DETERMINATION OF THE CORRELATION BETWEEN TYPES OF STRABISMUS AND CERTAIN MEDICAL CONDITIONS

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Abstract

Background: There are numerous subtypes of strabismus: esotropia where one eye deviates inward compared to the other, exotropia where one eye deviates outward compared to the other, hypertropia where one eyes is higher than the other, concomitant strabismus where the degree of deviation is the same in each gaze, incomitant strabismus where the degree of deviation varies in different gazes. Adult strabismus can be caused by various conditions including vasculopathic diseases (diabetes, hypertension, and stroke), compressive CNS lesions, myasthenia gravis, sensory strabismus, thyroid ophthalmopathy, multiple sclerosis, trauma, post-surgical strabismus, recurrent childhood strabismus, longstanding adult strabismus without proven cause, syndrome related strabismus, restrictive orbital masses, and congenital fibrosis of the extraocular muscles. It is currently unknown whether any of these underlying conditions correlate with a specific type of strabismus.

Purpose: The purpose of this study is to determine if underlying conditions correlate with a certain misalignment (i.e. esotropia, exotropia, hypertropia, concomitant, or incomitant). If there is a statistically significant correlation between a certain misalignment and systemic disease, this could add to the algorithm that physicians use to diagnose these systemic conditions.

Methods: This was a retrospective review of 692 patients >=21 years of age who presented to a pediatric ophthalmologist with adult strabismus from September 2008 to September 2015. The inclusion criteria were: (1) an age of 21 years or older, (2) a confirmed diagnosis of new-onset or recurrent childhood strabismus, (3) any severity and type of deviation, and (4) documentation of diplopia in any field of gaze. The variables that were extracted from the files were: the type of misalignment (esotropia, exotropia, hypertropia, concomitant, incomitant) and the underlying disorder (vasculopathic diseases (diabetes, hypertension, and stroke), compressive central nervous system (CNS) lesions, myasthenia gravis, sensory strabismus, thyroid ophthalmopathy, multiple sclerosis, trauma, post-surgical strabismus, recurrent childhood strabismus, longstanding adult strabismus without proven cause, syndrome related strabismus, restrictive orbital mass caused strabismus, and congenital fibrosis). Interpretation of the data consisted of determining if a correlation between type of misalignment and underlying condition exists.

Results: The average age of the population is 60.5 years with a standard deviation of 16.9, of which 49.6% were male. Results of this study indicate that multiple conditions that cause strabismus have a proclivity to negatively or positively predict a certain type of strabismus. Specifically, post-surgical patients are more likely to have hypertropia than esotropia or exotropia, sensory strabismus patients are more likely to have exotropia. Adult patients with recurrent childhood strabismus are more likely to have exotropia and concomitancy. Compressive CNS lesions, thyroid ophthalmopathy, and traumatic causes of strabismus are more likely to cause incomitant strabismus. Vasculopathic causes of strabismus do not have a tendency to cause any certain type of strabismus.

Conclusion: These findings will assist ophthalmologists in delineating a cause of their patient's strabismus based on which types of strabismus correlate with certain conditions.

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Introduction/Significance

CHILDHOOD STRABISMUS

Strabismus is the misalignment of one eye relative to the other. There are various types of strabismus that are defined according to the direction of the deviation relative to the other eye. The misalignment of the eyes can be horizontal, in which case one eye could deviate inward relative, called esotropia, or one eye could deviate outward relative to the other, called exotropia. The eyes could also be vertically misaligned, in which case one eye is said to be elevated compared to the other by convention, which is called hypertropia, but one eye could also be described as being depressed relative to the other eye, in which case it is called hypotropia. The angle of deviation could be present and consistent in all directions of gaze, in which case it is said to be concomitant, or it could vary in different directions of gaze, in which case it is said to be incomitant. Esotropia is the most common type of strabismus, with an incidence of 60.1%, followed by exotropia (32.7%) and hypertropia (6.7%).[8] The incidence of childhood esotropia is 111.0 per 100,000 in patients younger than 19 years old with an incidence of 1.94% in the first five years of life and 2.19% in the first ten years of life, but the incidence decreases with increasing age through 19 years of age.[5] The most common forms of childhood esotropia are fully accommodative esotropia, acquired nonaccommodative esotropia, esotropia associated with an abnormal central nervous system, and partially accommodative esotropia.[5, 8, 9] In fact, approximately half of childhood esotropia is either fully or partially accommodative esotropia.[5]

