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Surgical Correction of Childhood Intermittent Exotropia and the Risk of Developing Mental Illness

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Abstract

Purpose—To assess whether successful surgical intervention for intermittent exotropia, or the timing of intervention, has any effect on the development of mental illness.

Design—Retrospective observational case series

Methods—All patients (< 19 years) diagnosed with intermittent exotropia in Olmsted County, Minnesota, from January 1, 1975, through December 31, 1994, were retrospectively reviewed. 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 main outcome measures were the occurrence and severity of mental illness among those who underwent strabismus surgery compared to those who did not.

Results—Ninety-six (52%) of the 184 children identified were diagnosed with a mental illness at a mean age of 23.3 years (range 6 to 41 years). Thirty-five (36%) of the 96 children who developed mental illness underwent strabismus surgery. Success at surgery (< 10 prism diopters) was not associated with a decreased occurrence of mental illness ($p=0.30$). Of the 88 patients who did not develop mental illness, strabismus surgery was not more commonly performed ($p=0.54$) nor was it performed at a younger age ($p=1.0$), when compared to the 96 patients who later developed mental illness.

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Contributions of Authors: Design and conduct of the study (BGM, JAM); Collection of data (JAM); Management, analysis, and interpretation of the data (all authors); and Preparation, review, and approval of the manuscript (BGM, DOH, KPK).

Conclusions—Strabismus surgery for children with intermittent exotropia, regardless of success or age at surgery, did not alter the development of mental illness by early adulthood.

Keywords

Exotropia; strabismus; mental illness; surgery; surgical correction

Intermittent exotropia (Intermittent XT) afflicts 1% of children in the West^{1–3} and is the predominant form of ocular misalignment among Asians.^{4,5} Children with intermittent exotropia residing in Olmsted County, Minnesota were recently found to be three times more likely than age- and gender-matched controls to develop mental illness by early adulthood.^{6,7} A genetic link between constant exotropia and mental illness among adults has been reported,⁸ but environmental or other factors also likely play a role. The purpose of this study was to assess whether successful surgical intervention, or the timing of intervention, influences mental illness outcomes among a cohort of children diagnosed with intermittent exotropia as residents of Olmsted County, Minnesota over a 20-year period.

METHODS

The medical records of all patients younger than 19 years of age and residing in Olmsted County, Minnesota, when diagnosed with intermittent exotropia by an ophthalmologist from January 1, 1975, through December 31, 1994, were retrospectively reviewed. This study was approved by the Institutional Review Board of Mayo Clinic, Rochester, MN. It also conforms to the requirements of the United States Health Insurance Portability and Privacy Act.

Intermittent exotropia was defined as an acquired, intermittent exodeviation of at least 10 prism diopters (PD) in an otherwise healthy child. Patients with an underlying or associated developmental, neurologic, or sensory strabismus were excluded. The records of patients with intermittent XT were also reviewed for the use of psychotropic medication, mental health emergency department visits or hospitalizations, suicide attempts, suicidal or homicidal ideation, and diagnoses of mental illnesses included in the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* codes (specifically, Attention Deficit Hyperactivity Disorder (ADHD), adjustment disorder, learning disorder, substance abuse and depression). Each mental illness diagnosis was confirmed by a psychiatrist. The psychotropic medications recorded include antidepressants, stimulants, antipsychotics, and mood stabilizers. The full criteria for inclusion of information indicative of mental health problems were described in a preceding study.⁶

Potential cases were identified using the resources of the Rochester Epidemiology Project, a multicenter medical records database designed to capture data on any patient-physician encounter in Olmsted County, Minnesota.^{9,10} The racial 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. The population of this county (106,470 in 1990) is relatively isolated from other urban areas, and virtually all medical care is provided to residents by a largely unified medical care system (Mayo Clinic, Mayo Medical Group and

their affiliated hospitals) that has accumulated comprehensive medical records for nearly one century.^{10,11}

A total of 184 children were diagnosed with intermittent exotropia during the 20-year study period. The ophthalmic findings and subsequent mental health characteristics of the 184 patients and their controls have already been reported.⁷ The medical records of each of the 184 children with intermittent XT were reviewed for any surgical intervention for strabismus, age at surgery, total number of surgeries, and post-operative motor and sensory results. Each of these factors was analyzed to determine correlation with the occurrence and severity of mental illness.

Continuous data were presented as a mean and range. Categorical data were presented as counts and percentages. The Fisher exact test was used to compare categorical variables between groups. Wilcoxon rank-sum test was used for the comparison of continuous variables. All statistical tests were two-sided, and the threshold of significance was set at $\alpha=0.05$.

