The Turkish Journal of Pediatrics 2022; 64: 341-349
https://doi.org/10.24953/turkjped.2021.204

Original Article

Non-ocular risk factors in Turkish children with strabismus and amblyopia

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ABSTRACT

Background. To evaluate non-ocular risk factors including family history, febrile seizure, history of trauma, neurological diseases, and prematurity in Turkish children with strabismus and amblyopia.

Methods. The records of patients diagnosed with strabismus and/or amblyopia below 18 years old, were recruited. The current mean age, sex, types and subtypes of strabismus and amblyopia, family history, history of trauma, and febrile seizure were investigated. The presence of neurological diseases and prematurity were noted. Family history was investigated whether the presence of strabismus or amblyopia was maternal or paternal. Blood relatives were divided into 3 groups including first, second, and third-degree relatives. The relationship between blood relative degrees and types of strabismus or amblyopia were assessed.

Results. There were 803 patients with a current median age of 8 years (1-29 years). Of these patients, 786 patients could be evaluated and 55% had esotropia (ET), 32.6% had exotropia (XT) and 12.5% had amblyopia as a primary diagnosis. Positive family history of strabismus or amblyopia was more common among all risk factors. There was a statistically significant rate of patients with a positive family history in the first-degree relatives, in the esotropic patient group (p= 0.002). Maternal positive family history was more common in patients with refractive ET (p= 0.024) and paternal positive family history was more common in patients with intermittent XT (p= 0.009).

Conclusions. The rates of positive family history of amblyopia and strabismus were not statistically different. Family history of strabismus in first-degree relatives of patients with esotropia was markedly high. The family history of strabismus on the maternal or paternal side might be different in patients with different subtypes of strabismus.

Key words: strabismus, amblyopia, non-ocular risk factors, family history.

Ocular misalignment and amblyopia are common and important ocular diseases that might cause visual impairment if left untreated in childhood. Ocular misalignment or in other words, strabismus might be caused by abnormalities in binocular vision or by anomalies of neuromuscular control of ocular motility. Amblyopia can be defined as a unilateral or bilateral reduction of best-corrected visual acuity (BCVA) that can not be attributed directly to the effect of any structural abnormality of the eye or visual pathways.[1]

The prevalence of strabismus was 1.93% worldwide, in a recent meta-analysis.[2] Ocular risk factors for strabismus development were found to be hyperopia, moderate anisometropia, and amblyopia, in a recent study.[3] Other risk factors, including positive family history, additional neurological diseases, history of trauma, Down Syndrome, prematurity, and low birth weight were assessed previously, in the literature.[4-8]

The prevalence of amblyopia was reported to be 2.8% in a recent study that investigated

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Received 15th January 2021, revised 28th April 2021, 29th July 2021, 31st August 2021, 17th October 2021, accepted 7th November 2021.

This paper was presented online at the Turkish Ophthalmology Association 2020 National and Compound Congress, December 2020, Antalya, Turkey.

amblyopia among children in an Eastern European Country.[9] Ocular risk factors for amblyopia were strabismus, anisometropia, hyperopia, astigmatism, and congenital nasolacrimal duct obstruction.[9,10] Non-ocular risk factors, including a family history of amblyopia, prematurity, low birth weight, maternal age, neurological diseases were found, in previous studies.[5,7,11,12]

To the best of our knowledge, there have been no studies focusing on these risk factors in Turkish children. In the present study, we aimed to assess non-ocular risk factors, including family history, previous trauma, febrile seizure history, prematurity, and neurological diseases in Turkish children with different types of strabismus or amblyopia. We focused on children with strabismus and/or amblyopia because these disorders are the most common disorders we have to deal with in our Pediatric Ophthalmology Department and they are related closely with each other. We also investigated possible differences in maternal or paternal family history and the differences in family blood relative degrees.

Material and Methods

The present, retrospective study was conducted at Sakarya University hospital. Prior approval from the Institutional Review Board was taken (Sakarya University Ethical Committee, IRB number: 71522473/050.01.04/54). The study was performed in adherence to the Declaration of Helsinki.

A retrospective chart review of all records at the Pediatric Ophthalmology Department was performed. The chart reviews included medical records between January 2014 and December 2019. The records of patients with strabismus and amblyopia were enrolled. The number of patients with the primary diagnosis of esotropia (ET), exotropia (XT), hypertropia, and amblyopia was noted. When present, secondary and tertiary diagnoses were also noted. The inclusion criteria were the presence of ET, XT, hypertropia, and/or amblyopia in the patients who were diagnosed below the age of 18 years old. Patients who were diagnosed above the age of 18 years old and who had incomitant strabismus were the exclusion criteria of the study.

