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Retinal vascular speed <0.5 disc diameter per week as an early sign of retinopathy of prematurity requiring treatment

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Abstract

Purpose: To analyse the speed of temporal retinal vascularisation in preterm infants included in the screening programme for retinopathy of prematurity.

Material and methods: A total of 185 premature infants were studied retrospectively between 2000 and 2017 in San Cecilio University Hospital of Granada, Spain.

The method of binocular indirect ophthalmoscopy with indentation was used for the examination. The horizontal disc diameter was used as a unit of length. Speed of temporal retinal vascularisation (disc diameter/week) was calculated as the ratio between the extent of temporal retinal vascularisation (disc diameter) and the time in weeks.

Results: The weekly temporal retinal vascularisation (0–1.25 disc diameter/week, confidence interval) was significantly higher in no retinopathy of prematurity (0.73 ± 0.22 disc diameter/week) than in stage 1 retinopathy of prematurity (0.58 ± 0.22 disc diameter/week). It was also higher in stage 1 than in stages 2 (0.46 ± 0.14 disc diameter/week) and 3 of retinopathy of prematurity (0.36 ± 0.18 disc diameter/week). The rate of temporal retinal vascularisation (disc diameter/week) decreases when retinopathy of prematurity stage increases. The area under the receiver operating characteristic curve was 0.85 (95% confidence interval: 0.79–0.91) for retinopathy of prematurity requiring treatment versus not requiring treatment. The best discriminative cut-off point was a speed of retinal vascularisation <0.5 disc diameter/week, with a sensitivity and a specificity of 84.8% and 77%, respectively.

Conclusion: The rate of temporal retinal vascularisation is a quantifiable observation that can help to alert a clinician that treatment of retinopathy of prematurity may be required. However, before becoming a new standard of care for treatment, it requires careful documentation, with agreement between several ophthalmologists.

Keywords

Retinopathy of prematurity, temporal retinal vascularisation, treatment of retinopathy of prematurity

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Introduction

Retinal vascularisation starts from week 16 of pregnancy; the retinal vessels extend towards the periphery in response to stimuli such as hypoxia and release of angiogenic factors, advancing 0.1 mm per day.[1] The mean optic disc width in premature infants is 1.05 mm.[2,3] If the horizontal optic disc size is taken as the unit of length and the retinal area covered by the vessels in 1 week in premature infants is known, the speed of normal retinal vascular development can be measured.

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Our objective was to analyse the speed of temporal retinal vascularisation in preterm infants included in the screening programme for retinopathy of prematurity (ROP).

Material and methods

A total of 185 premature infants included in the screening programme for ROP were studied retrospectively between 2000 and 2017 in San Cecilio University Hospital of Granada, Spain. Clinical data were collected retrospectively from the inclusion of premature infants in the ROP protocol to the medical discharge.

The classification of ROP stage was carried out by an expert ophthalmologist. The gold standard method of binocular indirect ophthalmoscopy with indentation was used for the examination of preterm infants after pharmacological mydriasis (phenylephrine 1% and cyclopentolate 0.2%). A 20-diopter lens was used to complete the technique. This type of lens magnifies the image ×2.5, allowing a view of the retina of 8 disc diameters (DDs).[4–6]

A written informed consent from parents was obtained for using the clinical data for research. Patients included in the sample were born at a gestational age of ≤32 weeks and underwent at least three examinations. All of them had no ROP, stage 1, stage 2 or stage 3 of ROP. The No ROP group was composed of those preterm infants with avascular retina without any stage of ROP. The exclusion criteria were ophthalmologic or systemic congenital abnormalities and media opacity, which it made impossible to observe the retina. This study also excluded those cases in which examinations were insufficient to calculate the rate of vascularisation as well as patients with ROP stage 4, stage 5 and posterior aggressive ROP (APROP), due to lack of sufficient samples.

