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Original Article

Self-Reported Findings of the Korean Intermittent Exotropia Multicenter Study Questionnaire

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Purpose: To determine subjective symptoms and medical history of patients with intermittent exotropia in a large study population.

Methods: The Korean Intermittent Exotropia Multicenter Study (KIEMS) is a nationwide, observational, cross-sectional, multicenter study conducted by the Korean Association for Pediatric Ophthalmology and Strabismus including 5,385 patients with intermittent exotropia. Subjective symptoms and medical history of patients with intermittent exotropia were extracted by a comprehensive survey based on a self-administered questionnaire according to the study protocol of the KIEMS.

Results: The mean age of symptom onset was 5.5 years. The most common symptom reported in patients with intermittent exotropia was photophobia (52.1%), followed by diplopia at near fixation (7.3%) and distance fixation (6.2%). Preterm birth was found in 8.8%, and 4.1% had perinatal complications. A family history of strabismus was present in 14.9%, and 5.5% of patients had a family member who underwent strabismus surgery.

Conclusions: The KIEMS is one of the largest clinical studies on intermittent exotropia. Intermittent exotropia frequently caused photophobia and diplopia, and patients with a family history was not uncommon.

Key Words: Exotropia, Multicenter study, Surveys and questionnaires, Symptoms

Intermittent exotropia is the most common type of strabismus in children and adults in the Asian population [1–7]. The clinical characteristics of intermittent exotropia have been reported in various studies; however, a relatively small sample size and a lack of detailed history and clinical examination were limitations for providing comprehensive information about this condition [8]. The Korean

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Intermittent Exotropia Multicenter Study (KIEMS) is a nationwide, observational, cross-sectional, multicenter study conducted by the Korean Association for Pediatric Ophthalmology and Strabismus (KAPOS) dedicated to clinical research of pediatric eye disease and strabismus in South Korea [8]. We have described the study design and standardized protocol of the KIEMS in a previous report [8]. Comprehensive ophthalmologic examinations were performed by strabismus specialists throughout the country, providing reliable objective findings of intermittent exotropia in a large study population [9]. In this study, we presented the subjective symptoms and medical history of patients with intermittent exotropia based on a self-administered questionnaire that was collected at their initial visit according to the study protocol of the KIEMS.

Materials and Methods

The detailed method and study protocol of the KIEMS have been described elsewhere [8]. Study participants were recruited from March 1, 2019, to February 29, 2020, by 65 members of the KAPOS who were strabismus specialists in 53 institutions of South Korea [8]. When a patient visited multiple institutions, only the first reported data were used to avoid redundancy. Intermittent exotropia patients with at least 8 prism diopters (PD) of exodeviation during distant or near fixation were enrolled for a comprehensive ophthalmologic examination and self-administered questionnaire on their initial visit to the institution. Patients with congenital ocular anomalies, ocular myopathies, incomitant strabismus including neurologic or paralytic disorders, previous ocular surgery, corneal opacity, cataracts, retinal diseases, or blepharoptosis were excluded.

Questionnaire forms were pre-distributed to the investigators for the standardization of collected data [8]. Each investigator collected the questionnaires from all patients who met the inclusion criteria. The data collection was conducted in accordance with the Personal Information Protection Act of South Korea. Private information in the questionnaires were anonymized, encrypted, and collected by the KIEMS committee for further analysis [8]. The study protocol conformed to the tenets of the Declaration of Helsinki and was approved by the Institutional Review Board of each institution.

Self-administered questionnaire

Clinical information regarding subjective symptoms and medical history were collected from patients or their guardians using a self-administered questionnaire [8]. The questionnaire was constructed as a combination of open-ended and multiple-choice questions subdivided in three categories as follows.