ADULT STRABISMUS

While the incidence of strabismus in adults aged 19 years and older is 54.1 cases per 100,000, which is approximately half of that for children, the estimated lifetime risk of an adult developing some type of strabismus is approximately 4.0% for men and 3.9% for women.[7] The distribution of the types of strabismus that present in adults is also different than that for children. The four most common types of adult strabismus are paralytic (44.2%), convergence insufficiency (15.7%), small angle hypertropia (13.3%), and divergence insufficiency (10.6%).[7] In addition, incidence of adult strabismus increases with age and peaks in the 8th decade of life, and esotropia, exotropia, and hypertropia occur with similar frequency in adults.[7]

The causes of paralytic strabismus are similar to that of children. Sixth nerve palsy, fourth nerve palsy, and third nerve palsy are all present in adults as they are in children with sixth nerve palsy causing esotropia, fourth nerve palsy causing hypertropia, and third nerve palsy causing exotropia and/or hypotropia.[7, 8] Internuclear ophthalmoplegia related to multiple sclerosis and myasthenia gravis are causes of paralytic strabismus that are unique to adult strabismus. Internuclear ophthalmoplegia is a condition in which the medial longitudinal fasciculus, which connects the sixth cranial nerve nucleus to the third cranial nerve nucleus in the pons, is injured. Therefore, on horizontal gaze, the eye that must adduct does not receive the neurological stimulus and, consequently, does not adduct as it should. However, convergence ability of both eyes is retained.

Unlike internuclear ophthalmoplegia and the other forms of paralytic strabismus, myasthenia gravis does not cause a specific type of strabismus. In patients with myasthenia gravis, an auto-antibody attack the nicotinic acetylcholine receptors on the post synaptic cell of the neuromuscular junction causing fatigable weakness of muscles, including the extraocular muscles.[11] Ocular myasthenia gravis is thought to be a milder form of the illness that progresses to the more sever generalized form. Although rare, ocular myasthenia gravis can also occur in children. Hypertension, diabetes mellitus, and stroke are other causes of acquired paralytic strabismus in adults. These vasculopathic diseases cause ischemic extraocular motor nerve palsies.[10]

While convergence insufficiency occurs in children as well as adults, the frequency with which convergence insufficiency causes strabismus in children and adults are quite different. The percentage of strabismus cases that are caused by convergence insufficiency in children is 6.4%, whereas the percentage of strabismus cases that are caused by convergence insufficiency in adults is 15.7%. [10]

Other causes of strabismus in adults are sensory strabismus and restrictive strabismus. Sensory strabismus is caused by a pre-existing unilateral ocular condition decreasing visual acuity resulting in subsequent strabismus not resulting from another cause.[7] It is not known whether the type of strabismus caused by a sensory deficit is more like to cause a certain type of strabismus (esotropia, exotropia, or hypertropia). Restrictive strabismus is defined as a recent or pre-existing diagnosis of Grave's disease, trauma, space occupying lesion within the orbit, or ocular or facial surgery with evidence of extraocular muscle restriction.[7] In Grave's disease, the mechanism of thyroid-associated ophthalmopathy is not entirely known. Fibroblasts in the orbital tissue express thyroid stimulating hormone (TSH) receptor, to which the body produces auto-antibodies in Grave's disease. Therefore, the accumulation of T lymphocytes sensitized to the TSH receptor in the orbit leads to immunological abnormalities causing infiltration of mucopolysaccharides, inflammatory cells, and immune complexes into the orbital fat and extraocular muscles, resulting in increased orbital volume and pressure.[2] It is not known whether thyroid ophthalmopathy causes a specific type (esotropia, exotropia, or hypertropia) of strabismus more frequently than another.

Other less common types of adult strabismus are compressive lesions within the CNS, strabismus caused by underlying syndromes, and congenital fibrosis of the extraocular muscles.[3] Examples of lesions within the CNS that can cause compression of cranial nerves are CNS abscesses, aneurysms, and tumors. Some syndromes that cause strabismus in adults are Marfan syndrome, Engelmen syndrome, Rett syndrome as well as others. Congenital fibrosis of the extraocular muscles can present in adulthood as the fibrosis progresses in its restriction of the extraocular muscles.