Strabismus types of patients were classified. Subtypes of ET were refractive accommodative ET (RAET), partially refractive ET (PAET), infantile ET (IET), basic acquired nonaccommodative ET (BANAET), and sensory ET (SET). Subtypes of XT were intermittent XT (IXT), constant XT (CXT), infantile XT, and sensory XT (SXT). Amblyopia might be defined as the reduction of best-corrected visual acuity of one or both eyes that cannot be attributed exclusively to a structural abnormality of the eye.[13] Amblyopia was classified as isoametropic, anisometropic, strabismic, and visual deprivation (VD) amblyopia.

The mean age, gender, mean BCVA which was measured by Snellen chart, spherical equivalent (SE), the value of astigmatism, presence of myopia or hyperopia, presence of inferior oblique overaction (IO OA), and strabismus surgery requirement were noted. Refractive error measurements were done under cycloplegic conditions by using an auto refractometer (Nidek ARK-30) or retinoscopy. An alternate cover test in near and distance was performed by using prism bars to measure ocular deviations.

Positive family history was defined as the presence of the same type of strabismus or amblyopia in blood relatives. The presence of strabismus or amblyopia in the first, second, and third-degree relatives of patients were investigated. Additionally, the information, whether these relatives were maternal or paternal, was also assessed. These data were obtained from the parents of children besides first and second degree relatives were also examined in our strabismus department. The characteristics of family history were evaluated in different subtypes of strabismus and amblyopia.

Previous febrile seizure history of patients was noted and the rates of febrile seizure history was investigated in subtypes of strabismus or amblyopia.

Previous head trauma which was linked to the beginning of strabismus, in the infancy period was asked to all patients or parents of patients and noted. The distribution of the number of patients with trauma history, among patients with different types of strabismus, was also investigated.

Neurological diseases including hydrocephalus, developmental delay, cerebral palsy and attention deficit and hyperactivity disorder (ADHD) were found out and evaluated in strabismic or amblyopic patients. Besides, patients who had Down Syndrome were also noted and evaluated in this group.

Prematurity was investigated among patients with strabismus or amblyopia. The effect of prematurity on different types of strabismus was also evaluated. Besides, the mean birth weight, gestational age, and neonatal intensive care unit (NICU) requirement were noted.

Statistical Analysis

Statistical analysis was performed by using SPSS statistical software (IBM SPSS Statistics, Version 23.0. Armonk, NY: IBM Corp.) Descriptive analyses were performed to provide information on the general characteristics of the study population. Kolmogorov-Smirnov test was used to evaluate whether the distributions of numerical variables were normal. The numeric variables were presented as mean ± standard deviation. Categorical variables were compared by the Chi-Square test. A p-value <0.05 was considered significant.

Results

Totally 803 patients were enrolled in this study. Table I reveals the characteristics of patients. The mean age given in the Table I was the current age of patients. All patients were diagnosed with strabismus and amblyopia below 18 years old. The number of patients with solely vertical deviation was only 9 and 8 patients had unclassifiable diagnoses such as Duane syndrome, restrictive strabismus. So 786 patients with the diagnosis of exo-, esodeviations, and amblyopia could be analyzed in comparisons (Of these patients, 432 had ET, 256 had XT, and 98 had amblyopia as a primary diagnosis). The number of patients who had vertical deviations as a secondary diagnosis was 16. In Table II, subtypes of eso- and exodeviations and amblyopia are seen. Patients

Table I. General characteristics of patients.

The median age (minimum-maximum)	8 years (1-29 years)
Female/male ratio	412/391
The mean BCVA of right eyes (decimal) (n:687)	0.80±0.24
The median SE of right eyes (n:797) (min-max)	2.25D (-0.50-13.5D)
The median astigmatism of right eyes (n:797) (min-max)	0.50D (0D-5.25D)
The median astigmatism axe of right eyes (n:797)	65° (0°-180°)
The percentage of patients with ET	55 %
The percentage of patients with XT	32.6 %
The percentage of patients with amblyopia as a primary diagnosis	12.5 %
Presence of IO OA (%)	21%
Patients with surgery requirement (%)	31,3%
The mean GA of preterms (n:134)	32.0±3.6 week
The mean BW of preterms (n:134)	1856.3±787.6 gram

BCVA: best corrected visual acuity, SE: spherical equivalent, IO OA: inferior oblique overaction, GA: gestational age, BW: birth weight, ET: esotropia, XT: exotropia

Table II. Number of patients with subtypes of ET, XT, and amblyopia.

