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Congenital esotropia and the risk of mental illness by early adulthood

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Abstract

Objective—The purpose of this study is to investigate whether children with congenital esotropia are more likely than controls to develop mental illness by early adulthood.

Design—Retrospective, population-based cohort.

Participants—Children (<19 years) diagnosed with congenital esotropia while residing in Olmsted County, Minnesota, from January 1, 1965, through December 31, 1994, and their one-to-one non-strabismic birth- and gender-matched controls.

Methods—The medical records of patients with esotropia and their controls were retrospectively reviewed for the subsequent development of psychiatric disease.

Main Outcome Measures—The development of mental illness and associated co-morbidities among patients with congenital esotropia and their controls.

Results—A mental health disorder was diagnosed in 42 (33%) of the 127 patients with congenital esotropia followed to a mean age of 20.4 years compared to 16% of controls ($p=0.002$). Congenital esotropia increased the odds of developing a psychiatric illness 2.6 times (Confidence interval: 1.5–4.8) compared to controls. The number of mental health diagnoses ($p=0.019$) and the use of psychotropic medications ($p=0.015$) were significantly more common among esotropic patients compared to non-strabismic controls.

Conclusions—Congenital esotropia, similar to those with intermittent exotropia or convergence insufficiency, increases the odds of developing mental illness by early adulthood 2.6 times compared to controls. The etiology of this association does not appear to be associated with premature birth.

Strabismus is a common disorder of ocular alignment that affects 3–5% of children worldwide.^{1–5} Recently, a number of studies have reported a link between strabismus and mental illness in adulthood.^{6–9} At least one form of strabismus, constant exotropia, has been shown to be genetically associated with schizophrenia.⁶ Moreover, children with intermittent exotropia and convergence insufficiency, compared to controls without

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strabismus, have been shown to have a three-fold increased risk of developing mental illness by early adulthood.^{8,9} However, in the same population, children diagnosed with esotropia were no more likely than controls to develop a psychiatric illness when followed for a similar duration. Only children with congenital esotropia, one of the three forms of esotropia studied, were found to have an elevated risk, though not statistically significant, of being diagnosed with a mental illness.⁸ The purpose of this study is to further investigate the prevalence of psychiatric disorders among young adults who had congenital esotropia as children by extending the cohort to include patients who were diagnosed during a 30-year period.

METHODS

The medical records of all patients younger than 19 years of age who were residing in Olmsted County, Minnesota, when diagnosed with congenital esotropia (CET) by an ophthalmologist from January 1, 1965, through December 31, 1994, were retrospectively reviewed. Institutional review board approval was obtained for this study. Congenital esotropia was defined as a nonaccommodative esotropia that developed by 6 months of age in a neurologically intact child. The initial esotropic deviation was measured by the Hirschberg estimate or Krimsky test. A cycloplegic refraction was performed in all patients, most often using atropine or cyclopentolate. Children with a paralytic, sensory, or neurologic cause of their deviation, or in the setting of a developmental disorder, were specifically excluded from the study. Potential cases were identified using the resources of the Rochester Epidemiology Project (REP), a medical records database designed to capture data on any patient-physician encounter in Olmsted County, Minnesota.^{10–11} The REP is a centralized medical records linkage system that encompasses all health care that is delivered to residents of Olmsted County, Minnesota. The REP captures and classifies diagnostic information from the patients' complete medical records. The diagnoses that are assigned at each visit are coded and indexed continuously, including esotropia. 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, Olmsted Medical Group and their affiliated hospitals) that has accumulated comprehensive clinical records for nearly one century.

A total of 127 children were diagnosed with CET during the 30-year period. For each case of CET, we identified one control that did not have a diagnosis of strabismus. Potential controls were generated randomly by selecting three age- and sex-matched patients identified to be residents of Olmsted County matched for each of the index cases. Initially the ophthalmic history of potential control candidates were reviewed individually starting with the lowest medical record number. If no history of strabismus was identified, the entirety of the medical record was subsequently reviewed along with their corresponding CET patient. If a history of strabismus was identified in the potential control patient, they were excluded from the study and the next numerically higher clinic number was reviewed for the same criteria until an appropriate control was identified. Residence status, verified by trained residency checkers, was assessed for cases and controls at the time of birth and at diagnosis using information from city and county directories. Patients not residing 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 (DSM-IV codes), use of psychotropic medication, mental health emergency room visits or hospitalizations, suicide attempts, and suicidal or homicidal ideation. Mental illness was defined as a disease meeting the DSM-IV criteria diagnosed by a psychiatrist,