Divergence insufficiency is defined as diplopia at distance with an esotropia greater in distance than near and absence of double vision at near.[6, 7] Since divergence insufficiency incidence increases with age, peaking in the 8th decade of life, one proposed mechanism is medial rectus muscle shortening occurring in response to increased convergence tonus resulting from increased accommodative effort.[13] As people age, their lenses naturally become less elastic; therefore, the accommodation process becomes less effective, thereby leading to hyperopia.

This age related hyperopia caused by inelasticity of the lens is called presbyopia. Therefore, presbyopic adults can develop divergence insufficiency due to medial rectus muscle shortening. These patients have long standing strabismus that develops as an adult without any proven cause.

SIGNIFICANCE AND RATIONALE

It has yet to be determined whether certain conditions such as: vasculopathic diseases (diabetes, hypertension, and stroke), compressive CNS lesions, myasthenia gravis, sensory strabismus, thyroid ophthalmopathy, multiple sclerosis, trauma, post-surgical strabismus, recurrent childhood strabismus, longstanding adult strabismus without proven cause, syndrome related strabismus, restrictive orbital mass caused strabismus, and congenital fibrosis are associated with certain types of strabismus such as esotropia, exotropia, hypertropia, concomitant, or incomitant. If there is such a correlation, it could augment the diagnosis criteria for these conditions.

Research Methods and Materials

This study was a retrospective chart review of 692 patients at least 21 years of age who present to a pediatric ophthalmologist with adult strabismus from September 2008 through September 2015. The inclusion criteria was: (1) an age of 21 years or older, (2) a confirmed diagnosis of new-onset or recurrent childhood strabismus, (3) any severity and type of deviation, and (4) documentation of diplopia in any field of gaze. The variables that were extracted from the files were: age, gender, the type of misalignment (esotropia, exotropia, hypertropia, concomitant, incomitant), and the underlying disorder (vasculopathic diseases (diabetes, hypertension, and stroke), compressive CNS lesions, myasthenia gravis, sensory strabismus, thyroid ophthalmopathy, multiple sclerosis, trauma, post-surgical strabismus, recurrent childhood strabismus, longstanding adult strabismus without proven cause, syndrome related strabismus, restrictive orbital mass caused strabismus, and congenital fibrosis). The data was deidentified before being recorded onto a password protected computer.

Independent Covariates and Outcomes

The study had five binary outcomes: esotropia status, exotropia status, hypertropia status, concomitant status, and incomitant status. Furthermore, binary categorical independent predictors of vasculopathic diseases (diabetes, hypertension, and stroke), compressive CNS lesions, myasthenia gravis, sensory strabismus, thyroid ophthalmopathy, multiple sclerosis, trauma, post-surgical strabismus, recurrent childhood strabismus, longstanding adult strabismus without proven cause, syndrome related strabismus, restrictive orbital mass caused strabismus, and congenital fibrosis were assessed in this study.

Statistical Analysis

Patient demographic and clinical characteristics were determined using descriptive statistics including means, standard deviations for continuous variables, and frequencies, proportions for categorical variables. The T-test was implemented to assess differences in continuous variables between the presence and non-presence of the outcome. Chi-squared analysis was implemented to assess the differences in proportions. To determine the association between the potential predictors and the outcomes, two models were formed for each outcome by implementing logistic regression to estimate odds ratios and 95% confidence intervals. First, univariate analysis was used to assess each predictor separately with logistic regression. The second model contained all the predictors to assess whether the independent variables predict the outcomes as a group. The second model also was adjusted for the confounders age, gender and race. Since, there were five outcomes in the study, the proposed statistical analysis plan was implemented for each outcome.

Results

Overall population statistics

The average age of the population is 60.5 years with a standard deviation of 16.9, of which 49.6% were male. The breakdown of the outcomes were: 10.1% with esotropia, 42.6% with exotropia, 55.4% with hypertropia, 66.2% with concomitant status, 33.8% with incomitant status. The breakdown of the predictors were: vascular event 16.6%, compressive lesion 0.87%, myasthenia gravis 1.7%, sensory strabismus 3.0%, thyroid ophthalmopathy 12.3%, multiple sclerosis 0.29%, trauma 9.8%, post-surgical 13.9%, childhood strabismus 14.2%, long-standing adult strabismus without a proven cause 26.5%, syndrome related strabismus 2.8%, restrictive orbital mass 0.29%, and restrictive fibrosis 0.29% (Table 1).

