• Clinical Research •

Clinical characteristics of sibling patients with comitant strabismus

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Abstract

• AIM: To investigate the clinical characteristics of sibling patients with comitant strabismus.

• METHODS: Sibling patients who were diagnosed with comitant strabismus from January 2005 to December 2014 were retrospectively reviewed. Factors including age, sex, types of strabismus, refractive errors, angle of deviation, and coexistence of other strabismus were analyzed.

• RESULTS: A total of 62 patients (31 pairs of siblings) were included. Of these, 26 pairs had intermittent exotropia, 3 had accommodative esotropia, and 2 had infantile esotropia. There were no pairs with different subtypes of strabismus. The age at first visit was 3.7±2.6y and the mean follow-up period was 30.5±24.1mo. In siblings with intermittent exotropia, there was no difference in age of onset, age at operation, or refractive errors between the first and second-born children. The 20 (77%) pairs of siblings with exotropia showed more than 80% concordance of maximum angle of deviation during follow-up. In the 9 pairs in which both siblings had an operation, the final angle of deviation after the operation was 8.2±8.1 prism diopters (PD) in first-born children and 8.6±6.5 PD in second-born children.

• CONCLUSION: The subtypes of strabismus are the same in all pairs of siblings and clinical characteristics of strabismus are similar between the first and second-born children. This similarity could be an indicator for the diagnosis of second-born children. Further prospective study including a larger number of sibling patients is needed.

• KEYWORDS: siblings; clinical characteristics; strabismus
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INTRODUCTION

Strabismus is a misalignment of the visual axis and one of the most common childhood visual disorders, occurring in 3%-4% of the population[1-5]. Hippocrates[6] first suggested that strabismus was transmitted from parent to offspring, and there have been studies attempting to identify the genetics and environmental risk factors which influence the development of strabismus[2,7-9]. Although studying the heritability of strabismus is quite difficult because of different measuring methods and definitions, many studies have demonstrated a genetic contribution to strabismus. They reported that the prevalence in families with a history of strabismus was higher, ranging from 10% to 48.9%[10-13]. Previous twin studies showed that the concordance of strabismic phenotypes was higher in monozygosity than in multizygosity, suggesting a hereditary basis for the development of strabismus[14-15].

Similar to dizygotic or multizygotic twins, siblings share both genetic and environmental factors. However, there have been very few reports regarding the clinical characteristics of siblings with comitant strabismus. Therefore, we investigated the prevalence and clinical characteristics of comitant strabismus in siblings.

SUBJECTS AND METHODS

The Institutional Review Board (IRB) of Seoul National University Hospital ethically approved this study and the study protocol followed the tenets of the Declaration of Helsinki. The Ethics Committee study protocol number was 1506-050-679 and the IRB granted a waiver of consent for this retrospective chart review study. The view was performed for sibling patients who visited Seoul National University Children's Hospital and were diagnosed with comitant strabismus between January 2005 and December 2014. The following information was recorded: age of onset, age of first diagnosis of strabismus, sex, types of strabismus, refractive errors as determined using cycloplegic refraction, angle of deviation at near and distance, age at operation, and coexistence of other strabismus such as vertical deviations, oblique muscle over action, presence of nystagmus, and dissociated deviations.

The angle of deviation was measured by alternate prism cover test both at near (0.33 m) and at distance (6 m), and indicated as prism diopters (PD) with appropriate spectacle correction

Table 1 Demographics and clinical characteristics of sibling patients with different subtypes of comitant strabismus

Factors	Total	Intermittent exotropia	Accommodative esotropia	Infantile esotropia
Pairs of siblings	31	26 (84%)	3 (10%)	2 (6%)
Age at first visit (a)	3.7±2.6	4.0±2.6	2.6±1.6	0.8±0.7
Refractive error (diopters)	0.6±1.8	0.1±1.5	4.7±1.7	1.7±1.6
Duration of follow-up (mo)	30.5±24.1	29.7±24.6	33.8±17.2	35.8±15.5
Types of siblings (pairs)				
Sisters	9	6	2	1
Brothers	2	2	-	-
Brothers and sisters	20	18	1	1

when required. The cycloplegic refraction was performed with 1 drop of 1% cyclopean to late hydrochloride, repeated 3 times in 15min. The mean of the spherical equivalent in both eyes was used as the refractive error. All examinations at first visit and during follow-up were performed by one experienced examiner (Kim SJ), who determined the follow-up interval depending on the patients' age, frequency and angle of deviation.