		N	%
Subtypes of ET	RAET	207	26.3
	PAET	84	10.7
	IET	46	5.9
	BANAET	86	10.9
	Sensory ET	9	1.1
	Total	432	55
Subtypes of XT	IXT	189	24
	CXT	56	7.1
	Infantile XT	3	0.4
	Sensory XT	8	1
	Total	256	32,5
Subtypes of Amblyopia*	Strabismic	124	15.8
	Anisometropic	152	19.3
	Isometropic	39	5
	VD	12	1.5
	Total	327	41.6

ET: esotropia, RAET: refractive accommodative esotropia, PAET: partially refractive esotropia, IET: infantile esotropia, BANAET: basic nonaccommodative esotropia, XT: exotropia, IXT: intermittent exotropia, CXT: constant exotropia, VD: visual deprivation
*: patients with the diagnosis of amblyopia in all groups.

with RAET in the esodeviation group and IXT in exodeviation group were more common. In the amblyopia group, anisometropic amblyopia was more common. The number of patients who had amblyopia as a primary diagnosis was 98 (12,5%) but in total 327 amblyopic patients were evaluated (Fig. 1).

The percentage of patients with a non-ocular risk factor was 83.9%. Table III reveals these rates in detail. Positive family history was found to be more common among all risk

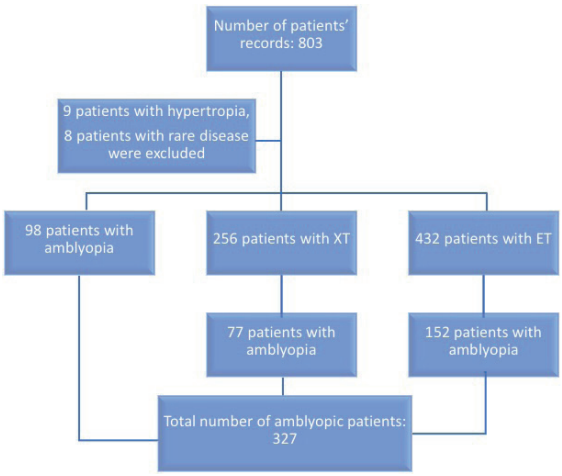

Fig. 1. The flow chart of the patients recruited in the study.

factors. Neurological diseases included global developmental delay, cerebral palsy, hydrocephalus, epilepsy, history of intracranial hemorrhage, attention deficit disorders, and 21 patients had Down Syndrome. The diagnosis of these neurological diseases were obtained from the records of patients in the hospital system and from the parents of the children.

Positive family history was more common in patients with esotropia but statistically, a significant difference was not seen between amblyopic patients and patients with eso- and exodeviatons (p= 0.088). Rates of other risk factors including febrile seizure, history of trauma, presence of neurological diseases, and prematurity were also not different between groups (p=0.16, p=0.50, p=0.20, p=0.42, respectively).

Table IV reveals positive family history rates of patients with subtypes of eso-, exodeviations,

Table III. Percentages of esotropic, exotropic, and amblyopic patients with nonocular risk factors.

	ET n (%)	XT n (%)	Amblyopia n (%)	Total n (%)
Positive family history	151(19.2)	75 (9.5)	42 (5.3)	268 (34.1)
Positive febrile seizure history	36 (4.6)	33 (4.2)	9 (1.1)	78 (9.9)
Previous trauma history	28 (3.6)	18 (2.3)	3 (0.4)	49 (6.2)
Presence of neurological diseases	80 (10.2)	50 (6.4)	12 (1.5)	142 (18.1)
Prematurity	81 (10.3)	40 (5.1)	12 (1.5)	133 (16.9)

ET: esotropia, XT: exotropia

Table IV. Positive family history in patients with different subtypes of ET, XT, and amblyopia.