RESULTS

The historical and clinical characteristics of the 184 subjects are summarized in Table 1. Sixty-three (34%) of the 184 children underwent surgery. The prevalence of a positive psychiatric family history between patients who underwent surgery and those who did not were similar. Similarly, the difference in the prevalence of a history of chemical dependency between patients in the surgical and non-surgical group was not statistically significant.

Ninety-six (52%) of the 184 study patients, followed to a median age of 21.8 years (range 1 to 41 years), were diagnosed with a mental illness at a median age of 13.3 years (range 7.9 to 17.5 years) (Table 2). Seven (7.3%) were diagnosed with a mental illness before they were diagnosed with intermittent XT, one (1.0%) was diagnosed with both on the same day, and the remaining 88 (91.7%) were diagnosed with intermittent XT before being diagnosed with a mental illness. Thirty-five (36%) of the 96 children who developed a mental illness underwent strabismus surgery at a median age of six years (range 3 to 29 years). A similar proportion, 28 (32%) of the 88 children who did not develop a mental illness also underwent strabismus surgery at a median age of six years (range 3 to 23 years). There was no statistically significant difference in the number of patients undergoing strabismus surgery, or the age at surgery, between those who developed mental illness and those who did not. There was also no statistically significant difference in either the number of patients who developed mental illness, or the total number of mental illness disorders, between those that underwent surgery and those that did not. The type and severity of mental health disorders were also similar between the two groups (Tables 3 and 4).

Strabismus surgery occurred by 6 years of age in 32 patients, and beyond this age in the remaining 31 patients. Surgical correction at age 6 years or younger, compared to that after 6 years of age, neither decreased nor increased the risk for the development of mental illness ($p=1.0$). Similarly, strabismus surgery at any age, neither increased nor decreased the risk for developing a psychiatric illness ($p=0.54$).

Forty (63%) of the 63 children who underwent surgery were greater than 10 prism diopters of orthotropia within one year of their first surgery (Table 5). Twelve (19%) required a second surgery while none of the patients had three surgeries. There was no difference in the rate of mental illness for those who were successfully aligned (< 10 prism diopters) compared to those who were not ($p=0.30$)

DISCUSSION

Strabismus surgery for children with intermittent exotropia, regardless of surgical success or age at surgery, did not decrease or otherwise alter the development of mental illness by early adulthood in this population-based cohort. There was no significant difference in the types of psychiatric diagnoses or their prevalence among intermittent XT patients who underwent surgical correction compared to those who did not undergo surgery. Of the patients who did undergo corrective surgery, there was no difference in psychiatric illness and psychiatric diagnosis profile between patients who underwent surgery before 6 years of age compared to 6 years or older. Moreover, successful post-operative alignment (< 10 prism diopters) did not decrease the risk of developing a psychiatric illness.

The association between strabismus and mental illness was reported in several recent studies.^{6-8,12-14} Toyota and co-investigators identified alanine-specific deletion mutations in PMX2B, a gene encoding a neurodevelopmental transcription factor, to be strongly associated with the development of schizophrenia and constant exotropia in adults.⁸ Schiffman et al has shown that subjects who eventually develop schizophrenia disorder demonstrate higher frequency of strabismus compared to matched subjects with an outcome of other psychopathology or those with no psychiatric diagnosis in adulthood.^{12,13} Patients with congenital esotropia have also been found to be 2.6 times more likely to develop a mental illness by early adulthood compared to those without the condition.¹⁴ These associations between mental illnesses and strabismus, both of which have strong genetic bases, suggest that certain genes may be redirecting neural development in ways that increase the risk for both. In the current study, there was no statistically significant association between parents with schizophrenia or another psychiatric illness, and the development of strabismus in their children, but whether there are specific neural mechanisms that lead to both mental illness and strabismus remain to be determined.

We observed a slightly higher rate of ADHD in patients who underwent surgery compared to those who did not, but there was no difference in ADHD diagnosis rates among patients who underwent surgery before, compared to after, age six years. An association between ADHD and the use of general anesthesia among children under two years of age has recently been reported,¹⁵ but our study was not designed to study ADHD specifically or to detect the improvement of ADHD symptoms with or without surgery.

