

Early Vitreous Surgery for Aggressive Posterior Retinopathy of Prematurity

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- **PURPOSE:** To assess the efficacy of early vitrectomy for aggressive posterior retinopathy of prematurity (ROP) to stop progression of retinal detachment.
- **DESIGN:** Retrospective, noncomparative, consecutive case series.
- **METHODS:** Twenty-two eyes (15 patients) with aggressive posterior ROP underwent vitrectomy with or without lens sparing, because retinal photocoagulation failed to stop progression of fibrovascular proliferation, despite being performed early, densely, and with early retreatment. We assessed the status of retinal attachment and foveal formation ophthalmoscopically and the presence or absence of fixation of visual behavior.
- **RESULTS:** Follow-up ranged from six to 12 months (mean, 9 months). Six eyes (100%) in which a lens-sparing vitrectomy was performed developed a large tractional retinal detachment. In contrast, the retinas were completely reattached in 16 eyes (100%) in which vitrectomy with lensectomy was performed, nine eyes (56%) had foveal configuration, and 14 eyes (88%) had steady fixation.
- **CONCLUSIONS:** These results suggest that early vitrectomy is effective for preventing retinal detachment in aggressive posterior ROP. (*Am J Ophthalmol* 2006; 142:636–643. © 2006 by Elsevier Inc. All rights reserved.)

IN EYES WITH RETINOPATHY OF PREMATURETY (ROP), visual outcomes are generally poor^{1,2} when the retina begins to detach and progresses to Stage 4B or 5. Surgical interventions for retinal detachment associated with progressive ROP, that is, scleral buckling,^{3–6} or vitrectomy for Stages 4 and 5,^{7–9} usually fail to obtain foveal formation, resulting in poor vision. Recent studies of

lens-sparing vitrectomy for Stage 4 ROP have reported retinal reattachment and foveal formation.^{10–14}

In contrast to the classical course described by the Committee for the International Classification of ROP,¹⁵ an unusual form of ROP rapidly progresses to a closed funnel of tractional retinal detachment within one to two weeks if left untreated. This severe form is referred to as type II ROP by the Japanese Diagnostic and Therapeutic Criteria for ROP^{16,17} or aggressive posterior ROP by the revised International Classification of ROP.¹⁸ Aggressive posterior ROP commonly occurs in zone I and sometimes posterior zone II, with substantial dilation and tortuosity of the vessels of the posterior pole. The flat network of neovascularization on the retinal surface at the deceptively featureless demarcation between the vascularized and nonvascularized area arises circumferentially, usually extends for 12 clock hours, and rapidly extends toward the posterior lens surface. Another characteristic of aggressive posterior ROP is that it may progress to Stage 5 without exhibiting the classical course that includes Stages 1 to 3.

Early intervention with photocoagulation or cryopexy is necessary but often fails to stop ROP progression to Stage 5.^{19,20} We report anatomic success after early treatment with vitrectomy in eyes with aggressive posterior ROP.

METHODS

- **PATIENTS:** All aspects of this study were approved by the institutional ethics committee, and the parents of the patients provided informed consent before the infants were enrollment in the study. We retrospectively reviewed the clinical charts and surgical outcomes of 15 infants (30 eyes) with aggressive posterior ROP. All eyes had previously undergone peripheral laser ablation at our clinic or elsewhere; however, the primary treatment stopped the progression of fibrovascular proliferation in eight eyes. Twenty-two eyes underwent early vitrectomy as a secondary treatment performed by one surgeon (N.A.) in our clinic between July 2004 and August 2005.

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• **OCULAR EXAMINATION AND LASER PHOTOCOAGULATION:** In our clinic and attendant clinics, the initial ocular screening examinations using binocular indirect ophthalmoscopy were performed as early as possible when systemic conditions stabilized, at the latest at three weeks of chronologic age or 29 weeks of postmenstrual age, in all premature infants less than 34 weeks of gestational age or weighing 1800 g or less at birth, and for all infants who underwent supplemental high-concentration oxygen treatment or surgical intervention. Aggressive posterior ROP, which is designated as type II ROP in Japan, especially should be treated as early as possible at the time of identification.¹⁶⁻¹⁸ The criteria that characterizes the early phase of aggressive posterior ROP by the Committee for the International Classification of ROP¹⁸ and type II ROP by the Japanese Diagnostic and Therapeutic Criteria for ROP^{16,17} are the same: (1) posterior location (usually zone I, and sometimes posterior zone II); (2) prominently increased dilation and tortuosity of the posterior pole arteries and veins in all four quadrants; and (3) shunting from vessel to vessel within the retina and not solely at the junction between the vascularized and nonvascularized retina, a flat network of neovascularization at the deceptively featureless junction between the vascularized and nonvascularized retina, or both. Although we usually perform laser ablation of prethreshold retinopathy based on the criteria of the Early Treatment for Retinopathy of Prematurity Study,²¹⁻²³ neovascularization in aggressive posterior ROP often progresses rapidly from the intraretinal to the extraretinal areas, circumventing the typical formation of the ridge. Thus vascular shunting sometimes associated with the presence of hemorrhage widely observed within the retina is an important initial sign.^{16,17}

