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Clinical Features of Comitant Strabismus Related to Family History of Strabismus or Abnormalities in Pregnancy and Delivery

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Purpose: To elucidate the genetic or environmental background for clinical features in the three major types of comitant strabismus.

Methods: Interview based on a questionnaire asking background factors such as family history of strabismus and abnormalities in pregnancy and delivery was conducted with 101 consecutive patients with infantile esotropia (5–180 months of age), 83 with accommodative or partially accommodative esotropia (6–201 months of age), and 143 with intermittent exotropia (3–216 months of age) seen during 7 months from May to November 1998. The clinical features of strabismus obtained from medical records were analyzed statistically by logistic regression to determine their relation with these background factors.

Results: In infantile esotropia, patients with family history of strabismus had a significantly higher chance of showing latent nystagmus (odds ratio, 3.553; 95% confidence interval [CI], 1.077–11.717; $P = .0373$, logistic regression analysis). In a subgroup of 40 patients with infantile esotropia whose birth followed no abnormalities in pregnancy or delivery, patients with family history of strabismus had a significantly higher chance of showing inferior oblique muscle overaction (odds ratio, 7.714; 95% CI, 1.246–47.761; $P = .0280$), dissociated vertical deviation (odds ratio, 6.667; 95% CI, 1.176–37.787; $P = .0321$), and latent nystagmus (odds ratio, 7.333; 95% CI, 1.168–46.060; $P = .0336$). In accommodative or partially accommodative esotropia and intermittent exotropia, no relation was found between the clinical features and the background factors.

Conclusions: Inferior oblique muscle overaction, dissociated vertical deviation, and latent nystagmus in infantile esotropia might have a genetic background. **Jpn J Ophthalmol 2003;47:208–213** © 2003 Japanese Ophthalmological Society

Key Words: Abnormalities in pregnancy and delivery, esotropia, exotropia, family history, strabismus.

Introduction

The etiology of comitant strabismus such as infantile esotropia, accommodative esotropia, and intermittent exotropia remains unknown. Population-based studies and case-control studies have revealed several risk factors for the development of comitant strabismus. These risk factors are family history of strabismus, maternal cigarette smoking, low birth weight, and neonatal hypoxia,[1–4] and can be classified largely into two entities, either hereditary influence or environmental influence. The heredity of comitant strabismus is also supported by high concordance of strabismic phenotypes between monozygotic twins compared with dizygotic twins.[5–7]

In the previous study, we demonstrated that family history of strabismus was found at a significantly higher rate in intermittent exotropia and accommodative or partially accommodative esotropia than in infantile esotropia.[8] The rate of abnormalities in

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pregnancy and delivery was, in contrast, significantly higher in infantile esotropia than in intermittent exotropia and accommodative or partially accommodative esotropia. In this study, we tried to find which clinical features of these three major types of strabismus would have a genetic background or an environmental background.

Materials and Methods

History data were collected by interview based on a questionnaire to the family members, often mothers, of 101 consecutive patients with infantile esotropia (5–180 months of age; mean, 35 months), 83 patients with accommodative or partially accommodative esotropia (6–201 months of age; mean, 91 months), and 143 patients with intermittent exotropia (3–216 months of age; mean, 95 months) seen at the Strabismus Service in Okayama University Hospital during 7 months from May to November 1998. Infantile esotropia was defined as nonaccommodative esotropia that developed within 6 months after birth and was not associated with any known central nervous system abnormalities. The entity of accommodative or partially accommodative esotropia included 50 patients with refractive accommodative esotropia (with normal accommodative convergence/accommodation (AC/A) ratio defined as lower than 6 prism diopters/diopter), 5 with nonrefractive accommodative esotropia (with high AC/A ratio defined as 6 or higher prism diopters/diopter), and 28 with partially accommodative esotropia. Accommodative or partially accommodative esotropia was defined as esotropia with deviation that could be reduced by 10 or more prism diopters with prescription glasses for hyperopia. In partially accommodative esotropia, 10 prism diopters or more deviation remained after 10 prism diopters or more reduction by glasses. The patients in this study included some patients from our previous study using the same questionnaire.[8] Exclusion criteria were strabismus associated with intraocular organic diseases including retinopathy of prematurity, systemic or central nervous system diseases, mental retardation, or fetal alcohol syndrome.

