Prevalence and Sex Differences of Psychiatric Disorders in Young Adults Who Had Intermittent Exotropia as Children

Jeff A. McKenzie, BA; Jason A. Capo, MD; Kevin J. Nusz, MD; Nancy N. Diehl, BS; Brian G. Mohney, MD

Objective: To evaluate the prevalence and sex differences of mental disorders diagnosed among young adults who had intermittent exotropia (IXT) as children.

Methods: The medical records of all children (<19 years) diagnosed as having IXT as residents of Olmsted County, Minnesota, from January 1, 1975, through December 31, 1994, and their randomly selected nonstrabismic birth-and-sex-matched controls (1:1) were retrospectively reviewed.

Results: A mental health disorder was diagnosed in 97 (53.0%) of the 183 patients with childhood IXT followed to a mean age of 22 years compared with 55 (30.1%) controls (P < .001). Patients with IXT were 2.7 (95% confidence interval, 1.7-4.1) times more likely to develop a psychiatric illness than controls. A mental health disorder was diagnosed in 63% (41 of 65) and 47% (56 of 118) of males and females with IXT, respectively, compared with 33% (22 of 66) and 28% (33 of 117) of male and female controls, respectively. Additionally, males with IXT had a greater use of psychotropic medication (P = .003), psychiatric emergency department visits (P < .001), psychiatric hospital admissions (P = .04), suicide attempts (P = .004), and suicidal ideation (P = .002) than controls, and females with IXT had more suicidal ideation (P = .02) than controls.

Conclusions: Children diagnosed as having IXT, especially males, are more likely to develop mental illness by the third decade of life compared with children without strabismus.


INTERRUPTED EXOTROPIA (IXT) occurs in approximately 1% of developmentally healthy children in the United States and, given its predominance over esodeviations among Asian populations, it may be the most prevalent form of strabismus worldwide. Published reports have suggested a link between strabismus and mental illness. A polyalanine length variant in a single gene, PMX2B, was recently shown to be associated with both a rare form of strabismus (constant exotropia) and adult schizophrenia. Moreover, we have reported that children diagnosed as having exotropia in Olmsted County, Minnesota, in a single decade, as opposed to those with esotropia, are at increased risk of developing mental illness by early adulthood compared with birth-and-sex-matched controls. This association appeared to be strongest for patients with IXT, but the study did not have sufficient power to perform an analysis based on sex. The purpose of this study is to further investigate the prevalence and sex differences of psychiatric disorders diagnosed among young adults who had IXT as children by extending the cohort to include patients who were diagnosed as having IXT during a 20-year period.

METHODS

The medical records of all patients younger than 19 years who were residing in Olmsted County, Minnesota, when diagnosed as having IXT by an ophthalmologist from January 1, 1975, through December 31, 1994, were retrospectively reviewed. Institutional review board approval was obtained for this study. Intermittent exotropia was defined as an acquired, intermittent esodeviation of at least 10 prism diopters in an otherwise healthy child. Patients with an underlying or associated developmental, neurologic, or ocular sensory disorder were excluded. Potential cases were identified using the resources of the Rochester Epidemiology Project, a medical records database designed to capture data on any patient-physician encounter in Olmsted County, Minnesota. The ethnic distribution of Olmsted County residents in 1990 was 95.7% white, 3.0% Asian American, 0.7% African American, and 0.3% each for Native American and other, as de-
Table 1. Historical and Clinical Characteristics of Patients With Intermittent Exotropia and Their Controls by Sex<sup>a</sup>