In addition to a possible genetic link between strabismus and mental illness, other factors such as environmental influences may also play a role. If so, earlier resolution of strabismus might be expected to lead to a lower risk of mental illness, but neither early surgery nor a successful surgical outcome was associated with improved mental illness outcomes. Surgical intervention before six years of age, compared to after this age, showed no significant

difference in mental health outcomes. Successful surgical correction of strabismus (< 10 prism diopters) was also not associated with a lower rate of mental illness, which suggests that having intermittent exotropia may predispose patients to the development of psychiatric disorders, regardless of the duration of the misalignment. For those children with exotropia who did not develop mental illness, they were not more likely to have had surgery, nor to have undergone surgery at an earlier age, compared to those who did develop mental illness. However, given the focused nature and size of this investigation, factors not captured by this study may explain the association between childhood intermittent XT and the later development of mental illness. For example, childhood intermittent XT may trigger mental illness at a critical stage of development before strabismus surgery for the intermittent XT is even contemplated. The patient's perception of surgical success following strabismus surgery has also been found to be significantly different from the standard definitions of surgical success.¹⁶ Perhaps the patient's perception, and not the actual alignment, is associated with the development of mental illness.

The results of this study should not be interpreted as a suggestion or indication on whether or not to perform surgery for patients with ocular misalignment. Strabismus is an ocular disorder with significant impact on vision as well as cosmesis, which has sociopsychological ramifications. Indeed, strabismus surgery has been demonstrated to result in substantial improvements to visual function, physical and psychological quality of life, patient self-evaluation of appearance, psycho-social interactions, self-esteem, anxiety, and depression.^{17–20} Patients with noticeable strabismus, in addition to poor self-esteem, suffer social and professional consequences.^{9,21,22} While some forms of intermittent exotropia can be managed without surgery, surgery is indicated in others for the preservation of binocular vision and cosmesis. Regardless of whether the strabismus is corrected, physicians treating children should be aware of the association between strabismus and mental illness in order to be alert to the earliest signs of psychiatric disorders and offer earlier intervention.

There are a number of limitations to this study. First, this population was relatively geographically and racially homogenous. Second, sample sizes for some of the reported variables, such as specific types of psychiatric diagnoses, or the number that underwent surgery, were so small that reported associations may be due to chance and lack of associations may be due to insufficient power. Moreover, because this study was not designed to detect differences in the various types of mental disorder, caution should be employed in drawing conclusions from Table 3. Third, given the stigma of mental illness, some patients from the Olmsted community may have sought medical or surgical intervention outside the geographic area, thus excluding these diagnoses from our database. Finally, follow-up monitoring for most patients extended to late adolescence or early adulthood. This limitation in follow-up time could exclude a number of mental illnesses that typically do not develop until middle or later adulthood.

Although children with intermittent exotropia have been found to be at an increased risk of developing a psychiatric disorder by early adulthood compared to controls without strabismus,⁷ surgical correction, regardless of timing or motor success, does not appear to decrease or otherwise alter this risk. Further studies are required to determine a causative relationship, if one exists, between intermittent XT and the development of mental illness.

