Prognostic Factors in the Natural Course of Retinopathy of Prematurity

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Background: There exists no reliable information that allows the ophthalmologist to predict with any degree of certainty a particular infant's chances of requiring surgical treatment for retinopathy of prematurity (ROP) or of reaching an unfavorable outcome on the basis of the retinal findings at the time of the nursery examination.

Methods: In the Multicenter Trial of Cryotherapy for Retinopathy of Prematurity (CRYO-ROP), 4099 infants weighing less than 1251 g at birth underwent eye examinations that began at 4 to 6 weeks after birth and subsequently continued at 2-week intervals. Independent variables in the population were studied using multiple logistic regressions.

Results: An increased risk of reaching threshold ROP was found associated with lower birth weights, younger gestational age, white race, multiple birth, and being born outside a study center nursery. For infants who developed ROP (66%), corresponding probabilities are presented for developing severe ("threshold") ROP or of having an unfavorable macular outcome. The risk of an unfavorable macular outcome was increased with zone 1 ROP, "plus" disease, the severity of the stage, and the amount of circumferential involvement. A higher risk also was associated with a rapid rate of progression of ROP to prethreshold disease but not with the postconceptional age at which ROP was first noted.

Conclusion: The findings indicate that the ocular characteristics of ROP, along with some easily identifiable and available basic systemic and demographic information about an infant, can assist the ophthalmologist in understanding variations in an individual baby's chance for a good or poor macular outcome.

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As advances in neonatology allow the survival of increasingly premature, lower birth weight babies, the frequency of retinopathy of prematurity (ROP) has risen.[1-5] The literature identifies numerous potential risk factors for ROP,[6] revealing that it is a multifactorial disease occurring most frequently in the smallest, sickest infants. Infants with a birth weight of 1200 g or less appear to be the group at greatest risk.[7] Other risk factors that have been reported include low gestational age, prolonged parenteral nutrition, an increased number of blood transfusions, oxygen therapy, apnea, episodes of hypoxemia, hypercarbia and hypocarbia, and sepsis.[2,7-9]

Recognizing the importance of ROP, the American Academy of Pediatrics[10] has recommended that "an individual experienced in neonatal ophthalmology and indirect ophthalmoscopy should examine the retinas of all premature neonates who require supplemental oxygen," with those less than 30 weeks gestation and/or under 1300 g birth weight having examinations "regardless of oxygen exposure." Examination is recommended "prior to hospital discharge or at least by 5 to 7 weeks of age" with follow-up as determined by the initial findings.

As previously reported, of the cohort of 4099 infants weighing less than 1251 g at birth in the Multicenter Trial of Cryotherapy for Retinopathy of Prematurity (CRYO-ROP), 2699 (65.8%) developed ROP of some degree.[5] (Whenever ROP incidence is stated, the reader must keep in mind that it means "ROP observed or documented on study examinations." We are not implying that our incidence rates are perfect, but they represent what our investigators documented. Consequently, when we mention "no ROP," we also mean "no ROP observed or documented on study examinations.")

Prethreshold ROP occurred in 17.8% and threshold ROP developed in 6.0% of the total population. Given prethreshold disease at any time, approximately one third (33.5%) went on to develop threshold,[11] and 51.4% of the untreated threshold eyes had an unfavorable macular outcome at 3 months after randomization.[12] Nowhere is there reliable information that allows the ophthalmologist to predict with any degree of certainty a particular infant's chances for requiring surgical treatment for ROP or of reaching an unfavorable outcome on the basis of the retinal findings at the time of the nursery examination.

Our study group has previously reported that treatment of stage 3+ ROP at threshold reduced the incidence of an adverse outcome by 45.8%.[13] We are continuing to systematically gather information on the natural history of ROP. This report presents data on the natural course of ROP and identifies prognostic factors that contribute to a rational basis for formulating new examination guidelines in these premature infants.