The interview was done with family members, often mothers who accompanied patients to the hospital. Background factors for strabismus included in the questionnaire were birthweight, maternal age at birth, conceptional age at delivery, family history of strabismus, as well as maternal use of antibiotics, alcohol, cigarettes, or exposure to irradiation or infection during pregnancy, and other factors during pregnancy and delivery as shown in Table 1. Premature labor was defined as labor that occurred at 36 weeks or earlier before full term and was not the same as premature birth which was defined as either labor at 36 weeks or earlier or a birthweight of 2500 g or less. Family history of strabismus was taken as positive when at least one member in the family within six-degree relatives (siblings, parents, grandparents, uncles, aunts, first and second cousins) had any type of strabismus in addition to the patient. All 327 patients included in this study were unrelated to one another except for one pair of sisters with infantile esotropia. Maternal cigarette smoking and alcohol drinking during pregnancy was taken as positive only when they were habitual and daily. Abnormalities in pregnancy and delivery were defined as having at least one of the 14 factors described in Table 1.

Clinical features of strabismus collected from the medical records of these 327 patients were the presence of inferior oblique muscle overaction, dissociated vertical deviation, latent nystagmus, and amblyopia for infantile esotropia, the AC/A ratio, the presence of partial components, the degree of hyperopia, the presence of amblyopia for accommodative or partially accommodative esotropia, the degree of deviation and the type of distant and near deviations for intermittent exotropia. The AC/A ratio was determined by the gradient method, and 6 or more prism diopters/diopter was interpreted as abnormal. The presence of partial components indicated that a patient had partially accommodative esotropia. The degree of hyperopia was defined as the greater spherical equivalent degree in either eye, and classified into two groups, 4 diopters or more and less than 4 diopters. The degree of deviations were determined by alternating prism cover test, and classified into two groups, 25 prism dipoters or more and less than 25 prism diopters in intermittent exotropia. The types of distant and near deviations in intermittent exotropia were classified into basic type, convergence insufficiency type, and divergence excess type, based on 15 prism diopters or greater difference between distant and near deviations. The data at the final visit were used in patients who had not undergone surgery and the data immediately before the surgery were used in patients with previous strabismus surgery. The age at data collection in patients with infantile esotropia was not significantly different between those with surgery and those without surgery ($P = .0523$, Mann–Whitney U-test, Table 2). Overall, the age at data collection in patients with infantile esotropia was significantly younger compared with the age at data collection in patients with accommodative or partially accommodative esotropia

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Table 1. Incidence of Risk Factors for Three Types of Strabismus

Risk Factor	Infantile Esotropia (%) (n = 101)	Accommodative or Partially Accommodative Esotropia (%) (n = 83)	Intermittent Exotropia (%) (n = 143)
Positive family history of strabismus	22 (22)	21 (25)	46 (32)
Antibiotic use during pregnancy	9 (9)	6 (7)	5 (3)
Alcohol drinking during pregnancy	7 (7)	8 (10)	15 (10)
Cigarette smoking during pregnancy	9 (9)	4 (5)	8 (6)
Irradiation during pregnancy	8 (8)	4 (5)	5 (3)
Infection during pregnancy	0 (0)	0 (0)	2 (1)
Abnormalities in pregnancy and delivery*	61 (60)	25 (30)	58 (41)
Threatened abortion	27 (27)	12 (14)	25 (17)
Toxemias of pregnancy	5 (5)	5 (6)	11 (8)
Vacuum extraction	6 (6)	1 (1)	2 (1)
Powerless labor	5 (5)	1 (1)	2 (1)
Protracted labor	1 (1)	0 (0)	0 (0)
Fetal or neonatal hypoxia or asphyxia	8 (8)	0 (0)	12 (8)
Caesarean section	20 (20)	3 (4)	17 (12)
Neonatal jaundice	16 (16)	2 (2)	3 (2)
Hemorrhage during pregnancy	8 (8)	7 (8)	10 (7)
Placenta previa	3 (3)	1 (1)	1 (1)
Premature rupture of the membranes	4 (4)	1 (1)	2 (1)
Abnormal (foot) position	4 (4)	0 (0)	2 (1)
Premature labor	26 (26)	7 (8)	14 (10)
Excess of amniotic fluid	0 (0)	0 (0)	1 (1)

*Abnormalities in pregnancy and in delivery are defined as involving at least one factor in the following 14 factors. $P = .0008$ (2×3 chi-square test).

($P < .0001$, Mann–Whitney U-test) and in those with intermittent exotropia ($P < .0001$, Table 2). Logistic regression analysis was done with clinical features designated as dependent factors and background factors as independent factors.