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Males (n=131)</th>
<th>Controls (n=235)</th>
<th>P Value</th>
<th>Males (n=65)</th>
<th>Controls (n=66)</th>
<th>P Value</th>
<th>Males (n=118)</th>
<th>Controls (n=117)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prematurity&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1/39 (3)</td>
<td>7/55 (13)</td>
<td>.13</td>
<td>4/61 (7)</td>
<td>3/87 (4)</td>
<td>.45</td>
<td>.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Birth weight, g</td>
<td>3342 (1850-4100) (n=27)</td>
<td>3376 (1210-4650) (n=54)</td>
<td>.37</td>
<td>3258 (955-4700) (n=48)</td>
<td>3354 (1810-4460) (n=67)</td>
<td>.53</td>
<td>.13</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>56/59 (95)</td>
<td>63/65 (97)</td>
<td>.67</td>
<td>95/103 (92)</td>
<td>105/106 (99)</td>
<td>.02</td>
<td>.13</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Product of a difficult pregnancy&lt;sup&gt;c&lt;/sup&gt;</td>
<td>33/63 (52)</td>
<td>42/65 (65)</td>
<td>.21</td>
<td>70/110 (64)</td>
<td>52/114 (46)</td>
<td>.008</td>
<td>.13</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Family history of psychiatric disease</td>
<td>15/47 (32)</td>
<td>9/47 (19)</td>
<td>.24</td>
<td>33/77 (43)</td>
<td>16/75 (21)</td>
<td>.006</td>
<td>.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maternal history of chemical abuse</td>
<td>6/43 (14)</td>
<td>5/45 (11)</td>
<td>.76</td>
<td>12/65 (18)</td>
<td>3/81 (4)</td>
<td>.005</td>
<td>.13</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Family history of chemical abuse</td>
<td>14/44 (32)</td>
<td>9/48 (19)</td>
<td>.16</td>
<td>18/74 (24)</td>
<td>9/69 (13)</td>
<td>.09</td>
<td>.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at psychiatric diagnosis, y</td>
<td>13.3 (3.4-33.8) (n=41)</td>
<td>15.2 (5.6-46.8) (n=22)</td>
<td>.59</td>
<td>13.9 (2.2-30.8) (n=56)</td>
<td>17.5 (5.1-35.3) (n=33)</td>
<td>.02</td>
<td>.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup>Categorical variables are presented as number (percentage) and compared between cases and controls using the Fisher exact test. Continuous variables are summarized as mean (range) and compared between cases and controls using the Wilcoxon rank sum test. Boldface values are significant at P < .05.

<sup>b</sup>Born at less than 37 weeks gestational age.

<sup>c</sup>Includes cesarean delivery, nuchal chords, and forceps delivery.

terminated by self-report. The population of this county (106,470 in 1990) is relatively isolated from other tertiary medical communities, and almost all medical care is provided to residents by a largely unified medical care system (Mayo Clinic, Olmsted Medical Group, and their affiliated hospitals) that has accumulated comprehensive clinical records for nearly 1 century.

A total of 183 children (aged 0-18 years) diagnosed as having IXT were included in the study. For each patient with IXT, we identified 1 control who did not have a diagnosis of strabismus. Controls were chosen by selecting Olmsted County residents who were of the same sex and whose year of birth and registration (within our 2 medical institutions) were matched for each of the index cases. Residency status, verified by trained checkers, was assessed for cases and controls at the time of birth and at diagnosis using information from city and county directories. Patients who did not reside in Olmsted County, Minnesota, at the time of their diagnosis were excluded from the study.

The medical records of the cases and their controls were reviewed for the diagnosis of mental illness (Diagnostic and Statistical Manual of Mental Disorders [Fourth Edition, Text Revision] codes),<sup>7</sup> use of psychotropic medication, mental health emergency department visits or hospitalizations, suicide attempts, and suicidal or homicidal ideation. The entirety of the medical record of a patient (both paper and electronic) from Olmsted County was reviewed for each case and control and included inpatient and outpatient psychiatric, psychological, primary care, and emergency department records. A history of mental illness diagnosed elsewhere was included when confirmed by a mental health care professional within Olmsted County. Data regarding the use of psychiatric medications included the type of medication, concurrent use of multiple medications, and total duration of use; this information was obtained from medication records by physicians and self-reports. A history of suicide attempts or ideation was elicited from the mental health care record, whereas substance abuse, a family history of psychiatric disease, or maternal substance abuse during pregnancy among cases and controls was determined from mental health and self-reporting primary care records. The obstetric history was recorded only for those children who were born in Olmsted County.

Continuous data are presented as mean (range). Categorical data are presented as numbers (percentage). Comparisons between cases and controls for continuous variables were completed using Wilcoxon rank sum tests, and the Fisher exact test was used in comparisons between cases and controls for categorical data. All statistical tests were 2-sided, and the threshold of significance was set at α = .05.

RESULTS

A total of 183 children were diagnosed as having IXT during the 20-year study period, with females comprising 118 (64.5%) of the cohort. The cases were followed up to a mean age of 21.9 years (range, 13 months to 41 years) compared with 22.2 years (range, 8 months to 46.8 years) for controls (P = .53). Table 1 gives the historical and clinical characteristics of the 183 children with IXT (by sex) and their controls. Refractive error was recorded in 50% of our total cohort but showed no correlation with mental illness or difference among groups and was not included in the tables. Females with IXT were more likely to be the product of a difficult pregnancy (P = .008), have a family history of psychiatric disease (P = .006), and have been born to mothers with a history of chemical abuse while pregnant (P = .02) compared with controls. These differences were not observed among males with IXT or their controls. None of the study children were diagnosed as having fetal alcohol syndrome or other known disorders associated with maternal chemical abuse during pregnancy. Females with IXT received their first psychiatric diagnosis earlier than controls at 13.9 vs 17.5 years (P = .02) compared with males at 13.3 and 15.2 years for cases and controls, respectively (P = .59).