Patients and Methods

Between January 1, 1986 and November 30, 1987, at each of the 23 CRYO-ROP Study Centers, all infants born weighing less than 1251 g were registered into a master log each week. The results presented here are from those 4099 infants who met the enrollment criteria for the natural history cohort as described previously.[5]

Examination techniques, inter- and intraobserver reliability, the timing of the serial examinations, and the 3-month outcome regimen are discussed in the original, detailed publications[11,12] of this study. The term *postconceptional age*, referring to gestational age at birth plus weeks after birth, as well as the ROP diagnostic descriptions and definition of an unfavorable macular outcome, also have been thoroughly explained.[5,11-13]

Retinal findings were recorded using the International Classification of Retinopathy of Prematurity (ICROP)[14] until the 3-month outcome evaluation, at which time an adaption of the 1953 Reese classification for cicatricial retrolental fibroplasia[15] was used as a summary diagnosis. "Plus" disease consisted of a standardized degree of dilatation and tortuosity of the vessels in the posterior pole,[11] and did not require iris engorgement, pupillary rigidity, vitreous haze, or retinal hemorrhages.

In this report, we include analysis of ROP stages in terms of the presence or absence of plus disease. To highlight this, we include the symbol "+" after the stage number whenever plus disease is present. When plus disease is absent, we use the symbol "−" to signify this. If neither "+" nor "−" is shown, the stage category includes cases both with and without plus disease.

Baseline characteristics of the study population were described in terms of the percentage of infants (or eyes) reaching a particular outcome for each 2 weeks of postconceptional age, with the corresponding 95% confidence limits for each percentage. Results were correlated separately for each zone and stage of the disease as well as whether plus disease was present. More detailed statistical analyses were performed using a multiple logistic regression model. This statistical technique permits assessment of the independent contribution each prognostic factor has on reaching threshold disease.[16] The multiple logistic model partitions the odds (risk) of developing an unfavorable macular outcome into component parts that are associated with various prognostic factors. It results in an estimate of the odds when a factor is present versus absent. All statistical tests were noted if $P < 0.05$.

Results

In the 4099 natural history infants reported in this article, the risk of progressing to threshold was studied by categorizing the data according to the postconceptional age at the time infants were examined. The results are listed in Table 1 according to the zone of vascular completeness or stage of ROP and presence or absence of plus disease in each eye. Except where the numbers were too small to make a meaningful calculation, Table 1 shows the percentage of eyes with a particular retinal finding at a given age that later developed threshold disease. For instance, it can be seen in the column titled 32 weeks or less postconceptional age that 32.8% of all the eyes having incomplete vasculature in zone 1 will subsequently develop threshold ROP. In contrast, incomplete vessels in zone 2

Table 1. Number of Eyes Examined in Each Successive Two-week Period with the Percentage of Eyes for Each Zone/Stage Category that Ultimately Reached Threshold ROP*

	Postconceptional Age											
	≤32 wks		*33–34 wks*		*35–36 wks*		*37–38 wks*		*39–40 wks*		*41–42 wks*	
	No.	*Percent*	*No.*	*Percent*	*No.*	*Percent*	*No.*	*Percent*	*No.*	*Percent*	*No.*	*Percent*
Z2												
Incomplete Z2	1991	9.3	2166	5.5	1161	2.8	588	1.4	206	2.4	81	0.0
Stage 1–†	358	7.5	1138	6.5	1186	4.5	742	1.5	365	1.4	194	1.0
Stage 2–	129	3.9	494	5.5	816	4.4	786	2.3	481	1.2	310	1.3
Stage 3–	9	NC	83	15.7	205	13.2	283	8.5	267	2.2	193	0.0
Stage 1+†	2	NC	12	83.3	12	41.7	6	NC	4	NC	0	NC
Stage 2+	2	NC	25	44.0	59	33.9	24	25.0	36	16.7	15	0.0
Stage 3+	2	NC	30	76.7	61	60.7	87	34.5	51	31.4	35	14.3
Z1												
Incomplete Z1	122	32.8	46	37.0	15	6.7	14	35.7	0	NC	0	NC
Stage 1–	11	18.2	27	33.3	8	NC	3	NC	0	NC	0	NC
All others	4	NC	7	NC	18‡	NC	7	NC	5	NC	2	NC

NC = not calculated due to small number.

* From 32 weeks to 42 weeks postconception, eyes were subdivided by zone and stage of disease and the presence/absence of plus disease.

† "+" means with plus disease, "–" means without plus disease.

‡ Insufficient sample for each category precludes risk analysis.

at this time led to threshold ROP in only 9.3% of the cases.

