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Incidence, Types, and Lifetime Risk of Adult-onset Strabismus

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Abstract

Objective—To describe the incidence and types of adult-onset strabismus in a geographically defined population.

Design—Retrospectively reviewed population-based cohort.

Participants—All adult (≥ 19 years of age) residents of Olmsted County, Minnesota diagnosed with new-onset adult strabismus from January 1, 1985, through December 31, 2004.

Methods—The medical records of all potential cases identified by the resources of the Rochester Epidemiology Project were reviewed.

Main Outcome Measures—Incidence rates for adult-onset strabismus and its types.

Results—Seven hundred fifty-three cases of new-onset adult strabismus were identified during the twenty-year period, yielding an annual age- and gender-adjusted incidence rate of 54.1 cases (95% confidence interval 50.2–58.0) per 100,000 individuals ≥ 19 years of age. The four most common types of new-onset strabismus were paralytic (44.2% of cases), convergence insufficiency (15.7%), small angle hypertropia (13.3%), and divergence insufficiency (10.6%). The incidence of adult-onset strabismus overall and its four most common forms significantly increased with age ($p < 0.001$ for all), with a peak incidence in the eighth decade of life. The lifetime risk of being diagnosed with adult-onset strabismus was 4.0% in females and 3.9% in males.

Conclusions—Paralytic strabismus was the most common subtype of new-onset adult strabismus in this population-based cohort. All of the most common forms of adult-onset strabismus increased with age, especially after the sixth decade of life. Further characterization of strabismus types found in this study is warranted to better define this common disorder.

Strabismus is a disorder of ocular alignment characterized by a horizontal, vertical, and/or torsional deviation of one eye relative to the other. Although commonly recognized among children, adults also develop strabismus secondary to a variety of conditions including

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trauma, surgical procedures, thyroid dysfunction, cranial nerve palsies, or other neurologic diseases.¹ While childhood strabismus has been well-characterized by epidemiologic studies worldwide,^{2–13} published reports of strabismus among adults are uncommon and are almost exclusively institution-based series of patients referred solely for surgical intervention.^{14–16} Such reports provide little data on the true incidence and demographics of the disorder in adults. The purpose of this study is to report the incidence of new-onset strabismus and its types in a population of adults (≥ 19 years of age) diagnosed over a twenty-year period using a population-based medical records linkage system.

Methods

Study population

The study population included all Olmsted County, Minnesota residents ≥ 19 years of age who were newly diagnosed with some form of strabismus from January 1, 1985, through December 31, 2004. Olmsted County is a small urban region approximately 90 miles (145 km) southeast of Minneapolis and in 2000, about 70 percent of the county's population (124,277) lived within the city limits of Rochester. The racial distribution of county residents in 2000 was 90.3% Caucasian, 4.3% Asian, 2.7% Black or African-American, 0.3% American Indian or Alaska Native, and 0.9% for other. Hispanic or Latinos of any race comprised 2.4% of the population.

Case Ascertainment

Institutional review board approval was obtained for this study. Potential cases of new-onset adult strabismus were identified through the Rochester Epidemiology Project (REP), a medical records-linkage system designed to capture all patient-physician encounters in Olmsted County, Minnesota.^{17,18} Since the county is relatively isolated from other urban areas, Mayo Clinic or Olmsted Medical Group and their affiliated hospitals provide the vast majority of the medical care received by county residents. Summary information on demographics, medical diagnoses, and surgical interventions from all participating providers is accumulated into a central computerized record for each patient, linking all medical care received by the individual within the county.

Potential cases of new-onset adult strabismus were ascertained by searching the REP linkage system for International Classification of Diseases 9 codes for strabismus and other disorders of binocular eye movements. A trained data abstractor (JMM) reviewed all medical records for subjects with at least one of the diagnostic codes for strabismus entered during the twenty-year period 1985 to 2004. The data abstractor used pre-determined inclusion criteria (described below) to confirm a diagnosis of new-onset strabismus and to classify subjects by the type of strabismus. Residency and age verification was ascertained using REP-provided information at the time of record review by the data abstractor.

Entry and Diagnostic Criteria

Predetermined inclusion and exclusion criteria were established to identify cases of new-onset adult strabismus (Table 1). Cases with a history of strabismus with documented onset

prior to the study dates or documented onset in childhood were included in the study only if they developed a new form of strabismus as an adult during the study period.

