

Factors Related to Poor Visual Outcome in Patients With Retinopathy of Prematurity After Xenon Arc Photocoagulation and/or Cryocautery

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Abstract: We evaluated long-term visual outcome following xenon arc photocoagulation and/or cryocautery in 28 patients (52 eyes) with retinopathy of prematurity. Outcomes were divided into two groups: 43 eyes had visual acuity of 0.6 or better, 9 eyes had visual acuity of 0.2 or worse. Poor visual outcomes resulted primarily from macular degeneration. Risk factors involved were low birthweight (Mann-Whitney's U test, $P = 0.03$); the presence of signs of possible rapid progression (χ^2 test, $P = 0.041$); treatment of more clock hours of the fundus (Mann-Whitney's U test; $P = 0.035$) as well as the inside of the vascular arcade (χ^2 test, $P = 0.0034$); and total (360°) cryocautery (χ^2 test, $P = 0.032$). Macular degeneration occurred either as an isolated small focus extending circumferentially around the fovea or as a result of extension from the temporal degeneration caused by treatment. This suggests that intensive treatment, in addition to prematurity and the severity of retinopathy, is involved in the development of macular degeneration. Overtreatment should be carefully avoided in zone I retinopathy of prematurity and zone II retinopathy with signs of possible rapid progression, which requires photocoagulation inside the vascular arcade. **Jpn J Ophthalmol 1997;41:428-435** © 1997 Japanese Ophthalmological Society

Key Words: Cryocautery, macular degeneration, signs of possible rapid progression (plus disease), retinopathy of prematurity, xenon arc photocoagulation.

Introduction

Photocoagulation and cryocautery have been the treatments of choice for retinopathy of prematurity (ROP) in Japan since the first use of xenon arc photocoagulation by Nagata¹ in 1968, and the introduction of cryocautery by Yamashita² in 1972. Numerous reports have confirmed the effectiveness of these procedures,^{1,3-16} but a lack of case-control studies has long caused doubt in other countries about their effectiveness. A recent American case-control study of cryocautery for ROP showed that it was indeed effective in preventing poor visual outcome, compared with the natural course of the disease.¹⁷⁻²¹ Photocoagulation by argon laser²²⁻²⁴ or diode laser²⁵⁻³⁰ is now recognized as a better alternative for cryocautery in North America and Europe.

More than 20 years have passed since the introduction of xenon arc photocoagulation in Japan. The earliest patients have become adults. A limited number of long-term follow-up studies of these patients appeared recently but did not address the factors related to poor visual outcome.³¹⁻⁴³ In the present study, we retrospectively reviewed the medical records of patients who have been followed for more than 10 years and attempted to identify those factors implicated in poor visual outcome.

Patients and Methods

Medical records of 28 consecutive patients (52 eyes) with ROP^{7,13} treated at Okayama University Hospital from February 1974 to January 1982, were reviewed. Follow-up periods ranged from 12 years 4 months to 21 years 2 months (mean: 18 years 4 months). Patients were born at 26-36 weeks gestation (mean: 30.9 weeks) and had birthweights of 865-2300 g (mean: 1461 g).

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The international classification for retinopathy of prematurity was used in this study.^{44,45} At various times, the classification of the stages of retinopathy of prematurity has been redefined. In 1984, it was decided that when dilatation and tortuosity of vessels occur in the posterior pole of the eye, it is an indication of activity and possible rapid progression. It was advocated that this development be indicated by placing a + sign after the stage number of the disease (stage 1⁺, stage 2⁺, etc). However, some researchers began to use a minus sign in the same way (stage 2⁻), causing confusion. Later, "stage plus disease" was used, in an effort to avoid confusion. In this paper we use the term "plus disease" to mean "the presence of posterior vascular dilatation and tortuosity," returning to the wording of the original classification.⁴⁴