From 2000 to 2004, the criteria of the multicenter trial of cryotherapy for ROP were used for the classification and treatment of ROP.[7] From 2005 to 2017, the Early Treatment for ROP Randomized Trial and the international criteria for classification of ROP were used.[8–12] Stage 1 is characterised by the presence of a demarcation line separating avascular from vascularised retina. In stage 2 of ROP, a ridge arises in the region of the demarcation line and in stage 3, extraretinal fibrovascular proliferation/neovascularisation extends from the ridge into the vitreous.

The horizontal DD was used as the unit of length. This measure was used to calculate the speed of temporal retinal vascular development. Time was measured in weeks. The speed of temporal retinal vascularisation is not considered a risk factor but is a quantifiable observation. Speed of temporal retinal vascularisation (DD/week) was calculated as the ratio between the extent of temporal retinal vascularisation (DD) and the time in weeks.

Speed of temporal retinal vascularisation (DD/week) = avascular temporal area (DD)/weeks needed for complete vascularisation of the retina.

Statistical analysis: data were analysed with the SPSS V.21.0 (SPSS Inc, Chicago, IL, USA). Student's t-test was applied to compare the results of means of temporal vascularisation speed in the different stages of ROP. Variance had been previously analysed by means of the Levene test or the non-parametric Mann–Whitney U-test. The receiver operating characteristic (ROC) curve and the area under the curve (AUC) were used to evaluate predictive performance and to determine the cut-off point in the speed of vascularisation. Thus, it was possible to determine and predict whether patients would need treatment or not.

Results

Demographic characteristics of the study population

A total of 612 premature infants born at a gestational age 32 weeks or less were reported between 2000 and 2017 in the Department of Paediatrics of San Cecilio University Hospital of Granada. 417 patients were excluded from this study considering the exclusion criteria previously mentioned. A retrospective study of the speed of temporal retinal vascularisation was carried out in 185 infants within no ROP group, Stage 1, 2 and 3 of ROP. There were 91 (49.2%) males and 94 (50.8%) females. The mean gestational age and birth weight were 28.95 (standard deviation (SD): 1.99 weeks) and 1119.35 (SD: 270.94) g, respectively. The sample included 92 (49.7%) patients with no ROP, 32 (17.3%) with stage 1 of ROP, 17 (9.2%) with stage 2 of ROP and 44 (23.8%) with stage 3 of ROP.

Temporal retinal vascular development associated with no ROP, stages 1, 2 and 3 of ROP. The temporal retinal vascularisation was calculated dividing the avascular temporal area (DD) by the number of weeks required to complete retinal vascularisation. The speed of temporal retinal vascular development calculated in our study was 0.73 ± 0.22 DD/week in no ROP group, 0.58 ± 0.22 DD/week in stage 1, 0.46 ± 0.14 DD/week in stage 2 and 0.36 ± 0.18 DD/week in stage 3 of ROP. The weekly retinal vascularisation (DD/week) was significantly higher in infants with no ROP than in those with stage 1 of ROP (Student's t was 3.21, $p = 0.0021$). It was also higher in stage 1 than in stages 2 and 3 (Student's t: 4.61, gl: 49, $p = 2.91E{-}05$). Comparing the rate of vascularisation in ROP stage 2 (0.46 ± 0.14 DD/week) and ROP stage 3 (0.36 ± 0.18 DD/week), no significant difference was observed (Student's t: 1.69, gl: 32;) (Figure 1).

ROC curve of temporal retinal vascular development: the capacity of the rate of vascularisation to determine whether patients need treatment or not. ROC curve showed that the speed of temporal retinal vascularisation <0.5 DD/week was the best cut-off point, with an AUC of 0.85 (95% confidence

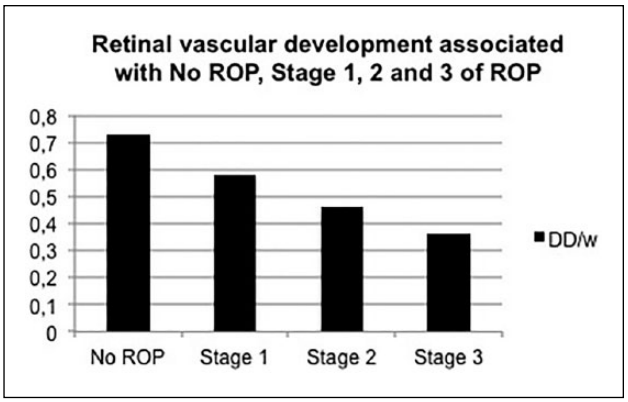

Figure 1. The most severe stage of ROP in the preterm infants. The speed of retinal vascularisation decreases when ROP stage increases.