Each incident case was counted only once even if a second form of strabismus developed later in the study period. Cases meeting the entry criteria were then classified by additional diagnostic criteria into strabismus categories (Table 2). Previously established criteria for children⁷⁻⁹ were used for forms of adult-onset exotropia, esotropia, or hypertropia not listed in Table 2. Cases that were difficult to categorize because they did not meet pre-established criteria were reviewed with senior investigators (JMH, BGM) and agreement reached by consensus. Study data were collected and managed using Research Electronic Data Capture (REDCap), a secure, web-based application designed to support data capture for research studies.¹⁹

Data Analysis

Annual age- and gender-adjusted incidence rates were estimated using the age- and gender-specific population figures for Olmsted County, Minnesota from the 1990 and 2000 United States census. Age- and gender-specific denominators for individual years were generated from linear interpolation of the 1980, 1990, and 2000 census figures and the State of Minnesota Demographer's Office projections for estimates between census years. Incidence rates were age- and gender- adjusted to the United States' Caucasian population for 2000. The 95% confidence intervals for incidence estimates were calculated assuming a Poisson error distribution. Trends over time, by age, and between genders were assessed using Poisson regression models. The sex-specific lifetime risk of diagnosis with adult-onset strabismus was estimated using the incidence rate estimates from this study and mortality rates from life tables for the general population. All statistical tests were two-sided and the threshold of significance was set at an alpha of 0.05. Statistical analyses were performed using SAS Version 9.2 (SAS Institute, Cary, NC).

Results

General Characteristics

A total of 753 individuals developed new-onset adult strabismus in Olmsted County, Minnesota during the twenty-year period. There were 340 (45.2%) male cases and the cohort was diagnosed at a median age of 65 years (range 19–100 years). Six-hundred and forty-nine cases (86.2%) had diplopia on initial presentation. Esotropia was the primary deviation for 261 (34.7%), exotropia for 251 (33.3%), and hypertropia for 241 cases (32.0%). There were no cases of torsional diplopia alone.

Incidence and Types of Adult-Onset Strabismus

The age- and gender- adjusted annual incidence rate for adult-onset strabismus was 54.1 cases per 100,000 people (95% confidence interval, 50.2–58.0 cases per 100,000 people). Paralytic strabismus was observed in 333 (44.2%) cases, convergence insufficiency in 118 (15.7%), small angle hypertropia in 100 (13.3%), and divergence insufficiency in 80 (10.6%). Table 3 provides the median age, frequency, and age- and gender- adjusted annual incidence rates for all observed types of adult-onset strabismus. The annual incidence rates

for subtypes of paralytic strabismus included 10.4 cases per 100,000 people (95% confidence interval, 8.7 – 12.2) for sixth nerve palsy, 6.3 cases per 100,000 people (95% confidence interval, 5.0 – 7.6) for fourth nerve palsy, and 3.5 cases per 100,000 people (95% confidence interval, 2.5 – 4.5) for third nerve palsy. The peak incidence of adult-onset strabismus occurred in the eighth decade of life (Figure 1). Paralytic strabismus peaked in the seventh decade, while convergence insufficiency, small angle hypertropia, and divergence insufficiency had a peak incidence in the eighth decade of life.

Incidence Trends

There was a significant increase in the incidence of adult-onset strabismus with increasing age ($p < 0.001$, Table 4). Figure 2 depicts this age trend in both males and females, with an increase in the incidence after the age of 60. There were no significant gender differences or changes in the incidence of adult-onset strabismus over the twenty-year study period.

Among the four most common types of new-onset adult strabismus, the incidence significantly increased with age. Males had a significantly higher incidence of paralytic strabismus compared to females ($p = 0.004$). When assessing subgroups of paralytic strabismus, males had a significantly higher incidence of fourth nerve palsy compared to females ($p = 0.003$), but no significant gender differences were identified for sixth nerve or third nerve palsy. With the exception of the gender differences for paralytic strabismus, there were no significant gender differences or differences in the incidence of each type of strabismus over the twenty-year period. Smaller subgroups of new-onset adult strabismus could not be assessed for incidence trends.

Lifetime Risk

Based on calculations of cumulative incidence from the above age- and gender- adjusted annual incidence, the estimated lifetime risk for being diagnosed with adult-onset strabismus was 4.0% for females and 3.9% for males (Table 5). Table 5 also provides the residual lifetime risks for both females and males by age group.

Discussion

The present study provides data on the incidence and various subtypes of adult-onset strabismus in a defined population from the upper Midwest region of the United States. The four most common types of new-onset strabismus were paralytic (44.2%), convergence insufficiency (15.7%), small angle hypertropia (13.3%), and divergence insufficiency (10.6%). Based on the age- and gender- adjusted annual incidence rate of 54.1 cases per 100,000 people, about 1 in 25 adults would be expected to develop strabismus during their lifetime, with a significant higher risk with increasing age.

