Nasotemporal Asymmetry of Retinopathy of Prematurity

Kieran Gallagher, BSc; Merrick J. Moseley, PhD; Anamika Tandon, FRCS; Martin P. Watson, MRCOphth; Kenneth D. Cocker, MSc; Alistair R. Fielder, FRCOphth

Objective: To quantify an apparent nasotemporal asymmetry in the location of retinopathy of prematurity with respect to the optic disc.

Methods: Twenty-four–bit color images were captured using a contact digital fundus camera during routine screening. Semiautomated measurements were undertaken to determine the distance between the optic disc and retinopathy located in the nasal and temporal regions of the retina.

Results: Forty-nine image pairs (17 right eye, 32 left eye) were captured from 10 infants during a period of 32 to 40 weeks postmenstrual age. For right eyes, averaged across age, the mean (SD) distance between the optic disc and temporal retinopathy was 426 (26) pixels and that between the optic disc and nasal retinopathy was 330 (26) pixels. Corresponding measurements for the left eye were 428 (30) and 332 (24) pixels. This observed asymmetry was found to be statistically significant in both left and right eyes (Mann-Whitney U test, \( P < .01 \)). While the distance between the optic disc and retinopathy increased with age by 10 to 17 pixels per week, the extent of the asymmetry did not vary systematically with age.

Conclusion: The location of retinopathy of prematurity is asymmetric along the horizontal meridian with respect to the optic disc—an observation germane to retinal vascular development, the pathogenesis of retinopathy of prematurity, and current disease classification by circular (symmetric) zones.

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SINCE THE introduction of an international classification,\(^1\) retinopathy of prematurity (ROP) has been the subject of intense clinical and basic research interest. The classification includes 3 cardinal taxonomic features: severity, by stage; location, by zone; and extent of involvement around the retinal circumference. The last 2 at least denote an acceptance that the location and extent of ROP are important clinically and as such are determinants of treatment and outcome.\(^2\)

Retinal vascularization commences at about the 14th week of fetal life,\(^3\) is centered on the optic disc, and proceeds centrifugally from this structure. The ROP lesion is located at the junction of the vascularized and yet to be vascularized retina, and its location by zone is determined by how far retinal vascularization has progressed. This coordinated developmental sequence permits the retina to be subdivided into 3 concentric circular zones. Zone I, the innermost zone, consists of a circle, the radius of which subtends an angle of 30° and extends from the disc to twice the distance from the disc to the center of the macula.\(^4\) Zones II and III are circular extensions to the area encompassed by zone I, with zone III being the “residual crescent of retina anterior to zone II.”\(^5\) The periphery of zone II in the nasal portion of the retina is the ora serrata, but in the temporal portion, the junction between zones II and III “cannot be accurately defined clinically.”\(^6\) Thus, all 3 retinal zones are derived from a spatial coordinate system centered on the optic disc.

Location by zone has major consequences for outcome. For example, in the Multicenter Trial of Cryotherapy for Retinopathy of Prematurity,\(^4\) studying infants with a birth weight less than 1251 g, the risk of reaching “threshold” ROP (current indication for treatment) was 54% if vascularization was incomplete in zone I; however, if vascularization had reached zone II (but not III), this was reduced to 8%. Thus, disease in zone I and posterior zone II carried a high risk of vision impairment,\(^7\) while in zone III (ROP that was always located in zone III), the risk of an unfavorable outcome was nil,\(^7\) indi-
cating the importance of location along the anteroposterior meridian.

Although circular zones reflect the centrifugal pattern of retinal vascularization, ROP does not usually develop simultaneously at every point of the advancing vascular front simultaneously. We have previously established that with respect to its temporal behavior, the location of ROP at onset is frequently asymmetrical, so that in the most immature infant, retinopathy has a tendency to develop in the nasal before the temporal portions of the retina.8 This observation led us to speculate whether this time-domain asymmetry has a corollary in the spatial domain, with ROP located asymmetrically with respect to the optic disc. If this were the case, it would have implications for our understanding of retinal zones and their clinical significance.

