Major Article

Longitudinal study of the association between thrombocytopenia and retinopathy of prematurity

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BACKGROUND An association between thrombocytopenia and retinopathy of prematurity (ROP) has been suggested but not been studied longitudinally. We sought to identify the time period in postnatal development during which thrombocytopenia and the subsequent development of severe ROP are associated.

METHODS This was a retrospective case–control study of 100 subjects who received laser photocoagulation for type 1 ROP between 2005 and 2009 and 100 controls with no ROP or only stage 1 ROP. The proportions of infants with thrombocytopenia, defined as a serum platelet level of <150,000/μL, among cases versus controls were compared on a weekly basis from birth through the time of laser during early (postmenstrual age [PMA] weeks 24-28), middle (PMA weeks 29-34), and late (PMA weeks 35-38) time periods. Main outcome measures were odds ratios for the association between thrombocytopenia and type 1 ROP from multivariate logistic regression models adjusted for gestational age, birth weight, culture-proven sepsis, and necrotizing enterocolitis.

RESULTS Thrombocytopenia was significantly associated with severe ROP during PMA weeks 24-28 (adjusted OR, 4.7; 95% CI, 2.0-1.1; $P = 0.001$) and 29-34 (adjusted OR, 2.8; 95% CI, 1.4-5.6; $P = 0.006$), but not during weeks 35-38 (adjusted OR, 2.0; 95% CI, 0.9-4.3; $P = 0.10$).

CONCLUSIONS Thrombocytopenia from birth through 34 weeks' PMA was associated with subsequent severe ROP. This time period corresponds to a period of poor retinal vascular growth, suggesting a possible proangiogenic effect of platelets in normal retinal vascular development in infants at risk for ROP. (J AAPOS 2018;■:1-5)

The pathogenesis of retinopathy of prematurity (ROP) is currently thought to involve phases of initial hyperoxia, followed by retinal hypoxia and finally vascular proliferation.[1] Disease development and progression are largely mediated by alterations in local vascular endothelial growth factor (VEGF) and systemic insulin-like growth factor 1 (IGF-1). Normally, hypoxia in the developing and increasingly metabolically active avascular retina induces VEGF secretion, which stimulates vessel growth.[2] However, VEGF activity requires sufficient levels of serum IGF-1, a systemic growth hormone.[2,3] In premature infants, lack of maternal sources and poor endogenous secretion result in low serum IGF-1 and poor retinal vessel growth despite hypoxia and upregulated local VEGF production. With time, endogenous serum IGF-1 levels rise[4] and permit VEGF activity, resulting in a proliferative retinopathy.[2]

In addition to hemostasis, platelet functions may include both pro- and anti-angiogenic regulation.[5,6] Platelets store, transport, and deliver key angiogenic factors,[7] including VEGF[5,6] and IGF-1,[8] and therefore may influence the development of ROP. In 2010 Vinekar and colleagues[9] found a relationship between thrombocytopenia and aggressive posterior ROP (AP-ROP). Based on a single serum platelet level prior to laser, they found lower mean serum platelet counts in 10 cases compared to 21 controls. We subsequently reported an association between thrombocytopenia immediately preceding laser and Early Treatment of ROP Study type 1 ROP in 91 cases versus 91 matched controls, again considering only a single serum

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Conflicts of interest: Gil Binenbaum, MD, participates as a site investigator in a retinopathy of prematurity treatment randomized controlled trial sponsored by Novartis.

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platelet level prior to laser.[10] In a subgroup analysis, the overall association seemed primarily attributable to zone I cases. However, it was unclear whether these findings reflected the timing of the platelet level being considered (earlier for zone I disease in our study and for AP-ROP in the Vinekar and colleagues[9] study) or the anatomic location of the disease, because the association between thrombocytopenia and ROP has yet to been investigated longitudinally. Recently, Lundgren and colleagues[11] found significantly lower serum platelet counts preceding aggressive-posterior ROP diagnosis among 9 infants who developed AP-ROP compared to 9 infants who developed ROP of stage 2 or less, although multivariable analysis was not performed to control for sepsis and NEC.

We sought to evaluate the temporal course of the association between thrombocytopenia and subsequent development of severe retinopathy of prematurity (ROP). We hypothesized that there would be a time period in postnatal development during which the association would be strongest.