Ocular misalignment among adults differs significantly from children. Pediatric strabismus is a well-characterized disorder of primarily young children in which 88% of patients are diagnosed by the sixth year of life.¹⁰ Two-thirds display an esotropic deviation, a large proportion have amblyopia, and diplopia is rare.¹ In contrast, new-onset ocular misalignment among adults is significantly associated with increasing age with the highest incidence among individuals in the eighth decade of life. Esotropia, exotropia, and

hypertropia occur with similar frequency. Adult-onset strabismus is not associated with amblyopia or decreased vision but instead, is more likely to be the result of a paralytic disorder or small but troubling deviations with persistent double vision. Convergence insufficiency and superior oblique palsies are forms of ocular alignment common among both children and adults. The remaining forms of adult-onset strabismus identified in this study are generally infrequent among children or vice versa.¹

Published reports on adult strabismus are primarily institution-based series that include both childhood and adult-onset forms.^{14,15} Paralytic (33% – 36%) and restrictive strabismus (9.8%–19%) were the most common types of adult-onset strabismus identified in these reports. While paralytic strabismus was the most common form of adult-onset strabismus in the present study (44.3%), a direct comparison between the studies is difficult given the referral bias of prior studies and the nearly universal focus on patients who underwent surgery. The sole exception is a recent study by Repka and coauthors²⁰ in which they investigated the diagnosis of strabismus among 5% of Medicare B claims during a 9-year period. Paralytic strabismus, esotropia, and exotropia were common diagnoses while strabismus surgery was performed in only 2.3% of the study patients. Although their findings are similar to the current study, including a statistically significant increase in the incidence of adult strabismus with increasing age, their study was a partial sampling of elderly adults and essentially excluded those younger than 65 years of age.

With regards to population-based studies of adult strabismus, we are only aware of a single report on the incidence and risk factors of sixth nerve palsy. Patel et al²¹ conducted a retrospective population-based study in Olmsted County, Minnesota from 1978 through 1992 to determine the incidence of sixth nerve palsy. Their age- and gender- adjusted annual incidence rate for sixth nerve palsy was 11.3 cases per 100,000 individuals (95% confidence interval 9.3–13.2), which is consistent with the incidence rate of 10.4 cases per 100,000 individuals 19 years of age found in this study.

Incidence rates for adult-onset strabismus significantly increased with age, with a sharp increase after the age of 60 as shown in Figure 3. This trend of increasing incidence with age was seen in each of the major forms of adult-onset strabismus: paralytic, convergence insufficiency, small angle hypertropia, and divergence insufficiency. For paralytic strabismus, the association between age and the incidence may be related to the age-dependent increase of vasculopathic diseases such as hypertension and diabetes. Prior referral-based series have commonly listed hypertension or diabetes as causes of acquired ocular motor nerve palsies.^{22–26} In addition, two case-control studies have reported an association between hypertension and/or diabetes and ocular motor nerve palsies.^{27,28} Patel et al,²⁸ who used a population-based approach to identify cases of sixth nerve palsy and controls, found that while hypertension alone was not associated with sixth nerve palsy (odds ratio = 1.62, 95% confidence interval = 0.85–3.08), there was an association between diabetes and sixth nerve palsy (odds ratio = 5.59, 95% confidence interval = 1.79–17.42) and an association between a combination of diabetes and hypertension and sixth nerve palsy (odds ratio = 8.36, 95% confidence interval = 1.83–38.18). A similar population-based case control study has not been reported for isolated fourth or third nerve palsies.

Paralytic strabismus was also significantly more common in males due primarily to the higher incidence of fourth nerve palsy. Head trauma is often reported as the most common identifiable cause of fourth nerve palsy,^{22–25} and the reported incidence of close head injury is higher in males than females.²⁹ While this may explain the higher incidence of fourth nerve palsy in males, a case-control study design would be necessary to assess the magnitude of the association.

Difficulty with near convergence in the elderly has been reported in several case series, supporting the finding in the current study that the incidence of convergence insufficiency increases with age.^{30–32} Pickwell³⁰ found that the percentage of individuals in an urban population with convergence insufficiency increased gradually until around the age of 55–60, with a marked increase from about 25% at 55 years to over 60% in the elderly. In addition, Oguro et al³¹ assessed the convergence of 113 healthy individuals and found that reduced convergence increased with age, affecting around 70% of individuals in their eighties.

