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Concordance of Strabismic Phenotypes in Monozygotic Versus Multizygotic Twins and Other Multiple Births

Toshihiko Matsuo, Mizue Hayashi,
Hirotake Fujiwara, Takashi Yamane and Hiroshi Ohtsuki

Department of Ophthalmology, Okayama University Medical School, Okayama City, Japan

Purpose: The concordance of strabismic phenotypes was examined in monozygotic versus multizygotic twins and other multiple births to study the role of genetic background in different types of comitant strabismus.

Methods: Medical charts of 45 consecutive pairs of twins (16 monozygotic and 18 dizygotic twins, and 11 with unknown zygosity), 3 sets of triplets (one monozygotic and 2 trizygotic triplets), and one set of quadruzygotic quadruplets examined at 6 institutions between 1973 and 1999 were reviewed retrospectively. The concordance was defined as both or all members having either esotropia or exotropia in common.

Results: The concordance of strabismic phenotypes was noted in 33 of 49 pairs or sets (67.3%): 14 of 17 monozygotic twins or triplets (82.4%), 10 of 21 multizygotic twins, triplets, or quadruplets (47.6%), and 9 of 11 twins with unknown zygosity (81.8%). The concordance rate was significantly higher in monozygosity than in multizygosity ($P = .043$, Fisher exact probability test). The predominant concordant phenotypes in monozygosity were accommodative esotropia and intermittent exotropia.

Conclusion: A high concordance rate of strabismic phenotypes, predominantly of accommodative esotropia and intermittent exotropia in monozygosity, suggests the genetic background for these types of strabismus. **Jpn J Ophthalmol 2002;46:59–64**

Key Words: Esotropia, exotropia, multiple births, strabismus, twin.

Introduction

The etiology of comitant strabismus remains unknown. Patients with comitant strabismus often have a family history of strabismus, indicating that genetic factors play a role in its development. On the other hand, comitant strabismus can occur in association, for example, with cerebral palsy, suggesting that environmental factors during pregnancy and delivery also contribute to its development. Periventricular leukomalacia, an underlying pathological lesion in cerebral palsy, is indeed found in some patients with infantile esotropia.[1]

The study of twins is one method of learning how genetic factors and environmental factors would contribute to the development of a disease. The concordance and discordance of phenotypes are compared between monozygotic and dizygotic twins. Until now, several studies have shown the concordance of strabismus in monozygotic twins.[2–9] However, it remains unknown which types of comitant strabismus are more concordant in twins. In this study, we examined the concordance and discordance of strabismic phenotypes in twins, triplets, and quadruplets to understand to what extent genetic factors play a role in each type of comitant strabismus.

Materials and Methods

Medical charts of 45 consecutive pairs of twins (16 monozygotic twins, 18 dizygotic twins, and 11 twins

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Correspondence and reprint requests to: Toshihiko MATSUO, MD, Department of Ophthalmology, Okayama University Medical School, 2-5-1 Shikata-cho, Okayama City 700-8558, Japan

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with unknown zygosity), 3 consecutive sets of triplets (1 monozygotic and 2 trizygotic triplets), and 1 set of quadruzygotic quadruplets, seen at six institutions between 1973 and 1999, were reviewed retrospectively. The six institutions were Okayama University Hospital (23 groups), Hiroshima City Hospital (15 groups), Kure Mutual Aid Hospital (2 groups), Himeji Red Cross Hospital (3 groups), Okayama Red Cross Hospital (one group), and Kochi Prefectural Central Hospital (5 groups). This was a referral population of patients with strabismus, with at least one sibling affected in each group and all siblings examined in each group. Both or all members of twins, triplets, or quadruplets were examined at least once or followed by ophthalmologists at each institution. The patients usually underwent routine strabismological examinations including cycloplegic refraction, deviation measurement at far and near by alternating prism cover test or Krimsky test, binocular fusion determination by Bagolini striated glass test, and stereopsis measurement by Titmus test or TNO test whenever these tests could be done. Cycloplegic refraction was done with atropine in esotropes and cyclopentolate in exotropes.

The concordance was defined as both or all members of twins, triplets, or quadruplets having either esotropia, exotropia, or dissociated vertical deviation in common. The discordance was defined as one of twins, triplets, or quadruplets having esotropia or exotropia in contrast with another member or other members of twins, triplets, or quadruplets having other types of strabismus or straight alignment. The zygosity was determined by obstetricians based on monochorionic or multichorionic placenta.