Classification into zone I, II, and III retinopathy was omitted in this study because of the difficulty in differentiating zone I and II from our medical records, which used the classification system of the Japanese Ministry of Health and Welfare.^{46,47} Xenon arc photocoagulation and/or cryocautery were usually done at stage 3, but were done at stage 2 when there were signs of possible rapid progression (plus disease).^{7,11} Xenon arc photocoagulation was done with the Model XC-550A (Nidek, Tokyo) at maximum power, size: 6 degrees; duration: 0.5 seconds. Transconjunctival cryocautery was done with a retinal probe (Amoils Cryo Unit, Keeler Instruments, Windsor, UK) at -70-50°C for 7-15 seconds. According to the stan-

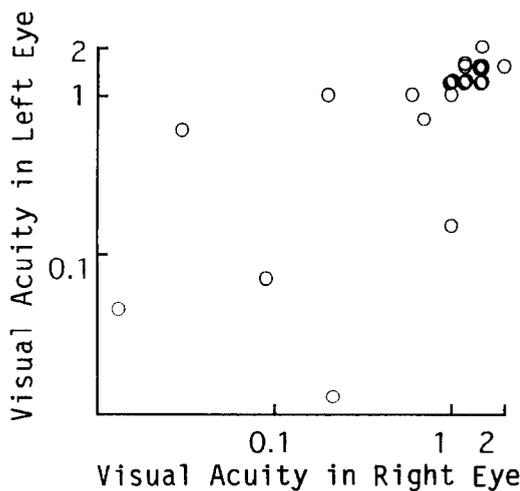


Figure 1. Visual acuity in patients with retinopathy of prematurity after xenon photocoagulation and/or cryocautery. Visual acuity in both eyes is correlated (Spearman's correlation, $P = 0.0001$) and falls into two groups, 0.6 or better and 0.2 and worse.

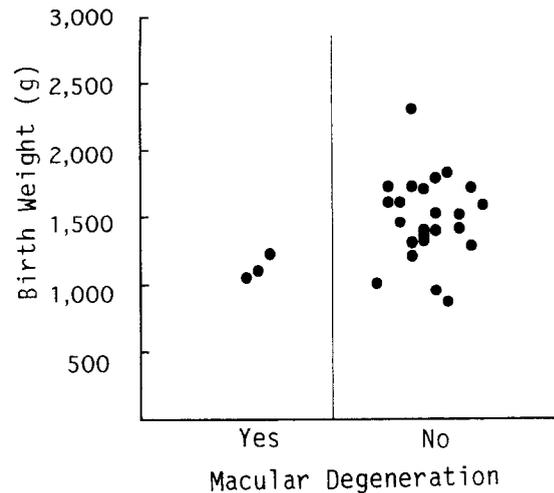


Figure 2. Development of macular degeneration in right eye in relation to birthweight. Macular degeneration occurs more with lower birthweight (Mann-Whitney's U test, $P = 0.03$).

dard method used at that time, scattered photocoagulations were placed on the ridge as well as to its avascular periphery.^{7,11} In ROP with plus disease, including type II (five patients; 10 eyes) and intermediate type (five patients; 10 eyes)⁴⁸ defined by a revised ROP classification of the Ministry of Health and Welfare,^{46,47} overlapping photocoagulations were made on the ridge and to the avascular area. There was also a row of scattered photocoagulations in the area posterior to the ridge at stage 2, in all eyes with type II, and in some intermediate type eyes.⁷