Several theories have been proposed to explain the mechanism of divergence insufficiency, otherwise known as distance esotropia, in the elderly.^{33–38} Both Mittelman³³ and Jacobson³⁴ found that the median age of individuals affected by divergence insufficiency was in the mid-seventies, which is consistent with the present study. They suggest a microvascular ischemic insult to a “divergence center” in the brain as a potential cause, with some investigators reporting focal lesions of the pons or midbrain post-mortem of individuals with divergence insufficiency.^{35,36} Rutar and Demer³⁷ propose an alternate theory regarding primary divergence insufficiency based on the degeneration of orbital connective tissues that occurs with aging. They imaged elderly patients with esotropia and hypotropia and found that both lateral rectus muscles were displaced inferiorly on MRI, suggesting that the displacement may be secondary to degeneration of the lateral rectus-superior rectus band that connects the lateral and superior recti pulleys. They propose that somewhat impaired abduction as a result of this displacement could contribute to divergence insufficiency in elderly individuals with an already existing esophoria or deficient fusional divergence amplitudes. Guyton proposes yet another theory, in which divergence insufficiency develops secondary to permanent shortening, or increased tone, of the medial rectus muscles as a response to a lifetime of near work.³⁸

Some individuals with convergence or divergence insufficiency in this study may have had ocular misalignment as children, yet were able to compensate and remained undiagnosed prior to becoming symptomatic in adulthood. This may also be the case for individuals with small angle hypertropia, some of which may have had small vertical phorias that went unnoticed until double vision emerged. Reasons as to why small angle hypertropia significantly increased with age are unclear. Some of these hypertropic cases could represent skew deviation secondary to brainstem, cerebellar, or unilateral vestibular lesions due to microvascular ischemia undiagnosed by conventional imaging.³⁹ The small angle hypertropia cases in the current study were comitant and skew deviations typically present as a comitant hypertropia.³⁹ However, limited data on the magnitude of any associated cyclodeviation and the absence of ocular tilt testing, or a four-step test, in the present study prevented formal classification of these cases as skew deviation.

There are a number of limitations to the findings of this study, the majority of which may result in an underestimation of the true incidence of adult-onset strabismus. While the Rochester Epidemiology Project allowed review of records from various medical institutions in Olmsted County, there was no access to records from optometrists practicing in the area. Based on the twenty-year study period, we assumed most cases initially evaluated by a local optometrist would seek referral to REP-affiliated institutions within the county, particularly if symptomatic and necessitating further management. Since the majority of new-onset strabismus cases were paralytic, they would have been captured by the REP upon visits to emergency departments or ophthalmologists and neurologists in the county. An additional weakness may be that other strabismus specialists might disagree with some of our classification criteria, but our criteria represent the consensus of two senior strabismus specialists who have had diverse training and experience.

The generalizability of the study results is also limited given the racial and ethnic composition of Olmsted County. Because the composition was 90.3% Caucasian during the years of the study, our results are best extrapolated to the small urban Caucasian populations of the United States. Recognizing these weaknesses and assuming a population of 209,128,094 individuals 19 years of age (2000 US Census), we estimate that approximately 113,000 new cases of adult-onset strabismus will develop each year in the United States. Roughly 50,000 adults will have some form of paralytic strabismus.

This study has presented population-based data on the incidence of new-onset adult strabismus, with a reported annual age- and gender- adjusted incidence rate of 54.1 cases per 100,000 adults, a peak incidence in the eighth decade of life, and an estimated lifetime risk of 4.0%.

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Figure 1.
Frequency of new-onset adult strabismus types by decade of life.

Figure 2.
Incidence rates of adult-onset strabismus by age in Olmsted County, Minnesota, from 1985 through 2004 (three-year running average).

Table 1**Inclusion and Exclusion Criteria for New-Onset Adult Strabismus****Inclusion criteria**

- Age ≥ 19 years of age on initial date of diagnosis
 - Resident of Olmsted County, Minnesota during the year of new-onset strabismus diagnosis and for at least one preceding year
 - New strabismus lasting for at least 24 hours consisting of:
 - Any size of tropia/phoria with documentation of double vision symptoms in any field of gaze or prescription of prisms with resolution of symptoms
- OR
- Intermittent or constant horizontal (≥ 10 PD) or vertical (≥ 3 PD) tropia at distance or near in primary position by any test of ocular alignment

Exclusion criteria

- History of strabismus with onset prior to study dates

PD=prism diopter

Table 2**Diagnostic Criteria for New-Onset Adult Strabismus Cases****Convergence insufficiency**

Symptoms of double vision while reading with an exophoria/tropia at near by any ocular alignment test and an absence of double vision at distance OR exophoria/tropia 10 PD at near on PACT with orthophoria or small (<10 PD) phoria at distance

Divergence insufficiency

Symptoms of double vision at distance with an esophoria/tropia greater in distance than near by any ocular alignment test and an absence of double vision at near