Results

The positive rate of family history of strabismus was not significantly different among the three types of comitant strabismus ($P = .1800$, chi-square test, Table 1). The rates of maternal antibiotic use, alcohol drinking, cigarette smoking, irradiation, or infection during pregnancy also did not show significant differences among the three types of comitant strabismus. In contrast, abnormalities in pregnancy and delivery were found at a significantly higher rate in patients with infantile esotropia (61 of 101, 60%) compared with patients with accommodative or partially accommodative esotropia (25 of 83, 30%, $P = .0007$, 2×2 chi-square test) and those with intermittent exotropia (58 of 143, 41%, $P = .0023$, Table 1). Of 22 patients with infantile esotropia who had family history of strabismus, 13 patients also had abnormalities in pregnancy and delivery, while the remaining 9 patients did not have any abnormalities in pregnancy and delivery.

Dissociated vertical deviation was significantly more prevalent in patients with infantile esotropia (21 of 101, 21%) compared with patients with accommodative or partially accommodative esotropia (4 of 83, 5%, $P = .0034$, 2×2 chi-square test with Yates correction) and those with intermittent exotropia (7 of 143, 5%, $P = .0001$, Table 3). Latent nystagmus was found at a significantly higher rate in patients with infantile esotropia (17 of 101, 17%) than in patients with accommodative or partially accommodative esotropia (3 of 83, 4%, $P = .0086$, 2×2 chi-square test with Yates correction, Table 3). No difference was found in the prevalence of inferior oblique muscle overaction among the three types of strabismus.

In infantile esotropia, patients with family history of strabismus had a significantly higher chance of showing latent nystagmus (odds ratio, 3.553; 95% confidence interval [CI], 1.077–11.717; $P = .0373$, logistic regression analysis). Dissociated vertical deviation and inferior oblique muscle overaction did not have significant correlation with family history of strabismus (Table 4). In a subgroup of 40 patients with infantile esotropia born after no abnormalities

Table 2. The Age of Patients with Three Types of Strabismus When Clinical Data Were Collected*

	Surgery	No. of Patients	Age at Data Collection† (months)
Infantile esotropia	Yes	86	5–104 (29)
	No	15	7–180 (66)
	Yes and No	101	5–180 (35)
Accommodative or partially accommodative esotropia	Yes	16	49–201 (94)
	No	67	6–180 (92)
	Yes and No	83	6–201 (92)
Intermittent exotropia	Yes	77	5–194 (100)
	No	66	3–216 (90)
	Yes and No	143	3–216 (95)

*Values in parentheses are means. Overall, the age at data collection is significantly younger in patients with infantile esotropia compared to those with accommodative or partially accommodative esotropia ($P < .0001$) and those with intermittent exotropia ($P < .0001$, Mann–Whitney U-test).

†Clinical data were obtained immediately before surgery for patients who had undergone surgery and at the final visit for patients without surgery.

in pregnancy or delivery, 9 patients with family history of strabismus had a significantly higher chance of showing inferior oblique muscle overaction (odds ratio, 7.714; 95% CI, 1.246–47.761; $P = .0280$), dissociated vertical deviation (odds ratio, 6.667; 95% CI, 1.176–37.787; $P = .0321$), and latent nystagmus (odds ratio, 7.333; 95% CI, 1.168–46.060; $P = .0336$), compared to 31 patients without family history of strabismus.

Dissociated vertical deviation was observed at a significantly lower rate ($P = .0074$, chi-square test) in patients with infantile esotropia who underwent surgery (14 of 86 patients), compared with those who did not undergo surgery during the study period (7 of 15 patients). The age at the initial visit of patients with infantile esotropia, which could be used as a cue for the age at the onset, did not correlate with family history. Dissociated vertical deviation, latent nystagmus, and inferior oblique muscle overaction also had no relation with the age at the first visit.

In accommodative or partially accommodative esotropia, clinical features including high AC/A ratio, the presence of partial components, the degree of hyperopia, and the presence of amblyopia had no relationship with the family history of strabismus or the presence of abnormalities in pregnancy and delivery (Table 4). In intermittent exotropia, clinical features such as the degrees of deviations and types of distant and near deviations did not have a significant relation with family history of strabismus or abnormalities in pregnancy and delivery (Table 4).