Given the millimeter scale of preterm retinal topography, it has hitherto been impossible to undertake the necessary measurements to determine if spatial asymmetry of ROP location exists. Until now, only qualitative observations could be undertaken using directview examination methods (eg, indirect ophthalmoscopy). Here, we employ a recently developed digital retinal imaging system with incorporated software of sufficient accuracy to allow detailed topographical measurements.

**METHODS**

**IMAGE CAPTURE**

During screening for ROP, 24-bit color images were captured using a contact digital fundus camera (RetCam120; Massie Research Laboratories Inc, Dublin, Calif). This handheld instrument (employed here with an interchangeable camera head optimized for imaging the preterm retina) incorporates an image archive and analysis software. Included among the latter is the facility to undertake linear topographical measurements of retinal structures. This semiautomated procedure requires that an observer position a mouse-driven screen cursor at points that spatially define a feature of interest. The analysis routine calculates the distance between the defined points and returns the value on screen. Authorization to undertake measurements on routinely captured images was granted by St Mary's Hospital NHS Trust Local Research Ethics Committee.

**IMAGE SELECTION AND ANALYSIS**

Criteria for the inclusion of images in the study were
- Images obtained from infants with both nasal and temporal ROP.
- The availability within a single examination of an image pair in which (1) the optic disc and nasal ROP and (2) the optic disc and temporal ROP could be visualized in one image each (image pairs are required [except for zone I ROP], as the RetCam does not have a sufficiently large field of view such that nasal and temporal retinopathy can be viewed to the full extent within a single image).
- Images that, in addition to the aforementioned criteria, were captured from infants on more than 1 occasion (minimal interval, 7 days).

Principal analysis compared the mean distance from the optic disc to the nasal ROP and that from the optic disc to the temporal ROP. The center of the optic disc was the reference point throughout. A single examiner (K.G.) undertook all measurements. Reference points between which distance measurements were recorded were the center of the optic disc to the center of the demarcation line of the retinopathy. To avoid arbitrary variation in the few images where this line was greatly thickened by extraretinal fibrovascular proliferation, the reference point was taken as the outermost edge. Although the center of the optic disc can, for the purposes of the exercise, be treated as a single point in space, retinopathy, when represented on screen, is a 2-dimensional (typically, curvilinear) structure. In consequence, its distance from the optic disc will vary, and it was therefore necessary to obtain measurements in a systematic fashion at equal intervals (2 mm) and to average them accordingly (Figure 1). Measurement errors arising from this strategy would not result in a systematic bias between measurements of nasal and temporal ROP to the optic disc.

**RELIABILITY AND ACCURACY OF MEASUREMENTS**

Retinal topographic measurements obtained in the manner described are subject to 2 principal sources of error: the inherent accuracy of the measurement system and the extent to which a human observer can consistently and accurately position the screen cursor. The instrument's manufacturer claims an accuracy of ± 100 µm for the measurement between any 2 points within a given image. In our published pilot studies,9 one of us (A.T.) obtained an intraobserver agreement score (mean difference and central 95% range) of 0.14±1.64 mm with 2 different sets of 22 images recorded from the same eyes within a single session. This score combines an estimate of the intrinsic reliability (between images) of the instrument with that of an observer's ability to consistently position the screen cursor. The interobserver agreement (mean difference and central 95% range) between 2 of us in our measurements of 90 sample images was 0.16±0.65 mm. In the present study, our concern was with the relative rather than the absolute physical distances between the optic disc and nasal and temporal retinopathy. Hence, all measurements reported here are expressed in camera pixel units. The image analysis routine in the RetCam120 used to calculate the distance between retinal locations of interest is based on a stated calibration that may vary between 0.025 and 0.03 mm/pixel (e-mail communication, Massie Research Laboratories, 2002).

**RESULTS**

Forty-nine image pairs (17 right eye, 32 left eye) captured from 10 infants met the stated inclusion criteria.
These were obtained during a period of 32 to 40 weeks postmenstrual age, with 2 to 5 examinations per infant. The site of ROP onset, its subsequent extension along the retinal circumference, and maximum stage are presented in the Table.

