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Original Article

Maternal Iron Deficiency Anemia as a Risk Factor for the Development of Retinopathy of Prematurity

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Abstract

Background

Retinopathy of prematurity is a proliferative vascular disease affecting premature newborns and occurs during vessel development and maturation. The aim of this study was to evaluate the maternal iron deficiency anemia as possible risk factors associated with the development of retinopathy of prematurity among premature or very low birth weight infants.

Methods

In this study, mothers of 254 infants with retinopathy of prematurity were analyzed retrospectively, and their laboratory results of medical records during pregnancy were reviewed for possible iron deficiency anemia.

Results

In a cohort of 254 mothers of premature infants with retinopathy of prematurity, 187 (73.6%) had iron deficiency, while the remaining 67 (26.4%) mothers had no deficiency. Babies born to mothers with iron deficiency anemia with markedly decreased hemoglobin, hematocrit, mean corpuscular volume, serum iron, and ferritin levels were more likely to develop retinopathy of prematurity.

Conclusions

Our results are the first to suggest that maternal iron deficiency is a risk factor for the development of retinopathy of prematurity. Our data suggest that maternal iron supplementation therapy during pregnancy might lower the risk of retinopathy of prematurity.

Keywords

anemia; iron deficiency; premature infants; retinopathy of prematurity

Introduction

Retinopathy of prematurity (ROP) is an abnormal vasoproliferative disorder that represents the main cause of visual impairment and blindness in preterm infants.[1] ROP begins to develop between 28 and 34 weeks after conception, regardless of gestational age at delivery.[1 and 2] With the progress in neonatology, the survival of extremely low birth weight infants has increased, in turn increasing the number of diagnosed ROP cases.[3] In general, there are about 70,000 children in the world suffering from ROP-induced blindness.[4] It is generally accepted that the rate of blindness caused by ROP varies greatly among countries, depending on their level of development, availability of sufficient neonatal care and neonatal outcomes, and whether effective screening and treatment programs exist. In Turkey extremely premature infants with low gestational ages have high incidence rates (47.6%) of advanced ROP and most of these infants (30.2%) require ROP treatment.[5]

The pathogenesis of ROP is not fully understood, despite a number of perinatal factors, such as prematurity, low birth weight, respiratory distress syndrome, and prolonged oxygen treatment having been recognized as contributory factors in the development of ROP.[1] Prematurity is the single most important preventable risk factor responsible for ROP. The incidence of ROP increases with decreasing gestation and birth weight.[6] ROP was associated with excessive oxygen use shortly after the initial description of the disease.[7] For many years, it was thought that oxygen therapy increased the risk of ROP in preterm infants, but we still are not able to control ROP in premature babies.[8 and 9]

ROP occurs during vessel development and maturation. A better understanding and management of this disease may help to significantly reduce poor outcomes in this disorder. Consequently, preventive and less destructive therapies for ROP would be much more desirable. Although the most important risk factors are oxygen therapy, anemia, blood transfusion, sepsis, and apnea, maternal risk factors are poorly understood. Therefore, the objective of this study was to investigate maternal iron deficiency anemia as a possible risk factor associated with the development of ROP among premature or very low birth weight infants.

Materials and Methods

Patient selection

In this retrospective study from March 2010 to July 2013, hospital records of premature infants who were referred to ophthalmology and pediatric neurology clinics for ROP were reviewed. In this analysis, 254 (36.4%) of 698 premature infants who met established criteria for ROP were evaluated. Mothers of infants with ROP were analyzed retrospectively, and their laboratory results of medical records during pregnancy were reviewed for possible iron deficiency anemia. Parental consent was obtained and approval of the local ethics committee was provided.

