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ORIGINAL RESEARCH ARTICLE

New pediatric risk factors for amblyopia: strabismic versus refractive

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ABSTRACT

Purpose: To assess the role of risk factors for amblyopia, such as family history and neonatal background, for the prediction of either strabismic amblyopia or refractive amblyopia.

Methods: In this retrospective case-control model, the study population included all children born at the Hospital de Braga during 1997-2012 (3 to 18 years old) with ophthalmologic consultation in 2014. Data collection was performed from the clinical database and through telephone questionnaire surveys.

Results: A total of 298 (50%) controls and 298 (50%) cases (120 [40.3%] strabismic amblyopia and 178 [59.7%] refractive amblyopia) were analyzed. A significantly lower birthweight was detected in patients with strabismic amblyopia (mean 2,961 g [95% confidence interval (CI) 2,827-3,096]) compared to controls (mean 3,198 g [95% CI 3,125-3,271]) ($p = 0.002$). Five-minute Apgar was significantly lower in patients with strabismic amblyopia (mean 9.57 [95% CI 9.37-9.77]) than in controls (mean 9.83 [95% CI 9.77-9.90]) ($p = 0.004$) or patients with refractive amblyopia (mean 9.79 [95% CI 9.69-9.89]) ($p = 0.031$). Family history of either amblyopia or strabismus was associated with amblyopia (χ^2 [2, n = 562] = 12.66; $p = 0.002$; Cramer V = 0.150; χ^2 [2, n = 561] = 11.0; $p = 0.004$; Cramer V = 0.140), but was significantly more associated with strabismic amblyopia ($p = 0.0023$ and $p = 0.0032$) than with refractive amblyopia ($p = 0.48$ and $p = 0.015$, respectively). Multinomial logistic regression model explained 50.8% of the variance in amblyopia development. Low 5-minute Apgar had a relevant odds ratio (OR) for either strabismic amblyopia (OR 3.44; $p = 0.066$) or refractive amblyopia (OR 3.30; $p = 0.077$).

Conclusions: This division in amblyopia subtypes gives a new perspective of the risk factors for amblyopia, with family history and some obstetrician/neonatal outcomes appearing to be more relevant in strabismic amblyopia. Educating health care providers to recognize these risk factors can result in an early ophthalmologic referral.

Keywords: Amblyogenic risk factors, Family history, Neonatal background

Introduction

Amblyopia is a neurodevelopmental vision disorder caused by sensory deficits during early life (1). It is a common ophthalmologic disorder in pediatric age, with considerably different prevalence rates according to the country and the criteria used in diagnosis (2). Since amblyopia is the effect of a pathologic process, recent studies propose to include in its diagnosis not only acuity-based criteria, but also the concomitant presence of causal factors, called amblyogenic risk factors (ARF) (3, 4). Functional eye anomalies, such as refractive error, strabismus, and media opacity, are established ARF (5). Amblyopia is regarded as an important public health problem as it is the main cause of vision loss in children and one of the leading causes of visual impairment in adults (6, 7). The prompt detection and treatment of amblyopia could prevent or cure this consequence (8, 9). Therefore, this pediatric ophthalmologic screening topic, in order to detect decrease in visual acuity and/or ARF, has gained widespread attention in recent decades. Also, it seems that screening high-risk

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children could be more efficient and cost-effective (10, 11), so further research has gradually focused on the ARF. Although some ocular conditions have already been established and validated, it is possible that amblyopic children have additional risk factors. Some personal or familial characteristics seem to be linked with amblyopia (5, 12-15), but there is no consensus among the scientific community as to predictive factors of amblyopia development. The neonatal background, such as the 5-minute Apgar score, is a helpful predictor of neurodevelopment and a relevant prognostic factor for infants with neonatal hypoxia (16). There is no consensus about the role of prematurity, low birthweight (LBW), neonatal hypoxia or admission to the intensive care unit (ICU) (13-15, 17). Family history is also controversial. In recent studies, an association with ophthalmologic history (refractive error, amblyopia, or strabismus) in relatives was revealed (17, 18). Current evidence concerning the ARF's predictive power is not clear. Thus, the main goal of this study was to assess the role of risk factors for amblyopia, such as family history and neonatal background, for the prediction of either strabismic amblyopia (SA) or refractive amblyopia (RA).