The mean distance between the optic disc and nasal and temporal retinopathy as a function of postmenstrual age, in left and right eyes, is shown in Figure 2. For right eyes, averaged across age, the mean (SD) distance between the optic disc and temporal retinopathy was 426 (26) pixels, and between the optic disc and nasal retinopathy was 330 (26) pixels. Corresponding measurements for the left eye were 428 (30) and 332 (24) pixels, respectively, for temporal and nasal retinopathy. The differences between the distances from the optic disc to nasal and the optic disc to temporal retinopathy were 426 (26) pixels, and between the optic disc and nasal retinopathy was 330 (26) pixels. Corresponding measurements for nasally located ROP. In the left eye, the corresponding figures were 17 (10) and 17 (12) pixels per week. This quantification of the observed trend is, however, subject to the bias of some infants contributing more images to the data set than others (Table).

A qualitative analysis of trend revealed by the lines of best fit in Figure 2 shows that for almost all infants’ eyes, the distance between the optic disc and retinopathy increases as a function of age. Averaged data, clarifying this trend, are shown in Figure 3. The mean (SD) increase in the right eye was 10 (13) pixels per week for temporally located retinopathy and 12 (9) pixels per week for nasally located ROP. In the left eye, the corresponding figures were 17 (10) and 17 (12) pixels per week. This quantification of the observed trend is, however, subject to the bias of some infants contributing more images to the data set than others (Table).

The extent to which the spatial asymmetry per se is dependent on the age of the infant is shown in Figure 4. Here, the average distance between the disc and temporal retinopathy subtracted from the average distance between the disc and nasal retinopathy is plotted as a function of age for left and right eyes. Inspection of the trend lines does not reveal any ordered relationship in these plots. Thus, while averaged across infants, the absolute differences between disc and retinopathy increase with age (Figure 3). The extent of the asymmetry does not appear to vary systematically with time.

We have systematically documented 2 features of ROP that we believe to be of significant clinical relevance: its asymmetric location in the nasal and temporal portions of the retina and its centrifugal migration with increasing postmenstrual age. Three possible explanations may account for the observed nasotemporal asymmetry: asymmetry of image capture, asymmetric retinal vascularization, and asymmetric ROP onset. First, we have now accumulated more than 10,000 images and have noted that measurements do not differ according to positioning or rotation of the camera head. Two studies on different image sets have produced the same findings.9 We have, post hoc, confirmed our quantified RetCam observations by the qualitative indirect ophthalmoscope. Once spotted, it is rather obvious, as shown in Figure 5. Citing this time-honored ophthalmic tradition makes a serious point—signs first observed only by fluorescein angiography could subsequently be seen, in the light of the insight gained by this technique, by ophthalmoscopy. What was not observed by many thousands of ophthalmoscopic examinations by us and others is now retrospectively obvious on digitally captured retinal images.

Second, asymmetry may reflect the normal pattern of retinal vascular development. It is a general tenet that neural development, with the increase in cell density and activity, generates a metabolic need that drives vascular development through a physiologic astrocytic hypoxia-induced vascular endothelial growth factor mechanism.10,11 However, this does not fully explain retinal blood vessel development, as there are important regional variations, and certain retinal regions never vascularize.3,11-14 For instance, at the fovea, the development of retinal vessels is both inhibited and retarded so that the major lobular vessels arch around the macular area, whereas in the nasal retina, blood vessels adopt a more direct route. Gariano et al13 reported that for each gestational age studied, vessel growth had proceeded farther in the nasal compared with the temporal region.

### Table: Image Details of ROP in Infants

<table>
<thead>
<tr>
<th>Subject No./ Gestational Age, wk</th>
<th>Birth Weight, g</th>
<th>Site of Onset (Eventual Circumferential Extent)</th>
<th>Maximum Stage</th>
<th>Left Eye</th>
<th>Right Eye</th>
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<tr>
<td>1/24</td>
<td>710</td>
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<td>3</td>
<td>13</td>
<td>9</td>
</tr>
<tr>
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<td>9</td>
<td>8</td>
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<tr>
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<td>2</td>
<td>6</td>
<td>1</td>
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<tr>
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<td>920</td>
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<td>5</td>
<td>1</td>
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<tr>
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<td>2</td>
<td>4</td>
<td>3</td>
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<td>10</td>
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<tr>
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<td>8</td>
<td>4</td>
</tr>
<tr>
<td>10/26</td>
<td>950</td>
<td>Temporal (360°)</td>
<td>3</td>
<td>9</td>
<td>1</td>
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</tbody>
</table>

Abbreviation: ROP, retinopathy of prematurity.