As shown in Table 1, of the eyes that have incomplete vasculature in zone 1 at 32 weeks or less postconceptional age, approximately one third overall will go on to develop threshold disease. When incomplete vessels extend to zone 2, the risk is much lower (9.3% at ≤32 weeks, decreasing to 0% at 41 to 42 weeks postconceptional age).

Among eyes that have zone 2 disease, those with stage 3 have a higher risk than those with stage 2 ROP. Comparing the percentages of stage 3– to stage 2– ROP (15.7%/5.5% at 33 to 34 weeks, reducing to 2.2%/1.2% at 39 to 40 weeks), indicates about a threefold excess risk associated with the increased stage of ROP. For zone 2 eyes with stage 3+ ROP compared with stage 2+, the ratio is approximately 2:1.

The large number of eyes with zone 2 disease allows a detailed presentation for this subgroup of eyes. The chance of an eye at a given postconceptional age reaching threshold disease from any given stage can be expressed graphically (Figs 1 and 2). Figures 1 and 2 show the effect of stage on zone 2 ROP, comparing stages 3– to 2– (Fig 1) and stage 3+ to 2+ (Fig 2). All curves show a declining risk as age postconception advances. The variation of the 95% confidence limits at each postconceptional age is due to the marked variation in sample sizes noted in Table 1 (i.e., larger confidence intervals are associated with smaller sample sizes).

To complete the analysis of this population of 4099 infants, multiple logistic regressions showing the relative independent effects of certain variables on reaching threshold are reported in Table 2. The first column in Table 2 shows the influence of each factor on an eye's chance of reaching threshold disease. An odds ratio less than one indicates that the chance decreases as the factor increases. The second category (5141 eyes) refers to only those eyes that have developed ROP, and reports the corresponding potential prognostic factors for threshold disease. The third category (1333 eyes) restricts attention to those eyes that progressed to prethreshold disease. The final category (162 eyes) repeats the logistic regression analysis for untreated (control) eyes that have already reached threshold disease. Here the potential prognostic factors reflect the influence each contributes to the risk of an unfavorable macular outcome 3 months after randomization for the cryotherapy trial.[12]

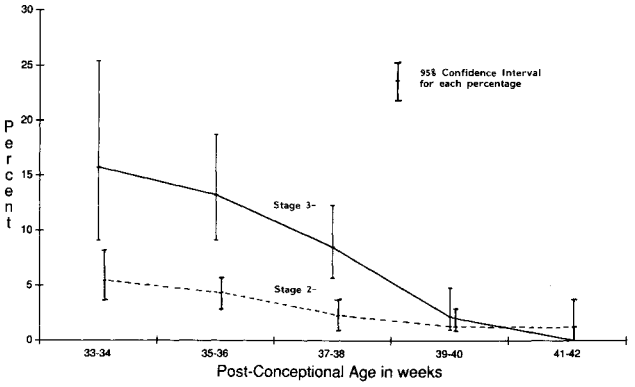

Figure 1. Percent of eyes reaching threshold for zone 2 patients without plus disease.

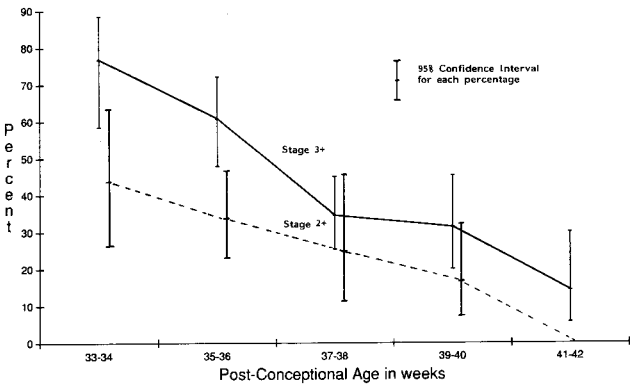

Figure 2. Percent of eyes reaching threshold for zone 2 patients with plus disease.

