Progression and Timing of Treatment of Zone I Retinopathy of Prematurity

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• PURPOSE: To clarify the progression of zone I retinopathy of prematurity (ROP) and elucidate the most suitable time and method of treatment.
• DESIGN: Interventional case series.
• METHODS: Forty-six eyes of 23 zone I ROP infants were studied at a single institution. Birth weight ranged from 448 to 954 g, and gestational age ranged from 22 to 26 weeks. Fundus examination was started at 29 or 30 weeks postmenstrual age and was performed once or more per week. The first treatment was performed using laser photocoagulation or cryotherapy when zone I ROP progressed to the following criteria. Treatment criteria A included 35 eyes of 18 cases of zone I any stage ROP with plus disease (Early Treatment for Retinopathy of Prematurity [ETROP] type 1), criteria B included five eyes of three cases of zone I stage 3 ROP with or without plus disease (ETROP type 1), criteria C included six eyes of four cases of stage 1 or stage 2 ROP without plus disease; the demarcation lines belonged, in large part, within the zone I area.
• RESULTS: Hazy media such as corneal opacity, miotic pupil, tunica vasculosa lentis, and hazy vitreous persisted until approximately 32 weeks postmenstrual age. The mean period between stage 1 and stage 3 mild was one week, that between stage 1 and stage 3 moderate was 1.7 weeks, and that between stage 1 and stage 3 severe was 1.3 weeks. The period between stage 1 and the first treatment was zero to 20 days, and 60.9% of all the cases were treated within 10 days after stage 1. Six of 46 eyes had unfavorable outcomes. Surgical results of our treatment were comparable or better than those of other reports.
• CONCLUSIONS: Immediate treatment was required when zone I ROP was diagnosed behind persistent hazy media. (Am J Ophthalmol 2008;146:369–374.

RETINOPATHY OF PREMATURITY (ROP) HAS BEEN A severe childhood ocular disease, leading to vision loss, for the last 40 years.[1] The Cryotherapy for Retinopathy of Prematurity (CRYO-ROP) Study proposed that threshold ROP was the critical time for treatment, but many cases resulted in unfavorable outcomes.[2] The Early Treatment for Retinopathy of Prematurity (ETROP) randomized trial defined eyes with prethreshold ROP that were at high risk for retinal detachment (RD) or blindness as type 1 ROP and demonstrated improved surgical results using the peripheral retinal ablation therapy at the early time.[3]

In 2005, the International Committee for the Classification of Retinopathy of Prematurity (ICROP) classified an uncommon, rapidly progressing, severe type of ROP as aggressive posterior ROP (AP-ROP),[4] referred to previously as rush-type ROP in Japan.[5] AP-ROP is observed most commonly in zone I or posterior zone I. Zone I ROP usually is diagnosed as some stage of retinopathy observed within zone I.[6,7] The visual outcome of zone I ROP has been reported to be extremely poor in several articles.[6–9] However, the natural history and progression of zone I ROP has never been reported in a computerized search using PubMed and is not clearly understood. We studied how rapidly zone I ROP progressed to stage 3 after the

TABLE 1. Methods of Treatment for Retinopathy of Prematurity

	No. of Cases	No. of Eyes
First treatment		
Laser photocoagulation	15	28
Cryotherapy	6	10
Laser and cryotherapy	5	8
Additional treatment		
Cryotherapy	4	7
Scleral buckling	4	5
Vitrectomy	3	5

TABLE 2. Period of Persistent Hazy Media in All 46 Eyes with Retinopathy of Prematurity

	No. of Eyes	Time of Disappearance (wks)
Corneal opacity	8	30 to 35 (mean, 32.6)
Miotic pupil	10	31 to 33 (mean, 32.6)
TVL	40	31 to 34 (mean, 32.5)
Hazy vitreous	26	30 to 32 (mean, 31.3)

TVL = tunica vasculosa lentis; wks = weeks.
Time is measured by postmenstrual weeks.

