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

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Running title: Questionnaire of Intermittent Exotropia in Korea
ABSTRACT

**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 (KAPOS) including 5385 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 of age. The most common symptom reported in patients with intermittent exotropia was photophobia (52.1%), followed by diplopia at near (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 photophoria and diplopia, and patients with a family history was not uncommon.

**Keywords**: Exotropia, Multicenter study, Questionnaire, Symptom
INTRODUCTION

Intermittent exotropia is the most common type of strabismus in children and adults in Asians[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 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 eight 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. 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.
Clinical information regarding subjective symptoms and medical history were collected from patients or their guardians using a self-administered questionnaire. The questionnaire was constructed as a combination of open-ended and multiple-choice questions subdivided in three categories as follows.

- **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; associated symptoms including abnormal head posture, photophobia, photophobia/glare, reading difficulty, headache, ocular pain, micropsia, or blurring; frequency of diplopia at distant or near viewing conditions.

- **Past medical history**: wearing glasses; duration, frequency, and laterality of occlusion therapy; developmental delay, systemic or neurologic diseases, previous surgery; birth history including type of delivery, gestational age, and birth weight; perinatal medical conditions.

- **Family history**: strabismus in parents and/or siblings, history of strabismus surgery.

The English version of the questionnaire is provided in Table I.

### RESULTS

A total of 5,385 cases were included for comprehensive history taking and ophthalmological examination. 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. Male and female participants were 2,592 (48.1%) and 2,793 cases (51.9%). The mean angle of exodeviation was of 23.5 ± 8.8 PD at distance and 25.1 ± 9.3 PD at near fixation.

### Symptoms

The mean age of symptom onset was 5.5 ± 5.2 years (range, 0-75.9). The mean interval between the time of symptom onset to the time of initial visit to a strabismus specialist was 2.4 ± 3.9 years (range, 0-59.5). Subjective symptoms of all patients are summarized in Table 2.

In children under the age of 19 years old (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%), 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. Children with poor fusional control during distance (46.8%) and near (42.8%) fixation had a significantly higher rate of concordance between subjective recognition and objective findings of the nondominant eye compared to those with fair (38.1%, 29.8%) and good (25.8%, 21.7%) fusional control (P<0.001, P<0.001 by likelihood ratio test).

The most common associated symptom reported in children was photophobia (51.5%), followed by diplopia at near (6.1%) and/or distance (5.2%) fixation, reading discomfort (2.6%), blurring (2.0%), headache (1.8%), eye pain (0.6%), 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%, 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. Adults with poor fusional control during distance (62.2%) and near (58.6%) fixation had a significantly higher rate of concordance between subjective recognition and objective findings of the nondominant eye compared to those with fair (45.1%, 50.7%) and good (33.3%, 33.8%) fusional control (P<0.001, P=0.010, likelihood ratio test).

The most common associated symptom reported in adults was photophobia (63.4%), followed by diplopia at near (30.2%) and/or distance (25.7%) fixation, reading discomfort (9.0%), eye pain (4.9%), blurring (4.5%), headache (3.4%), 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 2535 patients (47.1%) who had siblings, 15.1% had strabismus and 6.1% underwent strabismus surgery.

**DISCUSSION**

To the best of our knowledge, this is part of the largest clinical study including 5385 participants with intermittent exotropia who were enrolled in the Korean Intermittent Exotropia Multicenter Study (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. Sarah et al[20]. reported that children with intermittent XT frequently experience symptoms that impact the child’s health-related quality of life. The most frequently reported symptom
in children with intermittent XT 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 XT. 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 et al. reported that exotropia was more reliably detected by the parents than esotropia, particularly in older children and patients with a larger angle of deviation[10]. Son and Kim 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[21].

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., low gestational age (GA) was an independent risk factor for strabismus; strabismus was present in 2% of full-term infants, 12% of preterm infants with GA 29-32 weeks without ROP, 22% of preterm infants with GA ≤ 28 weeks without ROP and 26% with GA ≤ 32 weeks with ROP[23]. Gulati et al. reported that infants were at an increased risk of strabismus by 13% for every 250 g below a birthweight of 2500 g[22]. 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 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
4273 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. 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[33]. Ziakas et al. 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%), compared to infantile esotropia (14.9%) and hypermetropic accommodative esotropia (26.1%)[31]. 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 pre-populated 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.

The KIEMS study is one of the largest clinical studies on intermittent exotropia[8]. We investigated subjective symptoms, medical history and family history of 5385 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 symptoms were photophobia. A family history of strabismus was present in 14.9% of patients.