Methods

This was a retrospective case-control study. Study protocol and informed consent were reviewed and approved by the local ethical committee of Hospital de Braga. The study population corresponded to all children born in Hospital de Braga during 1997-2012 (3 to 18 years old at the time of collection) with an ophthalmologic consultation in 2014. Retrospective assess to all ophthalmologic information present in the electronic clinical database (Global Intelligence Technologies; Glintt®) was made.

Inclusion criteria included diagnosis of amblyopia and registration of occlusive treatment in addition to strabismus diagnosis or refractive error detection. In cases without occlusive treatment, the inclusion criteria for unilateral amblyopia were as follows: an intraocular difference of ≥2 lines in best-corrected visual acuity (BCVA) and an amblyogenic refractive error (ARE) (ARE defined as follows: myopia if sphere ≥-3 D; hyperopia if sphere ≥+1.50 D; or astigmatism if cylinder ≥± 2 D) (19). For bilateral amblyopia, the criteria were defined as ARE present plus bilateral BCVA ≤6/10 in 3- or 4-year-old subjects or ARE plus bilateral BCVA ≤8/10 in 5+-year-old subjects. Simultaneous SA and RA were categorized as strabismic amblyopia. Exclusion criteria included organic amblyopia, BCVA less than normal without ARE, or normal BCVA with ARE. All selected cases were reviewed by a trained ophthalmologist. The controls were selected among the study population, according to the exclusion criteria, stratified by age and sex.

Telephone questionnaire surveys, which included questions related to ophthalmologic and obstetrician/neonatal data, were applied in a blinded way, with a response rate of 94.5%. The questionnaire began in accordance with the ethical protocol, with an oral informed consent.

Statistical analyses were performed using Statistical Package for the Social Sciences (IBM SPSS Statistics 22®). The multiple logistic regression model was used to estimate the predictive power of new risk factors. For statistical purposes, low 5-minute Apgar score was ≤8 and LBW was considered as less than 2,500 grams. Kruskal-Wallis and Pearson χ^2 test were applied. The possible new risk factors were included in the multiple logistic regression. Two-sided p values <0.05 (95% confidence interval) were considered to be statistically significant.

Results

The sample had a total of 596 participants (306 female [51.3%]), aged on average 8.9 ± 3.76 years, of whom 298 (50%) were controls and 298 (50%) were cases. The cases included 178 (59.7%) RA and 120 (40.3%) SA.

Five-minute Apgar score had significant differences among the subgroups (χ^2 [2, n = 555] = 10.6; p = 0.005; ηp^2 = 0.019), with pairwise comparisons showing significant differences between the SA subgroups and control (p = 0.004), as well as between the SA subgroups and the RA subgroup (p = 0.031) (Tab. I). There was a statistically significantly different mean birthweight among the subgroups ($F_{2,579}$ = 5.74; p = 0.003; ηp^2 = 0.019), with Games-Howell post hoc test showing statistical differences between the SA subgroup and the controls (p = 0.002) (Tab. I). In respect to family history of amblyopia, there was a significant association (χ^2 [2, n = 562] = 12.66; p = 0.002; Cramer V = 0.150), with a statistically significantly greater association with amblyopia diagnosis in a relative with SA (Tab. II). Family history of strabismus also had a significant association with the tested outcome (χ^2 [2, n = 561] = 11.0; p = 0.004; Cramer V = 0.140), with a statistically significantly greater association with strabismus diagnosis in a relative in the SA subgroup than in the RA subgroup (Tab. II).