Data collection

Preterm infants with ROP were classified according to the criteria of the International Classification of Retinopathy of Prematurity.[10] This international classification was revised in 2005 (Table 1).[11] The International Classification of Retinopathy of Prematurity describes vascularization of the retina and characterizes ROP by its position (zone), severity (stage), and extent (clock hours). The infants with ROP were classified according to (1) occurrence of ROP in any of its five stages of development and (2) severity of ROP (requiring treatment to prevent vision loss) during the observation period (from the fourth and sixth weeks after birth through the 45th week of adjusted gestational age). There was no premature infant with ROP stage 5 in our study group.

Table 1.
Stages of Retinopathy of Prematurity Published by The International Classification of Retinopathy of Prematurity and descriptions of stages[10 and 11]

Stages	Features
Stage 1	**Demarcation line** that is identified as relatively flat and white and lies within the plane of the retina, distinguishes the avascular retina anteriorly from the vascularized retina posteriorly.
Stage 2	**Ridge** is the specific finding that arises in the demarcation line. White- or pink-colored appearance above the plane of retina and vessels that leave the plane of the retina posterior to the ridge to enter are characteristics for stage 2. Popcorn-shaped areas of neovascular tissue that produces several small heaps on the surface of the retina that are detected behind the ridge.
Stage 3	**Extraretinal fibrovascular proliferation** or neovascular tissue leads into the vitreous from the ridge. The increased proliferation results in a ragged appearance in which these neovascularization zones persist through the vitreous. Stage 3 lesions are classified according to the severity involve mild, moderate and severe types.
Stage 4	**Partial retinal detachment** consists of extrafoveal (stage 4A) and foveal (stage 4B) types. The duration of fibrovascular traction and degree of contraction may cause various grades of the retinal separation. During the ophthalmological examination, partial retinal detachments start at the fibrovascular areas, and lead to the vascularized retina.
Stage 5	**Total retinal detachment** has a funnel-shaped structure associated with occasionally exudative tractional separations on surface of the retina. This stage involves various subgroups due to division of funnel configuration as anterior and posterior. In first subgroup, the detachment tends to become a concave configuration and extends to the optic disc when open both anteriorly and posteriorly. The second subgroup has localized detachment behind the lens; the funnel structure is quite narrow in both its anterior and posterior aspects. Typically, the funnel is open anteriorly, but narrows posteriorly in third subgroup. In the end, the least common type is characterized by narrow anteriorly and open posteriorly funnel shape.

Table options

All eye examinations were performed at the Gaziantep University Hospital Ophthalmology Clinic. The infants were examined while hospitalized and as outpatients up to the 45th week of adjusted gestational age. The ophthalmological exam consisted of binocular indirect ophthalmoscopy with a 20-diopter lens (Volk, Germany) and a lid speculum. Pupils were dilated with 0.5% tropicamide and 2.5% phenylephrine eye drops applied 1 hour before the examination. All patients diagnosed with threshold ROP were treated with laser photocoagulation or surgery, if needed. The ophthalmological examinations were initiated between the fourth and sixth weeks of life and were repeated weekly or biweekly until full vascularization of the retina reached zone 3 (the most peripheral temporal retinal zone) or until full remission of ROP after treatment.

Complete blood values of all 254 mothers of infants with ROP in pregnancy were analyzed before labor. Maternal iron deficiency was evaluated for the infants in terms of morbidity and risk factor in ROP. In our study, the other factors causing anemia in mothers other than iron (i.e., vitamin B_{12} and folic acid deficiencies) were excluded. Premature infants with congenital malformation were also excluded from the study.

Statistical analysis

Results are expressed as the mean ± standard deviation or percentage. Statistical analysis was performed using GraphPad Instat (version 3.05; GraphPad Software, San Diego, CA) statistical software. Student *t* and chi-square tests were used for group comparisons and statistical conclusions. For all statistical tests, the *P* values were two-sided and $P < 0.05$ was considered statistically significant.