We excluded patients with a history of ophthalmic surgery, history of previously diagnosed with a congenital or acquired ophthalmic condition such as an optic nerve disease, glaucoma, media opacity, or cataract. We also excluded patients with systemic or central nervous system disease such as epilepsy, cerebral palsy, or mental retardation.

Statistical Analysis All statistical analyses were performed with Statistics Package for Social Sciences version 22.0 for Windows (SPSS, Inc., Chicago, IL, USA) The paired *t*-test, independent *t*-test, Chi-square test and one-way analysis of variance (ANOVA) test were used to compare the patients' characteristics and *P* value less than 0.05 was accepted as significant.

RESULTS

A total of 62 Asian patients (31 sibling pairs) were included. Of these, 9 were pairs of sisters, 2 were pairs of brothers, and 20 were pairs of brothers and sisters. The age at first visit was 3.7±2.6y and mean refractive error was 0.6±1.8 diopters. The mean follow-up period was 30.5±24.1mo. There were 26 pairs with intermittent exotropia, 3 with accommodative esotropia, and 2 with infantile esotropia. There were no pairs with different types of strabismus (Table 1).

In siblings with intermittent exotropia, the age of presumed onset and age at operation were 3.1±2.3, and 6.9±3.4y in first-born children and 2.8±2.5, and 5.9±2.9y in second-born children (*P*=0.446, 0.429, respectively). Among 26 pairs with intermittent exotropia, there were 6 pairs of sisters, 2 pairs of brothers, and 18 pairs of brothers and sisters, and the ages of presumed onset were 3.8±3.4, 2.3±1.6, and 6.0±2.6y, respectively (*P*=0.004 by one-way ANOVA test). Compared to pairs of only sisters or brothers, pairs of brothers and sisters show delayed onset of intermittent exotropia. However, there was no difference in the age of onset between the first-born children and second-born children in each subtype of siblings. There was no difference in refractive error in right and left eyes between first and second-born children (Table 2). In addition, 20 (77%) pairs of siblings showed more than 80% concordance of maximum angle of deviation during follow-up (Figure 1).

Table 2 Comparison of clinical characteristics in siblings with intermittent exotropia

Factors	First-born children	Second-born children	*P*
Age of presumed onset (a)			
Sisters	3.7±3.2	3.8±3.8	0.611[a]
Brothers	5.0±2.8	7.0±2.8	0.705[a]
Brothers and sisters	2.7±1.9	1.9±1.1	0.144[a]
Total	3.1±2.3	2.8±2.5	0.446[a]
Refractive error (diopters)			
R	0.0±1.2	0.3±1.0	0.242[a]
L	0.0±1.7	0.2±0.9	0.428[a]
Maximum angle of deviation during follow-up (PD)	28.2±8.5	29.0±7.2	0.687[a]
No. of patients who had an operation	12/26 (46%)	14/26 (54%)	0.259[b]
Age at operation (a)	6.9±3.4	5.9±2.9	0.429[a]
Final angle of deviation after operation (PD)	9.8±8.5	6.9±5.8	0.313[a]

PD: Prism diopters. [a]Independent *t*-test; [b]Fisher's exact test.