The multinomial logistic regression model (Tab. III) contained binary independent variables (familial refractive error during childhood, amblyopia in a relative, strabismus in a relative, 5-minute Apgar score, neonatal ICU admission, neonatal reanimation, high-risk pregnancy) and continuous independent variable (birthweight). Refractive errors were considered. With these variables, the model improved its statistical significance compared to the intercept alone (χ^2 [22, n = 473] = 307; p<0.001) and had goodness of fit (χ^2 [922, n = 473] = 955; p = 0.22). The set of independent variables included in the model explained 50.8% (Nagelkerke R^2) of the variance in amblyopia development. With this model, we found that amblyopia in a relative increased the odds of having SA and RA, in a factor of 2.64 and 2.02, respectively; strabismus in a relative added a 1.43 risk of having SA; and, finally, that 5-minute Apgar score increased the chance of SA and RA, 3.44 and 3.30 times, respectively.

Discussion

This is the first study that splits different subtypes of functional amblyopia, SA and RA, in the same study. Furthermore, it shows associations between newly considered risk factors and functional amblyopia subtypes, SA or RA, and some of the newly considered risk factors have also a predictive power for functional amblyopia development, SA or RA.

We found that SA is statistically predicted by family history of amblyopia and has a greater association than RA with family history of strabismus. Also, we observe statistically

TABLE I - Statistical tests for 5-minute Apgar score and birthweight among subgroups

	Central tendency measurements, mean ± SD; median (interquartile range)			Statistical test	Significance of pairwise comparisons, p			p value effect size
	Control	RA	SA		SA vs control	RA vs control	SA vs RA	
Apgar at 5 minutes (range 1-10)	9.83 (9.77; 9.90); 10 ± 0	9.79 (9.69; 9.89); 10 ± 0	9.57 (9.37; 9.77); 10 ± 0	χ^2 (2, n = 555) = 10.6	0.004	NS	0.031	0.005; ηp^2 = 0.019
Birthweight, g	3,198 (3,125; 3,271)	3,122 (3,035; 3,210)	2,961 (2,827; 3,096)	$F_{2,579}$ = 5.74	0.002	NS	NS	0.003; ηp^2 = 0.019

ηp^2 = (small 0.01, medium 0.06, large 0.14); NS = nonsignificant (p>0.05); RA = refractive amblyopia; SA = strabismic amblyopia.

TABLE II - Statistical tests for family history of amblyopia and strabismus among subgroups

	Statistical test	*p* value	Effect size, cramer v	Cross-tabulation			
				Control	RA	SA	Total
Amblyopia in a relative	χ^2 (2, n = 562)=12.66	0.002	0.150				
Count				24	25	25	74
% Within each subgroup				8.7	14.7	21.7	13.2
% Of Total				4.3	4.4	4.4	13.2
Adjusted residuals				-3.11	0.71	3.05	
p value				0.0019*	0.48	0.0023*	
Strabismus in a relative	χ^2 (2, n = 561)=11.0	0.004	0.140				
Count				29	10	21	60
% Within each subgroup				10.5	5.9	18.3	10.7
% Of Total				5.2	1.8	3.7	10.7
Adjusted residuals				-0.14	-2.43	-2.94	
p value				0.89	0.015†	0.0032*	

* If adjusted, p value with significance (<0.0083); Cramer V (small 0.1, medium 0.3, large 0.5).
† p<0.05.
% = Proportion × 100.
RA = refractive amblyopia; SA = strabismic amblyopia.

TABLE III - Multinomial logistic regression model: new risk factors for strabismic and refractive amblyopia

Independent variable		B	SE	Wald	df	p value	OOR	95% CI for OR	
Birthweight	RA	<0.001	<0.0001	0.59	1	0.44	1.00	0.999	1.00
	SA	<0.001	<0.0001	2.48	1	0.12	1.00	0.999	1.00
Neonatal reanimation	RA	-0.41	0.53	0.59	1	0.44	0.66	0.23	1.89
	SA	-0.22	0.51	1.49	1	0.70	0.82	0.30	2.22
Neonatal intensive care unit admission	RA	-0.16	0.40	0.17	1	0.68	0.85	0.39	1.85
	SA	0.096	39	0.060	1	0.81	0.91	0.42	1.95
Low Apgar at the fifth minute	RA	1.19	78	3.12	1	0.077	3.30	0.88	12.4
	SA	1.24	0.67	3.37	1	0.066	3.44	0.92	12.9
Familiar with refractive error in childhood	RA	-0.46	30	2.35	1	0.13	0.63	0.35	1.14
	SA	-0.50	0.31	2.66	1	0.10	0.61	0.33	1.11
Strabismus in relative	RA	-0.84	0.53	2.53	1	0.11	0.43	0.15	1.22
	SA	0.36	0.44	0.67	1	0.41	1.43	0.61	3.38