family physician, or emergency physician. The use of psychotropic medication, mental health emergency room visits/hospitalizations, suicide attempts, and suicidal or homicidal ideation were not used as individual criteria to diagnose mental illness by the reviewers. The entirety of a patient's medical record from Olmsted County was reviewed for each case and control and included paper and electronic records, in- and outpatient psychiatric, psychological, primary care and emergency room records. A history of mental illness diagnosed elsewhere was included when confirmed by a mental health care provider within Olmsted County. The use of psychiatric medications included the type, concurrent use, and total duration and was obtained from medication records by providers as well as self-reports. A history of suicide attempts or ideation was elicited from the mental health care record while a family history of psychiatric disease, substance abuse, or maternal substance abuse during pregnancy among cases and controls were collected from mental health and self-reporting primary care records.

Continuous data were presented as a mean and range. Categorical data were presented as counts and percentages. 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 two-sided, and the threshold of significance was set at $\alpha=0.05$.

RESULTS

A total of 127 pediatric patients were diagnosed with congenital esotropia during the 30-year study period, with males representing 52% (67/127) of the cohort. The cases were followed to a mean age of 20.4 (range, 6 months to 42.2 years), compared to 19.1 years (range, 1 month to 57.7 years) for the control group. Table 1 compares the historical and clinical characteristics of the patients with congenital esotropia and their controls. Subjects with CET were more likely than their controls to have been born prematurely ($p=0.022$) or have had some difficulty with pregnancy ($p=0.006$).

A mental health disorder was diagnosed in 42 (33%) of the 127 children with CET compared to 20 (16%) of the controls ($p=0.002$). A diagnosis of congenital esotropia increased the odds of being diagnosed with a mental illness by early adulthood 2.6 (Confidence Interval=1.45 to 4.84) times compared to controls. Table 2 provides the prevalence of specifically queried factors of mental illness among all patients with CET and their controls. The p-values were adjusted for significant difference in rates of premature birth and difficulty during pregnancy utilizing a multivariable logistic regression model. A mental health disorder was diagnosed in 22 (33 %) of the 66 men and 20 (30 %) of the 61 women with CET. Individuals with CET were also more likely than controls to have a greater number of mental illness diagnoses ($p=0.019$) and use psychotropic medications ($p=0.015$). The four most commonly diagnosed forms of mental illness disorders among males were major depression, ADHD, drug use and alcoholism; while major depression, depression not otherwise specified, adjustment disorder, and eating disorders were the most prevalent among females.

Table 3 shows the type and total number of psychiatric disorders diagnosed among cases and controls. Patients with CET were more likely to develop an adjustment disorder than were controls ($p=0.048$). A slightly higher percentage of patients with CET were also diagnosed with major depression, dysthymia, bipolar disorder, personality disorders, phobia-specific anxiety, and psychosis. However, the sample size of individual mental health disorders was too small to demonstrate statistical significance. There is also a suggestion that patients with CET were less likely than controls to develop attention deficit hyperactivity disorder (ADHD), alcoholism, learning disorders, or an eating disorder.

Table 4 compares the prevalence of mental illness among patients with CET who were reported as being born prematurely with those who were not. Premature children who developed CET were no more likely than those born at full term to be diagnosed with a psychiatric disorder ($p=0.54$). Nor were there significant differences in the number of psychiatric medications prescribed ($p=0.73$), psychiatric related emergency room visits ($p=0.24$), psychiatric inpatient admissions ($p=0.20$), suicide attempts ($p=0.072$), or reported suicidal ideation ($p=1.00$) between the two groups.

DISCUSSION

Olmsted County residents with congenital esotropia were 2.6 times more likely than controls to be diagnosed with a mental illness by early adulthood. Children with congenital esotropia were also found to be significantly more likely than controls to have a greater number of mental health diagnoses and to be prescribed psychotropic medications. Premature birth did not appear to significantly alter mental health outcomes.

These findings expand further the forms of childhood strabismus associated with the subsequent development of mental illness. Previously, common forms of childhood exotropia (constant exotropia, intermittent exotropia, and convergence insufficiency) were associated with an increased risk for developing mental illness while esotropia was found to have no greater risk than controls.^{6,8} However, when extending the cohort of children diagnosed with CET from 10 to 30 years, a statistically significant association was identified. It is unclear as to why the congenital form of esotropia is associated with an increased risk of mental illness while other forms are not.⁸ Any significant esodeviation, not corrected by spectacle correction, would be visible to the outside observer leading to a similar psychosocial burden. Perhaps the earlier onset of CET exposes patients to a more sensitive or prolonged period of stress compared to acquired forms of esotropia. However, there is no evidence to support the notion that the psychosocial stressors encountered by children with strabismus, including CET, are directly linked to the development of mental illness.

