

• Clinical Research •

Clinical features and changes of disease spectrum of zone II retinopathy of prematurity: a 10-year review

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Abstract

• **AIM:** To report the clinical features and evolution of zone II retinopathy of prematurity (ROP).

• **METHODS:** RetCam images of preterm infants with zone II ROP at our hospital between January 2009 and January 2019 were reviewed. The location, extent, and severity of ROP were recorded. Eyes were classified as type 1 zone II, type 2 zone II, and mild zone II ROP. The clinical features and evolution of zone II ROP were analyzed.

• **RESULTS:** In total, 184 infants (302 eyes) were enrolled. Of these, 55 eyes (18%) developed type 1 zone II ROP, 39 eyes (13%) developed type 2 zone II ROP, and 208 eyes (69%) developed mild zone II ROP. The proportion of type 1 zone II ROP significantly decreased over the 10y. The onset of type 2 zone II and mild zone II ROP were 1wk earlier than type 1 zone II, and both regressed at 45wk. Isolated neovascular tuft (popcorn) and double track signs were characteristic manifestations of zone II ROP. Eighty-seven percent of type 1 zone II ROP regressed completely with an unfavorable outcome that emerged in seven eyes after laser treatment.

• **CONCLUSION:** Zone II is an area with ROP disease at various risk levels. Zone II ROP has unique clinical presentations like popcorn and double track signs. Over time, the proportion of zone II ROP with high risk gradually decrease and respond well to therapy.

• **KEYWORDS:** retinopathy of prematurity; classification; natural evolution; zone

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INTRODUCTION

Retinopathy of prematurity (ROP) is a potentially blinding disease in premature infants^[1-2]. The current classification system of ROP (ICROP and revised-ICROP) denotes location, extent, and stage of the disease^[3-4]. Three concentric zones of retinal involvement have been described in order to define the anteroposterior location of the retinopathy. Dividing the retina into different zones may have important clinical significance in ROP because it provides a possible link between the spatial distribution and the severity of the disease^[5].

In ICROP^[3], the location is divided into zones I, II, and III. The location of ROP disease in different zones correlates to different risk levels. Zone I ROP, the innermost zone, is very high risk, affects the smallest and most premature infants, and correlates with relative insensitivity to laser/cryotherapy and poorer outcome^[6-7]. Conversely, ROP in zone III, the outermost zone, is a relatively safe condition. ROP in zone III or retinal vasculature extending anteriorly into zone III, without ROP disease previously existing in zone II, were positive prognostic indicators (with no or low risk)^[5].

However, ROP in zone II is quite different, consisting of a diverse disease spectrum and representing various kinds of risks. It is well known that retinal vascular development follows an eccentric model^[8]. At an early stage, vascular precursor cells (VPCs) exit from the optic nerve to form solid vascular cords, which known as vasculogenesis^[7-9]. Retinal vessels in zone I are of vasculogenic origin^[11]. The next stage, called angiogenesis, is the formation and spreading of new vessels from existing vessels that are responsible for the vascular development in zones II and III^[9-11]. From this point of view, zone II might be a mysterious transitional region where the development of retinal vessels transfers from two distinct clinical-pathologic processes. Understanding the detailed information about zone II ROP is a challenging but essential goal. The purpose of our study is to determine the clinical features and natural evolution of zone II ROP. We also examine the change in disease spectrum over 10y.

Evolution of zone II retinopathy of prematurity

Table 1 Characteristics of 184 infants with zone II ROP

Zone II ROP	Patients, n	Eyes, n (%)	Male	Female	GA, wk	mean±SD
Type 1 zone II (stage 2 or 3+)	34	55 (18)	19	15	29.48±1.99	1301.94±321.99
Type 2 zone II (stage 3-)	26	39 (13)	16	10	28.95±1.96	1284.80±305.54
Mild zone II (stage 2-, stage 1-)	124	208 (69)	62	62	29.95±2.34	1388.56±370.40
Total	184	302	97	87	29.72±2.25	1357.89±354.46
F					5.858	2.412
P					0.003	0.092

BW: Birth weight; GA: Gestational age; ROP: Retinopathy of prematurity.

SUBJECTS AND METHODS

Ethical Approval This study was designed as a retrospective, cross-sectional study that covered a 10-year period using data from the special clinic for ROP in our hospital. The Declaration of Helsinki was followed in our retrospective study, and protocol approval was obtained from the ethics committee of the hospital. Informed consent was waived due to the retrospective nature of the study. Enrolled in this study were 184 infants (302 eyes) who were admitted to our hospital with zone II ROP between January 2009 and January 2019. The infants were examined according to the 2004 Chinese Ministry of Health guidelines for ROP screening^[12]. Medical information, such as gestational age (GA), birth weight (BW), postmenstrual age (PMA), and systemic complications, were recorded.