Several factors were found to reduce the risk of developing threshold ROP. As shown in Table 2, there was an overall 27% (100% − 73%) lowering of the odds of reaching threshold for each additional 100 g of birth weight in the entire cohort of natural history infants (Table 2, category 1). With respect to eyes with ROP (category 2 in Table 2), there were 22% lower odds per 100 additional g of birth weight, but once prethreshold was reached (category 3), only a small benefit (10%) per 100 g was noted. A similar trend was seen when considering the gestational age of the neonates at birth, as there was a 19% lowering of the odds of reaching threshold for each additional week of gestational age for all natural history patients (category 1). Once ROP had occurred, the lowering of the odds per week was 14% (category 2), and, when considering only those eyes having prethreshold disease (category 3), gestational age at birth had no significant effect on the chances of progression to threshold ROP.

In the entire natural history cohort (Table 2, category 1), black infants had 65% lower odds of reaching threshold disease, and in the subgroup of eyes with any ROP (category 2), they had 64% lower odds. This significant racial difference held true even when considering only those eyes having prethreshold disease (category 3), where the black children had a 51% advantage.

Being born outside a study center nursery (outborn) or a product of a multiple birth were both associated with increased risk. Inborn babies have 36% lower odds of reaching threshold ROP (Table 2, category 1) than outborn infants, 32% lower odds once ROP occurred (category 2), but no significant difference once the level of prethreshold ROP was reached. A similar pattern was seen in single compared with multiple (twin or more) births: 36% lower odds for developing threshold ROP if a single birth, also in the eyes with ROP (category 2), and no significant benefit seen once prethreshold ROP was present (category 3).

Table 2 also shows that although there was no prognostic significance in the time of onset of ROP, the rate of progression of the disease was important. The longer the interval from the onset of ROP to prethreshold (under

Table 2. Multiple Logistic Regressions Showing the Relative Effects of Various Risk Factors on Reaching Threshold for All Natural History Eyes and for Eyes that Reached Threshold Showing the Relative Effects of Factors on an Unfavorable 3-month Outcome

	(1) 8198 Natural History Eyes with 448 Eyes Reaching Threshold		(2) 5141 ROP Eyes with 448 Eyes Reaching Threshold		(3) 1333 Prethreshold Eyes with 448 Eyes Reaching Threshold		(4) 162 Control Eyes with 81 Having Unfavorable Macular Outcome	
	P	*Odds Ratio*	P	*Odds Ratio*	P	*Odds Ratio*	P	*Odds Ratio*
Birth weight (100 gm)	<0.0001	0.73	<0.0001	0.78	0.02	0.90	0.03	0.73
Gestational age at birth (wks)	<0.0001	0.81	<0.0005	0.86	0.77	1.02	0.43	1.13
Race Black = 1 Other = 0	<0.0001	0.35	<0.0001	0.36	<0.0001	0.49	0.72	0.83
Inborn = 1/outborn = 0	<0.0005	0.64	0.0025	0.68	0.52	0.91	0.66	0.83
Single = 1/multiple = 0	<0.0005	0.64	00005	0.64	0.23	0.84	0.72	1.17
Onset of ROP (wks) (postconceptional age)	—	—	0.89	1.00	0.15	0.94	0.06	0.78
ROP to prethreshold (wks)	—	—	—	—	<0.0001	0.77	—	—
ROP to threshold (wks)	—	—	—	—	—	—	<0.0001	0.65
Zone at threshold Zone 1 = 1/Zone 2 = 0	—	—	—	—	—	—	0.02	8.24
No. of stage 3 sectors* at threshold	—	—	—	—	—	—	0.006	1.26

* A sector equals one clock-hour (30°).

Table 3. Number of Zone 2 Eyes Examined in each Successive 2-week Period with the Percentage of Eyes in each Staging Category Having an Unfavorable Macular Outcome by Physicians' Examination* (Postconceptional Age)

	≤32 wks		33–34 wks		35–36 wks		37–38 wks		39–40 wks		41–42 wks	
	No.	*Percent*	*No.*	*Percent*	*No.*	*Percent*	*No.*	*Percent*	*No.*	*Percent*	*No.*	*Percent*
Incomplete Z2	780	6.7	865	3.8	464	1.3	237	1.7	83	2.4	35	2.9
Stage 1–†	142	6.3	429	3.0	470	1.9	303	0.3	150	1.3	76	0.0
Stage 2–	52	0.0	208	3.4	333	2.4	339	0.9	199	0.0	132	2.3
Stage 3–	5	NC	31	3.2	95	2.1	130	5.4	137	4.4	90	1.1
Stage 1+†	0	NC	3	NC	6	NC	2	NC	3	NC	0	NC
Stage 2+	1	NC	11	27.3	24	29.2	10	20.0	16	12.5	12	33.3
Stage 3+	0	NC	29	62.1	80	47.5	129	34.9	95	30.5	60	31.7

NC = not calculated due to small number.

