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ARAŞTIRMA/RESEARCH

Factors associated with delayed vascular maturation in infants with retinopathy of prematurity not requiring treatment

Tedavi gerektirmeyen prematüre retinopatili yenidoğanlarda gecikmiş retina damar matürasyonuyla ilişkili faktörler

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Abstract

Purpose: The aim of this study is to determine risk factors associated with delayed regression of retinopathy of prematurity and prolonged vascular completion in patients not requiring treatment.

Material and Methods: Patients with acute retinopathy of prematurity not requiring treatment were grouped as control and delayed vascularization groups, on condition that retinal vascularization had completed before postconceptional age of 50 weeks or not. Patients with retinopathy of prematurity requiring treatment constituted treatment group. A total of 17 possible risk factors that may affect the time course of retinal vascularization in patients with acute retinopathy of prematurity were evaluated.

Results: Multivariate regression analysis showed that low Apgar score at fifth minute and blood transfusion were associated with an increased risk of delayed vascularization when compared with controls. Low gestational age and presence of patent ductus arteriosus were risk factors for retinopathy of prematurity that require treatment when compared with delayed vascularization group.

Conclusion: Low Apgar score and blood transfusion might be predictive factors for prolonged retinal vascularization in patients with retinopathy of prematurity not requiring treatment. Having a higher gestational age and absence of patent ductus arteriosus, appeared as reducing the risk of progressing to serious disease requiring treatment for an infant with retinopathy of prematurity that undergo regression slowly.

Key words: retinopathy of prematurity, prolonged regression, delayed retinal vascular maturation.

Öz

Amaç: Bu çalışmanın amacı tedavi gerektirmeyen prematüre retinopatisi olan hastalarda, retinopatinin gerilemesinde gecikme ve retina damar matürasyonunda uzama ile ilişkili olabilecek risk faktörlerini belirlemektir.

Gereç ve Yöntem: Tedavi gerektirmeyen prematüre retinopatili hastalar, retina damarlanmasının 50. postkonsepsiyonel haftadan önce tamamlanmış olup olmamasına göre kontrol ve gecikmiş matürasyon grubu olarak ikiye ayrıldı. Tedavi gerektiren prematüre retinopatili hastalar ise tedavi grubunu oluşturdu. Prematüre retinopatisi hastalarında retinanın damarlanma sürecini etkileyebilecek 17 olası risk faktörü gruplar arsında karşılaştırıldı.

Bulgular: Çoklu regresyon analizinde, 5. dakikadaki düşük Apgar skoru ve kan transfüzyonu öyküsü kontrol grubu kıyaslandığında gecikmiş matürasyon ile ilişkili bulundu. Gecikmiş matürasyonlu hastalar tedavi gerektiren prematüre retinopatili bebeklerle kıyaslandığında ise, düşük doğum haftası ve patent duktus arteriosus varlığı, tedavi gerektiren prematüre retinopatisi gelişmesi ile ilişkili bulundu.

Sonuç: Tedavi gerektirmeyen prematüre retinopatisi hastalarında 5. dakikadaki Apgar skorunun düşük olması ve kan transfüzyonu öyküsü, retina damarlanmasının uzun sürede tamamlanacağının habercisi olabilir. Doğum haftasının yüksek olması ve patent duktus arteriosus bulunmaması ise prematüre retinopatisi yavaş gerileyen infantlarda tedavi gerekecek evrelere ilerleme riskinin düşük olacağı konusunda fikir verebilir.

Anahtar kelimeler: prematüre retinopatisi, uzamış gerileme, gecikmiş retina damar matürasyonu.

