Chi-square = 33.533, degrees of freedom = 3, *p* < 0.001). Further pairwise comparison tests showed that tumor patients needed more time to recover than patients with traumatic, vascular, and idiopathic causes (*p* = 0.010; *p* < 0.001; *p* < 0.001, respectively). Trauma patients needed a longer time to recover than patients with vascular or idiopathic causes (*p* < 0.001; *p* = 0.002), but the difference in time to recovery was not significant between patients in the vascular and idiopathic groups (*p* = 0.677).

The unrecovery curves indicated recovery rates for the different types of disease cause (Fig. 1). This further demonstrated the same trend that tumor patients required the longest time to recover compared to patients with other causes of PS (Table 3). Cox proportional hazard regression analysis without adjustment for patient characteristics (age, sex, diabetes mellitus, hypertension, CN) revealed that disease cause was significantly associated with patient recovery (*p* < 0.001). Furthermore, after adjusting for the patient's characteristic data as the covariates, the result of Cox proportional hazard regression also showed this significant association, but the ratio of hazard rates (recovery rates) of patients in the trauma versus neoplastic group at any point in time became statistically insignificant (*p* = 0.081), which was the only result that differed from the result lacking adjustment for the effect of patient characteristic data on recovery. After adjustment, the hazard rates (recovery rates) of patients in the vascular and idiopathic at any point in time were 7.09 times and 7.86 times those of neoplastic patients (*p* = 0.002; *p* = 0.001), respectively; the hazard rates (recovery rates) for the patients with idiopathic and vascular causes at any point in time were 2.67 and 2.40 times those of patients who had undergone trauma (*p* < 0.001; *p* = 0.004), respectively (Table 4).

Table 3
Median of survival time of groups with different disease causes.

Cause	Median		
	Estimate (months)	Standard error	95% Confidence interval
Trauma	10.0	3.5	3.1–16.9
Vasculopathy	3.0	0.5	2.0–4.0
Idiopathic cause	4.0	0.7	2.7–5.3
Neoplasm	70.7 ^a	12.4	46.4–95.0
Overall	6.0	0.9	4.2–7.8

^a Number of cases = 18; censored = 15 (83.33%); events = 3; use the mean survival time in the neoplastic group.

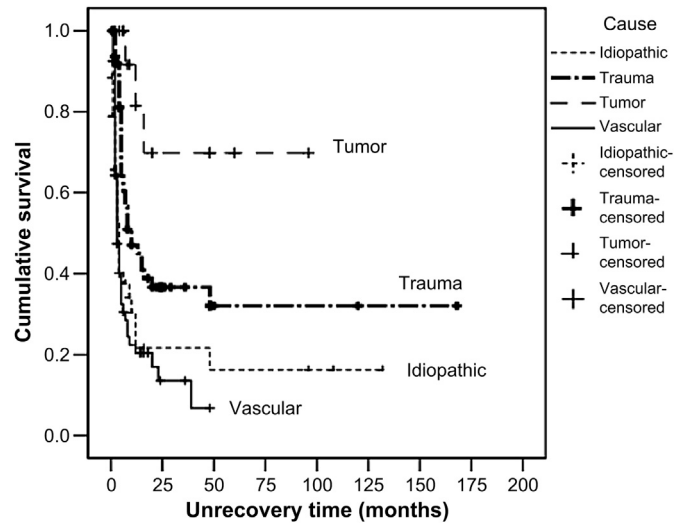


Fig. 1. The unrecovery curves for the different disease causes.

4. Discussion

In the past, a variety of interesting articles have been published focusing on PS, many of which have discussed diagnostic imaging techniques and management. Although acquired C3, C4, and C6 nerve palsies were not uncommon, the patients had different underlying pathologies and showed variable clinical courses.

Our data confirmed the distribution of acquired PS as being comparable to the results described by de Camargo et al and Mwanza et al, where CN6 was the most common and CN4 the least common palsy found.^{2,3} In a study of 4278 cases of acquired PS, the incidence of CN6, CN3, and CN4 palsy was 43.8%, 28%, and 15%, respectively.⁴ Our study showed that CN6 palsy was most prevalent, accounting for 41.33% of cases, followed by CN3 palsy (39.29%) and then CN4 palsy (19.39%) (Table 1).

The etiologies for acquired PS included vasculopathy, idiopathic causes, trauma, and neoplasm. A single most common etiology was not consistently found in previous studies. Idiopathy was the most common cause of strabismus

Table 4
Cox proportional hazard regression for the association between the patient's disease cause and recovery.