To be continued

TABLE III - Continued

Independent variable		B	SE	Wald	df	p value	OOR	95% CI for OR	
Amblyopia in relative	RA	0.70	0.45	2.46	1	0.12	2.02	0.84	4.84
	SA	0.97	0.43	5.14	1	0.023	2.64	1.14	6.10
High-risk pregnancy	RA	-0.43	0.38	1.25	1	0.26	0.65	0.31	1.38
	SA	-0.14	0.37	0.15	1	0.70	0.87	0.42	1.79

p value statistically significant when p<0.05.
CI = confidence interval; OR = odds ratio; RA = refractive amblyopia; SA = strabismic amblyopia.

significant differences regarding the 5-minute Apgar score and LBW, with lowest values in the SA subgroup. On the other hand, we find that the 5-minute Apgar score and the family history of amblyopia increase the risk of both SA and RA.

Relating to neonatal background, the results reveal that 5-minute Apgar score was statistically significantly lower in the SA subgroup than in the control or in the RA subgroups. Low 5-minute Apgar score increases the odds of functional amblyopia development in the SA subgroup as well as in the RA subgroup. In accordance with the prognostic power of 5-minute Apgar score already shown in the literature (20), the present study finds another statistically predicted comorbidity. The common definition of low 5-minute Apgar score is 6 or less (21), since it is associated with higher risk of neonatal encephalopathy, caused by peripartum hypoxia and consequent severe ischemia. The present study defined low 5-minute Apgar score as 8 or less to include less severe hypoxia and its effect on visual development. Until now, no study has analyzed the association of 5-minute Apgar score with SA or RA. The SA subgroup has a higher percentage of obstetrician and neonatal complications, such as high-risk pregnancy, low 1-minute Apgar score, neonatal reanimation, and ICU admission. Birthweight is statistically significantly lower in the SA subgroup than in controls, which is expected (15). The lack of significance related to 1-minute Apgar score in the present study is coherent with the literature (22), since low 1-minute Apgar score is not related to a worse prognosis or future neurodevelopmental complications.

Family history is also relevant. Strabismus in a relative is statistically significantly more associated with the SA subgroup than the RA subgroup. Amblyopia in a relative is a statistically significant predictor for SA and reveals a tendency of increased chance for RA development. This had not been proved before and the only study about this relation was done with another methodology (23). Therefore, family history of strabismus is a robust predictor only for strabismus in children and, in the same way, family history of amblyopia is a robust predictor only for amblyopia in children.

The main limitation of the present study is the hospital bias, with controls being selected from the hospital. When the retrospective data were collected, it was not possible to exclude previous amblyopia in patients who had normal BCVA besides the concomitant presence of ARE.

In the future, in order to determine the impact of these risk factors in strabismus development versus in SA development, a comparison study with squinty nonamblyopic controls versus squinty amblyopic cases should be done. Also, a prospective case-control study with controls selection from the general population could be performed to reinforce the findings of this study.

The present work establishes a predictive model for SA and RA development, including family history and some obstetrician/neonatal new risk factors. The division in amblyopia subtypes, SA and RA, gives a new perspective on the risk factors for amblyopia, with family history and some obstetrician/neonatal outcomes appearing to be more relevant in SA. The recognition of neonatal background and family history as possible risk factors for either SA or RA is important for the education and training of health care providers, either in the primary or in secondary health care system. This can result in early referral of at-risk children to an eye care professional.

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