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INTRODUCTION

Retinopathy of prematurity (ROP), one of the leading causes of preventable childhood blindness, is a proliferative retinal vascular disease affecting low birth weight premature infants. The leading fact in the pathogenesis of the disease is the completion of retinal vascularization of a preterm infant in a relatively hyperoxic environment rather than hypoxic conditions of the uterine cavity. Fortunately, it is observed that in patients with acute ROP, clinical findings often show spontaneous regression and retinal vascularization completes uneventfully with favourable outcome in the majority of cases[1]. However, some infants develop advanced stages of retinopathy that require treatment. Our current knowledge is not enough to reveal in which infants pathological process will occur. But some factors that determine the patients under risk have been reported with clinical experiences, low birth weight and small gestational age being the main and most common risk factors of all.

Duration of spontaneous resolution and completion of normal retinal vasculature varies among patients with ROP not requiring treatment. For some infants it may take only several weeks, however regression and full vascularization may be prolonged in a number of patients. Extensive studies have been conducted regarding the natural history of ROP and potential predictive factors associated with the severity of the disease, on the other hand little is known about the patients that undergo regression very slowly but never progress to serious disease requiring treatment[1,6]. In this study we aimed to evaluate systemic and ocular factors that may affect the duration of regression of ROP and completion of vascularization in patients with acute ROP not requiring treatment. Secondary goal of the study was to investigate the prognostic features of the infants with prolonged maturation that could be delineated from the patients requiring treatment.

MATERIAL AND METHODS

This retrospective study included inborn preterm infants with birth weight ≤ 2000 g or gestational age ≤ 34 weeks, who had been examined for ROP screening between March 2012 and March 2014 in a tertiary referral hospital. Initial fundus examination was performed at postnatal age of 4 weeks. Follow up examinations were performed on the basis of retinal findings as suggested in the guideline[7]. The ROP status of each infant was classified according to the International Classification of ROP including stage, zone, and extent of disease, and presence of plus disease[8]. Laser treatment was considered for the patients with pretreshold disease as recommended by the Early Treatment for Retinopathy of Prematurity Cooperative Group[9]. Patients with stage 4 and 5 ROP were referred for vitreoretinal surgery.

The stage of ROP was defined as the highest stage recorded in a given zone during fundus examinations. Complete regression of acute ROP findings and full retinal vascularization that reach ora serrata for 360° was defined as completion of vascularization. Patients with acute ROP not requiring treatment were grouped as control subjects on condition that retinal vascularization had completed before postconceptional age of 50 weeks, and delayed vascularization subjects with either any finding of ROP or avascular retina still existing after postconceptional age of 50 weeks. To constitute control group, 20 patients were selected randomly among infants that vascularization completed before the postconceptional age of 50 weeks. Patients with ROP requiring treatment constituted treatment group. One eye of each patient with more advanced stage of ROP was designated for analysis. One infant from each multiple gestations was included in the study as well. Infants who died or lost to follow-up before the termination of fundus examinations were not include in the study.

Medical records were analyzed to obtain data on demographic, perinatal, postnatal and ocular factors. Demographic and perinatal factors included birth weight, gestational age at delivery, gender, antenatal steroid medication, multiple gestation, Apgar scores in the first and fifth minutes. Postnatal factors were use of surfactant, intubation, mechanical ventilation duration, total respiratory support duration (mechanical ventilation, nasal continuous positive airway pressure, headbox), blood transfusion, sepsis, intracranial hemorrhage and patent ductus arteriosus (PDA). Ocular factors included stage and zone of ROP.

To investigate possible associations that may affect the course of retinal vascularization in patients with acute ROP findings, designated variables were compared between control, delayed vascularization and treatment groups. The study protocol was in accordance with the tenets of the Declaration of Helsinki.

Statistical analysis

All analyses were performed using SPSS 19.0 statistical software package (IBM SPSS Statistics). Categorical variables were expressed as numbers and percentages, whereas continuous variables were summarized as mean and standard deviation. Chi-square test was used to compare categorical variables between the groups. For non-normal distributed data, Kruskal Wallis test was used to compare the groups. Bonferroni adjusted Mann Whitney U test was used for multiple comparisons of the groups.

