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Clinical Studies of Ocular Motility Disturbances: Part 2. Ischemic Ocular Motor Nerve Palsy Risk Factors

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Abstract: A case-control study of 46 Japanese patients who were diagnosed by exclusion as having ischemic ocular motor nerve palsy and who exhibited spontaneous recovery within 4 months was done to evaluate the risk factors involved. We also evaluated the association between the number of risk factors and the spontaneous recovery or recurrence periods. Ischemic ocular motor nerve palsy is closely related to diabetes mellitus and coronary artery disease. Patients tended to be obese; many had two or more risk factors. Aging, in combination with two or more risk factors, seems to increase the likelihood of developing this disease. Diabetes mellitus is a particularly significant risk factor for this type of palsy, especially in combination with hypertension. **Jpn J Ophthalmol 1997;41:115–119** © 1997 Japanese Ophthalmological Society

Key Words: Coronary artery disease, diabetes mellitus, ischemic ocular motor nerve palsy, obesity, risk factor.

Introduction

Acquired motor nerve palsies in which trauma, infection, or tumor mass can be ruled out sometimes undergo rapid spontaneous recovery. This type of palsy is believed to be caused by ischemia of the microvessels supplying the ocular motor nerves. Diagnosis of this condition is made by ruling out other possibilities; there are no recognized signs specifically identifying ischemic ocular motor nerve palsy. A previous report[1] classified ischemic ocular motor nerve palsy according to the presence or absence of risk factors for such ischemic diseases as diabetes mellitus (DM), hypertension, and arteriosclerosis, but did not include a clear definition of this palsy. Jacobson et al[2] proposed that a definitive diagnosis can be made if the palsy heals spontaneously within 4 months of a diagnosis based on exclusion of the other types. By these criteria, the disease is closely related to DM, hematocrit levels, and left ventricular hypertrophy (LVH). If two or more risk factors are present, it is known that arteriosclerosis worsens; but the effects of multiple risk factors on ischemic ocular motor nerve palsy are not understood. Possible variations in risk factors between Japanese and non-Asian people should also be studied. The goals of the present study were to analyze the risk factors for ischemic ocular motor nerve palsy (as defined by Jacobson et al[2]), to assess the effects of multiple risk factors, to monitor spontaneous recovery, and to analyze recurrences.

Subjects and Methods

Between January 1989 and November 1995, 234 Japanese patients received a diagnosis of acquired ocular motor nerve palsy at our facility. Seventy of these met the following criteria: no history of head trauma within 3 months prior to onset, absence of coldlike symptoms or numbness of extremities prior to onset, no tumor mass detectable with diagnostic imaging, and no prior central nervous system disorder. Spontaneous recovery occurred within 4 months in 46 cases. These 46 patients were studied retrospectively.

The diagnosis of ocular motor nerve palsy was based on the results of qualitative and quantitative assessments of 9 diagnostic eye positions and the results of synoptophore (Clement Clarke, London,

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Table 1. Distribution of Ischemic Ocular Motor Nerve Palsy in 46 Patients

Age (y)	N (%)
40–49	2 (4)
50–59	6 (13)
60–69	23 (50)
70–79	15 (33)
Sex	
Male	32 (69)
Female	14 (31)

Table 2. Clinical Characteristics of Ischemic Ocular Motor Nerve Palsy in 46 Patients

	N (%)
Nerve Affected	
III	7 (15)
IV	22 (48)
VI	17 (37)
Pain	
Yes	13 (28)
No	33 (72)