Paralytic strabismus**Sixth nerve palsy**

Lateral rectus underaction on ductions AND esotropia on affected lateral gaze at least 6 PD greater than in primary on ocular alignment testing, OR esotropia with history of worsening double vision on corresponding lateral gaze

Fourth nerve palsy

Superior oblique underaction on ductions AND a positive three step test with hypertropia at least 2 PD greater in contralateral horizontal gaze and ipsilateral head tilt compared to primary by ocular alignment testing, OR hypertropia with history of worsening double vision on contralateral horizontal gaze and ipsilateral head tilt

Third nerve palsy

Underaction of any third nerve innervated muscles with or without complete or partial ptosis of affected eye AND exotropia and/or hypotropia of affected eye by any ocular alignment test

Internuclear ophthalmoplegia

Isolated adduction impairment of affected eye with worse double vision on contralateral gaze and associated abducting nystagmus of contralateral eye

Myasthenia gravis

Preexisting or recently diagnosed myasthenia gravis with subsequent or concurrent underaction of extraocular muscles on versions and double vision not due to another cause

Restrictive strabismus

Recent or preexisting diagnosis of Graves' disease, trauma, or ocular/facial surgery (e.g. scleral buckle) with evidence of restriction on ductions

Sensory strabismus

Preexisting unilateral ocular condition affecting visual acuity (e.g. ptosis or cataract) with subsequent strabismus not due to another cause

Small angle hypertropia

Comitant hypertropia <10 PD or prism prescription 3 PD on initial exam and symptoms of double vision with no evidence of oblique muscle dysfunction

PD=prism diopter, PACT=prism and alternate cover test

Note: Forms of adult-onset exotropia, esotropia, or hypertropia not fitting the criteria above were categorized using previously established criteria for children⁷⁻⁹ or remained unspecified

Table 3

Frequency and Annual Incidence of New-Onset Adult Strabismus

Type of Strabismus	Median Age in Years (Range)	n	%	Incidence per 100,000 people (95% CI)*
Paralytic	63 (19–100)	333	44.2	23.9 (21.3 – 26.5)
Convergence Insufficiency	69 (22–97)	118	15.7	8.4 (6.9 – 10.0)
Small Angle Hypertropia	72 (27–98)	99	13.1	7.5 (6.0 – 9.0)
Divergence Insufficiency	74 (19–92)	80	10.6	6.0 (4.7 – 7.3)
Restrictive	59 (29–93)	47	6.2	(2.4 – 4.3)
-Thyroid ophthalmopathy	49 (29–84)	21	2.8	1.41 (0.8 – 2.0)
-Other restrictive	63 (42–93)	26	3.5	1.9 (1.2 – 2.7)
Sensory	57 (20–94)	27	3.6	1.9 (1.2 – 2.6)
Intermittent Exotropia	40 (21–81)	21	2.8	1.3 (0.7 – 1.9)
High AC/A Ratio Esotropia	28 (25–93)	6	0.8	0.3 (0.1 – 0.6)
Constant Exotropia	43 (36–61)	4	0.5	0.3 (0.0 – 0.5)
ANAET [‡]	71 (70–73)	2	0.3	0.2 (0.0 – 0.4)
Unspecified	--	16	2.1	--
Overall	65 (19–100)	753	100.0	54.1 (50.2 – 58.0)

* Age- and gender-adjusted annual incidence rate with 95% confidence interval (CI)

[‡] ANAET=acquired non-accommodative esotropia

Table 4

Age-related, Gender-related, and Time-related Incidence Trends* for New-Onset Adult Strabismus

Type of Strabismus	Age trend (p-value) ^a	Gender trend (p-value) ^b	Time trend (p-value) ^c
Paralytic	<0.001	0.004	0.19
Convergence Insufficiency	<0.001	0.95	0.46
Small Angle Hypertropia	<0.001	0.32	0.80
Divergence Insufficiency	<0.001	0.45	0.18
Restrictive	<0.001	0.90	0.093
Strabismus Overall	<0.001	0.25	0.37

* Trends assessed only for groups with larger sample sizes.

^a Increasing incidence with increasing age

^b Greater in males than females

^c Greater in the second decade of the study period (1995–2004 versus 1985–1994)

Table 5
Estimated Residual Lifetime Risk (LR) of Diagnosis with New-Onset Adult Strabismus by Age Group

Age Group (years)	19–29	30–39	40–49	50–59	60–69	70–79	80–89
LR Female (%)	4.0	3.9	3.7	3.5	3.3	2.8	2.1
LR Male (%)	3.9	3.8	3.7	3.6	3.3	2.8	1.9