There were 12 first-born children and 14 second-born children who had an operation for intermittent exotropia during follow-up. In the 9 pairs in which both siblings had an operation, the final angle of deviation after operation was 8.2±8.1 PD in first-born children and 8.6±6.5 PD in second-born children (*P*=0.313 by paired *t*-test). Except for 2 pairs, each sibling pair showed similar final angle of deviation after operation (Figure 2).

In siblings with accommodative esotropia, the ages at first visit were 1.5±1.3y in first-born children and 3.7±1.6y in second-born children. Among 3 pairs of siblings with accommodative esotropia, there were 2 pairs of sisters, and 1 brother and sister pair. The mean refractive error was 4.5±1.6 diopters in first-born children and 4.8±2.7 diopters in second-born children.

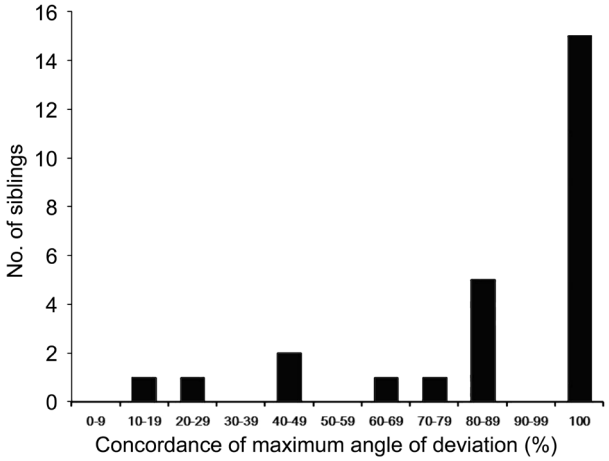

Figure 1 Distribution of concordance of maximum angle of deviation during follow-up between first and second-born children with intermittent exotropia.

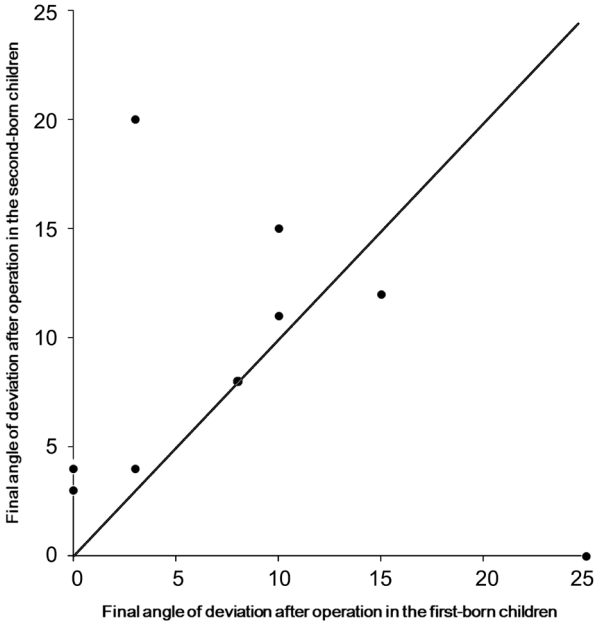

Figure 2 Final angle of deviation after operation in first- and second-born children with intermittent exotropia.

In 2 siblings with infantile esotropia, the ages at first visit were 0.5±1.9y in first-born children and 1.1±2.4y in second-born children. There was 1 pair of sisters and 1 pair of brothers. The maximum angle of deviation during follow up before surgery was 50 PD in first-born children and 42.5±10.6 PD in second-born children.

DISCUSSION

Strabismus is one of the earliest recorded genetic disorders. The genetics are complex because comitant strabismus does not follow a Mendelian inheritance pattern but instead has a multifactorial inheritance pattern including genetic and environmental factors. Furthermore, studying the heritability of strabismus including pedigree analysis is difficult, because the ocular manifestations such as angle of deviation are changeable over one's lifetime, and associated factors such as refractive errors are difficult to quantify.