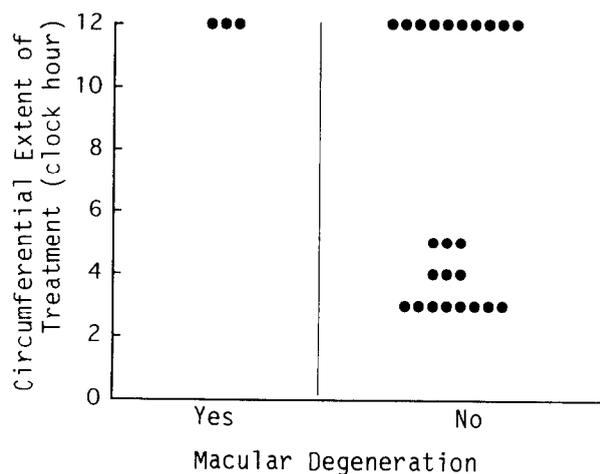


Figure 3. Development of macular degeneration in right eye in relation to circumferential extent of photocoagulation. Macular degeneration develops in eyes with treatment at more clock hours meridian (Mann-Whitney's U test, $P = 0.035$).

Table 1. Macular Degeneration in Right Eye With Plus Disease

Plus disease	Yes		No	
	Yes	No	Yes	No
Macular degeneration	3	7	0	17
No. of eyes				

Follow-up examinations included visual acuity, refraction, tonometry with applanation or Schiötz's tonometer, funduscopy, fluorescein and/or indocyanine green angiography. Factors examined were gestational weeks at birth, birth weight, oxygen administration and duration, corrected gestational weeks at treatment, presence of plus disease, area and location of treatment, and modalities used (photocoagulation, cryocautery). The area of treatment was expressed as clock hours meridian, as used in the international ROP classification;⁴⁴ the anteroposterior location was classified by location of scars inside or outside the vascular arcade. Patients were seen in the outpatient clinic twice a year. The StatView (Macintosh) software program was used for statistical analysis.

Results

1. Visual Outcome

The final visual acuity fell into two groups: 0.6 or better, and 0.2 or less (Figure 1). Poor visual acuity was caused by retinal detachment (2 eyes; 3.8%); and macular degeneration (7 eyes; 13.5%). Refractive errors included myopia (48 eyes) and emmetropia (4 eyes) with no hyperopia. Spherical equivalents ranged from -0.25 to -11.38 diopters (mean: -3.83). Visual acuity in both eyes was correlated (Spearman's correlation; $P = 0.0001$) (Figure 1). Right eyes were selected for statistical analysis.⁴⁹

When compared with 24 patients without macular degeneration in the right eye, 3 patients with this condition had significantly lower birthweights (Mann-Whitney's U test; $P = 0.03$; Figure 2); significantly more clock hours of fundus treated (Mann-Whitney's U test; $P = 0.035$; Figure 3); a significantly higher prevalence of plus disease (χ^2 test; $P = 0.041$; Table 1); and a significantly higher rate of scars inside the vascular arcade (χ^2 test; $P = 0.0034$; Table

Table 2. Macular Degeneration in Right Eye With Scars Inside Vascular Arcade

Scars inside vascular arcade	Yes		No	
	Yes	No	Yes	No
Macular degeneration	3	2	0	22
No. of eyes				

Table 3. Macular Degeneration in Relation to Type of Retinopathy Defined in Revised Classification of Retinopathy of Prematurity (Ministry of Health and Welfare of Japan⁴⁷)

Macular Degeneration		Number of Eyes		
		Type I	Intermediate	
			Type	Type II
Right Eyes	No	17	4	3
	Yes	0	1	2
Both Eyes	No	32	7	5
	Yes	0	3	5

2). Macular degeneration in the right eye developed at a significantly higher rate in patients with type II retinopathy (χ^2 test; $P = 0.0433$) and at a higher rate in those with intermediate type ($P = 0.2273$) than in patients with type I retinopathy. When data for both eyes were combined for statistical analysis, both type II and intermediate type retinopathy resulted in macular degeneration at a significantly higher rate than type I (χ^2 test; $P = 0.0003$ and 0.0105) (Table 3). Multivariate analysis of only right eyes or of both eyes did not prove all these factors to be significantly associated with macular degeneration. The development of macular degeneration was not correlated with oxygen administration or gestational weeks at birth.