Logistic regression analysis was performed to determine significant predictors for delayed vascularization group versus control and treatment groups. In univariate analysis, variables significant at the P <0.1 level were entered in logistic regression analysis. The statistical level of significance for all tests was considered to be 0.05.

RESULTS

Medical records of a total of 388 inborn infants who were examined for ROP were analyzed. Of the 218 infants with ROP, 197 (90.37 %) did not require treatment, however 21 (9.63%) developed advanced stages of ROP requiring treatment. Among 197 patients with ROP not requiring treatment, in 20 (10.15%) of them retinal vascularization did not complete until the postconceptional age of 50 weeks. In the control group retinal vascular completion was observed at the mean postconceptional age of 43.35±1.98 (range 40-47) weeks. In the delayed vascularization group, the mean of the postconceptional age that the follow-up examinations terminated was 55.2±5.42 (range 53-75) weeks.

Table 1, shows the demographic and perinatal characteristics of each group. No significant differences were observed between control and delayed vascularization groups with regard to birth weight and gestational age, however Apgar scores at the first and fifth minutes were lower in patients with delayed vascularization (p=0.041 and p=0.003 respectively).

When we compared treatment group with delayed vascularization group, gestational age was lower in patients with ROP requiring treatment (p<0.001), but birth weight was not. Gender, antenatal steroid administration and multiple gestation were not found to be correlated with any of the groups.

Table 1. Demographic and perinatal characteristics of control subjects, delayed vascularization and treatment groups.

	Control group (*n*=20)	Delayed vascularization group (*n*=20)	Treatment group (*n*=21)	p value
Birth weight (g)	1365.25 ± 327.52	1165.25 ± 351.53	939.25 ± 251.07	0.001[b]
Gestational age (week)	30.25 ± 1.68	28.90 ± 2.36	26.85 ± 1.57	<0.001[b,c]
Gender, male	11 (55.0)	12 (60.0)	10 (47.62)	0.817
Antenatal steroid	15 (75.0)	14 (70.0)	19 (90.48)	0.112
Multiple gestation	6 (30.0)	5 (25.0)	6 (28.57)	0.921
Apgar score at 1st min.	6.2 ± 1.8	4.8 ± 1.4	4.7 ± 1.7	0.012[a,b]
Apgar score at 5th min.	8.3 ± 0.8	7.3 ± 0.9	7.25 ± 1.0	0.001[a,b]

Data are given as mean ± standard deviation or *n* (%), a: p<0.05 for control versus delayed vascularization group, b: p<0.05 for control versus treatment group, c: for delayed vascularization versus treatment group, min: minute.

Table 2 shows the postnatal characteristics of each group. When compared with controls, use of surfactant and blood transfusion were found to be risk factors for delayed vascularization (p<0.05 for both) but there were no significant difference regarding intubation, mechanical ventilation duration, total respiratory support duration, presence of sepsis, intracranial hemorrhage and patent ductus arteriosus between these two groups. When compared with delayed vascularization group, duration of intubation was longer (p=0.022) and PDA was a risk factor (p<0.05) for treatment group. These two groups did not have significant difference regarding other postnatal systemic factors. Table 3 shows the ocular features of each group. Stage of ROP was more advanced in delayed vascularization group than control subjects (p<0.05) while the zone was not a risk factor for delayed maturation. Both advanced stage and posterior zone were found as ocular risk factors for treatment group when

compared with delayed vascularization group (p<0.05 for both).

Multivariate logistic regression analysis showed that Apgar score at fifth minute (p=0.041) and blood transfusion (p=0.047) are risk factors for patients with delayed vascularization when compared with controls (Table 4). Low gestational age (p=0.032) and presence of PDA (p=0.013) were risk factors for ROP that require treatment when compared with delayed vascularization group (Table 5).

Table 2. Postnatal characteristics of control subjects, delayed vascularization and treatment groups.