Results

The results are summarized in Table 1. Esotropia was noted as a common phenotype in 17 groups, while exotropia was noted as a common phenotype in 15 groups. Dissociated vertical deviation was found in common in one group. Overall, 33 of the 49 groups (67.3%) showed the concordance of strabismic phenotypes. From the viewpoint of zygosity, 14 of the 17 groups (82.4%) with monozygosity showed concordance of strabismic phenotypes, while 10 of the 21 groups (47.6%) with multizygosity showed concordance. Phenotypic concordance was noted in 9 of the 11 pairs (81.8%) of twins with unknown zygosity. The concordance rate was significantly higher in monozygosity than in multizygosity ($P = .043$, Fisher exact probability test). The most predominant phenotypes concordant in monozygosity were accommodative or partially accommodative esotropia and intermittent exotropia (Table 2).

The discordance of strabismic phenotypes was noted in 16 groups with either monozygosity or multizygosity (Table 1): the combination of esotropia and exotropia in 2 groups, that of exotropia and normal alignment in 2 groups, and that of esotropia and normal alignment in 12 groups. Of these 16 groups, 3 pairs of monozygotic twins showed the discordant phenotypes: 1 pair with the combination of accommodative esotropia and intermittent exotropia, 1 pair with the combination of accommodative esotropia and normal alignment, and 1 pair with the combination of constant exotropia and normal alignment.

In 16 pairs or sets with phenotypic discordance, one or all members of 7 pairs or sets (44%) had systemic or central nervous system diseases, or other ocular manifestations in addition to strabismus, such as epilepsy, mental retardation, cerebral palsy, or retinopathy of prematurity requiring photocoagulation. In contrast, such systemic or ocular complications were less frequently found in one or all members of pairs or sets with phenotypic concordance (6 of 33 groups, 18%, $p = .0856$, Fisher exact probability test).

Discussion

In this study, zygosity was determined by obstetricians based on gross morphology of the placenta, whether monochorionic, dichorionic, or multichorionic, but not based on karyotypes. The zygosity of 11 pairs of twins could not be confirmed on their medical records. Furthermore, the population of patients in this study is hardly representative of the population of multiple births as a whole. It is difficult to determine the total number of multiple births at these institutions over the period. From the viewpoint of data analysis, sensory aspects of strabismus such as fusion and stereopsis were not compared in this study because these sensory data were markedly changeable during the follow-up and could not be retrieved from medical records of all patients. In spite of these limitations, this study is the first to analyze which types of comitant strabismus are more frequently found in monozygotic twins and other types of multiple births.

This study showed that the concordance rate of strabismic phenotypes, either esotropia or exotropia, was higher in monozygosity than in multizygosity. Furthermore, accommodative esotropia and intermittent exotropia are the two predominant phenotypes of comitant strabismus that are concordant in

Table 1. Consecutive Series of Twins and Other Multiple Births Classified as Concordance and Discordance of Strabismic Phenotypes