Table 1: Overall Population Statistics

Variables	Values
Age (mean, SD)	60.5 (16.9)
Gender (male, %)	343 (49.6)
N(%)	
Esotropia	70 (10.1)
Exotropia	295 (42.6)
Hypertropia	383 (55.4)
Concomitant Status	458 (66.2)
Incomitant Status	234 (33.8)
Vascular Event	115 (16.6)
Compressive Lesion	6 (0.87)
Myasthenia Gravis	12 (1.73)
Sensory Strabismus	21 (3.03)
Thyroid Ophthalmopathy	85 (12.3)
Multiple sclerosis	2 (0.29)
Trauma	68 (9.83)
Post-Surgical	96 (13.9)
Childhood Strabismus	98 (14.2)
Long Standing Adult Strabismus	183 (26.5)
Syndrome	19 (2.75)
Restrictive Orbital Mass	2 (0.29)
Restrictive Fibrosis	2 (0.29)

The first table (Tables 2, 4, 6, 8, and 10) for each outcome shows how each predictor related to the outcome. The table demonstrates number and percentage of the patients with each predictor that have the outcome and do not have the outcome, as well as the p-value associated with that predictor.

In the second table (Tables 3, 5, 7, 9, and 11) for each outcome, all the predictors with p-values of less than 0.20 were added to a multiple logistic regression model to ascertain how well those characteristics predicted each outcome. Within the multiple logistic regression, any characteristic with a p-value less than 0.05 is a significant predictor. The area under the curve signifies how well the variables as a group in the multivariate model predicted the final outcome. Ideally, the area under the curve should be at least 0.70.

Esotropia

The predictors that were chosen to undergo multiple logistic regression based on a p-value of less than 0.02 were gender, post-surgical, long standing strabismus, and syndrome (Table 2). Of these variables, post-surgical status was a significant predictor of esotropia. Post-surgical patients were 72% less likely to have esotropia due to its odds ratio of 0.28 (Table 3). The area under the curve was 0.62 (Table 3).

Table 2: Univariate Analysis of Esotropia

Variables	No Esotropia N=622	Esotropia N=70	P-Value[1]
Age (mean, SD)	60.3 (17.2)	62.5 (13.9)	0.30
Gender (male, %)	315 (50.6)	28 (40.0)	0.09
N (%)			
Vascular Event	102 (16.4)	13 (18.6)	0.64
Compressive Lesion	6 (0.96)	0 (0.0)	1.0
Myasthenia Gravis	11 (1.77)	1 (1.43)	0.83
Sensory Strabismus	20 (3.22)	1 (1.43)	0.42
Thyroid Ophthalmopathy	77 (12.4)	8 (11.4)	0.81
MS	2 (0.32)	0 (0.0)	1.0
Trauma	60 (9.65)	8 (11.4)	0.63
Post-Surgical	93 (14.9)	3 (4.29)	0.02
Childhood Strabismus	88 (14.2)	10 (14.3)	0.97
Long Standing Adult Strabismus	160 (25.7)	23 (32.9)	0.20
Syndrome	15 (2.41)	4 (5.71)	0.12
Restrictive Orbital Mass	2 (0.32)	0 (0.0)	1.0
Restrictive Fibrosis	2 (0.32)	0 (0.0)	1.0

[1]P-values calculated via univariate analysis using Logistic regression.

Table 3: Multivariate Analysis of Esotropia

Variables	Odds Ratio (95% CI)	P-Value[1]
Gender (male)	0.64 (0.38, 1.07)	0.08
Post-Surgical	0.28 (0.09, 0.93)	0.04
Long Standing Adult Strabismus	1.30 (0.75, 2.24)	0.34
Syndrome	2.25 (0.71, 7.15)	0.16
Area Under the Curve	0.62	

[1]P-Values calculated using Multiple Logistic Regression adjusting for all other variables within the model

Exotropia

The predictors that were chosen to undergo multiple logistic regression were age, compressive lesion, sensory strabismus, post-surgical, childhood strabismus, and long standing strabismus (Table 4). Of these variables, age, sensory strabismus, post-surgical, and childhood strabismus were significant predictors for exotropia. For every one year of increase in age, patients are 2% less likely to develop exotropia. Post-surgical patients were 76% less likely to develop exotropia with its odds ratio of 0.24; childhood strabismus and sensory strabismus patients were 2.89 and 24 times more likely to have exotropia respectively. The area under the curve was 0.70, which demonstrates that these variables as a whole predict exotropia well (Table 5).