In evaluation of treatment modalities, macular degeneration was not significantly associated with photocoagulation or cryocautery, singly or in combination. Statistical analysis of either right or left eyes with the entire fundus (360°) treatment indicated that macular degeneration developed at a significantly higher rate in eyes with cryocautery applied to the whole circumference than in eyes treated with 360° photocoagulation alone and/or with cryocautery applied to part of the meridian (χ^2 test; $P = 0.032$) (Table 4). The most common complication immediately after treatment was retinal hemorrhage at the site of photocoagulation. One eye developed vitreous hemorrhage; two others had large preretinal hemorrhages reaching to the macula. There was no correlation between macular hemorrhage and degeneration.

Table 4. Macular Degeneration in Relation to Total (360°) or Partial Cryocautery in Eyes (Right and Left Eyes Combined)

Macular Degeneration	Partial Cryocautery		Total Cryocautery	
	Yes	No	Yes	No
Number of Eyes	2	12	6	4

Table 5. Timing for Development of Macular Degeneration in Course of Treatment of Plus Disease Eyes

Weeks	Right Eye	Weeks	Left Eye
Case 1			
4	Photocoagulation, total	4	Photocoagulation, total
5	Photocoagulation, temporal to superior	5	Photocoagulation, temporal to superior
7	Cryocautery, total	7	Cryocautery, total
33	Macular degeneration	13	Small degeneration temporal to fovea
		21	Whole macular degeneration
Case 2			
6	Photocoagulation, total		
7	Photocoagulation, total		
11	Cryocautery, total		
13	Cryocautery, total		
55	Macular degeneration		
Case 3			
		4	Cryocautery, total
		12	Small degeneration superior to fovea
		19	Whole macular degeneration
Case 4			
14	Cryocautery, total	14	Cryocautery, total
24	Cryocautery, temporal	24	Macular degeneration
25	Macular degeneration	130	Retinal detachment
Case 5			
6	Photocoagulation, total	6	Photocoagulation, total
?	Macular degeneration	?	Macular degeneration

Total: photocoagulation or cryocautery applied to whole 360° fundus.

2. Clinical Characteristics of Macular Degeneration

The development of macular degeneration in eight eyes of five patients is shown in Table 5. All eight eyes with plus disease (three with type II retinopathy; five with intermediate type retinopathy) under-

went photocoagulation or cryocautery to the entire 360° meridian in a single treatment; six of these had cryocautery of the whole area. Macular degeneration developed from 12 to 55 weeks after birth and from 6 to 44 weeks following 360° cryocautery (8–49 weeks after initial treatment). There was no pattern to the timing of macular degeneration development.

Macular degeneration was progressive in five eyes of four patients; two patterns of progression were noted (Figures 4, 5). One type was a small degenerative focus appearing on the macula and extending circumferentially around the fovea, resulting in degeneration of the whole macula in 7–8 weeks (two patients; two eyes). The other type involved photocoagulation scars in the temporal area which extended posteriorly to the macula (one patient; both eyes).

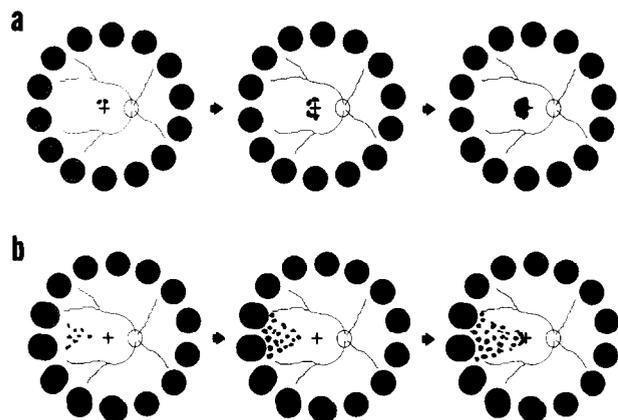


Figure 4. Two types of progressive macular degeneration. Type a: small macular degenerative focus extends circumferentially around fovea, resulting in total macular degeneration. Type b: photocoagulation scar on temporal side extends posteriorly to macula.