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Author contributions statement

REFERENCES


29. Korean Statistical Information Service. Live births by sex, period of pregnancy of provinces. [Updated


Table 1. Questionnaire for patients with intermittent exotropia or their guardians [8]

<table>
<thead>
<tr>
<th>Questions</th>
<th>Please check the appropriate box.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Who is answering this questionnaire?</td>
<td>□ Patient (self) □ Mother □ Father □ Grandparent □ Etc.</td>
</tr>
<tr>
<td>What is the reason for this visit?</td>
<td>Answer:</td>
</tr>
<tr>
<td>Have you ever visited other clinics?</td>
<td>□ No □ Yes Name of the clinic: Previous diagnosis:</td>
</tr>
<tr>
<td>Have you ever noticed ocular misalignment?</td>
<td>□ Yes □ No □ Not sure</td>
</tr>
<tr>
<td>- Who noticed the symptom first? (example: parents, teacher, doctor etc.)</td>
<td>Answer:</td>
</tr>
<tr>
<td>- When did you first notice the symptom?</td>
<td>Answer: years ago (years of age)</td>
</tr>
<tr>
<td>- How often in a day do you notice the symptom?</td>
<td>□ None □ Less than once □ Once or more</td>
</tr>
<tr>
<td>- What is the direction of ocular misalignment?</td>
<td>□ Inward □ Outward □ Upward □ Not sure □ Etc.:</td>
</tr>
<tr>
<td>- Which eye do you think is misaligned?</td>
<td>□ None □ Right □ Left □ Alternate □ Not sure □ Etc.:</td>
</tr>
<tr>
<td>Have you ever noticed abnormal head posture?</td>
<td>□ None □ Tilt □ Head turn □ Etc.</td>
</tr>
<tr>
<td>- How often do you notice abnormal head posture?</td>
<td>□ Always □ Sometimes □ Etc.</td>
</tr>
<tr>
<td>Please select all symptoms which the patient presents.</td>
<td>□ Photophobia: Blinking or Frowning at light</td>
</tr>
<tr>
<td></td>
<td>□ Discomfort at near sight □ Headache</td>
</tr>
<tr>
<td></td>
<td>□ Ocular pain □ Visual blurring □ Things look smaller than they really are</td>
</tr>
<tr>
<td></td>
<td>□ None □ Not sure</td>
</tr>
<tr>
<td>Any diplopia on near viewing?</td>
<td>□ None □ Not sure □ Less than once in a day □ Once or more in a day</td>
</tr>
<tr>
<td>Any diplopia on far viewing?</td>
<td>□ None □ Not sure □ Less than once in a day □ Once or more in a day</td>
</tr>
<tr>
<td>Has the patient ever received occlusion therapy?</td>
<td>□ Yes □ No</td>
</tr>
</tbody>
</table>
- 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?  (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? (example: 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
Table 2. Symptoms in Patients with Intermittent Exotropia

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Number</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Squint observed</td>
<td>4483</td>
<td>83.2%</td>
</tr>
<tr>
<td>Observed direction of deviation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exotropia</td>
<td>3395</td>
<td>63.0%</td>
</tr>
<tr>
<td>Esotropia</td>
<td>273</td>
<td>5.1%</td>
</tr>
<tr>
<td>Hypertropia</td>
<td>120</td>
<td>2.2%</td>
</tr>
<tr>
<td>Frequency of squint observed ≥ 1/day</td>
<td>3163</td>
<td>58.7%</td>
</tr>
<tr>
<td>Frequently deviated eye</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right</td>
<td>1277</td>
<td>23.7%</td>
</tr>
<tr>
<td>Left</td>
<td>1528</td>
<td>28.4%</td>
</tr>
<tr>
<td>Unremarkable or alternate</td>
<td>2580</td>
<td>47.9%</td>
</tr>
<tr>
<td>Abnormal head posture</td>
<td>1515</td>
<td>28.1%</td>
</tr>
<tr>
<td>Head tilt</td>
<td>660</td>
<td>12.3%</td>
</tr>
<tr>
<td>Head turn</td>
<td>619</td>
<td>11.5%</td>
</tr>
<tr>
<td>Others</td>
<td>236</td>
<td>4.4%</td>
</tr>
<tr>
<td>Photophobia</td>
<td>2804</td>
<td>52.1%</td>
</tr>
<tr>
<td>Reading difficulty</td>
<td>157</td>
<td>29.2%</td>
</tr>
<tr>
<td>Near diplopia</td>
<td>395</td>
<td>7.3%</td>
</tr>
<tr>
<td>Distant diplopia</td>
<td>333</td>
<td>6.2%</td>
</tr>
<tr>
<td>Visual blurring</td>
<td>114</td>
<td>2.1%</td>
</tr>
<tr>
<td>Headache</td>
<td>102</td>
<td>1.9%</td>
</tr>
<tr>
<td>Eye pain</td>
<td>44</td>
<td>0.8%</td>
</tr>
<tr>
<td>Micropsia</td>
<td>8</td>
<td>0.1%</td>
</tr>
<tr>
<td>No subjective symptom</td>
<td>1800</td>
<td>33.4%</td>
</tr>
</tbody>
</table>