	Control group (*n*=20)	Delayed vascularization group (*n*=20)	Treatment group (*n*=21)	p value
Intubation	9 (45.0)	12 (60.0)	17 (80.95)	0.030[b]
Intubation duration (day)	5.56±5.05	11±18.45	20.4±9.89	0.002[b,c]
Total respiratory support duration (day)	7.82±6.88	20.80±20.36	33.75±19.08	<0.001[b]
Use of surfactant	5 (25.0)	15 (75.0)	18 (85.71)	<0.001[a,b]
Blood transfusion	3 (15.0)	13 (65.0)	18 (85.71)	<0.001[a,b]
Intracranial hemorrhage	3 (15.0)	9 (45.0)	12 (57.14)	0.013[b]
Patent ductus arteriosus	5 (25.0)	5 (25.0)	16 (76.2)	0.001[b,c]
Sepsis	6 (30.0)	13 (65.0)	12 (57.14)	0.057

Data are given as mean ± standard deviation or *n* (%), a: p<0.05 for control versus delayed vascularization group, b: p<0.05 for control versus treatment group, c: for delayed vascularization versus treatment group.

Table 3. Ocular characteristics of control subjects, delayed vascularization and treatment groups.

	Control group (*n*=20)	Delayed vascularization group (*n*=20)	Treatment group (*n*=21)	p value
Stage of ROP				
1	16 (80.0)	4 (20.0)	0 (0.0)	
2	4 (20.0)	13 (65.0)	2 (9.52)	<0.001[a,b,c]
3	0 (0.0)	3 (15.0)	19 (90.48)	
Zone of ROP				
I	0 (0.0)	0 (0.0)	2 (9.52)	
II	2 (10.0)	5 (25.0)	17 (80.95)	<0.001[b,c]
III	18 (90.0)	15 (75.0)	2 (9.52)	

Data are given as *n* (%), a: p<0.05 for control versus delayed vascularization group, b: p<0.05 for control versus treatment group, c: for delayed vascularization versus treatment group.

Table 4. Multivariate analysis showing the relationship of independent variables with the risk of delayed vascularization when compared with control subjects in infants with ROP not requiring treatment.

Parameter	OR	95% CI	p value
Apgar score at fifth min.	0.224	0.053-0.941	0.041
Blood transfusion	10.086	1.035-98.338	0.047

OR: odds ratio, CI: confidence interval, min: minute.

Table 5. Multivariate analysis showing the relationship of independent variables with the risk of ROP requiring treatment when compared with delayed vascularization group.

Parameter	OR	95% CI	p value
Gestational age	0.621	0.401-0.960	0.032
Patent ductus arteriosus	7.170	1.512-34.006	0.013

OR: odds ratio, CI: confidence interval.

DISCUSSION

Spontaneous regression is the most favorable and desired outcome in the clinical course of acute ROP in premature infants. Fortunately, this is achieved by the majority of patients who are screened for ROP[10-12]. This process is defined as the downgrading of ROP stages and growth of retinal vasculature into a more peripheral zone observed during serial fundus examinations[12]. Vascularization reaching the ora serrata in all quadrants, providing normal capillary perfusion of the most peripheral retina, can be described as full vascularization.

It is not often possible to document the exact time of full retinal vascularization because intervals between follow-up examinations might be extended after the onset of involution. Besides, retinal examinations can be terminated by the clinician when the vascularization reaches zone III in a patient without zone I or II disease[7]. Hence investigators have preferred to document the time of onset of involution or duration of ROP[10,12-14]. However, it is also challenging to determine the precise time of the onset and termination of involution. In our clinical practice, we usually perform confirmatory examinations until we ensure that vascularization had completed uneventfully and record the information to the medical records for each patient, especially considering medico-legal problems. Regular and complete follow-ups enabled us to conduct a study regarding whether the vascularization had completed before the postconceptional age of 50 weeks or not.