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REFERENCES

1. Govindan M, Mohnney BG, Diehl NN, Burke JP. Incidence and types of childhood exotropia: a population-based study. *Ophthalmology*. 2005; 112(1):104–108. [PubMed: 15629828]
2. Chew E, Remaley NA, Tamboli A, Zhao J, Podgor MJ, Klebanoff M. Risk factors for esotropia and exotropia. *Arch Ophthalmol*. 1994; 112(10):1349–1355. [PubMed: 7945039]
3. Gnanaraj L, Richardson SR. Interventions for intermittent distance exotropia: review. *Eye (Lond)*. 2005; 19(6):617–621. [PubMed: 15359253]
4. Yu CB, Fan DS, Wong VW, Wong CY, Lam DS. Changing patterns of strabismus: a decade of experience in Hong Kong. *Br J Ophthalmol*. 2002; 86(8):854–856. [PubMed: 12140202]
5. Chia A, Roy L, Seenyen L. Comitant horizontal strabismus: an Asian perspective. *Br J Ophthalmol*. 2007; 91(10):1337–1340. [PubMed: 17475715]
6. Mohnney BG, McKenzie JA, Capo JA, Nusz KJ, Mrazek D, Diehl NN. Mental Illness in Young Adults Who Had Strabismus as Children. *Pediatrics*. 2008; 122(5):1033–1038. [PubMed: 18977984]
7. McKenzie JA, Capo JA, Nusz KJ, Diehl NN, Mohnney BG. Prevalence and sex differences of psychiatric disorders in young adults who had intermittent exotropia as children. *Arch Ophthalmol*. 2009; 127(6):743–747. [PubMed: 19506192]
8. Toyota T, Yoshitsugu K, Ebihara M, et al. Association between schizophrenia with ocular misalignment and polyalanine length variation in PMX2B. *Hum Mol Genet*. 2003; 13(5):551–561. [PubMed: 14709596]
9. Kurland LT, Molgaard CA. The patient record in epidemiology. *Sci Am*. 1981; 245(4):54–63. [PubMed: 7027437]
10. Melton LJ 3rd. History of the Rochester Epidemiology Project. *Mayo Clin Proc*. 1996; 71(3):266–274. [PubMed: 8594285]
11. St Sauver JL, Grossardt BR, Leibson CL, Yawn BP, Melton LJ 3rd, Rocca WA. Generalizability of epidemiological findings and public health decisions: an illustration from the Rochester Epidemiology Project. *Mayo Clin Proc*. 2012; 87(2):151–160. [PubMed: 22305027]
12. Schiffrman J, Ekstrom M, LaBrie J, Schulsinger F, Sorensen H, Mednick S. Minor physical anomalies and schizophrenia spectrum disorders: a prospective investigation. *Am J Psychiatry*. 2002; 159(2):238–243. [PubMed: 11823265]
13. Schiffrman J, Maeda JA, Hayashi K, et al. Premorbid childhood ocular alignment abnormalities and adult schizophrenia-spectrum disorder. *Schizophr Res*. 2006; 81(2–3):253–260. [PubMed: 16242918]
14. Olson JH, Louwagie CR, Diehl NN, Mohnney BG. Congenital esotropia and the risk of mental illness by early adulthood. *Ophthalmology*. 2012; 119(1):145–149. [PubMed: 21986557]
15. Sprung J, Flick RP, Katusic SK, et al. Attention-Deficit/Hyperactivity Disorder After Early Exposure to Procedures Requiring General Anesthesia. *Mayo Clin Proc*. 2012; 87(2):120–129. [PubMed: 22305025]
16. McBain HB, MacKenzie KA, Au C, et al. Factors associated with quality of life and mood in adults with strabismus. *Br J Ophthalmol*. 2014; 98(4):550–555. [PubMed: 24390164]
17. Fujiiike K, Mizuno Y, Hiratsuka Y, Yamada M. Quality of life and cost-utility assessment after strabismus surgery in adults. *Jpn J Ophthalmol*. 2011; 55(3):268–276. [PubMed: 21523376]
18. Jackson S, Harrad RA, Morris M, Rumsey N. The psychosocial benefits of corrective surgery for adults with strabismus. *Br J Ophthalmol*. 2006; 90(7):883–888. [PubMed: 16782950]
19. Archer SM, Musch DC, Wren PA, Guire KE, Del Monte MA. Social and emotional impact of strabismus surgery on quality of life in children. *J AAPOS*. 2005; 9(2):148–151. [PubMed: 15838442]

20. Durnian JM, Noonan CP, Marsh IB. The psychosocial effects of adult strabismus: a review. *Br J Ophthalmol*. 2011; 95(4):450–453. [PubMed: 20852320]
21. Olitsky SE, Sudesh S, Graziano A, Hamblen J, Brooks SE, Shaha SH. The negative psychosocial impact of strabismus in adults. *J AAPOS*. 1999; 3(4):209–211. [PubMed: 10477222]
22. Uretmen O, Egrilmez S, Kose S, Pamukçu K, Akkin C, Palamar M. Negative social bias against children with strabismus. *Acta Ophthalmol Scand*. 2003; 81(2):138–142. [PubMed: 12752051]

Biography

Khin P. Kilgore is a medical student at the Mayo Clinic College of Medicine. She has received a JD from Sandra Day O'Connor College of Law in Tempe, AZ, and a BA in Biology from Williams College in Williamstown, MA. Her research interests include congenital dacryostenosis, strabismus and mental illness, and the effects of correcting refractive errors on emmetropization in infants. She received the 2012 AOA Student Research Fellowship for the project on emmetropization.

Table 1

Comparing the clinical characteristics of the 184 patients diagnosed with intermittent exotropia between those who underwent surgery with those that did not undergo surgery

Variable	Total n=184	No Surgery n=121	Surgery n=63	p-value
<i>Male (%)</i>	66 (36)	46 (38)	20 (32)	0.42
<i>Family history of strabismus (%)</i>	58 (51)	36 (52)	22 (49)	0.85
<i>Family history of chemical dependency (%)</i>	32 (27)	21 (32)	11 (21)	0.21
<i>Premature birth (<37 weeks)</i>	10 (7)	6 (7)	4 (7)	1.00
<i>Difficult birth</i>	104 (60)	68 (61)	36 (58)	0.75
<i>Median birth weight in grams (range)</i>	3395 (2970, 3790)	3395 (2970, 3638)	3395 (3088, 3790)	0.67
<i>Median age at exotropia onset in years (range)</i>	2.8 (1.6,4.9)	3.2 (1.9,6.1)	2.0 (1.3,3.2)	0.04
<i>Median age at exotropia diagnosis in years (range)</i>	5.4 (3.3, 8.7)	6.9 (3.9, 9.9)	3.4 (2.2, 5.3)	<0.001