All eyes of all patients were treated immediately with argon green laser photocoagulation through an indirect ophthalmoscope (Lumenis, Santa Clara, California, USA) when the initial signs of aggressive posterior ROP were identified. The treatment was applied densely to the nonvascularized retina (duration 200 to 400 ms; power 300 to 400 mW). The adjacent vascularized retinal area posterior to the ridge, which contained marked vessel shunting, also was coagulated, because capillary nonperfusion seemed to be present in the already vascularized retina.²⁴ Laser photocoagulation often was applied repeatedly to the skip areas, because a remnant of the hyaloid vascular system including the tunica vasculosa lentis interrupts penetration of the laser light. Near-infrared diode laser that sometimes produces excessive coagulation with hardly distinguishable laser spots is difficult to use, when the density of the laser application should be varied on the nonvascularized and vascularized retina. By using argon green laser that is absorbed more by the hemoglobin in the tunica vasculosa lentis, subcapsular cataract does not develop after photocoagulation.^{25,26} When fibrovascular proliferation progressed circumferentially for six or more continuous clock hours and tractional retinal detachment

occurred simultaneously (Stage 4), the eye underwent vitreous surgery as a secondary treatment.

• **VITREOUS SURGERY:** In the patients who required secondary treatment, vitreous surgery was performed in each eye separately a few days to one week apart, or sometimes in both eyes on the same day, when ROP was suspected of having progressed rapidly to Stage 5 simultaneously in both eyes,¹⁶⁻¹⁸ or when a lengthy period of anesthesia was more acceptable in the presence of a systemic condition, such as a respiratory disorder, than a repeated period of anesthesia. Four infants (six eyes) underwent a lens-sparing vitrectomy that did not stop the progression of retinal detachment. Using a small contact lens designed for premature eyes, a core vitrectomy was performed in the six eyes.

In the other 11 patients (16 eyes), the lens was removed to perform vitrectomy in the periphery. In these eyes, a three-port vitrectomy was performed using the Accurus 25-gauge surgical system (Alcon, Fort Worth, Texas, USA) that includes cannulas, an infusion pipe, an illumination pipe, an endophotocoagulation probe, a vitreous cutter, scissors, and forceps. After performing conjunctival peritomy, 25-gauge sclerotomies were made 1.0 mm posterior to the limbus through the pars plicata. A wide-field vitrectomy was performed from the posterior pole to the vitreous base in the aphakic eyes. Dissection or removal of the fibrovascular tissues was minimized to avoid bleeding. A fluid-air exchange and endophotocoagulation were performed in three eyes in which an iatrogenic break developed. With the exception of these patients, no specific positioning was used postoperatively. No additional surgical intervention was performed in any of the 16 eyes.

• **ASSESSMENT OF SURGICAL RESULTS:** The infants were followed for six to 12 months (average, nine months) postoperatively. The preoperative and postoperative clinical charts and wide-field fundus photographs obtained using RetCam (Nidek, Gamagohri, Japan) were reviewed retrospectively. The six-month postoperative anatomic outcomes were determined by binocular ophthalmoscopy and photography with the patients under general anesthesia. Pediatric ophthalmologists assessed the visual behavior using suitable refractive correction. Central fixation was assessed by the corneal light reflex, and steady fixation was assessed using still and moving targets with the fellow eye occluded.

RESULTS

• **PATIENT CHARACTERISTICS:** Seven of the infants were girls and eight were boys. The gestational ages at birth ranged from 25 to 30 weeks (average, 25 weeks), and the birth weights ranged from 466 to 1676 g (average, 773 g). All but two patients weighed less than 1251 g at