* From 32 weeks to 42 weeks postconception, eyes were subdivided by zone and stage of disease and the presence/absence of plus disease.

† "+" means with plus disease, "–" means without plus disease.

category 3), the lower the chance of going to threshold. Each additional week that it took to go from onset of ROP to prethreshold resulted in a 23% reduction of the odds of getting threshold ROP.

To evaluate the effect of plus disease on the prognosis, it was necessary to look at the ROP result (unfavorable macular outcome) rather than the attainment of threshold, since plus disease was a prerequisite for the definition of threshold disease. Of the 4099 original natural history patients, 187 died before the 3-month outcome examination and 757 more were lost to follow-up, leaving 3155 infants with a 3-month summary diagnosis based on the ophthalmologists' examination.[5,11–12] Table 3 reports the eyes of these infants grouped, as in Table 1, by week of postconceptional age, stage, and presence or absence of plus disease. Since the number of eyes with plus disease in zone 1 at each examination interval was small, the data for this end point are given only for zone 2 disease. In this table, both the number and percentage of the eyes that ended with an unfavorable macular outcome according to the physician's examination[11,12] are provided. Where the numbers at a given postconceptional age were large enough, the strong effect of the plus disease parameter becomes obvious. For instance, at a postconceptional age of 33 to 34 weeks, eyes with zone 2, stage 3+ ROP had a 62% chance of having an unfavorable macular outcome, while eyes with zone 2, stage 3– (without plus) ROP had only a 3% chance of ending with this unfavorable diagnosis. This relationship of zone 2, stage 3+ compared with zone 2, stage 3– ROP from 33 to 42 weeks postconceptional age is shown in Figure 3 in graphic form with confidence intervals.

As previously shown in Table 2, the longer the interval between ROP onset and prethreshold, the lower the risk of progression to threshold. The rapidity of the course of ROP in the randomized control eyes in relation to either a favorable or unfavorable macular outcome is summarized in Table 4. For example, in those eyes with an unfavorable macular outcome,[12] the time span between onset of ROP to prethreshold, and from prethreshold to threshold ROP, usually is less than 10 days (average, 8 to 9 days). In contrast, the eyes with a favorable outcome had almost 2 weeks between ROP and prethreshold, and again

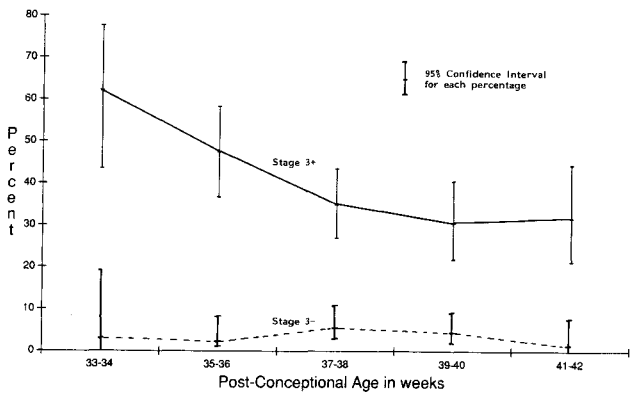

Figure 3. Percent of eyes having unfavorable outcome at 3-month examination for zone 2 patients.

Table 4. Time Course of ROP in 162 Randomized Control Eyes*

	Unfavorable Outcome (n = 81) Mean ± SE	Favorable Outcome (n = 81) Mean ± SE
ROP to prethreshold (days)	8.2 ± 1.2	12.3 ± 1.2
Prethreshold to threshold (days)	8.7 ± 0.9	13.2 ± 1.2
ROP to threshold (days)	16.9 ± 1.2	25.5 ± 1.7

SE = standard error.