Repka et al[10] reported that involution of ROP began before 44 weeks of postmenstrual age in 90% of patients, with a peak between 36 and 40 weeks. In a recent study by Ni et al[12] about natural involution of acute ROP not requiring treatment, it was reported that involution generally began between postmenstrual ages of 36.5 and 44.4 weeks (5%-95%). The authors also found that completion of involution was generally between 39.0 and 75.0 weeks (5%-95%). All these results show a significant variance in duration of regression and vascular completion among preterm infants. Likewise, we consider that there is a remarkable number of patients revealing an unusually prolonged maturation. Eliason et al[13] reported some cases that acute ROP persisted until 50 to 59 weeks of postconceptional age. In our study 10.15% of the patients with ROP not requiring treatment, still revealed either acute ROP findings or avascular retina, even after the postconceptional age of 50 weeks. In all these patients, retinal vascularization completed uneventfully until 53 to 75 weeks of postconceptional age.

There are numerous studies that have been conducted regarding risk factors for the development and severity of the disease[3-6,15-17]. However, there is currently little information about factors associated with delayed regression and vascular completion in patients with acute ROP not requiring treatment. Ni et al[12] found that continuous positive airway pressure, active stage 3 disease and anemia were significant risk factors associated with delayed involution of ROP. They also demonstrated that involution finished earlier in zone III and milder disease. In another study by Elison et al[13] Hispanic patients were reported to have longer duration of ROP when compared with non-Hispanic patients.

The present study demonstrated that Apgar score is lower in delayed vascularization group when compared with controls. The use of surfactant was more frequent in patients with delayed vascularization. So it can be postulated that status of the patient at birth may be predictive for the time course of retinal vascularization in a premature infant.

Blood transfusion is known as an independent risk factor for both development of ROP and its severity[17-22]. Our study demonstrated that duration of ROP and vascular completion was affected unfavorably by blood transfusions. Previously, it was reported that damaging effects of transfusions on the immature retina are mediated not only by increasing oxygen delivery, but also by an increase in free iron and oxygen radicals[21,22]. Thus we believe that the same mechanism can be considered to be responsible for the delay in involution of ROP and vascular maturation.

We found that spontaneous regression of ROP and vascular maturation time was independent of the zone of the disease. Although it was previously reported that involution of ROP finished earlier in zone III disease, our study demonstrated that in eyes with posteriorly located ROP, advancement of retinal blood vessels could be achieved as early as anterior disease[12]. However full vascularization was found to be prolonged in patients with more advanced stage than milder disease.

In our study, birth weight and gestational age were found to have no significant affect on vascularization time in patients not requiring treatment. Therefore, prolonged regression and vascular completion might also be expected in relatively mature patients as well as patients with lower birth weight and gestational age.

Patients with delayed vascularization were exposed to mechanical ventilation for shorter time than treatment requiring patients. This situation may be a considerable indicator to emphasize the importance of minimum possible duration of intubation for a premature infant. Also having a higher gestational age significantly reduced the risk of progression of the disease to treatment requiring stages. So it has emerged once again that one of the most valuable factors for a premature not to develop treatment requiring ROP is the maturity at the delivery. Presence of PDA is found as another factor for a premature infant that increases the risk of developing treatment requiring ROP, as reported previously[23]. Premature infants with PDA were even reported to have a higher risk for progression of ROP despite laser treatment[24].

The major shortcoming of our study is the small number of the patients. Delayed vascularization in acute ROP not requiring treatment is not a frequent situation. In the period of two years, among 338 infants screened for ROP, there were only 20 cases who had been in such a course. More definite results may be obtained by evaluating larger number of patients.

In conclusion, in this study we aimed to draw attention to the patients with acute ROP that undergo regression very slowly but never progress to treatment requiring stages. Our findings might help to clarify factors that affect the course of retinal vascularization. Determining which conditions cause a delay in vascularization and which prevent progression might also enlighten etiopathogenesis of the disease. The prediction concerning the duration of regression and vascular completion might also help the clinicians to schedule an individualized follow-up program.

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