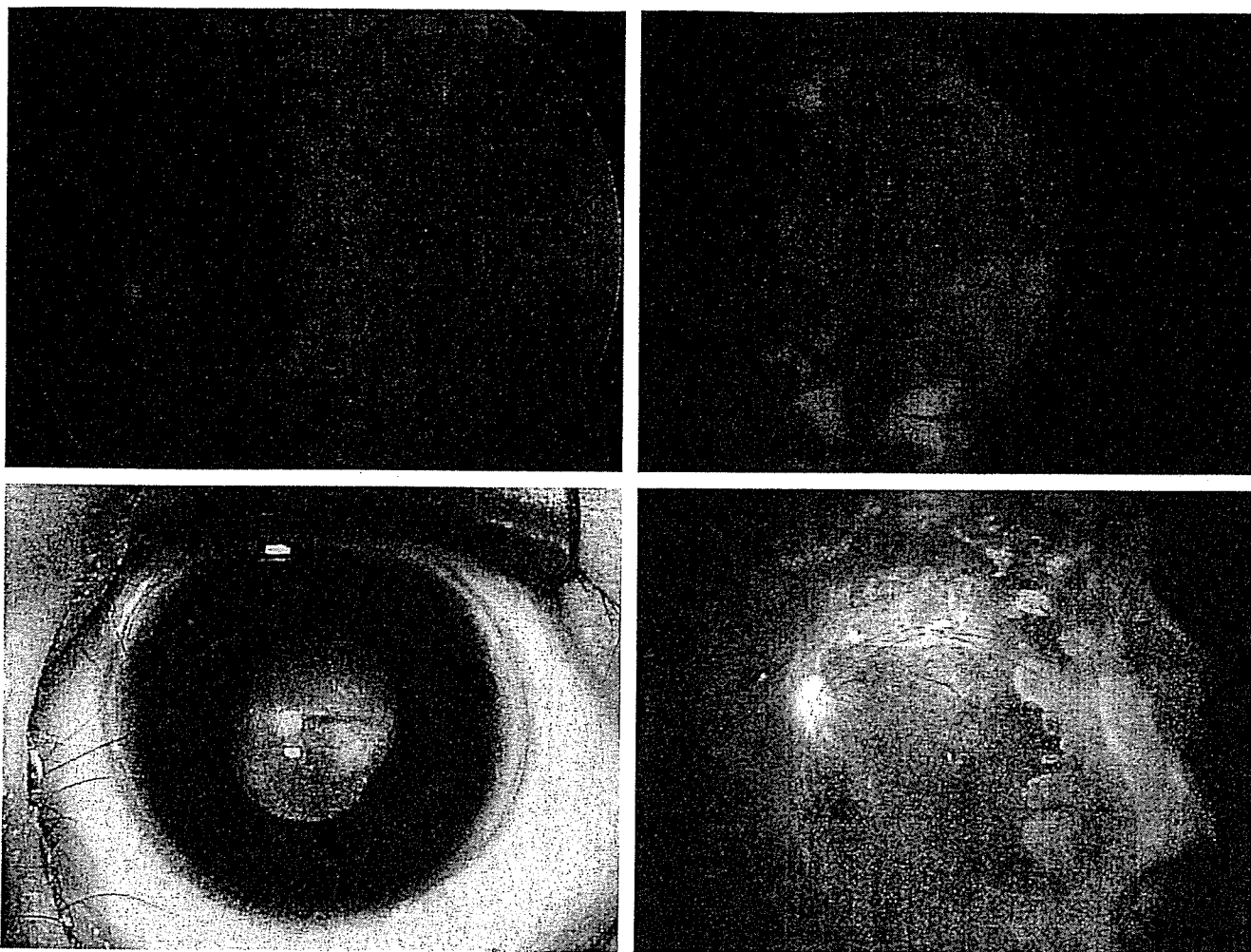


FIGURE 1. Fundus images of fibrovascular tissue (FT) growth and preoperative and postoperative lens-sparing vitrectomy in the left eye of Patient 2 with aggressive posterior retinopathy of prematurity (ROP) (gestational age 22 weeks; birth weight 479 g). (Top left) Ten weeks after birth, when the initial signs of aggressive posterior ROP were identified, the first photocoagulation was performed. (Top right) FT grew from the photocoagulation scars at 18 weeks, despite repeated applications of photocoagulation. (Bottom left) Although an early lens-sparing vitrectomy was performed at 18 weeks, the retinopathy progressed to Stage 5. (Bottom right) The secondary vitrectomy was performed one month after the initial vitreous surgery; however, retinal folds and significant degeneration persist.