Discussion

A major problem in this study is the timing of data collection for clinical features. Clinical features of strabismus such as deviations, the presence of inferior oblique muscle overaction, dissociated vertical deviation, or latent nystagmus, and binocular function usually change during the follow-up. In addition, strabismological examinations such as stereoacuity testing and fusion determination naturally require patients' understanding and collaboration. Deviations, the presence of inferior oblique muscle overaction, dissociated vertical deviation, or latent nystagmus, and binocular function can be also changed by strabismus surgery.[9–11] The older the patients are, the more accurate are the results of testing for such clinical features. In this study, the time for data collection was set at the final visit for patients without strabismus surgery and immediately before

Table 3. Inferior Oblique Muscle Overaction, Dissociated Vertical Deviation, and Latent Nystagmus in Three Major Types of Comitant Strabismus*

Manifestations	Infantile Esotropia (n = 101)	Accommodative Esotropia (n = 83)	Intermittent Exotropia (n = 143)
Inferior oblique muscle overaction	32 (32)	27 (33)	46 (32)
Dissociated vertical deviation	21 (21)	4 (5)	7 (5)
Latent nystagmus	17 (17)	3 (4)	0 (0)
The absence of all three	57 (56)	52 (63)	97 (68)

*Values in parentheses are percentages. Dissociated vertical deviation ($P = .0006$, 2×3 chi-square test) and latent nystagmus ($P = .0086$, 2×2 chi-square test with Yates correction) are significantly more prevalent in infantile esotropia compared with accommodative or partially accommodative esotropia and intermittent exotropia.

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Table 4. Relation Between Clinical Features and Background Factors in Three Types of Strabismus

Types of Strabismus	Clinical Features*	Background Factors†	Odds Ratio	95% Confidence Interval	*P*-value
Infantile esotropia	IO overaction	Family history	1.619	0.585–4.478	0.3537
		Abnormalities in P&D	0.630	0.258–1.537	0.3100
	DVD	Family history	2.885	0.961–8.657	0.0588
		Abnormalities in P&D	0.477	0.164–1.384	0.1732
	Latent nystagmus	Family history	3.553	1.077–11.717	0.0373
		Abnormalities in P&D	0.753	0.234–2.422	0.6344
	Amblyopia	Family history	1.189	0.086–16.477	0.8975
		Abnormalities in P&D	1.224	0.093–16.075	0.8778
Accommodative or partially accommodative esotropia	AC/A ratio	Family history	0.411	0.081–2.073	0.2813
		Abnormalities in P&D	0.429	0.094–1.965	0.2756
	Partial components	Family history	0.915	0.299–2.799	0.8763
		Abnormalities in P&D	0.283	0.072–1.106	0.0695
	Degree of hyperopia	Family history	0.639	0.227–1.803	0.3977
		Abnormalities in P&D	1.244	0.436–3.549	0.6829
	Amblyopia	Family history	1.333	0.397–4.474	0.6418
		Abnormalities in P&D	1.467	0.479–4.493	0.5020
Intermittent exotropia	Types of distant and near deviations	Family history	0.838	0.129–5.431	0.8527
		Abnormalities in P&D	1.812	0.130–25.227	0.6581
	Degree of deviations	Family history	0.678	0.248–1.854	0.4484
		Abnormalities in P&D	1.505	0.364–6.219	0.5726

*IO overaction: inferior oblique muscle overaction; DVD: dissociated vertical deviation.
†Abnormalities in P&D: abnormalities in pregnancy and delivery.

the surgery for those undergoing surgery. The age at data collection for clinical features, therefore, somewhat varied, although not significantly, between the patients with surgery and without surgery. Binocular function testing could not be done for a large part of the patients with infantile esotropia or for those with accommodative or partially accommodative esotropia, because of their younger age. The timing of data collection in patients with surgery was set before the surgery since surgical alignment would have a profound effect on the motor and sensory aspects of strabismus.

Another problem is the accuracy of history data in a questionnaire-based study. Family history of strabismus and abnormalities in pregnancy and delivery were not based on medical charts but obtained by mainly interviewing the mothers of patients. Furthermore, many smokers and heavy drinkers usually discontinue their intake during pregnancy. Such patients would have responded negatively to the questionnaire even if heavy smoking and/or drinking early in pregnancy could have contributed to the child's strabismus.