* With readable photographs at 3-month outcome.

between prethreshold and threshold ROP. Overall, the eyes resulting in an unfavorable macular outcome went from the onset of ROP to threshold in only about 17 days, which was about 9 days faster than eyes that fared well.

Presented in category 4 of Table 2 are the 162 natural history eyes that reached threshold disease and had gradable photographs at the 3-month outcome; 81 had unfavorable outcomes. The number of eyes published[11–13] for the results of cryotherapy was larger, because later referrals were included in the clinical trial in addition to this natural history cohort. Of the ocular factors recorded, the most striking effect is by the zone in which ROP was observed: almost all zone 1 ROP eyes result in an unfavorable outcome (there was an 8.24 times greater risk for an eye with zone 1 ROP going bad than for a zone 2 eye). Sector involvement was also important, as each additional sector over 5 clock hours (the minimal prerequisite for threshold) was associated with a 26% increase in the odds for an unfavorable result. The rate of progression, when adjusted for the factors noted in Table 2, lowered the odds of an unfavorable outcome by 35% for each week longer that it took to go from onset ROP to threshold.

The remainder of the risk factors noted in Table 2, category 4, involve the baseline characteristics of the infants. Again, the importance of the birth weight is noted, with each 100 g of additional birth weight resulting in a 27% reduction of the odds of an adverse outcome. Once threshold was reached, apparently neutral variables in governing the ultimate outcome were gestational age, race, being inborn, or a single delivery.

Discussion

This report considers the relationship of these and other risk factors as they relate to the development of severe (threshold) ROP and unfavorable retinal outcome. It has been previously reported[5–8,17,18] that the smallest babies (i.e, those with the lowest birth weight as well as those with the youngest gestational age) have both the greatest incidence and severity of ROP. Our results specify the rising risk to an infant of reaching threshold ROP with each 100 g lower birth weight, or with each week of greater prematurity (lower gestational age at birth).

Multiplicity of birth was originally identified as a potential risk in a 1956 cooperative ROP study,[17] although it was not shown to be an influencing factor in a 1977 collaborative study.[7] Multiple birth is again found to be a risk factor in this report. Although the *incidence* of ROP is independent of multiple birth,[5] the analysis reported in Table 2 shows multiple birth increases the risk of reaching threshold ROP, yet *not* the risk of then developing an unfavorable macular outcome.

We also found that infants had a lower chance of reaching threshold ROP when born within one of the participating hospitals of a study center. Babies requiring transfer into tertiary (level III) nurseries are generally smaller and sicker, which could help to explain this finding. Other possible differences that could contribute are local perinatal care practices and standards.

White infants did not fare as well as black infants. Indeed, the fact that black infants are less susceptible to ROP was an unexpected outcome of subgroup analysis. This result should be interpreted cautiously, as the protocol was not designed to make this comparison, and further verification of this finding in other studies is needed.[5,19]

Although the various systemic factors noted above play a role in altering the risk of an infant's likelihood of developing severe (threshold) ROP, it appears that local ocular factors can overtake and preempt the control of the systemic components. In Table 2, column 4, where ocular characteristics are included in the model for the 3-month outcome, the important features are zone, number of sectors of disease, time of onset of ROP, and progression from onset to threshold. Being inborn or the product of a multiple birth all appeared to be less influential than birth weight, losing their predictive value once an eye developed prethreshold disease. Surprisingly, even gestational age proved less valuable than birth weight as a prognostic indicator and lost its predictive value when prethreshold ROP occurred.

Like birth weight, race (being black) persists as a significant predictive risk factor when considering the data by infant or by the subgroup of eyes with ROP, and even when analyzing only those eyes with prethreshold ROP. However, once threshold ROP occurs, the various local ocular factors that predispose to an adverse macular outcome of the untreated eye seem to supersede any beneficial influence of the black race of the infant.

In addition to the general or "systemic" factors that may place a particular infant in a particular category of risk, we analyzed the "local" ocular variables, as the ROP developed, in terms of their individual prognostic significance. These factors, which provide important new prognostic (predictive) information, are comprised of: (1) the anterior–posterior location (zone) of the ROP demarcation line or ridge, (2) the presence or absence of plus disease, (3) the stage of ROP, (4) the circumferential extent (clock-hours) of the disease, and (5) the rapidity (rate) of its progression. This last variable was found to introduce a useful additional dimension to the classification of ROP severity.