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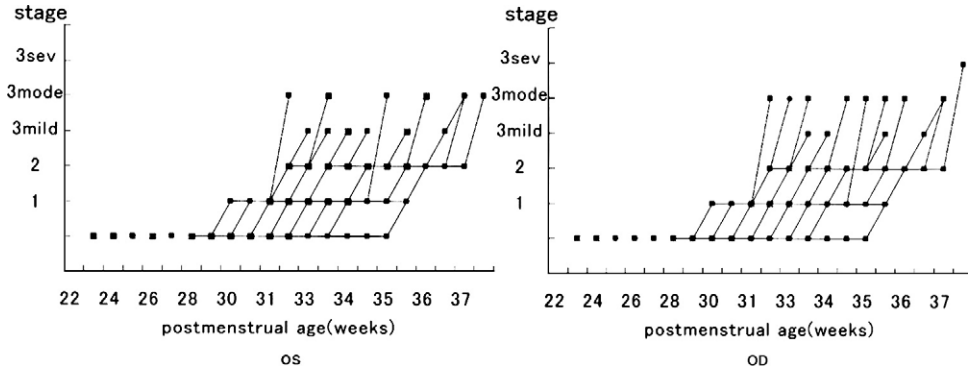

FIGURE. Graphs demonstrating the progression of stage of zone I retinopathy of prematurity. (Left) Progression course in the left eye. (Right) Progression course in the right eye. The endpoint of each line indicates the time of treatment. Mode = moderate; OD = right eye; OS = left eye; Sev = severe.

demarcation line appeared in the zone I area. We report the characteristics of progression and surgical results of zone I ROP.

METHODS

FORTY-SIX EYES OF 23 ZONE I ROP CONSECUTIVE CASES were studied. If any stage of retinopathy was observed within the zone I area, we diagnosed it as zone I ROP. Eleven infants were male, and 12 were female. All infants were born between January 1, 2000 and December 31, 2006 with birth weights of less than 1250 g at Osaka Medical Center and Research Institute for Maternal and Child Health. Mean birth weight of patients was 645.2 g (range, 448 to 954 g), and mean gestational age was 24.4 weeks (range, 22 to 26 weeks).

The first examination was performed at age 3 to 4 weeks, or 29 to 30 weeks postmenstrual age, whichever was tolerated by the infants. The examinations were performed once weekly, and increased to twice or more times per week after stage 1. Because the subdivision of stage 3 ROP of ICROP is rather subjective, stage 3 ROP is subdivided in our hospital into mild, moderate, and severe phases according to the vascular activity of the ridge proliferation. Stage 3 mild ROP is designated with white; stage 3 moderate ROP with yellow-orange; and stage 3 severe ROP with red.[9]

The first treatment was performed using a diode-pumped solid-state green laser photocoagulation or cryotherapy within 24 hours after stage 1 of zone I ROP progressed to the more severe stage. We treated 40 eyes according to the criteria of ETROP Study, and six eyes before then. Treatment criteria A included 35 eyes of 18 cases of zone I any stage ROP with plus disease (ETROP type 1); criteria B included five eyes of three cases of zone I stage 3 ROP with or without plus disease (ETROP type 1); criteria C included six eyes of four cases of zone I stage 1 or stage 2 ROP without plus disease whose demarcation line belonged within the zone I area in large part or when AP-ROP with very rapid progression was anticipated.

TABLE 3. Cicatricial Retinal Changes after Treatment for Retinopathy of Prematurity

	No. of Cases	No. of Eyes
Intact macula	18	36
Macular degeneration	2	4
Dragged disk	2	4
Retinal fold	1	1
Retrolental fibroplasia	3	6

The first treatment was performed using laser photocoagulation, cryotherapy, or a combination of both methods. Cryotherapy was used when photocoagulation was considered not effective because of advanced proliferative fibrovascular tissues or exudative RD. The ablation therapy was performed over the ridge–extraretinal fibrovascular proliferative complex and anterior avascular retina. It also was performed over the flat neovascularization in the posterior vascular retina. When additional treatments were needed, we performed cryotherapy, scleral buckling, or vitrectomy (Table 1).