Group No.	Gender	Zygosity*	Phenotype†	Other Features‡	Surgery	Final Refractive Errors§		Birth Weight (g)	Gestational Age at Birth (weeks)
						Right Eye	Left Eye		
Esotropia as a Concordant Phenotype									
1	M	Mono	Accom. ET		No	+5.8	+5.8	2795	40
	M		Accom. ET		No	+4.3	+4.0	2515	40
2	M	Mono	Accom. ET		No	+5.0	+4.5	2700	34
	M		Accom. ET		No	+6.5	+6.3	2540	34
3	F	Mono	Accom. ET		No	+3.0	+2.8	2378	34
	F		Accom. ET		No	+4.9	+5.1	2726	37
4	M	Mono	Accom. ET		No	+1.5	+1.8	1685	33
	M		Accom. ET		No	+2.5	+3.0	1900	33
5	F	Mono	P. accom. ET		No	+0.5	0	1865	33
	F		ET	LE:amblyopia	No	+0.8	0	2100	33
6	M	Mono	Infan. ET		Yes	+0.5	+0.8	1630	32
	M		Infan. ET	PDA	Yes	+2.5	+2.8	1520	32
	M		Infan. ET		No	Unknown	Unknown	1930	32
7	F	Di	P. accom. ET		Yes	+3.8	+4.0	2930	40
	F		P. accom. ET		Yes	+2.0	+1.8	2725	40
8	M	Di	P. accom. ET		No	−3.0	−2.5	2900	40
	M		Accom. ET		No	−2.5	−3.4	2600	40
9	M	Di	Infan. ET		Yes	+1.0	+0.8	2462	37
	M		Infan. ET		Yes	+1.6	+1.3	2532	37
10	F	Di	Infan. ET		No	+1.0	+1.0	1914	34
	F		Infan. ET		No	+0.5	+0.5	1544	34
11	F	Di	Acquired ET		Yes	−1.5	−2.3	2080	38
	F		Acquired ET		Yes	−1.5	−0.5	Unknown	38
12	F	Tri	Infan. ET	IO-OA	Yes	+4.0	+4.0	1265	30
	M		Infan. ET	IO-OA	Yes	+2.6	+2.3	1180	30
	F		Infan. ET		No	Unknown	Unknown	1300	30
13	F	Unknown	P. accom. ET	LE:amblyopia	No	+2.0	+2.5	Unknown	39
	F		P. accom. ET	LE:amblyopia	Yes	+2.8	+2.8	2250	39
14	F	Unknown	P. accom. ET	High AC/A	No	+2.8	+2.0	Unknown	Unknown
	F		P. accom. ET	High AC/A	No	+1.3	+2.3	Unknown	Unknown
15	M	Unknown	Infan. ET		Yes	+1.3	+0.8	2580	40
	M		Infan. ET		No	Unknown	Unknown	2800	40
16	F	Unknown	Acquired ET	DVD	Yes	−2.0	−2.0	2040	36
	F		Acquired ET	DVD, LE:amblyopia	Yes	+0.5	0	1650	36
17	F	Unknown	ET	Congenital rubella	No	+3.8	+4.0	1508	34
	F		ET	Congenital rubella	No	+4.5	+3.0	1480	34
Exotropia as a Concordant Phenotype									
18	F	Mono	Intermit. XT		Yes	−0.5	−0.5	2050	35
	F		Intermit. XT		Yes	−0.8	−0.8	2110	35
19	F	Mono	Intermit. XT		No	−3.0	−2.8	2860	37
	F		Intermit. XT		No	−2.5	−0.8	2860	37
20	F	Mono	Intermit. XT		Yes	+0.5	+0.3	1380	40
	F		Intermit. XT		Yes	−1.3	−1	1250	40
21	F	Mono	Intermit. XT		Yes	−6.3	−7.1	2040	36
	F		Intermit. XT		Yes	−10.3	−8.5	2090	36
22	M	Mono	Intermit. XT		No	+9.5	+9.3	2700	38
	M		Intermit. XT		No	+8.8	+9.5	2750	38
23	F	Mono	Constant XT	IO-OA	Yes	−4.4	−4.5	2280	Unknown
	F		Constant XT		Yes	−5.0	−5.0	2080	Unknown
24	M	Mono	Constant XT	ROP	No	Unknown	Unknown	1096	26
	M		Constant XT	ROP, CP	No	Unknown	Unknown	1088	26

(*continued*)