		N	% within each group
Subtypes of ET	RAET	78	51.7
	PAET	32	21.2
	IET	14	9.3
	BANAET	24	15.9
	Sensory ET	3	2
Total ET		151	100
Subtypes of XT	IXT	58	77.3
	CXT	12	16
	Sensory XT	3	4
	Infantile XT	2	2.7
Total XT		75	100
Subtypes of amblyopia*	Strabismic	28	27.5
	Anisometropic	54	52.9
	Isometropic	15	14.7
	Visual deprivation	5	4.9
Total amblyopia		102	100

ET: esotropia, RAET: refractive accommodative esotropia, PAET: partially refractive esotropia, IET: infantile esotropia, BANAET: basic nonaccommodative esotropia, XT: exotropia, IXT: intermittent exotropia, CXT: constant exotropia, VD: visual deprivation
*: all amblyopic patients with positive family history.

and amblyopia. There were no statistically significant differences in patients with different subtypes of diseases (p=0.08). All amblyopic patients were assessed to find out the possible differences between subtypes.

Table V reveals information about the degrees of relatives in patients with positive family history. A positive family history of strabismus in the first-degree relatives was more common in patients with esotropia (43.3%). There was a significant difference between esotropia, exotropia and amblyopia groups in terms of degrees of relatives (p=0.002).

Table VI reveals whether the family history of strabismus was maternal or paternal. Of 268 patients with positive family history, we could receive 213 patients' information (79,5%) about this item. There was no statistically significant difference between patients with eso-, exodeviations, and amblyopia (p=0.08). When evaluating patients with subtypes of these diseases, there was a statistically significant difference among patients with subtypes of ET (p= 0.024) and positive maternal family history was more common in patients with RAET and PAET (38 %). A statistically significant difference was found among patients with XT

Table V. Degrees of relatives in esotropic, exotropic, and amblyopic patients with positive family history.

	First degree (n/%)	Second degree (n/%)	Third degree (n/%)	Total
(n/%)				
Esotropic patients	116/43.3	31/11.6	4/1.5	151/56.3
Exotropic patients	47/17.5	23/8.6	5/1.9	75/28
Amblyopic patients*	39/14.6	2/0.7	1/0.4	42/15.7
Total	202/75.4	56/20.9	10/3.7	268/100

*: patients who had amblyopia as a primary diagnosis and had positive family history.
Chi-square test, p=0.002

Table VI. Differences between suptypes of ET, XT, and amblyopia in terms of positive maternal and paternal family history.

		Maternal family history (n/%)	Paternal family history (n/%)
Subtypes of ET	RAET	38/25.3	25/16.7
	PAET	19/12.7	8/5.3
	IET	5/3.3	5/3.3
	BANAET	6/4	11/7.3
	Sensory ET	1/0.7	1/0.7
ET Total	ET	69/26.8	50/19.2
Subtypes of XT	IXT	22/29.3	30/40
	CXT	4/5.3	6/8
	Sensory XT	2/2.7	0/0
XT Total	XT	28/10.7	36/13.8
Subtypes of amblyopia	Strabismic	11/10.8	14/13.7
	Anisometropic	25/24.5	16/15.7
	Isometropic	5/4.9	3/2.9
	Visual deprivation	3/2.9	1/1
Amblyopia Total	Amblyopia	44/6.5	34/5

Chi-square test, p=0.024 in ET group, p=0.009 in XT group, p=0.32 in amblyopia group.
ET: esotropia, RAET: refractive accommodative esotropia, PAET: partially refractive esotropia, IET: infantile esotropia, BANAET: basic nonaccommodative esotropia, XT: exotropia, IXT: intermittent exotropia, CXT: constant exotropia, VD: visual deprivation.

(p=0.009) and a positive paternal family history was more common in patients with IXT (40 %).

Discussion

In this current study, 33,7% of patients with strabismus or amblyopia had a positive family history of strabismus or amblyopia. Cotter et al.[14] reported that positive family history of strabismus was independently associated with a greater risk for exotropia. In another study, children with a family history of strabismus were observed and the development of constant or intermittent esotropia occurred in 17,6% of these children.[15] Positive family history of strabismus seems to be an important risk factor for the development of strabismus in a child thus this entity should be asked during the ophthalmic examination of a child.

In the literature, family history was found to be positive in only 2.6% of patients with IXT. The sample of this study was composed of 1228 patients from South China.[16] In our study, 30,7 % of patients with IXT had a positive family history of strabismus. Differences in race, ethnicity, and sample sizes could explain these results. Further evaluation should be performed on these patients to find out the possible genetic factors.