Table 2 gives the prevalence of specifically queried factors of mental illness among all patients with IXT and their controls. A mental health disorder was diagnosed in 97 (53.0%) of the 183 patients with a history of childhood IXT compared with 55 (30.1%) of controls (P < .001). These disorders were diagnosed by a psychiatrist or psychologist in 67.0% of cases, by a primary care
physician in 30.2%, and in the emergency department in the remaining cases. Children with IXT were also significantly more likely than controls to have a greater number of psychiatric disorders (P < .001), use psychotropic medications (P = .003), require psychiatric hospitalizations (P = .03), make emergency department visits (P < .001), have suicidal ideation (P < .001), and attempt suicide (P = .03). The most common medications used, from most common to least, were selective serotonin reuptake inhibitors, tricyclic antidepressants, stimulants, and benzodiazepines. These were used for a median of 70, 54, 42, and 126 months, respectively. For other medications, 3 males and 4 females with IXT used antipsychotic medications, and 1 male with IXT and 1 male control used mood stabilizers. During the follow-up period of this study, children with IXT were 2.7 (95% confidence interval, 1.7-4.1) times more likely than their controls to develop a mental illness, to have a greater number of mental illnesses, and to express suicidal ideation compared with their controls, whereas females with IXT developed more attention-deficit/hyperactivity disorder, anxiety or phobia, and learning disabilities. They were also significantly less likely to have obsessive-compulsive or eating disorders compared with controls. Depression not otherwise specified, major depression, attention-deficit/hyperactivity disorder, adjustment disorder, and drug or alcohol abuse were the most common disorders diagnosed among all patients.

Table 2. Mental Health Characteristics in Young Adults Who Had Intermittent Exotropia as Children and Their Controls

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total Cohort (n=366)</th>
<th>Females (n=118)</th>
<th>Controls (n=117)</th>
<th>Males (n=65)</th>
<th>Controls (n=66)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. (%) of patients with mental illness</td>
<td>97 (53.0)</td>
<td>56 (48)</td>
<td>33 (28)</td>
<td>41 (63)</td>
<td>22 (33)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>No. of total disorders, mean (range)</td>
<td>1.5 (0-6)</td>
<td>1.3 (0-6)</td>
<td>0.6 (0-6)</td>
<td>1.7 (0-6)</td>
<td>0.7 (0-5)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>No. (%) of patients using psychotropic medication</td>
<td>46/107 (43)</td>
<td>30/71 (42)</td>
<td>19/61 (31)</td>
<td>16/36 (44)</td>
<td>8/55 (15)</td>
<td>.003</td>
</tr>
<tr>
<td>No. (% of patients with psychiatric ED visits</td>
<td>30/166 (18)</td>
<td>10/109 (9)</td>
<td>5/114 (4)</td>
<td>20/57 (35)</td>
<td>4/64 (6)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>No. (% of patients with psychiatric inpatient evaluation</td>
<td>16/167 (10)</td>
<td>6/110 (6)</td>
<td>3/114 (3)</td>
<td>10/57 (18)</td>
<td>3/64 (5)</td>
<td>.04</td>
</tr>
<tr>
<td>No. (% of patients with suicide attempts</td>
<td>11/165 (7)</td>
<td>4/109 (4)</td>
<td>3/114 (3)</td>
<td>7/56 (12)</td>
<td>0/64</td>
<td>.004</td>
</tr>
<tr>
<td>No. (% of patients with suicidal ideation</td>
<td>25/166 (15)</td>
<td>12/109 (11)</td>
<td>3/114 (3)</td>
<td>13/57 (23)</td>
<td>2/64 (3)</td>
<td>.002</td>
</tr>
</tbody>
</table>

Abbreviation: ED, emergency department.

aBoldface values are significant at P < .05.

Table 3 lists the types and total number of psychiatric disorders diagnosed among cases and controls separated by sex. Males with IXT were more likely to develop depression and adjustment disorder compared with their controls, whereas females with IXT developed more attention-deficit/hyperactivity disorder, anxiety or phobia, and learning disabilities. They were also significantly less likely to have obsessive-compulsive or eating disorders compared with controls. Depression not otherwise specified, major depression, attention-deficit/hyperactivity disorder, adjustment disorder, and drug or alcohol abuse were the most common disorders diagnosed among all patients.