The increased risk for developing mental illness by early adulthood among children with CET may be explainable by environmental factors such as prenatal exposures. Similar to the findings in this study, children with CET are more likely than controls to have been born prematurely.^{8,12} The study subjects with strabismus were significantly more likely to have had some difficulty at the time of delivery, including a cesarean-section birth, forceps delivery, involvement of nuchal chords, the presence of meconium, or a low initial or 5 minute Apgar score. Recent studies have suggested a link between prematurity and poor neurobehavioral outcomes.^{13–15} Moreover, a recently published meta-analysis confirmed that children who were very preterm and/or of very low birth weight (< 33 weeks gestation or 1500 grams, respectively) have moderate-to-severe deficits in academic achievement, attention problems, and internalizing behavioral problems and poor executive functioning.¹⁶ Premature patients diagnosed with congenital esotropia from this study were found to be at a slightly higher risk of being born before 33 weeks gestation compared to controls (7% ($n=5/69$) vs 1% ($n=1/85$); $p = 0.090$). The neurobehavioral disorders reported among children born prematurely may partially explain the increased risk of CET patients having a higher risk of developing mental illness by early adulthood.

In addition to the potential role of prematurity and birth trauma, hereditary factors may also play a part in the development of mental illness among children with CET. Although a genetic locus for concomitant strabismus, including CET, has not been identified, it is thought to be the product of a complex genetic trait that is phenotypically manifest through multiple susceptibility gene interactions.¹⁷ Such a complex inheritance pattern makes it

unlikely that an inheritable trait alone can cause the association between CET and mental illness. However, Toyota and colleagues⁶ have reported a population of adults with constant exotropia to have a single gene mutation associated with schizophrenia. It remains to be seen if other such genetic variants can bridge the now uncertain connection between other forms of strabismus and mental health disorders.

The findings from this study may raise questions regarding the prevalence of mental illness among young adults in the United States. In a prior report from Olmsted County Minnesota, 30.7 % (125 of 407) of patients with no history of strabismus were diagnosed with a mental illness at a similar age to the control group in this study (average age = 12.7–15.9 years).⁸ Similarly, a study of randomly selected children aged 9, 11, and 13 years, living in a rural community in the southeastern United States, reported that a psychiatric illness was present in 20.3% of the children.¹⁸ A rate of 16% among nonstrabismic controls in this study is consistent with the prior reports in which mental illness occurred in approximately 15–30% of young adults.

There are a number of limitations to the findings in this study. First, this investigation was performed in a racially homogeneous population in a single geographic area. Extrapolating the findings from this study to groups not represented within our community is problematic. Caution is warranted in interpreting some of the reported factors until similar results are confirmed in other populations. Second, given the social stigma of mental illness, some patients from the community may have sought care outside of Olmsted County. We attempted to account for this potential bias by tracking patients with multiple records at both major health care institutions (Mayo Clinic and Olmsted Medical Group). Moreover, we would expect the numbers of case and control subjects who did seek outside care to be similar between the two groups. Lastly, because the average follow-up for the study patients was just beyond the second decade of life, associations for diseases with the tendency for later diagnosis, such as schizophrenia, may be under appreciated.

This population-based, nested-control study confirmed a previously suggested association between congenital esotropia and mental illness. A diagnosis of congenital esotropia increased the odds of being diagnosed with a mental illness by early adulthood 2.6 times compared to controls. Patients with CET were found to be significantly more likely to have a greater number of mental health diagnoses and to be prescribed psychotropic medications, compared to controls.

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Table 1

Historical and clinical characteristics of patients with esotropia and their controls

Characteristic	Cases (n=127)		Controls (n=127)		p-value
	N	%	N	%	
Male, n (%)	127	66 (52%)	127	66 (52%)	1.00
Prematurity, ^a n (%)	108	13 (12%)	115	4 (3%)	0.022
Mean birth weight in grams (range)	3276 (1050–4630)		3334 (1530–4700)		0.54
Caucasian, n (%)	116	116 (100%)	122	119 (98%)	0.25
Family History of strabismus	28	15 (54%)	7	2 (29%)	0.40
Difficulty with Pregnancy, ^b n (%)	102	38 (37%)	114	23 (20%)	0.006
Mean age in years at last follow-up (range)	109	20.4 (6mos–42.2)	127	19.1 (1mo–57.7)	0.26
Mean age in years at psychiatric diagnosis, (range)	33	16.0 (3.1–37.7)	19	14.4 (3.2–32.0)	0.66

Categorical variables are summarized as number (%) and compared between Cases and Controls using Fisher's Exact test. Continuous variables are summarized using mean (min, max). Cases and Controls are compared using the Wilcoxon rank-sum test. Please see table for number of observations used per comparison between cases and controls.