The first eye examination was performed at the postnatal age of four weeks. During each examination, dilation was performed using phenylephrine 2.5% and cyclopentolate 0.5%. A RetCam II or III (Clarity Medical Systems, Pleasanton, CA, USA) wide-angle fundus imaging device recorded ocular fundus images. Following the revised-ICROP^[4], the stage, extent, zone, and presence or absence of “plus” disease were classified.

All of the 302 eyes of the 184 infants developed at least one clock hour of acute ROP in zone II, stages 1 through 3. Eyes were classified as type 1 zone II (stage 2 or 3+) ROP, type 2 zone II (stage 3-) ROP, and mild zone II (stage 1 or 2-) ROP. The spectrum of zone II ROP and its change over time were analyzed. The clinical features of each type were recorded and compared. The age of onset of disease and completion of regression were defined as the mean age between the two serial retinal examinations.

Student’s *t*-test and one-way analysis of variance (ANOVA) were the statistical methods used. A *P* value of <0.05 was considered significant for all tests.

RESULTS

A total of 184 infants (302 eyes) had acute ROP in zone II. There were 97 males (52.71%) and 87 females (47.28%). Thirty-nine infants were from multiple births (21.19%). The mean BW was 1357.89±354.46 g, and the mean GA was

29.72±2.25wk for the entire population. Table 1 compares the three groups in terms of their BW and GA. There was no significant difference between the mean BW among the groups, while the GA of the type 1 zone II group was significantly lower than the other two groups (One-way ANOVA, *P*<0.05; Table 1).

The changes in the spectrum of zone II ROP over time were investigated. The number of eyes with zone II ROP in each subgroup significantly decreased during years 2014-2019 when compared with years 2009-2013 (One-way ANOVA, *P*<0.05; Figure 1A). The proportion of eyes with type 1 zone II ROP (which required treatment) decreased from 22% to 11% from years 2009-2013 to years 2014-2019 (Student’s *t*-test, *P*<0.05; Figure 1B).

The onset of type 1 zone II ROP was at a mean PMA of 38.2wk, about one week later than type 2 zone II (37.4wk) and mild zone II ROP (37.1wk). The ROP disease of both the type 2 zone II and mild zone II groups regressed at 45wk PMA. The clinical features and natural evolution of zone II ROP were demonstrated by the RetCam images (Figure 2). For type 1 zone II ROP, fibrovascular proliferation on the ridge was the typical manifestation (Figure 2). The posterior veins were dilated and the arterioles were tortuous, constituting the “plus” disease (Figure 2). Some small isolated white spots, called popcorn, scattered posterior to the ridge or fused into the ridge (Figure 2). For type 2 zone II ROP, a small amount of fibrovascular proliferation was recognized on the ridge with slight dilation of the posterior veins (Figure 2). The popcorn converged into a linear form and grew into the more peripheral region together with the ridge, which formed a double-track sign (Figure 2). For mild zone II ROP, quite a bit of popcorn had scattered just posterior to the ridge (Figure 2). The ridge gradually became flattened and blurred during the course of natural regression (Figure 2).

In the study, 127 eyes (42.05%) showed the presence of double-track signs, including 37 eyes (67.27%) with type 1 zone II ROP, 15 eyes (38.46%) with type 2 zone II ROP, and 75 eyes (36.05%) with mild zone II ROP. Popcorn was found only combined with zone II, stage 2 ROP. About 160 (52.98%) eyes were found with popcorn, including 23 (41.82%) eyes

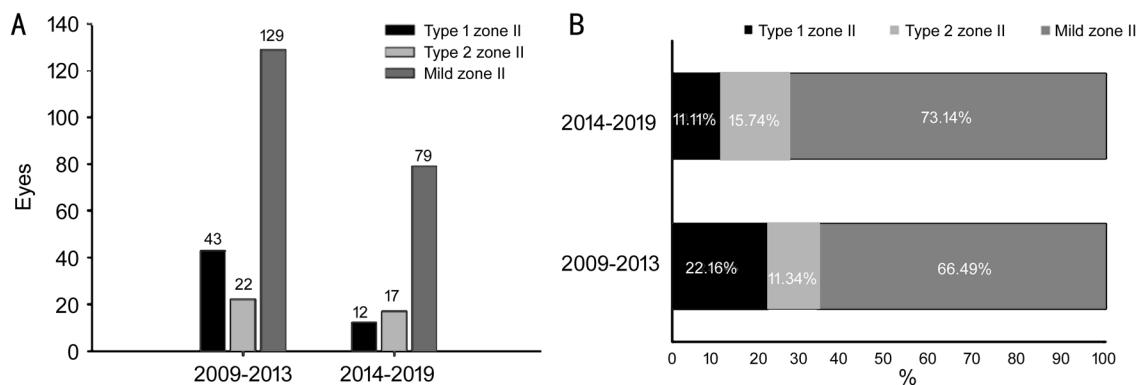


Figure 1 The timeline of changes in the spectrum of zone II ROP A: The number of eyes with zone II ROP; B: The proportion of eyes with type 1 zone II ROP.