- Information was unavailable for the following variables: race (n=8), family history of strabismus (n=70), family history of chemical dependency (n=65), prematurity (n=49), difficult birth (n=10), mean birth weight (n=50), age at onset (n=124), age at diagnosis (n=2).
- Difficult birth includes cesarean-section birth, nuchal chords, forceps delivery, low Apgar, meconium, and so forth.
- Categorical variables are reported as n (%), continuous variables are reported with median (min, max). Median – 25th and 75th percentiles.
- P-values result from Fisher's exact test or a Wilcoxon Signed Rank test.

Table 2

Management of intermittent exotropia in the 184 patients, with or without

Variable	Total (n=184)	No Surgery (n=121)	Surgery (n=63)	p-value
<i>Number with psychiatric disorders (%)</i>	96 (52)	61 (50)	35 (56)	0.54
<i>Median age at psychiatric diagnosis in years (range)</i>	13.3 (7.9,17.5)	12.3 (7.9,18.6)	13.6 (7.9,17.3)	0.85
<i>Number of psychiatric disorders per patient (range)</i>	2.0 (1.0,4.0)	2.0 (1.0,3.0)	2.0 (1.0,4.0)	0.85

- Categorical variables are reported as n (%), continuous variables are reported with mean (min, median, max). Median – 25th and 75th percentiles.
- P-values result from Fisher's exact test or a Wilcoxon Signed Rank test.

Characterization of surgical intervention among patients with intermittent exotropia and mental illness

Table 3

Variable	Total (n=184)	No Surgery (n=121)	Surgery (n=63)	p-value	Surgery 6 y.o. (n=32)	Surgery > 6 y.o. (n=31)	p-value
<i>Psychiatric disease</i>	96 (52)	61 (50)	35 (56)	0.54	11 (58)	24 (55)	1.0
<i>ADHD</i>	28 (15)	15 (12)	13 (21)	0.19	7 (22)	6 (19)	1.0
<i>Adjustment disorder</i>	29 (16)	20 (17)	9 (14)	0.83	4 (13)	5 (16)	0.73
<i>Learning disorder</i>	12 (7)	5 (4)	7 (11)	0.11	4 (13)	3 (10)	1.0
<i>Substance abuse</i>	19 (10)	12 (10)	7 (11)	0.80	2 (6)	5 (16)	0.26
<i>Major depression</i>	24 (13)	15 (12)	9 (14)	0.82	4 (13)	5 (16)	0.73

- Categorical variables are reported as n (%)
- P-values result from Fisher's exact test or a Wilcoxon Signed Rank test.
- ADHD: Attention-deficit hyperactivity disorder

Surgical intervention among patients with intermittent exotropia and factors often associated with mental illness

Table 4

Variable	Total (n=184)	No Surgery (n=121)	Surgery (n=63)	p-value	Surgery 6 y.o. (n=32)	Surgery > 6 y.o. (n=31)	p-value
<i>Using psych med</i>	57 (31)	37 (31)	19 (30)	1.0	9 (28)	10 (32)	0.78
<i>Psych ED visit</i>	36 (20)	25 (21)	11 (17)	0.70	5 (16)	6 (19)	0.75
<i>Suicide ideation</i>	31 (17)	23 (19)	8 (13)	0.31	2 (6)	6 (19)	0.15
<i>Suicide attempt</i>	17 (9)	14 (12)	3 (5)	0.18	0 (0)	3 (10)	0.11

- Categorical variables are reported as n (%)
- P-values result from Fisher's exact test or a Wilcoxon Signed Rank test.
- Psych ED visit: Psychiatric Emergency Department visit

Table 5

Post-operative profile of the 63 patients with intermittent exotropia who underwent strabismus surgery

Variable	Total (n=63)
<i>10 prism diopters of orthotropia within one year of first surgery (%)</i>	40 (63)
<i>Required second surgery (%)</i>	12 (19)
<i>Mental illness in patients with 10 prism diopters post-surgery (%)</i>	15(65)
<i>Mental illness in patients with >10 prism diopters post-surgery (%)</i>	20(50)