RESULTS

IN SOME CASES, AT THE FIRST EXAMINATION, THE FUNDI were hardly visible because of persistent hazy media. Corneal opacity persisted until 30 to 35 weeks (mean, 32.6 weeks) postmenstrual age in eight eyes, miotic pupil persisted until 31 to 33 weeks (mean, 32.6 weeks) postmenstrual age in 10 eyes, tunica vasculosa lentis (TVL) persisted until 31 to 34 weeks (mean, 32.5 weeks) postmenstrual age in 40 eyes, and hazy vitreous persisted until 30 to 32 weeks (mean, 31.3 weeks) postmenstrual age in 26 eyes (Table 2).

TABLE 4. Characteristics of 23 Cases of Zone I Retinopathy of Prematurity

Case No.	Eye	First Examination	Corneal Opacity	TVL	Hazy Vitreous	Miotic Pupil	Stage 1 (Postmenstrual wks)	Preoperative Stage	Extent in Zone I (hrs)[a]	Criteria of Treatment	Type of First Operation	Time of First Operation (Postmenstrual wks)	Birth Weight (g) and Gestational Age (Postmenstrual wks)
1	Right	29	−	+	+	−	35.7	3 severe+	6	A	PC+CR	37.0	626
	Left		−	+	+	−	35.7	3 moderate+	4	A	PC+CR	37.0	25
2	Right	29	−	+	−	+	31.6	3 moderate+	9	A	PC	33.4	642
	Left		−	+	−	+	31.6	3 mild+	9	A	PC	33.4	24
3	Right	30	−	−	−	−	33.0	3 moderate+	1	A	PC	35.0	954
	Left		−	−	−	−	33.0	3 moderate+	0	A	PC	35.0	26
4	Right	29	−	+	−	−	33.9	3 moderate+	12	A	CR	35.0	568
	Left		−	+	−	−	33.9	3 moderate+	3	A	CR	35.0	25
5	Right	29	−	+	−	−	31.6	2+	12	A	PC	33.3	508
	Left		−	+	−	−	31.6	1 preplus	9	C	PC	33.3	23
6	Right	27	−	+	+	−	30.4	3 mild+	4	A	CR	32.7	590
	Left		−	+	+	−	30.4	3 mild+	4	A	CR	32.7	24
7	Right	27	−	+	−	−	30.7	3 moderate+	3	A	PC+CR	32.1	515
	Left		−	+	−	−	30.7	3 moderate+	4	A	PC	32.1	24
8	Right	29	−	−	−	−	33.6	3 moderate+	2	A	PC	34.3	580
	Left		−	−	−	−	33.6	3 mild+	2	A	PC	34.3	24
9	Right	30	−	+	+	−	33.0	2+	1.5	A	PC+CR	34.3	580
	Left		−	+	+	−	34.0	2+	1.5	A	PC+CR	34.3	23
10	Right	29	+	−	−	−	33.7	3 mild+	0	A	CR	35.7	514
	Left		+	−	−	−	33.7	3 mild+	1	A	CR	35.7	22
11	Right	29	−	+	+	−	32.3	1+	12	A	PC	34.6	800
	Left		−	+	+	−	32.3	1+	12	A	PC	34.6	25
12	Right	29	−	+	−	−	31.4	1+	12	A	PC	32.15	812
	Left		−	+	−	−	31.4	1+	12	A	PC	32.15	25
13	Right	28	+	+	+	+	31.7	2+	2	A	PC	33.6	502
	Left		+	+	+	+	32.6	3 mild+	2	A	PC	33.6	23
14	Right	29	−	+	+	−	32.1	3 mild+	2	A	PC	33.1	656
	Left		−	+	+	−	32.1	3 moderate+	3	A	CR	33.1	24
15	Right	30	−	+	+	−	33.6	1+	6	A	PC	35.1	448
	Left		−	+	+	−	34.1	1+	4	A	PC	35.1	26
16	Right	29	−	+	+	−	35.1	3 moderate+	0	A	PC+CR	36.7	690
	Left		−	+	+	−	35.1	3 moderate+	12	A	CR	36.7	25
17	Right	29	+	+	−	−	32.3	3 moderate	3	B	PC	33.0	620
	Left		+	+	−	−	32.3	3 mild	7	B	PC	33.0	24
18	Right	30	−	+	+	+	32.7	3 mild	12	B	PC	33.7	768
	Left		−	+	+	+	32.7	3 mild	12	B	PC	33.7	25