UK) examination. At the first examination, blood pressure was recorded and hematology results were obtained, including hematocrit, total cholesterol, and HbA1c. The patients were seen at 1-month intervals. Patients were considered to have underlying DM if they were receiving diabetic therapy at the beginning of the study or if the blood glucose level at the initial visit was above the upper limit of the normal range and they were diagnosed as having DM based on the oral glucose tolerance test (OGTT) done. Patients whose OGTT suggested borderline diabetes were not regarded as diabetic patients; the OGTT was not given to patients whose blood glucose level was within the normal range on the first visit. A diagnosis of hypertension was made if the systolic pressure was over 140 mm Hg or the diastolic pressure was over 90 mm Hg, as recommended by WHO/ISH (the World Health Organization/International Society of Hypertension) in 1993[3] or if the patient was taking oral hypotensive medication. Patients who were receiving oral antihyperlipidemic medication or whose blood cholesterol level was > 240 mg/dL were regarded as having hypercholesterolemia. A judgment of obesity was made if the body mass index (BMI = weight in kilograms/height^2 in meters) was over 26.4, according to the criteria proposed by the Japanese Society of Obesity. Patients who had smoked more than 10 cigarettes a day during the 5 years prior to onset were regarded as smokers.[4] Patients who had confirmed history of myocardial infarction or angina pectoris were regarded as having underlying coronary artery disease (CAD). Risk factors were compared, using a case-control method. The control group of age- and sex-matched individuals was selected at random from patients who received health examinations at the Okayama Red Cross Hospital during the same period.

The odds ratios of risk factors in the ischemic ocular motor nerve palsy group (subject group) and the control group were determined; the unpaired *t*-test was used to determine the significance of intergroup differences in HbA1c, cholesterol, BMI, and hematocrit levels. The Kaplan-Meier method was used to analyze spontaneous recovery in relation to the number of risk factors present. The significance of intergroup differences in spontaneous recovery was evaluated using the Cox-Mantel method.

Results

Age Distribution

Ages of the 46 subjects ranged from 40 to 79 years (mean: 65.9) (Table 1).

Table 3. Distribution of Risk Factors for Ischemic Ocular Motor Nerve Palsy Group and Control Group With Odds Ratio

Risk Factor	Cases N (%)	Controls N (%)	Odds Ratio	(95% Confidence Interval)
Diabetes mellitus	20 (43)	7 (15)	4.29	(1.59–11.57)
Hypertension	27 (57)	21 (45)	1.85	(0.78–1.14)
Hypercholesterolemia	13 (28)	7 (15)	2.04	(0.71–6.37)
Smoking	15 (33)	16 (35)	0.97	(0.41–2.31)
Obesity	6 (13)	1 (2)	6.75	(0.78–58.50)
Coronary artery disease	11 (24)	1 (2)	14.15	(1.74–114.83)
Prior ocular motor palsy	6 (13)	0		
Prior facial nerve palsy	4 (9)	0		

Table 4. Distribution of Continuously Measured Risk Factors in Ischemic Ocular Motor Nerve Palsy Group and in Control Group

	Subjects			Controls			
Factor	Mean	SD	N	Mean	SD	N	*P* Value
HbA1c (%)	8.26	1.96	18	7.76	2.45	6	0.50
Total cholesterol (mg/dL)	211.09	74.30	39	199.04	36.70	46	0.44
Hematocrit	42.34	4.81	38	40.53	3.20	46	0.25
Body mass index	23.13	2.56	46	22.47	2.53	46	0.043

Table 5. Number of Risk Factors in Ischemic Ocular Motor Nerve Palsy Group and in Control Group

Risk Factors (N)	Subjects (N)	Controls (N)
None or one	18 (3)	34 (1)
Two or more	28 (17)	12 (6)

( ) = number of patients with diabetes mellitus.

Clinical Characteristics

Trochlear nerve palsy occurred more frequently than oculomotor nerve or abducens nerve palsy. ($P < 0.05$, Fisher's exact test). No patient had multiple ocular motor nerve palsy (Table 2).

Ratio of Risk Factors: Subject/Control Groups

DM and CAD were significantly more prevalent in the subject group than in the control group (Table 3): 11 subjects had CAD (old myocardial infarction, 6; angina pectoris, 5); 5 of these 11 also had DM.

Comparison of Risk Factors

The BMI was significantly higher in the subject group ($P < 0.05$). There were no intergroup differences in cholesterol, hematocrit, and HbA1c levels (Table 4). HbA1c is an indicator of the state of DM control during the past month. Hematocrit reflects blood viscosity.[5]

Comparison of Number of Risk Factors

Five risk factors closely related to ischemic disease were analyzed: DM, hypertension, hypercholesterolemia, obesity, and smoking. Individuals who had two or more of these risk factors and individuals who had none or only one were compared with the control group. The percentage of those with two or more was significantly greater in the subject group than in the control group ($P < 0.05$; chi-squared test) (Table 5). In the subject group, 28 patients had two or more risk factors; 18 (64%) of these patients also had DM. The most frequent combination of risk factors was hypertension and DM (9 patients), followed by combined hypertension, DM, and hypercholesterolemia, then by combined hypertension and hypercholesterolemia (Figure 1).