In spite of these limitations, we could reveal a few risk factors for specific clinical features of strabismus in this study. For example, the presence of family history of strabismus is a risk factor for developing latent nystagmus in patients with infantile esotropia. In our previous study[8] as well as in this study, patients with infantile esotropia reported a higher rate of abnormalities in pregnancy and delivery compared to patients with accommodative or partially accommodative esotropia and those with intermittent exotropia. These results suggest that environmental background during pregnancy and delivery would play a larger role in the development of infantile esotropia than would genetic background. In a subgroup of patients with infantile esotropia who did not have abnormalities in pregnancy and delivery, family history of strabismus became a risk factor for developing three clinical features such as inferior oblique muscle overaction, dissociated vertical deviation, and latent nystagmus. Under the circumstances of the general environmental background, specific clinical features of infantile esotropia such as inferior oblique muscle overaction, dissociated vertical deviation, and latent nystagmus would have a genetic background. Dissociated vertical deviation and latent nystagmus are usually associated with each other and often seen in patients with infantile esotropia.[12] These two features were, indeed, observed at a higher rate in patients with infantile estropia than in those with the other two types of strabismus in this study. The present results were also consistent with a previous finding that dissociated vertical deviation tended to occur more often in some families.[12]

Dissociated vertical deviation and latent nystagmus tend to emerge or become more apparent after horizontal muscle strabismus surgery.[9,10] The incidence of these manifestations, reported so far, also becomes high according to the age.[11] In this study, the age at data collection was somewhat younger, although not significantly, for patients with infantile esotropia who underwent surgery compared with those who did not undergo surgery during the study period. Dissociated vertical deviation was indeed less prevalent in the patients with surgery than in those without surgery. These facts indicated that younger patients with infantile esotropia had dissociated vertical deviation at a lower rate. The preoperative data collection in this study would, therefore, create low estimates of dissociated vertical deviation.

From an etiologic point of view, it would be interesting to know whether the patients with hereditary background would have infantile esotropia more often at birth or within the first few months of life since there have been no studies that directly address this issue. Furthermore, it remains to be answered whether a greater rate of dissociated vertical deviation and latent nystagmus is related to the age of the onset of esotropia. In this study, the presence of family history was not related to the age at the first visit which could serve as an estimate of the age at the onset. Dissociated vertical deviation and latent nystagmus had also no relation with the age at the first visit. These results suggest that hereditary background would not necessarily predispose patients to develop esotropia earlier in life.

In conclusion, risk factors for certain clinical features of comitant strabismus could be found by logistic regression analysis. Family history of strabismus was a risk factor for the development of inferior oblique muscle overaction, dissociated vertical deviation, and latent nystagmus in infantile esotropia. This kind of study will help elucidate the influence and interaction of both genetic and environmental background in the development of comitant strabismus.

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References

1. Hakim RB, Tielsch JM. Maternal cigarette smoking during pregnancy. A risk factor for childhood strabismus. Arch Ophthalmol 1992;110:1459–1462.
2. Chew E, Remaley NA, Tamboli A, Zhao J, Podgor MJ, Klebanoff M. Risk factors for esotropia and exotropia. Arch Ophthalmol 1994;112:1349–1355.
3. Mohney BG, Erie JC, Hodge DO, Jacobsen SJ. Congenital esotropia in Olmsted County, Minnesota. Ophthalmology 1998;105:846–850.
4. Abrahamsson M, Magnusson G, Sjostrand J. Inheritance of strabismus and the gain of using heredity to determine populations at risk of developing strabismus. Acta Ophthalmol Scand 1999;77:653–657.
5. Reynolds JD, Wackerhagen M. Strabismus in monozygotic and dizygotic twins. Am J Orthop 1986;36:113–119.
6. Matsuo T, Hayashi M, Fujiwara H, Yamane T, Ohtsuki H. Concordance of strabismic phenotypes in monozygotic versus multizygotic twins and other multiple births. Jpn J Ophthalmol 2002;46:59–64.
7. Paul TO, Hardage LK. The heritability of strabismus. Ophthalmic Genet 1994;15:1–18.
8. Matsuo T, Yamane T, Ohtsuki H. Heredity versus abnormalities in pregnancy and delivery as risk factors for different types of comitant strabismus. J Pediatr Ophthalmol Strabismus 2001;38:78–82.
9. Helveston EM, Neely DF, Stidham B, Wallace DK, Plager DA, Sprunger DT. Results of early alignment of congenital esotropia. Ophthalmology 1999;106:1716–1726.
10. Neely DE, Helveston EM, Thuente DD, Plager DA. Relationship of dissociated vertical deviation and the timing of initial surgery for congenital esotropia. Ophthalmology 2001;108:487–490.
11. Wilson ME, Parks MM. Primary inferior oblique muscle overaction in congenital esotropia, accommodative esotropia, and intermittent exotropia. Ophthalmology 1989;96:950–957.
12. Kubota N. The study on dissociated vertical deviation. Part 5. Nippon Ganka Gakkai Zasshi (Acta Soc Ophthalmol Jpn) 1968;72:368–373.