^aBorn at < 37 weeks gestational age

^bIncludes cesarean-section birth, nuchal chords, forceps delivery, low Apgar, meconium, etc

Table 2

Mental health characteristics in patients who had esotropia and their controls

Characteristic	Cases	N used	Controls	N used	p-value
Number (%) of patients with mental illness	42 (33%)	127	20 (16%)	127	0.025
Number of total disorders, mean (range)	0.7 (0–6)	127	0.3 (0–3)	127	0.019
Number (%) of patients using psychiatric medication	31 (24%)	127	13 (10%)	127	0.015
Number (%) of patients with psychiatric emergency room visits	9 (10%)	84	2 (2%)	126	0.14
Number (%) of patients with psychiatric inpatient	7 (8%)	86	2 (2%)	126	0.22
Number (%) of patients with suicide attempts	3 (4%)	85	1 (1%)	126	0.33
Number (%) of patients with suicidal ideation	8 (9%)	85	2 (2%)	126	0.15

Categorical variables are summarized as number (%). Number of total disorders is summarized using mean (min, max). P-values result from multivariable logistic regression models where prematurity and difficulty with pregnancy were adjusted for in the multivariable analysis as they were the variables showing the most highly single variable association with the endpoint of esotropia.

Table 3

Type and prevalence of all mental illnesses diagnosed

Type of Diagnosis Reported	Cases (n=42)	Controls (n=20)	p-value
Depression NOS	7 (17%)	3 (15%)	1.00
ADHD	8 (19%)	6 (30%)	0.35
Adjustment D/O	9 (21%)	0 (0%)	0.048
Drug Use	8 (19%)	4 (20%)	1.00
Encopresis/Enuresis	2 (5%)	0 (0%)	1.00
Alcoholism	5 (12%)	5 (25%)	0.27
Generalized Anxiety	8 (19%)	4 (20%)	1.00
Major Depression	21 (50%)	7 (35%)	0.29
Learning Disabilities	1 (2%)	2 (10%)	0.24
Dysthymia	4 (10%)	0 (0%)	0.30
Personality D/O	3 (7%)	0 (0%)	0.54
Anxiety Panic D/O	0 (0%)	0 (0%)	NA
Anxiety OCD	1 (2%)	0 (0%)	1.00
Eating D/O	2 (5%)	3 (15%)	0.32
Anxiety Phobia	2 (5%)	0 (0%)	1.00
Bipolar	3 (7%)	0 (0%)	0.54
Somatoform/Conversion	0 (0%)	0 (0%)	NA
Psychoses	2 (5%)	0 (0%)	1.00
Aggression D/O	0 (0%)	0 (0%)	NA
Schizophrenia	0 (0%)	0 (0%)	NA
Pervasive Development D/O	0 (0%)	0 (0%)	NA
Total	86	34	

Categorical variables are summarized as number (%) and compared between Cases and Controls using Fisher's Exact test.

NOS: not otherwise specified; ADHD: attention deficit hyperactivity disorder; D/O: disorder; OCD: obsessive compulsive disorder

Table 4

Mental health characteristics among patient's with congenital esotropia born at normal gestational age versus prematurely

Characteristic	Normal GA (N=95)	Prematurity (N=13)	p-value
Any psychiatric diagnosis reported	29 (31%)	5 (38%)	0.54
Number (%) of patients using psychiatric medication	23 (24%)	4 (31%)	0.73
Number (%) of patients with psychiatric emergency visits	4/63 (6%)	2/12 (17%)	0.24
Number (%) of patients with psychiatric inpatient	3/64 (5%)	2/13 (15%)	0.20
Number (%) of patients with suicide attempts	1/64 (2%)	2/13 (15%)	0.072
Number (%) of patients with suicidal ideation	4/63 (6%)	1/12 (8%)	1.00

Prematurity was defined as less than 37 weeks gestation, and full-term being a total of 37 weeks gestation or greater at the time of birth. Categorical variables are reported using number (percent) and p-values were obtained using Fisher's Exact test. GA: gestational age