First, the zone in which threshold ROP develops appears to have major importance. The more posterior zone 1 location carries an 8.24 times greater odds of proceeding to an unfavorable outcome than does the zone 2 area. Indeed, even when an eye has incomplete vascular development limited to zone 1 *without* any ROP (a normal finding for an infant ≤32 weeks of age), there is still a 33% chance that threshold disease will result. It is important to understand that these supposedly "normal" eyes must continue to be carefully monitored.

The second most strikingly influential parameter appears to be the presence of plus disease (Table 3) (Fig 3). It would seem reasonable to ascribe this ominous vascular finding to some aspect of the residual avascular retina and/or the arteriovenous shunt.[20] The more posteriorly this shunt occurs, the greater the area of immature, avascular retina, possibly resulting in a greater angiogenic

stimulus and, in turn, a larger arteriovenous shunt with perhaps increased blood flow through the shunt. This hemodynamic change is heralded by the dilatation and tortuosity of retinal arterioles and venules that is designated as plus disease, which appears to be associated with more posterior involvement of ROP. Persistence of these vascular alterations may then become associated with vitreous haze, engorged iris vessels, and iris resistance to mydriatics,[14] a combination of signs that indicates worsening of an already bad situation.

Third, the prognostic value of ROP staging is shown in Table 1 and Figures 1 and 2, where the higher stages are associated with a greater chance of reaching threshold ROP and, therefore, also a higher risk for ending in a less favorable outcome.

Fourth, the circumferential extent (clock hours or sectors) of stage 3 involvement also was significantly predictive, with each sector more than five adding a 26% increase in the odds for an unfavorable macular outcome (Table 2, category 4).

Finally, as noted in Table 2, the rate of progression of ROP to prethreshold was significant in that each week of lengthening interval was associated with a 23% decrease in the odds that threshold ROP would occur (category 3), and each week of delay in reaching threshold disease was associated with a 35% improvement in the odds of developing an unfavorable macular outcome at 3 months (category 4). This importance of the rate of progression of ROP was not considered in the ICROP,[14] although it had been previously recognized clinically that the more posteriorly located ROP may progress very rapidly ("rushed").[21]

The importance of the influence of the time of onset and the rate of progression of ROP deserves emphasis. However, the direct clinical applicability of this finding in particular is contingent on understanding the protocol used in this study, wherein many of the infants already had ROP at the time of the first examination at age 4 to 6 weeks after birth.[5] It is tempting to explore for factors that could be manipulated to slow the appearance and progression of ROP and thus improve the prognosis. In this respect, the finding that antioxidants may play a role in retarding the onset and rate of progression of ROP[22] suggests further investigation.

In conclusion, the general impression of severity or the "clinical gestalt" described by experienced examiners in speaking of ROP is a perception that is based on an integrated clinical sense of several specific prognostic indicators that we have described. This gestalt already guides the ophthalmologist in planning observation intervals and in discussing the disease with an ROP patient's parents. Separating and examining the individual components that comprise this clinically derived sense of prognosis will surely improve our understanding of the nature of ROP.

It appears that this natural history report may justify shortening the interval between examinations from every 2 weeks to weekly once prethreshold disease is discovered, and then maintaining heightened concern until either treatment is required or resolution begins. In addition, it appears clear that the prognostic nature of the various ROP parameters governs the stepwise method of the examination itself, as previously suggested in our protocol.[5] Since prolonged contact with the eye can result in the posterior retinal vasculature becoming dilated and more tortuous, thus simulating plus disease, one should initially look at the posterior pole to see if plus disease is present in the first place. Once this predictive factor is found or ruled out, the remainder of the examination can then proceed in an orderly fashion, as zone, stage, and number of involved sectors are not subject to change by the examination techniques. In this respect, programs involved with teaching residents and fellows should ideally arrange that the individual who initially examines the infant be the physician responsible for the diagnosis and follow-up planning.

Finally, it should be stressed that the examiner should be aware of both the results and dates of any previous ocular examinations, since the rate of progression helps to shape the clinician's concern and the patient's prognosis.

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