(1) Symptoms: onset of symptoms; the first person who noticed associated symptoms; frequency of manifest exotropia noticed per day; guardian's recognition of exotropia manifestations such as direction of deviation and fixation dominance [10]; associated symptoms including abnormal head posture, photophobia, reading difficulty, headache, ocular pain, micropsia, or blurring [11–13]; frequency of diplopia at distant or near viewing conditions [14]

(2) Past medical history: wearing glasses; duration, frequency, and laterality of occlusion therapy [15]; developmental delay, systemic or neurologic diseases, previous surgery; birth history including type of delivery, gestational age (GA), and birth weight [16]; perinatal medical conditions

(3) Family history: strabismus in parents and/or siblings, history of strabismus surgery [16]

The English version of the questionnaire is provided in Fig. 1 [8].

Results

A total of 5,385 cases were included for comprehensive history taking and ophthalmological examination [8]. The mean age of study participants were 8.2 ± 7.6 years at the time of examination and 95.0% of the subjects were under 19 years of age. The age distribution of the study population can be found in a previous report [8]. Male and female participants were 2,592 (48.1%) and 2,793 (51.9%), respectively. The mean angle of exodeviation was of 23.5 ± 8.8 PD at distance fixation and 25.1 ± 9.3 PD at near fixation [8].

Symptoms

The mean age of symptom onset was 5.5 ± 5.2 years (range, 0–75.9 months). The mean interval between the

Question	Answer (please check the appropriate box)
Who is answering this questionnaire?	□ Patient (self) □ Mother □ Father □ Grandparent □ Other
What is the reason for this visit?	Answer:
Have you ever visited other clinics?	□ No □ Yes (name of the clinic: ___; previous diagnosis: ___)
Have you ever noticed ocular misalignment?	□ Yes □ No □ Not sure
- Who noticed the symptom first (e.g., parents, teacher, doctor, etc.)?	Answer:
- When did you first notice the symptom?	Answer: years ago (years of age)
- How often in a day do you notice the symptom?	□ None □ Less than once □ Once or more
- What is the direction of ocular misalignment?	□ Inward □ Outward □ Upward □ Not sure □ Other:
- Which eye do you think is misaligned?	□ None □ Right □ Left □ Alternate □ Not sure □ Other:
Have you ever noticed abnormal head posture?	□ None □ Tilt □ Head turn □ Other
- How often do you notice abnormal head posture?	□ Always □ Sometimes □ Other
Please select all symptoms which the patient presents.	□ Photophobia: blinking or frowning at light □ Discomfort at near sight □Headache □ Ocular pain □ Visual blurring □ Things look smaller than they really are □ None □ Not sure
Any diplopia on near viewing?	□ None □ Not sure □ Less than once in a day □ Once or more in a day
Any diplopia on far viewing?	□ None □ Not sure □ Less than once in a day □ Once or more in a day
Has the patient ever received occlusion therapy?	□ Yes □ No
- Prescribed period and duration?	Period: ~ Duration in a day:
- Which eye?	□ Right □ Left □ Alternate
- Applied period and duration?	Period: ~ Duration in a day:
Does the patient wear glasses?	□ Never □ Yes (since when:)
Did the patient ever undergo any type of surgery (including ocular surgery)?	□ None □ Yes (name of the surgery: ___)
Has the patient ever been diagnosed with any medical condition (e.g., systemic disease, developmental delay, ADHD, brain disease, etc.)?	□ None □ Yes (diagnosis: ___)
Birth history	□ Normal spontaneous vaginal delivery □ Caesarean section □ Not sure
- Gestational age, birth weight, prematurity?	Answer: weeks, kg □ Prematurity
- Any problems at birth (e.g., breathing difficulty, lung disease, delivery complications)?	□ None □ Yes (diagnosis: ___)
Does the patient's mother have any form of strabismus?	□ No □ Yes (diagnosis: ___) □ Not sure
- Any strabismus surgery history?	□ No □ Yes □ Not sure
Does the patient's father have any form of strabismus?	□ No □ Yes (diagnosis: ___) □ Not sure
- Any strabismus surgery history?	□ No □ Yes □ Not sure
Does the patient's sibling have any form of strabismus?	□ No □ Yes (diagnosis: ___) □ Not sure
- Any strabismus surgery history?	□ No □ Yes □ Not sure

Fig. 1. Questionnaire for patients with intermittent exotropia or their guardians in English [8]. ADHD = attention deficit hyperactivity disorder.

time of symptom onset to the time of initial visit to a strabismus specialist was 2.4 ± 3.9 years (range, 0–59.5 months). Subjective symptoms of all patients are summarized in Table 1.