Table 4: Univariate Analysis of Exotropia

Variables	No Exotropia N=397	Exotropia N=295	P-Value[1]
Age (mean, SD)	63.9 (15.6)	55.9 (17.6)	<0.001
Gender (male, %)	195 (49.1)	148 (50.2)	0.78
(N %)			
Vascular Event	62 (15.6)	53 (17.9)	0.41
Compressive Lesion	6 (1.51)	0 (0.0)	0.04
Myasthenia Gravis	7 (1.76)	5 (1.69)	0.94
Sensory Strabismus	1 (0.25)	20 (6.78)	<0.001
Thyroid Ophthalmopathy	53 (13.4)	32 (10.9)	0.32
MS	0 (0.0)	2 (0.68)	1.0
Trauma	40 (10.1)	28 (9.49)	0.79
Post-Surgical	81 (20.4)	15 (5.08)	<0.001
Childhood Strabismus	28 (7.05)	70 (23.7)	<0.001
Long Standing Adult Strabismus	114 (28.7)	69 (23.4)	0.11
Syndrome	9 (2.27)	10 (3.39)	0.37
Restrictive Orbital Mass	2 (0.50)	0 (0.0)	1.0
Restrictive Fibrosis	1 (0.34)	1 (0.34)	1.0

[1]P-values calculated via univariate analysis using Logistic regression.

Table 5: Multivariate Analysis of Exotropia

Variables	Odds Ratio (95% CI)	P-Value[1]
Age (per 1 year increase)	0.98 (0.97, 0.99)	0.006
Compressive Lesion	0.19 (0.02, 1.70)	0.14
Sensory Strabismus	24.4 (3.21, 185.1)	0.002
Post-Surgical	0.29 (0.16, 0.54)	<0.001
Childhood Strabismus	2.89 (1.72, 4.86)	<0.001
Long Standing Adult Strabismus	0.84 (0.57, 1.24)	0.40
Area Under the Curve	0.70	

[1]P-Values calculated using Multiple Logistic Regression adjusting for all other variables within the model.

Hypertropia

The predictors that were chosen to undergo multiple logistic regression were age, compressive lesion, sensory strabismus, post-surgical, childhood strabismus, and syndrome (Table 6). Of these variables, sensory, post-surgical, and childhood strabismus were significant predictors for hypertropia. Sensory and childhood strabismus were protective predictors with sensory and childhood strabismus patients being 96% and 75% less likely to have hypertropia respectively. Post-surgical patients were 10.5 times more likely to develop hypertropia. The area under the curve was 0.72, which demonstrates that these variables as a whole predict hypertropia well (Table 7).

Table 6: Univariate Analysis of Hypertropia

Variables	No Hypertropia N=309	Hypertropia N=383	P-Value[1]
Age (mean, SD)	56.3 (17.5)	63.9 (15.7)	<0.001
Gender (male, %)	153 (49.5)	190 (49.6)	0.98
N (%)			
Vascular Event	56 (18.1)	59 (15.4)	0.34
Compressive Lesion	0 (0.0)	6 (1.57)	0.14
Myasthenia Gravis	5 (1.62)	7 (1.83)	0.83
Sensory Strabismus	21 (6.80)	0 (0.0)	0.001
Thyroid Ophthalmopathy	35 (11.3)	50 (13.1)	0.49
MS	2 (0.65)	0 (0.0)	1.0
Trauma	26 (8.41)	42 (10.9)	0.26
Post-Surgical	6 (1.94)	90 (23.5)	<0.001
Childhood Strabismus	75 (24.3)	23 (6.01)	<0.001
Long Standing Adult Strabismus	79 (25.6)	104 (27.2)	0.36
Syndrome	13 (4.21)	6 (1.57)	0.04
Restrictive Orbital Mass	0 (0.0)	2 (0.52)	1.0
Restrictive Fibrosis	1 (0.32)	1 (0.26)	1.0

[1]P-values calculated via univariate analysis using Logistic regression.