*Eventual circumferential extent does not denote the extent of the maximum stage, but of any ROP.
of the retina, and at 21 weeks’ gestational age, this difference was 1.55 mm. Others, however,\textsuperscript{3,11,14} have reported more advanced retinovascular development in the temporal compared with the nasal region of the retina, although according to Hughes et al.\textsuperscript{14} this differential was greater in the outer compared with the inner vascular plexus.

Third, our findings may reflect asymmetric ROP. In the preterm neonate, it is postulated that hyperoxia induces down-regulation of vascular endothelial growth factor, causing cessation of retinal vessel growth and vasoobliteration, setting the scene for the subsequent vascular endothelial growth factor up-regulation that characterizes the hypoxic-neovascular response—ROP.\textsuperscript{3} Our finding that in an eye with an internal diameter of 14 to 16 mm, ROP is located 2 to 3 mm (for pixel to millimeter conversion, see the “Methods” section) closer to the optic disc in the nasal compared with the temporal region of the retina points to a local perturbation of vascular development, as growth of the nasal, but not the temporal vessels, is retarded. These changes have not been reported in animal models of oxygen-induced retinopathy, but technological advances present new opportunities for frequent non-invasive monitoring of retinal development, which may provide clues to the mechanisms of human disease. The importance of regional retinal factors has already been alluded to as retinopathy in the most immature infant frequently develops first in the nasal portion of the retina,\textsuperscript{9}

Figure 2. Distance from the optic disc to retinopathy as a function of postmenstrual age for each infant, with lines of best fit. The plot symbols correspond to individual infants.
which might permit further progression of retinal vascularization temporally, thus contributing to nasotemporal asymmetry. This is unlikely to fully explain our findings because neither retinal neural density nor vascular development can fully explain why ROP only infrequently involves the vertical retinal meridia, and when it does, it appears later than in other parts of the retina. Asymmetric retinal vascularization and asymmetry of ROP onset coexist and may contribute to nasotemporal asymmetry. However, we recognize that other mechanisms, as yet unknown, may contribute to this finding.

Location by zone is one of the most powerful predictors of ROP outcome. However, if ROP is located in an oval rather than a circular pattern, then the point of reference that determines zonal location precisely becomes problematic. Our results also demonstrate that the ROP lesion migrates centrifugally between 32 and 40 weeks’ postmenstrual age, during the period of ROP screening. This, we assume, reflects the symmetrical growth of all coats of the eyeball during this period. Thus, the point of reference that defines location by zone merits attention because not only is it spatially asymmetric, it also migrates peripherally with time. Zone I is defined by the field of view of a 25-diopter condensing lens, with the nasal edge of the optic disc as one border and the retina at the opposite edge of the field of view as the other border. As zone I is measured from the optic disc, it is possible that with eye growth, the ROP migrates from zone I to posterior zone II. Repka et al reported centrifugal zone change from zone I to II in some patients. However, migration of ROP in peripheral zone II or III would probably not cause zone changes, as the parameters that
delineate the junction between these 2 zones are not measured from the optic disc.

To conclude, ROP location is asymmetric along the horizontal meridian with respect to the optic disc. This poses interesting questions concerning retinal vascular development and the pathogenesis of ROP. Explicitly, this suggests that the current International Classification of Retinopathy of Prematurity (ICROP)—based on spatial zoning of disease—may require modification for it to reflect the clinicopathologic nature of the disease as we now observe it.

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Corresponding author and reprints: Alistair R. Fielder, FRCOphth, Department of Ophthalmology, Imperial College London, Room 9LO2, Charing Cross Campus, St Dunstan’s Road, London W6 8RP, England (e-mail: a.fielder@imperial.ac.uk).

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