Table 1. *Continued*

Group No.	Gender	Zygosity*	Phenotype†	Other Features‡	Surgery	Final Refractive Errors§		Birth Weight (g)	Gestational Age at Birth (weeks)
						Right Eye	Left Eye		
25	M	Di	Intermit. XT		Yes	−0.8	0	960	25
	M		Intermit. XT		No	Unknown	Unknown	850	25
26	F	Di	Constant XT	CP	No	Unknown	Unknown	2256	37
	F		Constant XT	CP	No	Unknown	Unknown	2027	37
27	F	Di	Intermit. XT		Yes	+1.3	0	2400	40
	M		Constant XT		Yes	−1.0	−1.0	2600	40
28	M	Di	X		No	−0.8	−0.5	2390	36
	M		X		No	0	0	2510	36
29	F	Unknown	Intermit. XT		No	−0.5	−0.5	1700	Unknown
	F		Intermit. XT		No	+0.5	0	Unknown	Unknown
30	F	Unknown	Intermit. XT		Yes	+0.8	0	2150	38
	F		Intermit. XT		Yes	−0.8	−0.5	Unknown	38
31	F	Unknown	Constant XT	MR	No	Unknown	Unknown	2034	38
	F		Constant XT	MR	No	Unknown	Unknown	1840	38
32	F	Unknown	Constant XT	CP, DVD	Yes	−3.0	−3.5	800	25
	F		X		No	−5.5	−5.1	630	25
Phenotypic Discordance									
33	F	Mono	Accom. ET		No	−2.5	−3.8	3060	40
	F		Intermit. XT		Yes	−2.5	−4.3	2940	40
34	M	Mono	Accom. ET		Yes	+1.8	+1.0	2258	Unknown
	M		Non		No	0	0	2202	Unknown
35	F	Mono	Constant XT		No	+0.8	0	850	27
	F		Non		No	−1.0	−0.8	900	27
36	F	Di	ET	Epilepsy	No	−0.5	−1.0	2200	39
	F		Constant XT	DVD	Yes	−0.4	−0.8	2820	39
37	F	Di	Accom. ET		No	+6.3	+6.9	3048	40
	F		Non	LE:amblyopia	No	+1.3	+5.5	2308	40
38	F	Di	P. accom. ET		Yes	+3.5	+4.5	1760	34
	F		Non		No	Unknown	Unknown	2100	34
39	F	Di	P. accom. ET		Yes	+0.5	+0.5	2495	37
	F		Non		No	+0.8	+0.4	2505	37
40	M	Di	Infan. ET	CP	No	+4.8	+6.0	1584	32
	M		Non		No	+5.5	+5.0	1546	32
41	M	Di	Infan. ET	DVD	Yes	−4.0	−2.8	1300	31
	F		Non		No	Unknown	Unknown	Unknown	31
42	F	Di	ET	DVD, CP	No	−0.8	+1.0	2548	38
	F		Non		No	+0.8	+1.9	2980	38
43	F	Di	ET	MR, ROP	Yes	Unknown	Unknown	1028	26
	F		Non	ROP	No	Unknown	Unknown	735	26
44	M	Di	Intermit. XT	DVD	Yes	+0.3	+0.3	1743	31
	F		Non	CP	No	Unknown	Unknown	1355	31
45	F	Tri	ET	ROP	Yes	−7.8	−11.8	962	32
	M		ET	ROP	Yes	+0.8	+0.6	1446	32
	F		Non	ROP	No	−2.0	−2.3	1428	32
46	F	Quadru	Infan. ET	IO-OA, DVD	Yes	−1.0	−1.0	1658	33
	F		Non		No	Unknown	Unknown	Unknown	33
	M		Non		No	Unknown	Unknown	Unknown	33
	M		Non		No	Unknown	Unknown	Unknown	33
47	F	Unknown	Accom. ET		No	+2.5	+2.0	1820	35
	F		Non		No	+2.5	+1.5	1800	35
48	F	Unknown	ET	MR	No	+0.3	0	1752	34
	F		Non		No	Unknown	Unknown	1942	34

(*continued*)

Table 1. *Continued*

Group No.	Gender	Zygosity*	Phenotype†	Other Features‡	Surgery	Final Refractive Errors§		Birth Weight (g)	Gestational Age at Birth (weeks)
						Right Eye	Left Eye		
DVD as a Concordant Phenotype									
49	F	Mono	DVD, ET		Yes	+0.5	+0.5	1750	Unknown
	F		DVD		Yes	+1.3	0	Unknown	Unknown

*mono: monozygotic, di: dizygotic, tri: trizygotic, quadru: quadruzygotic.

†accom. ET: accommodative esotropia, p. accom. ET: partially accommodative esotropia, ET: esotropia, infan. ET: infantile esotropia, acquired ET: acquired esotropia, intermit. XT: intermittent exotropia, constant XT: constant exotropia, X: exophoria, non: nonstrabismus.

‡PDA: persistent ductus arteriosus, IO-OA: inferior oblique muscle overaction, AC/A: accommodative convergence/accommodation ratio, DVD: dissociated vertical deviation, ROP: retinopathy of prematurity requiring laser photocoagulation, CP: cerebral palsy, MR: mental retardation.