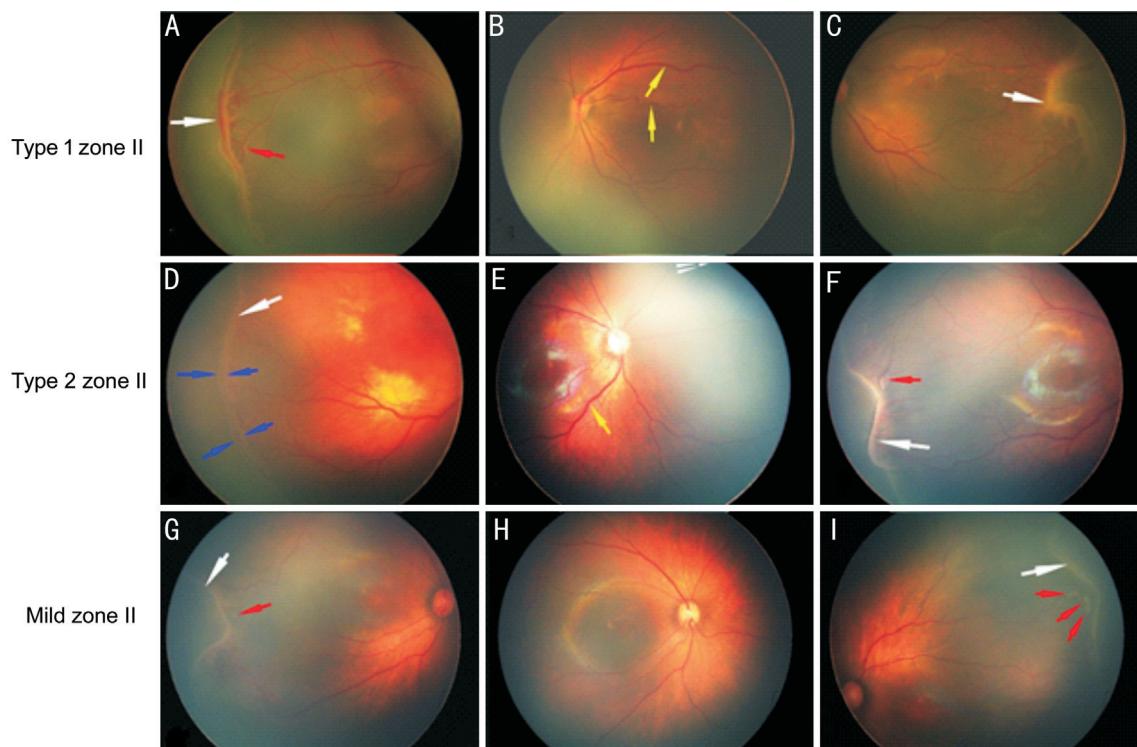


Figure 2 The evolution of zone II ROP A-C: Type 1 zone II; D-F: Type 2 zone II; G-I: Mild zone II. Red arrow: Popcorn; White arrow: Ridge; Yellow arrow: Dilated vein; Blue arrow: Double track sign.

with type 1 zone II ROP and 137 eyes with mild zone II ROP. Preretinal hemorrhages were found in 35 eyes (11.59%) with zone II ROP, while the mild zone II ROP had the smallest percentage of 1.44%. Zone II ROP regressed with a favorable outcome in 295 (97.68%) eyes. Seven eyes (2.31%) with type 1 zone II ROP progressed to an unfavorable outcome, such as stable stage 4a even after laser treatment. About 53.85% of eyes in the type 2 zone II group and 100% of eyes in the mild zone II group were vascularized into zone III before 45wk PMA (Table 2).

DISCUSSION

In the current study, we demonstrated that almost 69% of zone II ROP were at the low risk level, while 18% of zone II ROP was at high-risk (treatment required) and 13% of zone II ROP was at moderate-risk. In the postnatal growth ROP (G-ROP)

cohort^[13], the overall rate of type 1 and type 2 ROP was 12%. Although the subject cohorts of our study and the G-ROP study were different, the data reached the same conclusion that the condition of ROP was known to be a favorable clinical event in 90% of infants. A decreased trend of zone II ROP, especially the high-risk type 1 zone II ROP during the 10-year period, was observed. In spite of the increasing number of premature infants screened by about 2% a year in our hospital, the number of eyes with zone II ROP in each subgroup significantly decreased. The incidence of type 1 zone II ROP requiring treatment also decreased from 22% (2009-2013) to 11% (2014-2019). This outcome might be related to improvements in neonatal care for premature infants. In 2005, the Chinese Ministry of Health published guidelines for the prevention and treatment of ROP^[12]. Increased awareness of the