Results

Of the 254 mothers of infants with ROP, there were 187 (73.6%) and 67 (26.4%) preterm infants with ROP with and without maternal anemia, respectively. The frequency of advanced ROP in premature infants born to mothers with iron deficiency was significantly increased ($P < 0.0001$, Table 2). Stage 1 ROP occurred frequently in mothers with normal iron levels (88.1%) when compared with mothers with iron deficiency anemia (50.8%). However, stage 2 was more prominent in mothers with iron deficiency anemia (36.4% versus 11.9%). Stages 3 and 4 have not been observed in mothers with normal blood iron values. In mothers with iron deficiency anemia, stages 3 and 4 had frequencies of

10.7% and 2.1%, respectively.

Table 2.
Stages of ROP and Low and Normal Hemoglobin Levels of the Mothers Having Infants with ROP

ROP	Mothers with Normal Iron Level (n = 67) n (%)	Mothers with Iron Deficiency (n = 187) n (%)
Stage 1	59 (88.1)	95 (50.8)*
Stage 2	8 (11.9)	68 (36.4)*
Stage 3	0 (0.0)	20 (10.7)*
Stage 4	0 (0.0)	4 (2.1)

Abbreviation:

ROP = Retinopathy of prematurity

* $P < 0.0001$.

Table options

There were marked decreases in hemoglobin, hematocrit, mean corpuscular volume, serum iron, and ferritin levels in mothers with iron deficiency anemia when compared with the levels measured in mothers with normal iron levels (Table 3). Overall, ROP has been found more often in infants whose mothers are iron deficient during pregnancy in all stages of this disease. Also, 20 infants with ROP who underwent laser treatment (stage 3) and four who underwent retinal surgery (stage 4) had mothers who had anemia secondary to iron deficiency, and their iron levels were low.

Table 3.
Characteristics of Hemoglobin and Blood Values of the Mothers of Premature Infants with ROP at the Last Trimester

ROP	n	Hemoglobin Levels (g/dL)	Hematocrit (%)	MCV (fL)	Serum Iron Levels (μg/dL)	Serum Ferritin Levels (ng/mL)
Mothers with normal iron levels						
Stage 1	59	14.0 ± 3.4	45.9 ± 3.6	84.0 ± 5.8	44.6 ± 2.8	56.6 ± 5.7
Stage 2	8	13.8 ± 3.0	42.0 ± 4.0	82.5 ± 3.7	42.8 ± 3.2	38.1 ± 3.6
Stage 3	0	-	-	-	-	-
Stage 4	0	-	-	-	-	-
Mothers with iron deficiency anemia						
Stage 1	95	10.6 ± 2.4*	37.5 ± 3.5*	71.7 ± 3.0*	18.0 ± 2.3*	15.2 ± 4.6*
Stage 2	68	9.7 ± 2.7*	36.0 ± 3.0*	64.1 ± 2.5*	11.5 ± 3.0*	12.2 ± 4.0*
Stage 3	20	10.2 ± 2.0	37.1 ± 3.4	68.4 ± 4.1	9.5 ± 2.9	10.9 ± 4.1
Stage 4	4	9.2 ± 2.1	35.1 ± 2.2	64.4 ± 3.8	8.9 ± 1.9	11.1 ± 3.4

Abbreviations:

MCV = Mean corpuscular volume

ROP = Retinopathy of prematurity

* $P \leq 0.0001$.

Table options

We found no significant differences between the groups in regard to referral centers (152 from a university hospital, 18 from a children's hospital, 17 from a state hospital), birth weight, and gestational age. However, there were marked differences in the duration of neonatal intensive care unit admission (3.0 ± 0.4 weeks in mothers with normal iron levels versus 31.3 ± 1.6 weeks in mothers with iron deficiency anemia, $P < 0.0001$) and

the number of blood transfusions (1.9 ± 0.3 in mothers with normal iron levels versus 14.2 ± 1.1 in mothers with iron deficiency anemia, $P < 0.0001$). However, the average mother's age was found to be high in stage 1 and low in stage 2 mothers with iron deficiency anemia (Figure). Blood vitamin B_{12} and folic acid levels were within normal range for all groups.