Time From Onset to Spontaneous Recovery and Number of Risk Factors

There was no significant difference in the time from onset to spontaneous recovery in the 28 cases with two or more of the five risk factors, or the 18 cases with one or no risk factors ($P = 0.47$, Cox-Mantel). The number of risk factors was not correlated with the time required for spontaneous recovery (Figure 2).

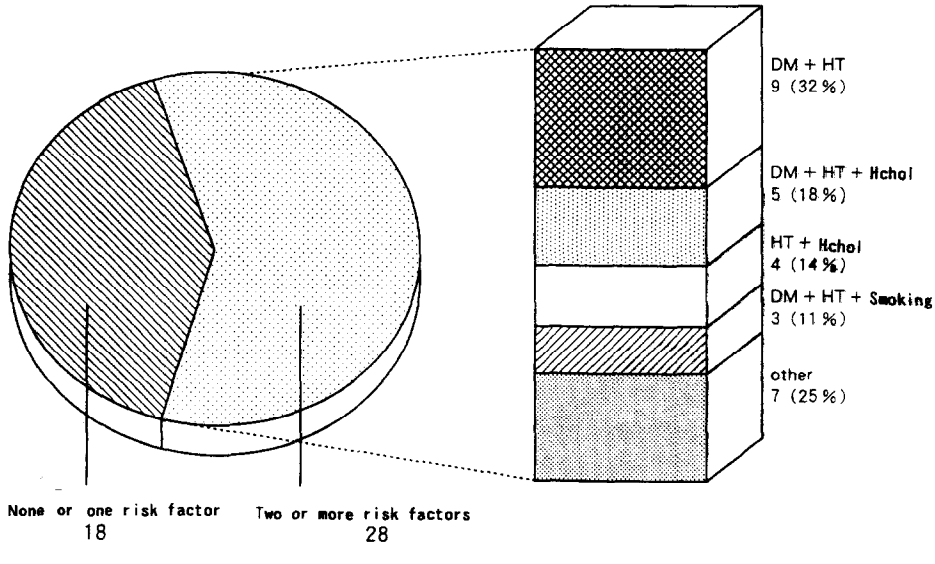

Figure 1. Risk factors in 46 cases of ischemic ocular motor nerve palsy. DM, diabetes mellitus; HT, Hypertension; Hchol, Hypercholesterolemia. Combinations of risk factors: No risk factor, 5 cases; One risk factor, 13 cases (DM 3 HT 3 Hchol 1 Smoking 5 Obesity 1); Two or more risk factors; 7 cases (HT + Obesity + Smoking, 2; Hchol + Smoking, 2; Obesity + Smoking, 2; HT + Hchol + Obesity + Smoking, 1).

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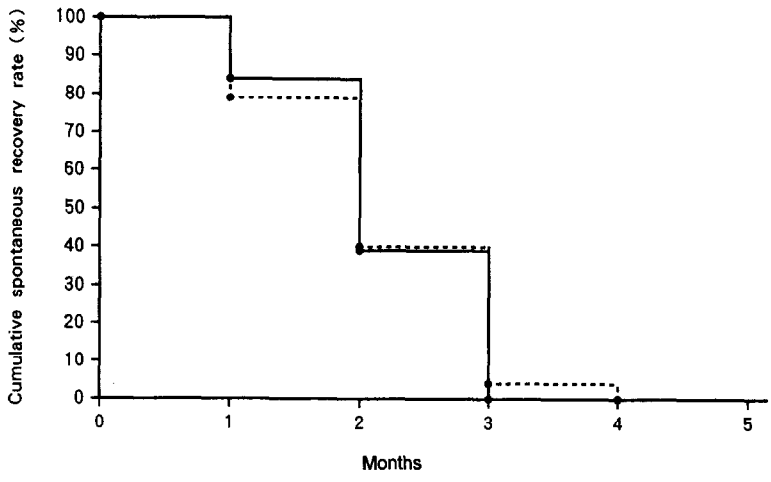

Figure 2. Time from onset to spontaneous recovery and number of risk factors. Dotted line, none or one risk factor; solid line: two or more risk factors.