Discussion

The present study found that most patients (20; 71%) retained visual acuity of 1.0 or better in both eyes after xenon arc photocoagulation for ROP. Only five patients had a poor visual outcome (0.2 or less) in both or either eyes which was primarily caused by macular degeneration. The development of macular degeneration was statistically associated with low

A



B

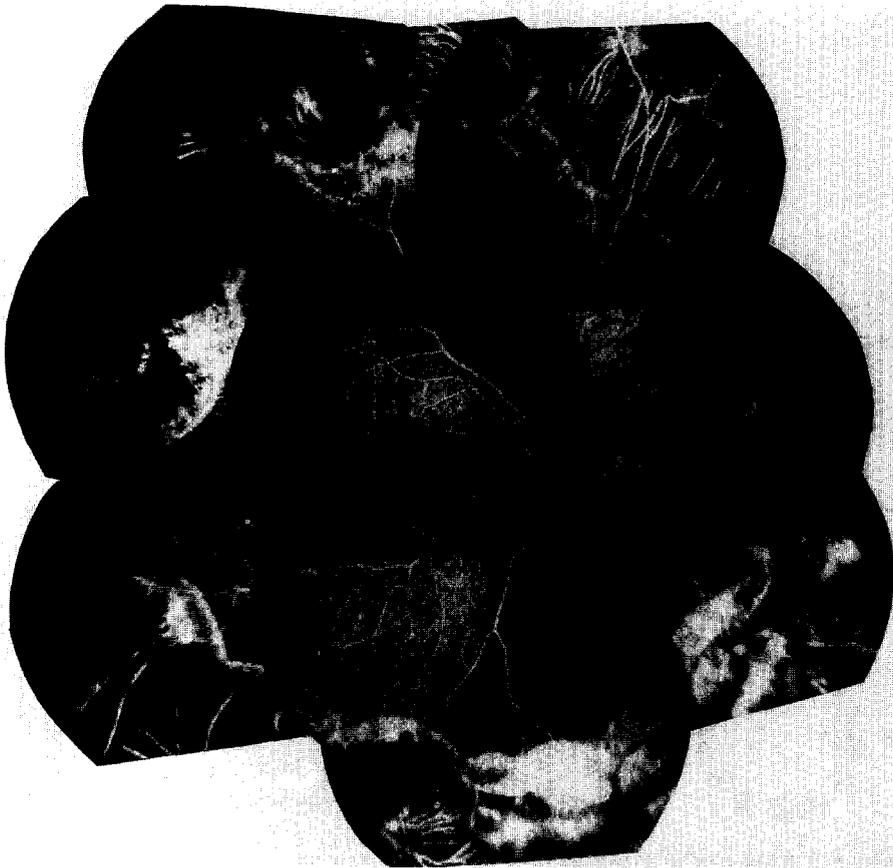
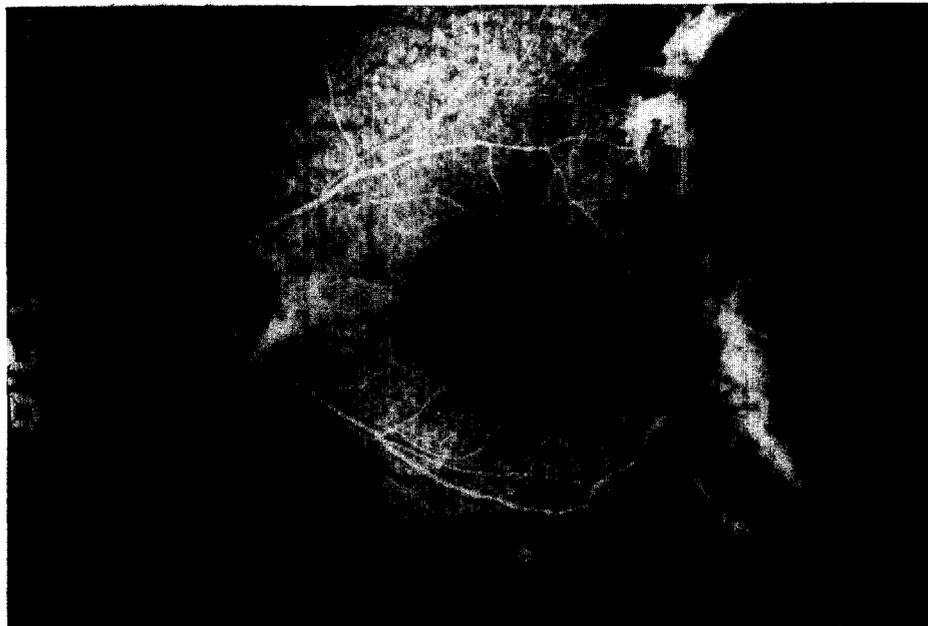