Figure.
Distribution of average birth weights of infants (A), average gestational age (B), and average mothers age (C) according to retinopathy of prematurity (ROP) stages (stage 1, demarcation line; stage 2, ridge; stage 3, extraretinal fibrovascular proliferation; stage 4, partial retinal detachment). *$P < 0.05$.

Figure options

Discussion

We observed a marked increase in ROP development in premature infants born from mothers with iron deficiency when compared with infants born from mothers with normal iron levels. Our study suggests for the first time that maternal iron deficiency anemia is an important risk factor for ROP development.

Numerous factors contribute to the genesis of ROP. Although some studies have reported that multiple gestations, apnea, race, intraventricular hemorrhage, exposure to light, anemia, sepsis, prolonged mechanical ventilation, and multiple transfusions are risk factors for ROP,[12] the precise individual role of these factors in the development of the disease have not yet been determined. On the other hand, low birth weight and gestational age as well as high postnatal oxygenation have consistently been shown to increase the risk of ROP.[2]

Although maternal hyperthyroidism is associated ROP,[13] maternal preeclampsia is

associated with a reduced risk of ROP in preterm births.[14 and 15] On the contrary, there is also evidence that maternal preeclampsia is associated with increased ROP development risk in premature infants.[16] Maternal systemic inflammation[17] and older maternal age[18] may play a role in the pathogenesis of ROP in premature babies. Our results suggest that maternal iron deficiency plays an important role in the pathogenesis of ROP, and maternal iron deficiency anemia is a newly identified risk factor for the development of ROP in premature babies.

The diagnosis and treatment of pregnant women with iron deficiency are cost-effective and easy in clinical practice. We believe that diagnosis and treatment have even more importance in women who have a high risk of premature birth. Morbidity resulting from ROP is very high in extremely premature infants.[19] Our findings imply that treating the anemic mother with iron supplements during prenatal period may provide protection for the premature babies against possible complications.

It is reported that gestational age, blood transfusion volume, and iron load by transfusions are associated with the risk of occurrence of ROP in premature infants.[20, 21 and 22] It is well known that an increased amount of free iron may catalyze Fenton reactions, which produce free hydroxyl radicals[23] from superoxide and hydrogen peroxide that are capable of damaging the retina. Thus, excess exogenous iron may contribute to oxidative injury in preterm babies, causing or exacerbating conditions such as retinopathy of prematurity.[24]

Understanding the molecular basis of the ROP is important to the development of successful medical interventions. ROP is also associated with additional serious ocular complications such as an increased incidence of refractive errors, amblyopia, strabismus, cataracts, and glaucoma.[25] Our data imply that screening and early intervention of the mother for iron deficiency may be an important factor in prevention of ROP development and possibly its complications.

There are many limitations of the present study. Because the study design is retrospective in nature, no information was provided concerning the duration of anemia, the potential onset before onset of pregnancy, the progression of the iron deficiency anemia, the therapy type, or duration of the therapy. Additionally, risk factors related to maternal and neonatal complications, which may play a potential role in genesis of ROP, were not provided. So, prospective studies with detailed analysis of maternal and neonatal issues are required.

In conclusion, our results suggest that ROP frequency in premature infants born of mothers with iron deficiency is higher when compared with the infants born from mothers without iron deficiency. Our data imply that maternal iron deficiency is a risk factor for ROP development in premature babies.

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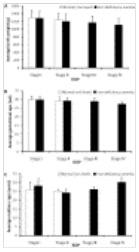

Distribution of average birth weights of infants (A), average gestational age (B), and average mothers age (C) according to retinopathy of prematurity (ROP) stages (stage 1, demarcation line; stage 2, ridge; stage 3, extraretinal fibrovascular proliferation; stage 4, partial retinal detachment). *P < 0.05.

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