**COMMENT**

Children diagnosed as having IXT in Olmsted County, Minnesota, were nearly 3 times more likely than controls to develop a mental illness by early adulthood. Males with IXT displayed a significantly greater number of psychiatric diagnoses and morbidities than their controls, including significant increases in the number of emergency department visits, hospitalizations, and suicide attempts. Females, although still more likely to develop mental illness, to have a greater number of mental illnesses, and to express suicidal ideation compared with controls, did not display the same level of psychiatric disease as that observed in males.

An association between exotropia and mental illness has previously been described. Toyota and coauthors have recently reported that a polyalanine length variant in the gene PMX2B is associated with schizophrenia and constant exotropia in adults. Although the population and form of strabismus differ from those of our study, the finding documents a genetic link between strabismus and mental illness. We have demonstrated an elevated risk for the development of mental illness in children with exotropia (IXT and convergence insufficiency) that is not present among children with esotropia (congenital, accommodative, and acquired nonaccommodative types).
The current study, undertaken in the same population, extended the original cohort from 10 to 20 years and limited the focus to patients diagnosed as having IXT. The findings from the current study demonstrate a greater statistical significance of the association between IXT and mental illness and indicate that this association is stronger for males than for females.

Why IXT would be associated with the development of mental illness by early adulthood remains unclear. Studies regarding the psychosocial impact of strabismus have reported that individuals with IXT are not judged more poorly than individuals with orthotropia by adult observers. However, a genetic argument for the association between IXT and mental illness is complicated by our finding that females with IXT were more likely to have a family history of psychiatric illness but had less mental illness than males with IXT. Moreover, IXT occurs at a higher rate in females than males,15 and additional study is needed to determine whether there is a genetic component to the association between IXT and mental illness.

The findings in this study have a number of limitations. This investigation was performed in an ethnically homogenous population of a single geographic area and may not be representative of other ethnic groups or diverse populations. Moreover, this study was not designed to detect differences in the various types of mental disorder, so caution should be used in drawing conclusions from Table 3. Also, further study is warranted to determine whether the association between IXT and mental illness persists throughout adulthood. Finally, 1 patient with IXT was originally miscoded as a male and was found to be a female on review after all data had been collected. For this reason, there is an extra case of IXT in the female group and 1 extra control in the male and was found to be a female on review after all data had been collected. For this reason, there is an extra case of IXT in the female group and 1 extra control in the male.

given that males are nearly twice as likely as females to successfully complete suicide.14

Hereditability is another possible cause of the association between IXT and mental illness. The more prevalent forms of strabismus and most childhood mental illnesses are believed to result from interactions between multiple susceptibility genes. Toyota and coauthors3 have demonstrated that disorders of ocular alignment can be genetically linked to the same locus as psychiatric disorders. However, a genetic argument for the association between IXT and mental illness is complicated by our finding that females with IXT were more likely to have a family history of psychiatric illness but had less mental illness than males with IXT. Moreover, IXT occurs at a higher rate in females than males,15 and additional study is needed to determine whether there is a genetic component to the association between IXT and mental illness.

The findings in this study have a number of limitations. This investigation was performed in an ethnically homogenous population of a single geographic area and may not be representative of other ethnic groups or diverse populations. Moreover, this study was not designed to detect differences in the various types of mental disorder, so caution should be used in drawing conclusions from Table 3. Also, further study is warranted to determine whether the association between IXT and mental illness persists throughout adulthood. Finally, 1 patient with IXT was originally miscoded as a male and was found to be a female on review after all data had been collected. For this reason, there is an extra case of IXT in the female group and 1 extra control in the male.

The reason why the association between IXT and mental illness is stronger for males than females is also unclear. Females with strabismus have been reported to have more difficulty securing gainful employment compared with controls, whereas the same is not true of males.12 Menon and colleagues11 found that 83% of males vs 75% of females experienced problems in their social lives due to strabismus. In addition, the increased rates of mental illness in males with exotropia is of particular concern.

The current study, undertaken in the same population, extended the original cohort from 10 to 20 years and limited the focus to patients diagnosed as having IXT. The findings from the current study demonstrate a greater statistical significance of the association between IXT and mental illness and indicate that this association is stronger for males than for females.