Table 7: Multivariate Analysis of Hypertropia

Variables	Odds Ratio (95% CI)	P-value[1]
Age (per 1 year increase)	1.01 (0.99, 1.02)	0.14
Compressive Lesion	5.86 (0.66, 51.8)	0.11
Sensory strabismus	0.04 (0.005, 0.28)	0.002
Post-Surgical	10.5 (4.46, 24.5)	<0.001
Childhood Strabismus	0.25 (0.15, 0.43)	<0.001
Syndrome	0.39 (0.14, 1.06)	0.06
Area Under the Curve	0.72	

[1]P-Values calculated using Multiple Logistic Regression adjusting for all other variables within the model.

Concomitant

The predictors that were chosen to undergo multiple logistic regression were age, compressive lesions, sensory strabismus, thyroid ophthalmopathy, childhood, and long standing strabismus (Table 8). Of these variables, compressive lesions, thyroid ophthalmopathy, and childhood strabismus were significant predictors for concomitancy. Compressive lesions and thyroid ophthalmopathy were protective factors for concomitancy with compressive lesion patients and thyroid ophthalmopathy patients being 83% and 42% less likely to have concomitant strabismus respectively. Childhood strabismus patients were 1.95 times more likely to have concomitant strabismus. The area under the curve was 0.63, indicating that there may be another characteristic that exists to help predict concomitant strabismus that was not included (Table 9).

Table 8: Univariate Analysis of Concomitancy

Variables	No Concomitant N=234	Concomitant N=458	P-Value[1]
Age (mean, SD)	59.3 (15.9)	61.1 (17.4)	0.18
Gender (male, %)	123 (52.6)	220 (48.0)	0.26
N (%)			
Vascular Event	38 (16.2)	77 (16.8)	0.84
Compressive Lesion	4 (1.71)	2 (0.44)	0.05
Myasthenia Gravis	5 (2.14)	7 (1.53)	0.56
Sensory Strabismus	4 (1.71)	17 (3.71)	0.12
Thyroid Ophthalmopathy	39 (16.7)	46 (10.0)	0.01
MS	0 (0.0)	2 (0.44)	1.0
Trauma	38 (16.2)	30 (6.6)	<0.001
Post-Surgical	31 (13.3)	65 (14.2)	0.73
Childhood Strabismus	23 (9.8)	75 (16.4)	0.02
Long Standing Adult Strabismus	51 (21.8)	132 (28.8)	0.04
Syndrome	132 (28.8)	4 (1.71)	0.21
Restrictive Orbital Mass	2 (0.85)	0 (0.0)	1.0
Restrictive Fibrosis	1 (0.43)	1 (0.22)	1.0

[1]P-values calculated via univariate analysis using Logistic regression.

Table 9: Multivariate Analysis of Concomitancy

Variables	Odds Ratio (95% CI)	P-Value[1]
Age (per 1 year increase)	1.01 (0.99, 1.02)	0.07
Compressive Lesions	0.17 (0.03, 0.93)	0.04
Sensory Strabismus	2.51 (0.81, 7.82)	0.11
Thyroid Ophthalmopathy	0.58 (0.35, 0.97)	0.04
Childhood Strabismus	1.95 (1.08, 3.51)	0.03
Long standing adult strabismus	1.29 (0.84, 1.99)	0.23
Area Under the Curve	0.63	

[1]P-Values calculated using Multiple Logistic Regression adjusting for all other variables within the model.

Incomitant

The predictors that were chosen to undergo multiple logistic regression were age, compressive lesion, sensory strabismus, thyroid ophthalmopathy, trauma, childhood and long standing strabismus (Table 10). Of these variables compressive lesion, thyroid ophthalmopathy, trauma, and childhood strabismus were significant predictors for incomitancy. Those patients with childhood strabismus were 49% less likely to have incomitant strabismus. Patients with compressive lesions, thyroid ophthalmopathy, and traumatic strabismus were 5.68, 1.70, and 2.28 times more likely to have incomitant strabismus. The area under the curve was 0.63, indicating that there may be another characteristic that exists to help predict incomitant strabismus that was not included (Table 11).