Matsuo et al.[17] studied risk factors for different types of comitant strabismus. They reported that when compared with patients with infantile esotropia, positive family history was found to be a marked risk factor in patients with IXT, constant XT, and accommodative esotropia. Eroğlu et al.[18] reported that the risk of strabismus development was high in esotropic patients with positive family history. The most common form was found to be the non-Mendelian type. In our study, there was no statistically significant difference between esotropic, exotropic, and amblyopic patients in terms of positive family history of strabismus or amblyopia.

Mocanu et al.[9] reported an association between amblyopia development and family history

of amblyopia. Guimaraes et al.[11] reported that positive family history was more common in patients with strabismic amblyopia. Not only amblyopia but also the presence of strabismus might have affected this result. When we investigated positive family history in patients with different subtypes of amblyopia, we found no statistically significant difference. Further studies are needed to clarify this.

In this current study, positive family history of strabismus was more common in the first-degree relatives of patients with esotropia. Ziakas et al.[19] reported that first-degree family history was remarkably common in patients with hyperopic accommodative esotropia.

Having a first-degree relative with amblyopia was also found to be a risk factor for amblyopia, in the literature.[20]

The origin of the family history of strabismus was also investigated in this current study. Statistically, a significant difference was not found between patients with eso-, exodeviations, and amblyopia. On the other hand, positive maternal family history of strabismus was more common in patients with RAET and PAET and positive paternal family history of strabismus was more common in patients with IXT. Although genetic-based studies were available, this item was not deeply discussed in previous studies.[19-21] The origin of the family history of strabismus might be important in the development of strabismus.

In this current study, 16,7% of patients had a history of prematurity. Prematurity was also found to be associated with a higher risk of having eso- and exotropia in a study.[7] Low BW and preterm delivery were also found to be risk factors for isolated strabismus. In a recent review; prematurity was found to be a risk factor for amblyopia, too.[22] Prematurity was also found to be associated with a high risk of esotropia.[23] Subtypes of strabismus or amblyopia did not differ in preterm born patients, in our study. The alterations in the results might be due to the characteristics and sizes of samples.

Both patients with esotropia (17,2%) and exotropia (21,3%) were found to be associated with neurological diseases such as cerebral palsy and developmental delay.[24] In a review, the incidence of strabismus was found to be higher in patients with cerebral palsy than neurologically normal patients. Esotropia was the most common ocular misalignment according to this review.[25] In our study, 17,7% of patients had neurological diseases and neurological diseases were not different between patients with different types of strabismus or amblyopia.

In our country, the prevalence of febrile seizures in children was also found to be 4,3%, compatible with the literature.[26] In this current study, the prevalence of the history of febrile seizure was 9,7% in patients with strabismus or amblyopia. This higher rate was remarkable and in our opinion, further studies just focused on the possible link between febrile seizures and decompansation of binocular fusion might give us more accurate results. In the literature, there was no information about this item.

The prevalence of patients with a history of head trauma possibly linked with strabismus was 6,2% in this current study. This rate was not high and did not enlighten us about the effect of trauma history on comitant strabismus and amblyopia. Further studies might explain the effect more precisely.

The major limitation of this current study might be the relatively small sample size and the retrospective manner. Because of the retrospective manner, the characteristics of febrile seizures, the severity of neurological diseases and head trauma were not avaliable. Besides, additional factors such as maternal smoking and factors associated with birth were not investigated. On the other hand, the investigation of head trauma linked with the beginning of strabismus or amblyopia, febrile seizure, and comparisons between subtypes of strabismus and amblyopia in terms of all risk factors were the positive sides of this current study. The evaluation of only Turkish children

with strabismus and amblyopia was also the unique side of the study.

In conclusion; the rates of positive family history of amblyopia and strabismus were not statistically different between esotropic, exotropic, and amblyopic patients. Family history of strabismus in first-degree relatives of patients with esotropia was markedly high. The positive maternal family history of strabismus was common in patients with RAET and PAET. Finally, the positive paternal family history of strabismus was more common in patients with IXT.

Ethical approval

Prior approval from the Institutional Review Board was taken (IRB number: 71522473/050.01.04/54).

Author contribution

The authors confirm contribution to the paper as follows: study conception and design: BÇ; data collection: ÖB, SÖ; analysis and interpretation of results: BÇ, NÖA, ÖB; draft manuscript preparation: BÇ, NÖA. All authors reviewed the results and approved the final version of the manuscript.

Source of funding

The authors declare the study received no funding.

Conflict of interest

The authors declare that there is no conflict of interest.

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