Cause	B ^a	<i>p</i> ^a < 0.001	Hazard ratio ^a	B ^b	<i>p</i> ^b < 0.001	Hazard ratio ^b
Trauma vs. neoplasm	1.35	0.025	3.87	1.08	0.081	2.95
Vasculopathy vs. neoplasm	2.19	<0.001	8.91	1.96	0.002	7.09
Idiopathic cause vs. neoplasm	2.08	0.001	8.00	2.06	0.001	7.86
Vasculopathy vs. trauma	0.83	<0.001	2.30	0.88	0.004	2.40
Idiopathic cause vs. trauma	0.73	0.004	2.07	0.98	<0.001	2.67
Vasculopathy vs. idiopathic cause	0.11	0.65	1.11	-0.10	0.762	0.90

B = coefficient of Cox regression.

^a Unadjusted for age, sex, diabetes mellitus, hypertension, and CN.

^b Adjusted for age, sex, diabetes mellitus, hypertension, and cranial nerve.

in Rush and Younge's study, and trauma in the report of de Camargo et al.^{2,5} Recently, the study by Park et al revealed that vasculopathy was the most frequent cause encountered.⁶ In our study, vasculopathy was the most common cause, followed by trauma, idiopathic causes, and neoplasms (Table 1). The different diagnosis between a vascular and an undetermined (or idiopathic) etiology may be challenging, and was usually based on the presence of vascular risk factors.

Diabetes mellitus and arterial hypertension are widely held to be the most common risk factors for vasculopathic nerve palsies. Studies also suggest other risk factors including hyperlipidemia, hypercholesterolemia, coronary artery disease, and cigarette smoking.^{5,7,8} Sanders et al studied 59 patients with vasculopathic CN6 and found no statistically significant difference in patient recovery in terms of sex, age, hypertension, or diabetes mellitus.⁹ In our study, diabetes mellitus and hypertension also showed no statistically significant difference in the association of recovery from PS.

Rush and Younge reported the prognosis and causes of 1000 cases and found that patients with palsies caused by vascular causes often recovered (71%), regardless of the nerve affected. Their study also reported recovery rates for idiopathic causes (50%), trauma (40%), and neoplasms (14.3%).⁵ The results of our study showed that, overall, about half of all patients recovered within 6 months. Vasculopathy was the most common cause (35.12%) and showed a shorter recovery time than the other causes. The presumed mechanism underlying vasculopathic nerve palsy may involve thickening and hyalinization of the nutrient vessels, which results in ischemic demyelination of a portion of the nerve. As time goes by, the area of ischemic demyelination subsequently undergoes remyelination, accounting for the clinical recovery.¹⁰ The vasculopathic nerve palsy usually spontaneously improves within 3–6 months.^{11,12} These findings were similar to those of our study, which showed that half of vascular patients recovered within 3 months.

In the largest referral-based series, from Richards et al,⁴ 21% of CN6 palsies were associated with neoplasm. In our study, CN6 palsy caused by neoplasms had the highest incidence of all groups. Several studies support our findings, including those of Rush and Younge, and Rucker.^{5,8} Our study showed that patients in the neoplastic group had the worst recovery rate and needed more time to recover, with a recovery rate significantly lower ($p < 0.05$) than that of the vascular and idiopathic groups.

When our study is compared with the 1986 study of Sheu et al,¹³ our results are consistent in that the vascular group had the best recovery rate and the neoplastic group had the poorest prognosis in both studies. Additionally, we also noted that the CN6 palsy was the most commonly acquired paralytic ocular motor nerve condition. Their report mentioned that head trauma was the most common cause of the palsies, but we

found vascular causes to be the most common. This difference may be attributed to legislation passed in 1997 that now requires motorcycle riders to wear helmets while riding in Taiwan. This has noticeably decreased the incidence of head trauma, and thus repositioned the order of causes of acquired ocular motor nerve palsies. It is interesting to note that Robert et al also concluded that enhanced bicycle safety was highly effective in preventing head injury.¹⁴

There were some limitations of our study: the small sample size and the retrospective study design. The patients in this study came only from a single medical center, which could have caused a selection bias. Consequently, we are cautious about generalizing our results to all patients with acquired PS. Therefore more extensive, large-scale, prospective, longitudinal studies with a greater number of patients are needed.

In conclusion, our investigation suggested that CN6 palsy is the most common palsy found in a patient group with acquired PS. PS caused by microvascular insults has the best recovery rate and for the shortest recovery time. Those palsies caused by a neoplasm had the worst recovery rate and the longest recovery time.

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