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TABLE 4. Characteristics of 23 Cases of Zone I Retinopathy of Prematurity *(Continued)*

Case No.	Eye	First Examination	Corneal Opacity	TVL	Hazy Vitreous	Miotic Pupil	Stage 1 (Postmenstrual wks)	Preoperative Stage	Extent in Zone I (hrs)[a]	Criteria of Treatment	Type of First Operation	Time of First Operation (Postmenstrual wks)	Birth Weight (g) and Gestational Age (Postmenstrual wks)
19	Right	30	–	+	+	–	33.3	3 mild preplus	1.5	B	PC	35.0	716
	Left		–	+	+	–	33.3	2	0	C	PC	35.0	23
20	Right	30	–	+	–	–	32.4	2	2	C	PC	33.3	828
	Left		–	+	–	–	32.4	2	2	C	PC	33.3	25
21	Right	30	–	+	+	+	32.3	2+	12	A	PC+CR	34.3	826
	Left		–	+	+	+	32.3	2+	12	A	PC+CR	34.3	25
22	Right	30	+	+	+	+	35.0	1 preplus	12	C	CR	35.0	488
	Left		+	+	+	+	35.0	1 preplus	12	C	CR	35.0	22
23	Right	30	–	+	+	–	32.3	3 moderate+	4	A	PC	36.6	608
	Left		–	+	+	–	32.3	3 moderate+	12	A	PC	36.6	23

CR = cryotherapy; PC = laser photocoagulation; TVL = tunica vasculosa lentis; + = yes; – = no.

A: Zone I any stage retinopathy of prematurity (ROP) with plus disease; B: Zone I stage 3 ROP with or without plus disease; C: Zone I stage 1 or stage 2 ROP without plus disease whose demarcation line belonged to the zone I area in large part or when aggressive posterior ROP (AP-ROP) with very rapid progression was anticipated.

[a]Clock hours of retinopathy in zone I.

The progression of stage in 46 eyes of 23 cases is shown in the Figure. Both eyes of each case progressed to a more severe stage at almost the same time. The endpoint of each line indicates the time of treatment. The demarcation line (stage 1) was observed at 29 to 35 weeks postmenstrual age. The period between stage 1 and stage 2 was 0.6 to 2.7 weeks (mean, 1.2 weeks) in 11 cases. The period between stage 1 and stage 3 mild was 0.7 to 1.9 weeks (mean, 1.0 weeks) in eight cases, the period between stage 1 and stage 3 moderate was 0.7 to 3.6 weeks (mean, 1.7 weeks) in 10 cases, and the period between stage 1 and stage 3 severe was 1.3 weeks in 1 case. The first treatment was performed at 30 to 37 weeks (mean, 34.0 weeks). The period between stage 1 and the first treatment was zero to 20 days (mean, 9.2 days), and most cases (60.9%) were treated within 10 days after stage 1.

The first treatment was performed by laser photocoagulation in 28 eyes of 15 cases, by cryotherapy in 10 eyes of six cases, and by a combination of both methods in eight eyes of five cases. Additional treatments were performed by cryotherapy in seven eyes of four cases, by scleral buckling procedure in five eyes of four cases, and by vitrectomy in five eyes of three cases. Cicatricial retinal changes after treatment were shown in Table 3.