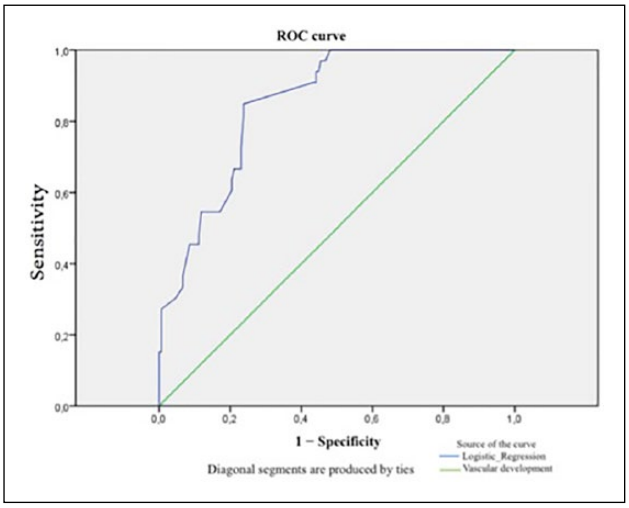

Figure 2. ROC curve showing sensitivity and specificity of predictive modelling of ROP requiring treatment using either the logistic regression model or the vascular development <0.5 DD/week.

interval (CI): 0.79–0.91). Sensitivity was 84.8% (95% CI: 61.9–100) and specificity 77% (95% CI: 71.1–82.2). The positive predictive value and the negative predictive value were 44.4% (95% CI: 36.6–55.3) and 96% (95% CI: 85.5–100), respectively (Figure 2). Positive (+) profitability index (PI)=0.848/0.23=3.7. Vascular development <0.5 DD/week is 3.7 times more likely to be present in patients with need for treatment of ROP than in those who do not require treatment. Negative (−) PI−=0.152 /0.77=0.2 (Figure 2). Vascular advancement ≥0.5 DD/week is five times more likely to be present in patients with untreated ROP than in those requiring treatment.

In this study, we analysed the results of the speed of temporal retinal vascularisation ≥0.5 DD/week or <0.5 DD/week both in premature infants that required treatment, and in those that did not need treatment (Table 1).

Discussion

A single paediatric ophthalmologist carried out all the examinations according to the screening programme for ROP, using the gold standard method of binocular indirect ophthalmoscopy with scleral indentation. Although the method used is subjective and may present limitations in our study, it is easy to perform and allows a correct examination of the peripheral retina. RetCam® has some disadvantages as it does not allow detailed examination of the peripheral retina and is not available at all hospitals.[13,14]

The progression of the avascular phase to the proliferative phase is attributed to the downregulation of growth factors due to an exposure to relative hyperoxia. This results in retinovascular growth attenuation and an increased metabolic demand of the developing retina.[15,16]

It has been described that ROP is genetically conditioned, with an estimated heritability of 70.1%–72.8%.[5,17] Furthermore, there are many factors that delay vascular development such as nitric oxide, adenosine, apelin, β-adrenergic receptor and Norrin-Fzd4. These factors increase the avascular area of the retina and play an important role in the development of ROP.[15,18,19] According to Harnett and Penn,[20] in ROP, there is a delay in physiologic retinal vascular development rather than vasoobliteration, with subsequent vasoproliferation in some infants with ROP. Hellström et al.[21] confirmed that the optimisation of oxygen saturation, nutrition and normalisation of concentrations of essential factors such as insulin-like growth factor 1 and ω-3 polyunsaturated fatty acids, as well as the reduction of the effects of infection and inflammation promote postnatal growth and improve retinal vascular development.

For the paediatric ophthalmologist, it is extremely important to know and predict whether or not a child will need treatment, especially in very low gestational age neonates with high comorbidity and large areas of avascular retina.