Table 10: Univariate Analysis of Incomitancy

Variables	No Incomitant N=458	Incomitant N=234	P-Value[1]
Age (mean, SD)	61.1 (17.4)	59.3)	0.18
Gender (male, %)	220 (48.0)	123 (52.6)	0.26
N (%)			
Vascular Event	77 (16.8)	38 (16.2)	0.84
Compressive Lesion	2 (0.44)	4 (1.71)	0.05
Myasthenia Gravis	7 (1.53)	5 (2.14)	0.56
Sensory Strabismus	17 (3.71)	4 (1.71)	0.12
Thyroid Ophthalmopathy	46 (10.0)	39 (16.7)	0.01
MS	2 (0.44)	0 (0.0)	1.0
Trauma	30 (6.55)	38 (16.2)	<0.001
Post-Surgical	65 (14.2)	31 (13.3)	0.73
Childhood Strabismus	75 (16.4)	23 (9.83)	0.02
Long Standing Adult Strabismus	132 (28.8)	51 (21.8)	0.04
Syndrome	15 (3.28)	4 (1.71)	0.24
Restrictive Orbital Mass	0 (0.0)	2 (0.85)	1.0
Restrictive Fibrosis	1 (0.22)	1 (0.43)	1.0

[1]P-values calculated via univariate analysis using Logistic regression.

Table 11: Multivariate Analysis of Incomitancy

Variables	Odds Ratio (95% CI)	P-Value[1]
Age (per 1 year increase)	0.99 (0.97, 1.00)	0.07
Compressive Lesion	5.68 (1.06, 30.2)	0.04
Sensory Strabismus	0.39 (0.12, 1.23)	0.11
Thyroid Ophthalmopathy	1.70 (1.02, 2.84)	0.04
Trauma	2.28 (1.28, 4.06)	0.005
Childhood Strabismus	0.51 (0.28 (0.92)	0.03
Long Standing Adult Strabismus	0.77 (0.50, 1.18)	0.23
Area Under the Curve	0.63	

[1]P-Values calculated using Multiple Logistic Regression adjusting for all other variables within the model

Discussion

As was hypothesized, different conditions in adult patients act as positive or negative predictors for a certain type of strabismus. These results can now augment the physician's algorithm for determining the cause of an adult patient's strabismus.

Esotropia

Our results indicated that post-surgical status of a patient is a negative predictor for esotropia. Therefore, when a patient presents with esotropia, it is unlikely that an ocular surgery is the cause of this condition. Although post-surgical status was the only predictor that had an odds ratio with statistical significance on multiple linear regression, the area under the curve was 0.62 indicating that there may be another characteristic that exists to help predict esotropia that was not included.

Exotropia

Increasing age was a negative predictor of exotropia, which was consistent with previous theories that stated age related presbyopia caused divergence insufficiency, a specific type of esotropia.[13] Post-surgical status was also a negative predictor of exotropia, as it was with esotropia. Therefore, in older patients and patients post-surgery, exotropia is less likely to be their presenting type of strabismus.

In contrast, childhood strabismus and sensory strabismus were strong positive predictors of exotropia. Since childhood strabismus is a positive predictor for exotropia, it is possible that exotropia in children is more likely to recur later in life, but this has yet to be validated. In addition, prior to this sensory causes of strabismus were not known to cause any specific type of strabismus, but with an odds ratio of 24, it is clear that diminished visual acuity that causes strabismus has a strong proclivity for causing exotropia.[7] The mechanism for this is unknown. However, if presbyopia causes medical rectus shortening in aging adults yielding esotropia, it is possible that prolonged diminished visual acuity can cause lateral rectus shortening yielding exotropia.

Hypertropia

Sensory and childhood strabismus were negative predictors of hypertropia. As previously discussed sensory strabismus is a strong positive predictor for exotropia; therefore, it would make sense that it would be a strong negative predictor for the other types of strabismus including hypertropia as is demonstrated with an odds ratio of 0.04. It is unclear why sensory status was not a strong negative predictor for esotropia, but as previously noted the area under the curve for esotropia was 0.62, meaning there may be more predictors not included in the statistical analysis for esotropia that are required for more complete analyses. Since childhood strabismus is a negative predictor of hypertropia, it is possible that hypertropia in children is more easily treated and less likely to recur in adulthood.

Post-surgical status is a strong positive predictor for hypertropia. Transient strabismus after ocular surgery is thought to result from anesthetic effects on the extraocular muscles, soft tissue swelling, or an exposition of previously unnoticed strabismus.[1, 12] One theory for the observed complication of hypertropia after ocular surgery is that a common local anesthetic administration location during ocular surgeries is the inferior orbit, which could result in transient paralysis or paresis of the inferior rectus muscle.