In previous twin studies, higher concordance level in monozygotic compared to in dizygotic twins revealed that there are strong genetic factors in strabismus. However, the concordance rate in monozygotic twins was not 100%, which supports the fact that environmental factors also play an important role[14]. Abrahamsson *et al*[16] reported that in a study of 1571 children with a positive family history of strabismus, there was a three-fold increase in the risk of developing strabismus. Chia *et al*[12] also stated the importance of family history in the development of strabismus. However, these studies did not analyze the subtypes of strabismus and family members in detail.

In this study, we investigated the prevalence, clinical characteristics and subtypes of comitant strabismus in siblings. The subtypes of strabismus were the same in all pairs of siblings. In siblings with intermittent exotropia, there was no difference in the age at onset, refractive error, maximum angle of deviation during follow-up, and the final angle of deviation after operation. These similar clinical characteristics in siblings show the important role of both genetic and environmental factors in strabismus.

With regard to subtypes of strabismus, exotropia predominates in Asian and African populations, while esotropia is 3 times more common than exotropia among Caucasians[3-4,8,17]. Some reports stated that esotropia has a greater genetic link than exotropia[18-19]. Another recent study reported an independent association between positive family history of strabismus and exotropia[13]. Yet another study showed that accommodative esotropia and intermittent exotropia were the 2 predominant subtypes of comitant strabismus concordant in monozygosity, suggesting a stronger genetic background[15]. However, there is still no agreement as to which subtype of strabismus has a greater genetic component.

Among a total of 31 pairs of siblings in this study, the most common subtype of strabismus was intermittent exotropia. The mean age of patients with intermittent exotropia at first visit was 4.0±2.6y, which reflects the general prevalence of strabismus in children. The 20 pairs of siblings with intermittent exotropia showed more than 80% concordance of the maximum angle of deviation during follow-up. The clinical course of siblings with intermittent exotropia before and after operation was similar between first and second-born children. In addition, other subtypes of strabismus showed similar results, even if only a small number of patients were included.

Similar to our results, Kim and Chang[20] reported that the difference in the amount of deviation was less than 10 PD in 23 pairs (76.7%) among total 32 sibling pairs and the result of operation in twins and sibling pairs was similar. In 2009, Wilmer and Backus[21] reported that deviation of angle in twins with phoria was similar and hypothesized that strabismus can result from gene-environment interactions. Schlossman and Priestley[10] also reported that if the subtype of strabismus was the same, the result of operation in siblings was similar, and that this result could be used as an indicator

in managing siblings with strabismus. Based on these results, we suggest that there would be the similarity in the subtypes, clinical characteristics such as angle of deviation and surgical outcomes in siblings. Even if the strabismus is multifactorial, once strabismus is developed in siblings, the clinical manifestations would be similar because of both genetic and environmental factors. Furthermore, this similarity would be helpful for diagnosis of other siblings with suspected ocular misalignment. Young infants in these families at risk could be screened earlier and potentially obtain a better outcome. Participation of families in genetic studies may also lead to a better understanding of the genetic basis and to better intervention and therapeutic trials.

There are some limitations in our study. First, we retrospectively searched medical records of siblings using keywords such as sisters or brothers, so there could be missed data such as total number of patients who had siblings without a diagnosis of strabismus. Further investigation including both affected and healthy siblings is needed. In addition, there were only 2 children in each family in our research. More families including more than 2 children should be also included in the future study. Second, we included several subtypes of strabismus, and there was a small number in each subtype. Because the clinical course and characteristics are quite different among the subtypes of strabismus, this heterogeneity needs further analysis for each subtype.

In conclusion, the type of strabismus was the same in all pairs of siblings and there was no significant difference in the age of onset, treatment, and maximum angle of deviation during follow-up in siblings with intermittent exotropia, which indicated that the clinical characteristics of strabismus are similar in siblings. The cause of strabismus is multifactorial, but this similarity could be used as an indicator when diagnosing second-born children. Further prospective study including a larger number of sibling patients with each specific type of strabismus would be needed for any definitive conclusions.

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