The revised international classification of ROP defined the location of the disease in the retina and the extent of the developing vasculature involved.[10] In addition to the location and stage of ROP, the results of this study support that the rate of weekly temporal retinal vascularisation is a good prognostic indicator. In addition, measuring the speed of temporal retinal vascularisation helps paediatricians to know if they need to adjust modifiable risk factors to avoid the worsening of ROP.

Some authors have described the extent of progression of retinal vascularisation measured in DD. Tahija et al.[22] used fluorescein angiography to measure the avascular area of the retina in DD in patients with incomplete peripheral retinal vascularisation after intravitreal injection of bevacizumab (IVB). In addition, Isaac et al.[23] described in their work the initial and final extent of the temporal retina

Table 1. A rate of retinal vascularisation <0.05 DD/week is a good cut-off point for the screening of preterm infants that need ROP treatment.

DD/week	Treated infants	Untreated infants	Total
<0.5	28 (15.1%)	35 (18.9%)	63 (34.1%)
≥0.5	5 (2.7%)	117 (63.2%)	122 (65.9%)
Total	33 (17.8%)	152 (82.2%)	185 (100%)

ROP: retinopathy of prematurity; DD: disc diameter.

vascularisation measured in DD. They compared in the same patient the retinal vascularisation between treated and untreated eyes after unilateral IVB treatment. In an article written by Mintz-Hittner et al.,[24] the avascular area in the temporal periphery measured in DD was compared between patients with those without recurrence of ROP, the latter being higher. The rate of vascularisation was also compared between the two groups, concluding that it was lower in patients with recurrence (0.11 DD/week) versus infants without recurrence (0.23 DD/week). For 17 years in San Cecilio University Hospital, weekly temporal vascularisation has been used as a clinical indication in the final evolution of ROP in a broad sample of patients with no ROP and stages 1, 2 and 3 of ROP. Several authors have found that from 28 weeks of gestational age, the internal vascular plexus of the retina grows 0.094–0.1 mm/day, which is equivalent to a vascularisation rate of 0.7 DD/week.[1,25] In this study, similar results were found in preterm infants with no ROP (0.73 ± 0.22 DD/week). The more time to vascularise the temporal retina, the lower the rate of vascularisation will be.[26] Our study corroborates the fact that a higher stage of ROP is related to a lower rate of vascularisation.

Vascularisation ≥0.5 DD/week indicates good vascular development of the retina and provides guidelines about the behaviour of ROP. In the sample, 96% of the preterm infants did not require treatment; therefore, a rapid vascularisation of the retina reduces the risk of severe ROP stages. Among the patients in the sample who received treatment, 85% had a rate of temporal retinal vascularisation <0.5 DD/week. Other studies support these results, since the total sample of Mintz-Hittner et al.[24] study was composed of premature patients who required treatment and in all of them a rate of lower than 0.5 DD/week was observed. A value of <0.5 DD/week is not by itself an indication that treatment is required. This indication for ROP treatment must be accompanied by the return of plus disease; the formation of extraretinal fibrovascularisation proliferation; zone I with any stage with plus disease; zone I, stage 3 without plus disease; or zone II, stage 2 or 3 with plus disease.[10–12] Decreased rate of temporal retinal vascularisation may be an important early sign that ROP requiring treatment may occur.

Limitations

The references that discuss the extent of progression of temporal retinal vascularisation in ROP published between 2014 and 2016[22–24] were documented by fundus photography and in some patients by fluorescein angiography. They can be measured repeatedly, exactly and by masked technicians. The values in this article are done clinically (moving, awake infants) and were not examined by multiple observers.

In conclusion, the rate of temporal retinal vascularisation is a quantifiable observation that can help to alert a clinician about when treatment may be required. Appropriate retinal vascular development reduces the need for treatment. The speed of temporal retinal vascularisation is one of several clinical indications that should be recorded before treatment is performed. Characterisation of clinical retinal vascularisation to set a new standard of care for treatment requires careful documentation, with agreement between several ophthalmologists.

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