Concomitant

Compressive CNS lesions and thyroid ophthalmopathy were negative predictors of concomitant strabismus. Thyroid disease, specifically Grave's disease, causes an accumulation of mucopolysaccharides, immune complexes, and inflammatory cells in the orbital fat and extraocular muscles leading to mass effect within the orbit as well as restriction within the extraocular muscles.[2] This mass effect within the orbit can cause varying degrees of restriction of ocular movements in different gazes based on where the mass effect is located. Therefore, it follows that thyroid disease would not cause concomitant strabismus. The compressive CNS lesions such as aneurysms, tumors, or abscesses compress one of the cranial nerves that control ocular movements leading to strabismus; however, it is unclear why this would protect against concomitancy. However, the area under the curve was 0.63, indicating that there may be another characteristic that exists to help predict concomitant strabismus that was not currently included.

Childhood strabismus status positively predicted concomitancy with an odds ratio of 1.95 indicating that potentially concomitant childhood strabismus is more likely to recur in adulthood.

Incomitant

Conversely, childhood strabismus status negatively predicted incomitancy with an odds ratio of 0.51 indicating that potentially incomitant childhood strabismus is less likely to recur in adulthood.

Compressive CNS lesions, thyroid ophthalmopathy, and traumatic strabismus were all positive predictors of incomitant strabismus. As previously described, the mass effect within the orbit from thyroid disease causes varying degrees of eye movement restriction in different gazes; therefore, it makes sense that thyroid ophthalmopathy is a positive predictor of incomitancy. Traumatic strabismus caused by entrapment of extraocular muscles within a fracture or soft tissue swelling also conforms with the result of varying degrees of eye movement restriction in different gazes.[10] It is unclear why compressive CNS lesions would yield incomitant strabismus; however, the area under the curve was 0.63, indicating that there may be another characteristic that exists to help predict incomitant strabismus that was not included.

Vasculopathic diseases such as (diabetes, hypertension, and stroke), myasthenia gravis, multiple sclerosis, longstanding adult strabismus without a proven cause, syndrome related strabismus, restrictive orbital mass caused strabismus, and congenital fibrosis were not significant predictors for any specific type of strabismus. Each of these predictors, with the exception of vasculopathic diseases and longstanding adult strabismus without a proven cause, did not have a large sample size, which is most likely why there was no statistical significance associated with these variables. One study found an association between diabetes and diabetes in combination with hypertension with sixth nerve palsies, but no such studies have been conducted to ascertain if such an association also exists with third and fourth nerve palsies.[16] Another article looking at the primary care perspective of diabetic eye disease stated that microvascular mononeuropathy can occur in any of the cranial nerves innervating the eye without preference.[4] Our results are consistent with this study as the vasculopathic diseases did not have a preference for causing any certain type of strabismus. Longstanding adult strabismus without a proven cause also did not predict any certain type of strabismus. Since there was no identifiable cause, there were likely various origins of these patients' strabismus making it implausible to identify a unifying predictor.

Future Directions

Future studies are needed to verify the results of this study, as this is the first study of its kind. Specifically, future studies need to identify more patients with myasthenia gravis, multiple sclerosis, syndrome related strabismus, restrictive orbital mass caused strabismus, and congenital fibrosis to increase their sample size in order to hopefully find a correlation with these conditions and certain types of strabismus. Since vasculopathic diseases are so prevalent, this category could be separated into its specific conditions to determine if diabetes, hypertension, or stroke cause different types of strabismus.

Conclusions

Results of this study indicate that multiple conditions that cause strabismus have a proclivity to negatively or positively predict a certain type of strabismus. Specifically, post-surgical patients are more likely to have hypertropia than esotropia or exotropia, sensory strabismus patients are more likely to have exotropia. Adult patients with recurrent childhood strabismus are more likely to have exotropia and concomitancy. Compressive CNS lesions, thyroid ophthalmopathy, and traumatic causes of strabismus are more likely to cause incomitant strabismus. Vasculopathic causes of strabismus do not have a tendency to cause any certain type of strabismus. These findings will assist ophthalmologists in delineating a cause of their patient's strabismus based on which types of strabismus correlate with certain conditions.

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