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Table 2 Disease characteristics and outcomes of zone II ROP

Clinical features	Type 1 zone II (stage 2 or 3+) (n=55 eyes)	Type 2 zone II (stage 3-) (n=39 eyes)	Mild Zone II (stage 2-, stage 1-) (n=208 eyes)	Overall (n=302 eyes)
Double track sign	37 (67.27)	15 (38.46)	75 (36.05)	127 (42.05)
Popcorn	23 (41.82)	0	137 (65.87)	160 (52.98)
Preretinal hemorrhages	16 (29)	16 (41)	3 (1.44)	35 (11.59)
Complete regression	48 (87.27)	39 (100)	208 (100)	295 (97.68)
Zone III vascularization (before PMA 45wk)	/	21 (53.85)	208 (100)	/
Unfavorable outcome	7 (12.72)	0	0	2.31

risk of blindness caused by ROP has led to the standardization of oxygen supplementation and expansion of a comprehensive screening program in the neonatal intensive care unit (NICU), resulting in a significant decrease of severe ROP in China. With routine ROP screening, we observed small isolated tufts (commonly known as popcorn) and double-track signs in the zone II ROP group. Interestingly, these manifestations could not be traced in either zone I or zone III ROP. About 42.05% of the eyes with zone II ROP had the presence of a double-track sign and 52.98% had popcorn. The double-track signs were composed of converged popcorn in a linear form parallel to the ridge. The type 1 zone II group had the highest incidence of double-track signs, while the mild zone II group had the highest incidence of popcorn. We also observed that the appearance of popcorn was associated only with zone II, stage 2 disease. The reason for this might be that the nature of popcorn is a special type of stage 2 and can be understood as regressed stage 3a. Our previous study^[14] identified that popcorn might be a clinical marker for the decreased risk of zone II, stage 2 ROP progression, which was consistent with other ophthalmologists' understanding of the phenomenon^[15-16]. Zone II ROP has been reported to be better responsive to treatment with either cryopexy or laser therapy than zone I^[17-18]. The CRYO-ROP^[17] reported 26.1% unfavorable outcomes in eyes with zone II ROP compared with 77.8% in zone I. In the ETROP study^[18], 38.8% of eyes with zone II ROP had an unfavorable outcome compared with 55.2% in zone I eyes. In our study, 87.27% of eyes with type 1 zone II ROP regressed completely after laser treatment, while seven eyes (12.72%) still progressed to unfavorable outcomes. Clinical features of those eyes were analyzed to reveal a high incidence (71.42%) of preretinal hemorrhages and lower BW of the infants. As widely seen, unfavorable outcomes could not be eliminated completely by laser ablation. Uncontrolled retinal neovascularization was triggered by local secretion of vascular endothelial growth factor (VEGF)^[19]. Anti-VEGF agents could therefore be used to eliminate uncontrolled retinal neovascularization, whether alone or in combination with laser treatment^[20-21]. The RAINBOW trial^[22] was the first multi-

center clinical trial to include ROP in all zone II locations. Their results demonstrated that the efficacy of ranibizumab was similar (or superior) to laser in both zone I and zone II, while the success was higher in zone II than in zone I. Following publication of the study, the trend to treat with anti-VEGF agents increased, while the safety questions, including specific ocular, neurological, pulmonary, renal, or bone complications, should be taken into account.

Evidence has been presented that ROP in different zones can be attributed to two distinct pathologic pathways of disease^[11]. In contrast to zone I ROP which occurs through vasculogenesis, zone II ROP takes place in the areas that are vascularized through angiogenesis^[10]. Angiogenesis is a process that proliferating endothelial cells form new vessel and extend the vascular network from pre-existing vessels^[11]. In our study, we have demonstrated the characteristic lesions of zone II ROP as popcorn and double-track sign. Those structures, we suggest, are typical of arrested angiogenesis. Moreover, formation of retinal vessels in zone II through angiogenesis appears to be dependent of metabolic demand and hypoxia-induced VEGF 165 expression^[11]. In this sense, this is why zone II ROP is clinically better responsive to cryopexy or laser therapy than zone I ROP.

The limitation of the present study was the retrospective design, meaning that infants without consistently documented data were excluded. Furthermore, laser ablation had been the only way to treat type 1 zone II ROP in our hospital, leading to the one-sided view toward the evaluation of therapeutic effect. In conclusion, our present study demonstrated the detailed disease spectrum of zone II ROP. The proportion of high-risk zone II ROP decreased with time. Popcorn and double-track signs were a specific manifestation of zone II ROP during its natural evolution. Zone II ROP responded well to laser therapy, with only 2.31% having an unfavorable outcome.

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