The characteristics of progression of all the cases are described in Table 4. Cases 1 through 20 had favorable outcomes, and Cases 21 through 23 had unfavorable outcomes. We obtained favorable outcomes in 40 eyes of 20 cases and unfavorable outcomes in six eyes of three cases. Favorable outcomes were achieved in 92.8% of cases with laser therapy, in 80.0% with cryotherapy, and in 75.0% with combination therapy.

DISCUSSION

WE FOUND THAT INFANTS WITH ZONE I ROP HAD PERSISTENT hazy media that disturbed the examination and the treatment thereafter. Hazy media consisted of two factors. One was ocular prematurity. Most infants with zone I ROP were born at early postmenstrual weeks, so the immaturity of the ocular structure caused a variety of ocular problems.[10] Atrophy of TVL begins centrally at approximately 28 weeks postmenstrual age and generally is completed by 34 weeks.[11] Premature infants of fewer than 30 weeks gestational age have hazy corneas because of corneal thickness, which precludes fundus examination. The corneal thickness decreases after 31 weeks, associated with increase in corneal diameter,[12,13] and there is sufficient corneal clarity to permit funduscopy. Hazy vitreous clears within 4 to 5 weeks after birth.[13] TVL, corneal opacity, and hazy vitreous persisted longer and existed during the treatment in many of our cases (Table 2). The other factor is severe ROP plus disease. Iris vascular engorgement or poor pupillary dilatation (rigid pupil) may be signs of severe ROP, referred to as a *plus disease*.[4] Iris congestion

associated with poor mydriasis may be a grave sign indicating an advanced stage of disease.[10,14–16] If zone I ROP was diagnosed late because of hazy media, the case likely resulted in an unfavorable outcome.

The Figure reveals that progression from stage 1 to stage 3 was rapid in zone I ROP. In 60.9% of such eyes, the period between stage 1 and the time of treatment was very short, within 10 days (mean, 9.2 days; Table 4). The first treatment was performed at 30 to 37 weeks postmenstrual age (mean, 34.1 weeks), earlier than the 30 to 42 weeks (mean, 35.2 weeks) of ETROP or other reports,[10,14,17–20] except for one report.[15] We treated four cases earlier than the ETROP treatment criteria called for (criteria C). Case 20 had dense TVL, and a part of the demarcation line appeared in zone I at 32 weeks postmenstrual age, and after six days, we treated when the demarcation line became a ridge (stage 2) in all clock hours of the retina. Case 22 had dense corneal opacity and TVL. We treated when the hazy media cleared a little at 35 weeks, and the posterior pole was diagnosed as zone I stage 1 pre-plus. ETROP reported 92.3% of patients with zone I stage 1 or 2 without plus disease were at high risk of poor structural outcomes. Zone I ROP has been reported as the most predictive risk factor of unfavorable prognosis.[3,8,9,21,22] Because Cases 5 and 19 progressed rapidly and AP-ROP was anticipated, we treated earlier than the ETROP criteria called for.

Laser photocoagulation and cryotherapy were used for treatment. The ablation therapy is applied over the ridge itself as well as the anterior avascular retina because this extensive treatment seems more effective for advancing ROP.[9,23] Laser photocoagulation currently is accepted as the first treatment for zone I ROP. However, a relatively clear medium is required for treatment with laser. Infants with persistent hazy media may be difficult to treat[24,25] and sometimes may not be suitable for laser treatment. Cryotherapy is available for the treatment of eyes with dense hazy media[10,16,26,27] or with severely advanced proliferative fibrovascular tissues or exudative RD.[9,10,16] Zone I ROP rapidly progresses to severe ROP with RD,[16,22,26] and so has to be treated immediately and completely.[25,26] In cases that can not be treated completely with laser photocoagulation, cryotherapy or the combination of laser and cryotherapy are effective for decreasing unfavorable outcomes.