Subjects and Methods

This study was approved by the institutional review boards of the Children's Hospital of Philadelphia and the Hospital of the University of Pennsylvania and complied with all requirements of the US Health Insurance Portability and Accountability Act of 1996 and the tenets of the Declaration of Helsinki. The medical records of premature infants at risk for ROP at both institutions between January 1, 2005, and December 31, 2009, were reviewed retrospectively. Cases were infants who received ROP laser photocoagulation surgery; decisions to treat were made using Early Treatment for ROP (ETROP) Study type 1 ROP criteria.[12] Controls infant received inpatient ROP examinations at either hospital during the same time period and developed either no ROP or at worst stage 1 ROP prior to documentation of one of the following: mature retinal vasculature, immature vasculature in zone III without prior disease, and regressing or regressed stage 1 disease. Although some of these case and control infants were included in a prior report,[10] only a single serum platelet level for each infant was considered; in the current study, new longitudinal data are collected and reported. In addition, the inclusion criteria for the prior and current studies differed. In the prior study cases had to have "matchable" controls with regard to birth weight (BW) and gestational age at birth (GA) and have platelet data available within 1 week prior to laser (cases) or within 2 weeks' postmenstrual age (PMA) of matched (controls). Neither were required in the current study.

Data were collected from inpatient and outpatient medical records at the study hospitals, including outside hospital transfer summaries. All available serum platelet levels were abstracted from birth through day of laser treatment for cases and through 38 weeks' PMA or hospital discharge for controls, whichever occurred first. Platelets were obtained as part of complete blood counts, which were drawn routinely at least weekly for the majority of patients at both study hospitals. For each ROP examination, stage, zone, and presence or absence of plus disease were recorded. BW, GA, episodes of culture-proven sepsis, and diagnosis of Bell's stage IIA or greater necrotizing enterocolitis (NEC)[13] were abstracted as potential confounders.

Data Analysis

Thrombocytopenia was defined as a serum platelet count of $<150{,}000/\mu L$.[14,15] For all analyses, a subject was considered to have thrombocytopenia during a given week of PMA if any of the available serum platelet levels during that week were $<150{,}000/\mu L$. The proportion of cases with thrombocytopenia was compared to that of controls during each week PMA until the time of laser treatment using the Fisher exact test. A two-sided P value of <0.05 was considered statistically significant. The association between thrombocytopenia and type 1 ROP was evaluated during early (PMA weeks 24-28), middle (PMA weeks 29-34), and late (PMA weeks 35-38) time periods by using multivariate logistic regression with adjustment for BW, GA, sepsis, and NEC. These time periods were chosen to approximately correspond to the initial hyperoxic, middle hypoxic, and later neovascular periods thought to occur in ROP pathogenesis,[1] although these definitions were known to be somewhat imprecise due to the varying GA of the infants studied. The study was designed to be an exploratory hypothesis-generating study; therefore, no corrections for multiple comparisons were made. The primary analysis considered all cases and controls. Subgroup analyses were performed by zone of disease, because prior studies suggested an association specifically for posterior disease. Consideration of confounding by sepsis and NEC depended upon the date of the platelet level being considered. Thrombocytopenia may precede other identifiable signs of neonatal sepsis or NEC up to 24 hours, continues until sepsis or NEC is controlled, and typically resolves over 1-2 weeks.[16] Therefore, an episode of sepsis was considered as a potential confounder if it occurred within a period ranging from one week prior to one week following the serum platelet level being considered. We considered a given serum platelet level as potentially being affected by a diagnosis of NEC made any time prior to through two weeks after the date of the platelet level. All analyses were performed using SAS statistical software version 9.2 (SAS INC, Cary, NC).

Results

During the study period, 110 infants underwent ROP laser photocoagulation surgery. Ten treated infants, all of whom had been transferred from an outside hospital for laser, were excluded because platelet data were lacking. Baseline characteristics for the remaining 100 cases and 100 controls appear in Table 1. The mean PMA at laser for the cases was 37.3 ± 3.0 weeks (standard deviation).

The proportions of cases and controls with thrombocytopenia for each PMA week from 24 to 38 appear in Table 2 and Figure 1. There was a significant association between thrombocytopenia and type 1 ROP during PMA weeks 24-28 (OR adjusted for BW, GA, sepsis, and NEC, 4.7; 95% CI, 2.0-1.1; $P = 0.001$), PMA weeks 29-34 (adjusted OR 2.8; 95% CI, 1.4-5.6; $P = 0.006$), and the combined period, PMA weeks 24-34 (adjusted OR 2.9; 95% CI,

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