§Refractive errors are determined under cycloplegics (atropine in esotropes and cyclopentolate in exotropes) and given in spherical equivalent.

monozygosity. These facts suggest that genetic background plays a greater role in the development of these two types of strabismus. The present finding is consistent with our previous finding that patients with accommodative or partially accommodative esotropia and those with intermittent exotropia have a higher rate of family history of strabismus, indicative also of the genetic background.[10] Considering the high strabismic concordance in monozygosity found in this study, the fact that all unknown zygosity patients were the same sex within pairs and showed high strabismus concordance suggested that most or all of these patients were monozygous, although this remained unknown.

We did not exclude from this study either the patients with systemic or central nervous system manifestations such as epilepsy, cerebral palsy, congenital rubella, mental retardation, or the patients with retinopathy of prematurity who underwent laser photocoagulation. These manifestations are sequelae of environmental problems in pregnancy and delivery, and known to be often associated with comitant strabismus. They could be, therefore, used as the cue to consider the environmental effect on strabismic phenotypes. In the present series of patients, such systemic and ocular manifestations tend to be found in twins and other multiple births who showed the discordance of strabismic phenotypes, suggesting that environmental factors underlie strabismus in these members and give rise to the phenotypic discordance.

Table 2. Phenotypic Concordance and Discordance in Twins and Other Multiple Births

	Twins, Triplets, or Quadruplets (pair or set)		Twins with Unknown Zygosity (pair)
	Monozygotic	Multizygotic	
Concordance (in total)	14	10	9
Esotropia (in total)	6	6	5
Accommodative	4	2	2
Infantile	1	3	1
Acquired	0	1	1
Others	1	0	1
Exotropia (in total)	7	4	4
Intermittent	5	1	2
Constant	2	1	1
Others	0	2	1
Dissociated vertical deviation	1	0	0
Discordance	3	11	2

The discordance of strabismic phenotypes in multizygosity is easily explained by a difference in genetic background. In the present study, a phenotypic discordance was noted in three pairs of monozygotic twins. One pair showed a combination of accommodative esotropia and intermittent exotropia, while another pair showed the combination of accommodative esotropia and normal alignment without hyperopia. A previous report described two pairs of monozygotic twins, with one member showing accommodative esotropia and the other member showing only hyperopia with normal alignment.[11] In those patients, hyperopia was present as a common underlying factor between the twins, irrespective of the presence or the absence of accommodative esotropia. Hyperopia, in contrast, was not found as a common factor in each member of two pairs of monozygotic twins in the present series, suggesting that factors other than genetic background also contribute to the development of accommodative esotropia in a limited number of cases such as the two pairs of monozygotic twins in this study.

In conclusion, the concordance of strabismic phenotypes was higher in monozygosity than in multizygosity. Accommodative esotropia and intermittent

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exotropia were the two predominant phenotypes of comitant strabismus concordant in monozygosity, suggesting a stronger genetic background for these types of strabismus.

References

1. Ohtsuki H, Kori Y, Hasebe S, Kono R, Harada Y. Comparative study of brain lesions detected by magnetic resonance imaging between strabismus and nonstrabismus in infancy. Ophthalmologica 2000;214:105–10.
2. de Decker W, Feuerhake C. Schielen bei eineiigen Zwillingen. Eine Analyse von 30 Paaren. Bericht ueber die Zusammenkunft der Deutschen Ophthalmologischen Gesellschaft 1978;75:490–3.
3. de Vries B, Houtman WA. Squint in monozygotic twins. Doc Ophthalmol 1979;46:305–8.
4. Kato E, Otsubo M, Yamamoto K, Adachi K. A study of strabismus in monozygous twins. Nippon Ganka Kiyo (Folia Ophthalmol Jpn) 1979;30:202–5.
5. Reynolds JD, Wackerhagen M. Strabismus in monozygotic and dizygotic twins. Am Orthop J 1986;36:113–9.
6. Lang J. Genetische Aspekte bei der Esotropie eineiiger Zwillinge. Klin Monatsbl Augenheilkd 1990;196:275–8.
7. Ahmed S, Young JDH. Late onset esotropia in monozygous twins. Br J Ophthalmol 1993;77:189–91.
8. Podgor MJ, Remaley NA, Chew E. Associations between siblings for esotropia and exotropia. Arch Ophthalmol 1996;114:739–44.
9. Paul TO, Hardage LK. The heritability of strabismus. Ophthalmic Genet 1994;15:1–18.
10. 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.
11. Bucci FA Jr, Catalano RA, Simon JW. Discordance of accommodative esotropia in monozygotic twins. Am J Ophthalmol 1989;107:84–5.