In children under the age of 19 years (95.0%), the first person who noticed strabismus or associated symptoms were family members in 53.4%, nonfamily members including teachers and primary care physicians in 41.5%, and 0.9% of patients had a self-reported sense of deviation. The frequency of manifested exotropia noticed at least once a day was 58.2%. The guardian's recognition of the direction of deviation was exodeviation (62.8%), esodeviation (5.1%), and hyperdeviation (2.2%). The frequently deviated eye was noted in the right eye (23.8%) or left eye (28.1%),

Table 1. Symptoms in patients with intermittent exotropia (n = 5,385)

Symptom	No. of patients (%)
Squint observed	4,483 (83.2)
Observed direction of deviation	
Exotropia	3,395 (63.0)
Esotropia	273 (5.1)
Hypertropia	120 (2.2)
Frequency of squint observed ≥1/day	3,163 (58.7)
Frequently deviated eye	
Right	1,277 (23.7)
Left	1,528 (28.4)
Unremarkable or alternate	2,580 (47.9)
Abnormal head posture	1,515 (28.1)
Head tilt	660 (12.3)
Head turn	619 (11.5)
Other	236 (4.4)
Photophobia	2,804 (52.1)
Reading difficulty	157 (2.9)
Near diplopia	395 (7.3)
Distant diplopia	333 (6.2)
Visual blurring	114 (2.1)
Headache	102 (1.9)
Eye pain	44 (0.8)
Micropsia	8 (0.1)
No subjective symptom	1,800 (33.4)

whereas it was not remarkable in the rest of patients (48.1%). The guardian's recognition of the frequently deviated eye was the same as the nondominant eye during distance and near fixation on prism and alternate cover testing in 37.6% and 29.1%, respectively. The rate of concordance between subjective recognition and objective findings of the nondominant eye was higher in children with poor fusional control during distance fixation (46.8%) and near fixation (42.8%) compared to those with fair fusional control (38.1% at distance, 29.8% at near) and good fusional control (25.8% at distance, 21.7% at near) (likelihood ratio test, $p < 0.001$ at distance and $p < 0.001$ at near).

The most common associated symptom reported in children was photophobia (51.5%), followed by diplopia at near (6.1%) and/or distance fixation (5.2%), reading discomfort (2.6%), blurring (2.0%), headache (1.8%), eye pain (0.6%), and micropsia (0.1%), while no specific symptoms were reported in 34.6%. Abnormal head posture was noticed in 28.1% of children.

In adults of age 19 years or older (5.0%), the first person who noticed strabismus or associated symptoms were family members in 25.0% and nonfamily members in 39.2%, while 29.5% of patients had a self-reported sense of deviation. The frequency of manifested exotropia noticed at least once a day was 69.8%. The recognition of the direction of deviation was exodeviation (67.5%), esodeviation (4.9%), and hyperdeviation (2.2%). The frequently deviated eye was noted in the right eye (22.8%) or left eye (32.8%), whereas it was not remarkable in the rest of patients (44.4%). The patient's recognition of the frequently deviated eye was the same as the nondominant eye during distance and near fixation on prism and alternate cover testing in 47.7% and 46.4%, respectively. The rate of concordance between subjective recognition and objective findings of the nondominant eye was higher in adults with poor fusional control during distance fixation (62.2%) and near fixation (58.6%) compared to those with fair fusional control (45.1% at distance, 50.7% at near) and good fusional control (33.3% at distance, 33.8% at near) (likelihood ratio test, $p < 0.001$ at distance and $p = 0.010$ at near).