Recurrence and Number of Risk Factors

There was no significant difference in the six patients who experienced a recurrence and the 40 who had only one episode (Fisher's exact test) (Table 6).

Discussion

Although there have been studies[2,6] of relationships between ischemic ocular motor nerve palsy and various risk factors in Western countries, none included studies of Japanese people. The present study, analyzing these factors in Japanese, revealed that DM and CAD were significantly correlated with this palsy and that these patients tended to be obese. DM was found to be the most significant risk, supporting the previous reports[2,6] and the view held by many other investigators.[1,7] Patients with ischemic ocular motor nerve palsy often show abnormal glucose tolerance results with the OGTT, even with a normal fasting blood glucose level,[7] suggesting a need to screen all patients with an OGTT.

One interesting finding in the present study is that CAD correlated closely with ischemic ocular motor nerve palsy. Prior to this, no investigators have referred to CAD when describing ischemic ocular motor nerve palsy other than Jacobson et al[2] who, in fact, reported that CAD did not correlate with this palsy. The incidence of CAD in Japan is reported to be one of the lowest in the world[8]; the death rates due to CAD in Japanese men and women are one-sixth and one-fifth of those for American men and women.[8] Our present study revealed a close correlation between CAD and ischemic ocular motor nerve palsy in Japanese, despite the low incidence of CAD in the country. Electrocardiography and echocardiography are therefore recommended when managing patients suspected of having ischemic ocular motor nerve palsy.

When the relationship with obesity was analyzed, we found that the BMI was significantly high in our subjects, suggesting a tendency toward obesity among these patients, although the percentage of individuals with a BMI over 26.4 (the decisive level for obesity) was not very high. Obesity apparently can indirectly precipitate ischemic ocular motor nerve palsy by promoting arteriosclerosis. When the effects of multiple risk factors were examined, the most frequent combination observed in our patients was DM and hypertension. Diabetes mellitus is often complicated by hypertension and hyperlipidemia. More recently, there was a suggestion that genetic factors are responsible for both DM and the associated hypertension.[9] DM primarily influences arteriosclerosis of relatively large arteries, while the ischemic lesions associated with DM in reality result from arteriole changes caused by hypertension.[10] This view was supported by the present study. A close relationship between hypertension and ischemic ocular motor nerve palsy has been recognized for some time[1,6]; however, the results of our study lead us to believe that hypertension,[9] as an independent factor, does not correlate closely with this palsy, but that a combination of hypertension and DM is closely related to its onset.

Table 6. Recurrence of Ischemic Ocular Motor Nerve Palsy and Number of Risk Factors

Risk Factors (N)	No Recurrence (N)	Recurrence (N)
None or one	17	1
Two or more	23	5

Teuscher et al[6] also found that DM, obesity, and hypertension were the most frequent complications in patients with ischemic ocular motor nerve palsy. The present study supports their findings, with the exception of the conclusion about hypertension. Jacobson et al[2] reported that ischemic ocular motor nerve palsy correlated with DM, LVH, and hematocrit levels. No ECGs were done with our subjects in this study, so we could not evaluate the possible influence of LVH. According to the WHO classification of hypertension,[3] LVH and stenosis of the retinal arteries are among the first complications of hypertension. Although no studies have been done of the relationship between ischemic ocular motor nerve palsy and arteriosclerosis of the ocular fundus, it is reasonable to believe that a relationship exists, if the fundus change correlates closely with LVH.

The present study has demonstrated that ischemic ocular motor nerve palsy among Japanese people is closely related to DM, CAD, and obesity. With an awareness of a recently noted tendency toward increasing DM among Japanese people, it is essential that patients with ocular motility disturbances that have no clear and evident cause be evaluated for DM, using the OGTT, and for CAD with an ECG and echocardiography.

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