Why IXT would be associated with the development of mental illness by early adulthood remains unclear. Studies regarding the psychosocial impact of strabismus have reported that individuals with IXT are not judged more poorly than individuals with orthotropia by adult observers. However, a genetic argument for the association between IXT and mental illness is complicated by our finding that females with IXT were more likely to have a family history of psychiatric illness but had less mental illness than males with IXT. Moreover, IXT occurs at a higher rate in females than males,15 and additional study is needed to determine whether there is a genetic component to the association between IXT and mental illness.

The findings in this study have a number of limitations. This investigation was performed in an ethnically homogenous population of a single geographic area and may not be representative of other ethnic groups or diverse populations. Moreover, this study was not designed to detect differences in the various types of mental disorder, so caution should be used in drawing conclusions from Table 3. Also, further study is warranted to determine whether the association between IXT and mental illness persists throughout adulthood. Finally, 1 patient with IXT was originally miscoded as a male and was found to be a female on review after all data had been collected. For this reason, there is an extra case of IXT in the female group and 1 extra control in the male.

The current study, undertaken in the same population, extended the original cohort from 10 to 20 years and limited the focus to patients diagnosed as having IXT. The findings from the current study demonstrate a greater statistical significance of the association between IXT and mental illness and indicate that this association is stronger for males than for females.

Why IXT would be associated with the development of mental illness by early adulthood remains unclear. Studies regarding the psychosocial impact of strabismus have reported that individuals with IXT are not judged more poorly than individuals with orthotropia by adult observers. However, a genetic argument for the association between IXT and mental illness is complicated by our finding that females with IXT were more likely to have a family history of psychiatric illness but had less mental illness than males with IXT. Moreover, IXT occurs at a higher rate in females than males,15 and additional study is needed to determine whether there is a genetic component to the association between IXT and mental illness.

The findings in this study have a number of limitations. This investigation was performed in an ethnically homogenous population of a single geographic area and may not be representative of other ethnic groups or diverse populations. Moreover, this study was not designed to detect differences in the various types of mental disorder, so caution should be used in drawing conclusions from Table 3. Also, further study is warranted to determine whether the association between IXT and mental illness persists throughout adulthood. Finally, 1 patient with IXT was originally miscoded as a male and was found to be a female on review after all data had been collected. For this reason, there is an extra case of IXT in the female group and 1 extra control in the male.

The results of this study have a number of limitations. This investigation was performed in an ethnically homogenous population of a single geographic area and may not be representative of other ethnic groups or diverse populations. Moreover, this study was not designed to detect differences in the various types of mental disorder, so caution should be used in drawing conclusions from Table 3. Also, further study is warranted to determine whether the association between IXT and mental illness persists throughout adulthood. Finally, 1 patient with IXT was originally miscoded as a male and was found to be a female on review after all data had been collected. For this reason, there is an extra case of IXT in the female group and 1 extra control in the male.
group. These numerical differences have no effect on the statistical calculations or outcomes.

This population-based, nested-control study found that children with IXT have a nearly 3-fold increased risk of developing mental illness by early adulthood compared with controls. Although IXT has been reported to occur more frequently in females, males with IXT were significantly more likely than controls or females with IXT to have mental health emergency department visits or hospitalizations, suicidal or homicidal ideation, and suicide attempts. Further study is needed to determine whether interventions for IXT can decrease or otherwise alter the future development of mental illness.

Submitted for Publication: September 24, 2008; final revision received December 9, 2008; accepted December 23, 2008.

Correspondence: Brian G. Mohney, MD, Department of Ophthalmology, Mayo Clinic, 200 First St SW, Rochester, MN 55905 (mohney@mayo.edu).

Financial Disclosure: None reported.

Funding/Support: This study was supported in part by the National Institutes of Health, National Institute of Mental Health (MH45863), New York, New York.

The editorial staff of Archives of Ophthalmology is pleased to announce a new section in the journal. In 2008 the Surgeon’s Corner was phased in as a regular feature in Archives to focus on surgical aspects of ophthalmology. The goal for this section is to provide readers with current information on surgical techniques, devices and outcomes and perioperative management. Consideration for inclusion in Surgeon’s Corner will be given to manuscripts addressing broadly applicable techniques using reasonably accessible technology. Preference for publication will be given to concise manuscripts whose results and conclusions are adequately supported by data and rigorous statistical analysis. Manuscripts submitted along with high-quality videos for online publication in Archives of Ophthalmology (http://www.archophthalmol.com) are strongly encouraged, and the accompanying video will be considered during the review process. Papers should fit into existing categories for Clinical Trials, Clinical Science, New Instruments, Surgical Techniques, or Research Letters as described in Instructions for Authors. A desire to be considered for this new section should be indicated by the authors at the time of manuscript submission.

REFERENCES