Consequently, the favorable outcomes were 92.8% in laser treatment cases, 80.0% in cryotherapy cases, and 75.0% in combination cases. We obtained unfavorable outcomes in 3 of 23 cases (Cases 21, 22, and 23; Table 4). The surgical results of our treatment are considered to be comparable or better than those of other reports.[3,6,7,14,17–19] Although some infants may recover spontaneously from the severe retinopathy, it is impossible to predict such an outcome during the progress of the disease. Too much observation is apt to cause a delay of treatment. There were no infants with severe general complications after the treatment. Our results strongly suggest immediate, rather than early, treatment with laser photocoagulation or cryotherapy is necessary when zone I ROP is diagnosed behind persistent hazy media.

THE AUTHORS INDICATE NO FINANCIAL SUPPORT OR FINANCIAL CONFLICT OF INTEREST. INVOLVED IN DESIGN OF STUDY (Y.S., Y.H.); conduct of study (Y.S.); collection, management, analysis, and interpretation of the data (Y.S., T.F.); and preparation and review of the manuscript (Y.S., Y.H.). The Institutional Review Board of Osaka Medical Center and Research Institute for Maternal and Child Health approved this study.

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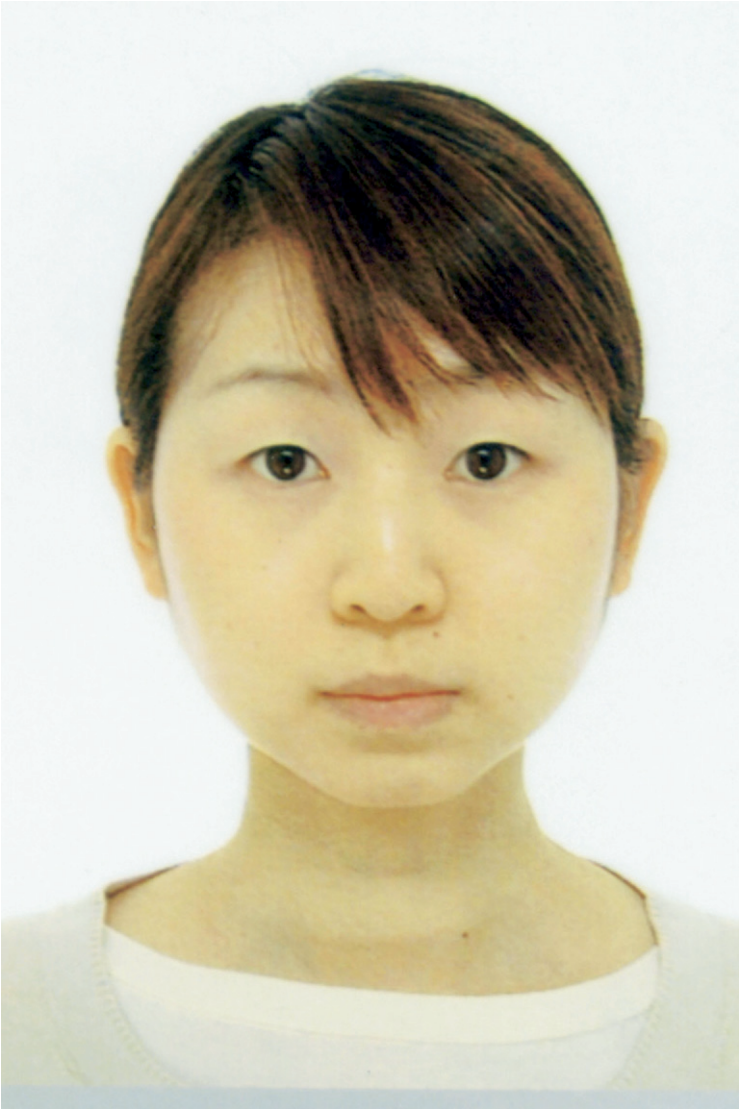

Biosketch

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