Figure 5. Fundus photographs (A,C) and fluorescein angiograms (B,D) of (A) type (a) macular degeneration (A,B) and (B) type (b) (C,D).



Figure 5. Continued.



birth weight, retinopathy with plus disease, and treatment inside the vascular arcade, indicating that both prematurity and the severity of the retinopathy affected the development of macular degeneration. The retrospective nature of this study did not allow precise classification into zone I, II, and III retinopathy of prematurity since the international classification⁴⁴ was established only in 1984. Treatment of the entire fundus, however, could be interpreted as zone I or II retinopathy, and treatment inside the vascular arcade as zone I retinopathy.

It should be noted that the macular degeneration was progressive; the two patterns of progression suggest that circulatory disturbance of the choroid is responsible for the development of degeneration involving the entire macula. Cryocautery and xenon arc photocoagulation are known causes of more insults to the choroid than the recently used argon laser photocoagulation. Damage not only to the superficially located choriocapillaris but also to larger vessels of the deep choroid naturally results in circulatory disturbance of the choriocapillaris outside

the areas of photocoagulation and cryocautery. The damage would be more severe in premature babies whose macula is still in the developmental phase.^{50,51}

Cryocautery of the entire 360° meridian was one factor leading to macular degeneration. This also can be understood as the result of choroidal circulatory disturbance since cryocautery causes more damage to the choroid than xenon arc photocoagulation. It is evident that the macular degeneration in this series of patients was caused by the adverse effects of photocoagulation and cryocautery.

The presence of plus disease has been known to indicate a rapid progression of ROP, usually leading to retinal detachment.⁴⁸ The standard treatment for retinopathy with plus disease in Japan has been, and still is, overlapping photocoagulation, not only in the avascular area, but also on the ridge, with scattered photocoagulation in the area posterior to the ridge.^{7,11} The hazy media, one sign of plus disease, limits the choice of treatment to cryocautery; treatment scars inside the vascular arcade and the use of cryocautery in addition to 360° photocoagulation, in the present series, were indeed necessary procedures for the severe retinopathy with plus disease. Low birth weight related to the development of macular degeneration, as in this study, has also been recognized as a factor in the development of plus disease.^{3,5,52-53}

Argon laser photocoagulation has recently become the primary modality for treatment of ROP.⁵⁴⁻⁵⁷ Argon laser allows smaller spots with well-controlled power, causing less damage to the choroid than xenon arc photocoagulation. The present results indicate that great care should be taken in placement of photocoagulation spots inside the vascular arcade in zone I retinopathy and zone II retinopathy with plus disease, in order to avoid overtreatment. Further study is necessary to determine the precise extent of photocoagulation required for retinopathy with plus disease, and whether or not photocoagulations must be placed posterior to the ridge.

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