The most common associated symptom reported in adults was photophobia (63.4%), followed by diplopia at near fixation (30.2%) and/or distance (25.7%) fixation, reading discomfort (9.0%), eye pain (4.9%), blurring (4.5%), headache (3.4%) and micropsia (0.4%), while no specific symptoms were reported in 10.8%. Abnormal head posture was noticed in 27.3% of adults.

Past medical history

Childbirth history of preterm birth was found in 8.8%, and 4.1% had perinatal complications. There was a higher rate of preterm birth in those with a younger age at onset (9.6% in 0–6 years of age) compared to children with an older onset age (8.6% in 7–12 years, 7.5% in 13–18 years; $p < 0.001$).

Of all patients, 26.5% were wearing glasses and 15.7% of patients had a history of occlusion therapy of the dominant eye (8.5%) or alternate patching (7.2%).

Family history

Family history of strabismus and/or strabismus surgery

in parents and siblings were noted [16]. Overall, a family history of strabismus was found in 14.9% of patients and 5.5% had underwent strabismus surgery. In detail, strabismus was present in 4.7% of mothers and 4.2% of fathers, of whom underwent strabismus surgery in 1.7% and 1.2%, respectively. Among the 2,535 patients who had siblings (47.1%), 15.1% had siblings with strabismus and 6.1% had siblings who underwent strabismus surgery.

Discussion

To the best of our knowledge, this is part of the largest clinical study including 5,385 participants with intermittent exotropia who were enrolled in the KIEMS. Subjective symptoms and medical history of patients with intermittent exotropia were extracted by a comprehensive survey based on a self-administered questionnaire. The mean age of symptom onset was 5.5 years of age and the mean interval between the time of symptom onset to the time of initial visit to a strabismus specialist was 2.4 years. The most common symptoms reported in children and adults were photophobia (51.5% and 63.4%, respectively), followed by diplopia at near and/or distance fixation. Preterm birth was found in 8.8%, and 4.1% had perinatal complications. A family history of strabismus was present in 14.9%, and 5.5% of patients had a family member who underwent strabismus surgery.

Subjective symptoms in patients with intermittent exotropia have been reported in few studies [17,18]. While photophobia represented as eye blinking or frowning at bright light is the most commonly recognized symptom [11,19], it is also believed that intermittent exotropia is asymptomatic due to well-developed mechanisms of suppression [17,20]. Overall, the mean age of symptom onset was 5.5 years of age and the mean interval between the time of symptom onset to the time of initial visit to a strabismus specialist was 2.4 years. In our study, photophobia was the most common symptom in both children and adults and the order and frequency of symptoms were somewhat similar in all age groups. Hatt et al. [20] reported that children with intermittent exotropia frequently experience symptoms that impact the child's health-related quality of life. The most frequently reported symptom in children with intermittent exotropia was rubbing the eye in 83%, problems with eyes in the sun 63%, and the eyes feeling tired in 63%. This is comparable to our results as rubbing the eyes is also related to photophobia and/or diplopia. However, only 35 patients were included in their study which is relatively small compared to our study [20].

The guardian's recognition of strabismus is important for healthcare seeking behavior in children with intermittent exotropia. In our study, the frequency of manifest exotropia noticed in children at least once a day was 58.2%. Mostly the guardian's recognition of the direction of deviation was exodeviation (62.8%); however, a small proportion of patients thought their children had esodeviation (5.1%) or hyperdeviation (2.2%). Han and Lim [10] reported that exotropia was more reliably detected by the parents than esotropia, particularly in older children and patients with a larger angle of deviation. Son and Kim [21] found that parental observation and clinical examination findings on the usually deviated eye showed good concordance in 74%, and that the degree of parental awareness was associated with the worsening level of fusional control rather than the amount of deviation.

Preterm children are known to be at a greater risk of strabismus [22,23]. Preterm birth is not only associated with retinopathy of prematurity (ROP), but it can also affect the development of brain structures associated with visual processing, such as global motion perception and visuomotor integration [24]. In a cross-sectional study by Fiess et al. [23], low GA was an independent risk factor for strabismus; strabismus was present in 2% of full-term infants, 12% of preterm infants with GA 29 to 32 weeks without ROP, 22% of preterm infants with GA ≤28 weeks without ROP, and 26% of preterm GA ≤32 weeks with ROP. Gulati et al. [22] reported that infants were at an increased risk of strabismus by 13% for every 250 g below a birthweight of 2,500 g. However, this study used claims data source lacking information on important clinical parameters such as the type and degree of strabismus, refractive error, or any known family history [22]. Several factors have been postulated as the neurodevelopmental mechanisms of intermittent exotropia in prematurity [25,26]. Abnormal development of neuronal activity in the oculomotor system may lead to abnormal extraocular proprioceptive inputs from extraocular muscles to the ophthalmic division of the trigeminal nerve, abnormal activity of the vergence neurons, superior colliculus, cerebellum, and/or vestibular pathways [27]. In our study, preterm birth was found in 8.8% of all patients, and there was a higher

rate of preterm birth in those with a younger age at onset which supports the theory of abnormal development of binocular fusion in premature children. Nevertheless, the percentage of preterm birth was not higher than the national preterm birth rate reported in South Korea, which has increased from 5.9% in 2011 to 9.1% in 2021 [28–30],

Inheritance is recognized as one of the various etiologies of strabismus [31]. In a cross-sectional study involving 4,273 children from Hong Kong, a family history of strabismus, maternal smoking during pregnancy, and advanced maternal age at childbirth (>35 years) were associated with a higher risk of strabismus [32]. However, subgroup analyses regarding the type of strabismus were not performed in their study. Taira et al. [33] analyzed the relation of background factors and the type of strabismus, showing that there was no relation found between the clinical features of intermittent exotropia and the presence of family history. Ziakas et al. [31] completed a three-generation pedigree for 96 cases with various types of strabismus and found that a family history of strabismus was less frequent in first degree relatives of patients with exotropia (4.0%), compared to infantile esotropia (14.9%) and hypermetropic accommodative esotropia (26.1%). In a longitudinal study of Swedish children between 3 months and 4 years of age with a family history strabismus, six of 34 children (17.6%) developed constant or intermittent esotropia [34]. In our study, a family history of strabismus was present in 14.9% of patients with intermittent exotropia, which was higher than the previous reports. More detailed investigation of the role of heredity in different types of strabismus according to race and ethnicity is necessary in further studies.

There are certain limitations that should be addressed for better interpretation of the results. First, as for the self-administered nature of the questionnaire in our study, we could not control the quality of data that may be potentially biased, exaggerated, or understated by the respondent, causing a deviation between self-reported findings and the true characteristics. Nevertheless, a detailed questionnaire is one of the best ways to collect clinical information on subjective symptoms which is in scope of our study. Second, the recall of perinatal history and family history may be unreliable in adults [35]. Thus, we included two generations of only siblings and parents in the family history data. However, as most of the patients were children (95%) with their parents involved in reporting their own history, recall bias was minimized and would not affect the quality of our results. Third, to simplify the questionnaire for better response rates and data clarification, questions regarding subjective symptoms were closed-ended with prepopulated answers. As for this reason, symptoms were combined into groups and certain symptoms were not investigated separately, such as blinking to regain fusion. In a previous report, nearly half of the patients with exotropia reported blinking to control their eyes (43%) or blinking a lot (40%) [20]. In our report, symptoms of blinking were included in photophobia, eye discomfort, and/or diplopia, which are the most common symptoms in both children and adults. Finally, as for the cross-sectional nature of the study, we could not evaluate the natural history or evolution of symptoms according to the duration or severity of the condition.

In conclusion, the KIEMS study is one of the largest clinical studies on intermittent exotropia [8]. We investigated subjective symptoms, medical history and family history of 5,385 patients with intermittent exotropia using a comprehensive list of questions in a self-administered questionnaire [8]. The mean age of symptom onset was 5.5 years of age, and the most common symptom was photophobia. A family history of strabismus was present in 14.9% of patients.

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