birth; however, posterior aggressive ROP also developed in Patient 14 whose birth weight was 1280 g with multiple malformation syndrome and Patient 15 whose birth weight was 1676 g with hydrops fetalis. The initial ocular examination was conducted between one to four weeks (average, three weeks) of chronologic age (27 to 31 weeks of postmenstrual age; average, 28 weeks). At this time, the retina was vascularized within zone I in 22 eyes and in posterior zone II in eight eyes. In all eyes, the ROP extended for 12 clock hours in zone I or posterior zone II and was characterized by prominent dilation and tortuosity of the vessels in the four quadrants of the posterior pole at four to 11 weeks (average, eight weeks) of chronologic age (29 to 36 weeks of postmenstrual age; average, 33 weeks). Argon laser photocoagulation was applied densely to the nonvascularized retina and the adjacent vascularized area

that contained prominent vessel shunting two to five times (average, three times) repeatedly during a period of two to seven weeks (average, four weeks) in all 30 eyes, because insufficient regression of the hyaloid vascular system interrupted penetration of the laser light. Photocoagulation stabilized the ROP in eight eyes. In the other 22 eyes, the dilation and tortuosity of the retinal vessels and elevation of the ridge transiently decreased to some extent; however, they increased again, and the fibrovascular proliferation present circumferentially for nearly 12 clock hours then progressed and extended toward the posterior lens surface, and tractional retinal detachment occurred (Figure 1, Top row). Thus the vascularity of ROP remained active at the time of vitreous surgery in all 22 eyes; the fovea was not involved with the retinal detachment (Stage 4A) in 15 of the 22 eyes. The fovea was involved (Stage 4B) in seven

TABLE. Characteristics of Eyes Undergoing Surgery for Aggressive Posterior Retinopathy of Prematurity

Patient No.	Gender	GA (wks)	BW (gr)	Eye	Zone	PMA at PHC (weeks)	PMA at Vitrectomy (weeks)	Stage	FT & VB Adhesion (clock hours)	Surgical Procedures	IOC	POC	Additional Surgical Procedures	Retinal Attachment (Final)	Foveal Formation	SCF	Systemic Complications
1	M	22	466	OD	I	32-39	40*	4A	N	LSV	H	RRD	V	Y	N	N	Hydrocephalus
2	M	22	479	OS	I	32-39	40*	4A	N	LSV	H	RRD	V	Y	N	N	Hydrocephalus
3	F	26	857	OS	I	33-38	39*	4A	N	LSV	H	RRD	V	Y	N	N	
4	F	27	946	OS	II	34-37	39	4B	N	LSV	H	RRD	V	Y	N	N	
5	M	22	470	OD	I	32-38	40*	4B	Y, <3	V	H	RRD	V	Y, DR	Hypoplastic	Y	Hydrocephalus
6	M	23	510	OD	I	32-38	40*	4A	N	V	H		V	Y	Y	Y	
7	F	24	526	OS	I	32-36	37*	4A	N	V	H		V	Y	Y	Y	
8	M	23	610	OS	I	34-38	41	4B	Y, ≥3	V	H		V	Y, DR	N	Poor	
9	F	23	612	OD	I	36-38	40	4B	Y, ≥3	V, FE, PHC	H, IB		V	Y, DR	N	Poor	
10	M	25	678	OD	I	32-35	36	4A	N	V	H	OH	V	Y	Y	Y	
11	F	25	798	OD	II	33-37	39	4A	N	V, FE, PHC	H, IB		V	Y, DR	Hypoplastic	Y	
12	M	24	803	OD	I	32-35	36	4A	N	V	H		V	Y	Y	Y	
13	M	26	897	OD	I	29-33	35	4B	Y, <3	V	H		V	Y, DR	Hypoplastic	Y	Hydrocephalus
14	F	28	1280	OS	II	34-38	40	4B	N	V, FE, PHC	H, IB	OH	V	Y, DR	Hypoplastic	Y	Prosoposisis Hydrocephalus
15	F	30	1676	OD	II	34-36	37	4A	N	V	H		V	Y	Y	Y	Hydrops fetalis
				OS	II	34-36	38	4A	N	V	H		V	Y	Y	Y	

GA = gestational age; BW = birthweight; OD = right eye; OS = left eye; M = male; F = female; PMA = postmenstrual age; PHC = photocoagulation; * = vitrectomy was performed in both eyes on the same day; FT = fibrovascular tissue; VB = the ciliary body and peripheral retina at vitreous base; LSV = lens-sparing vitrectomy; V = lensectomy-vitrectomy; FE = fluid-gas exchange; Y = yes; N = no; IOC = intraoperative complications; H = slight hemorrhage; IB = iatrogenic break; POC = postoperative complications; RRD = regrowth of the fibrovascular tissue and retinal detachment; OH = transient ocular hypertension; DR = dragging or folds of the retina; SCF = steady central fixation; retinal attachment (final) = results of initial vitreous surgery; in Patients 5 to 15 and results of the additional vitreous surgery in Patients 1 to 4.

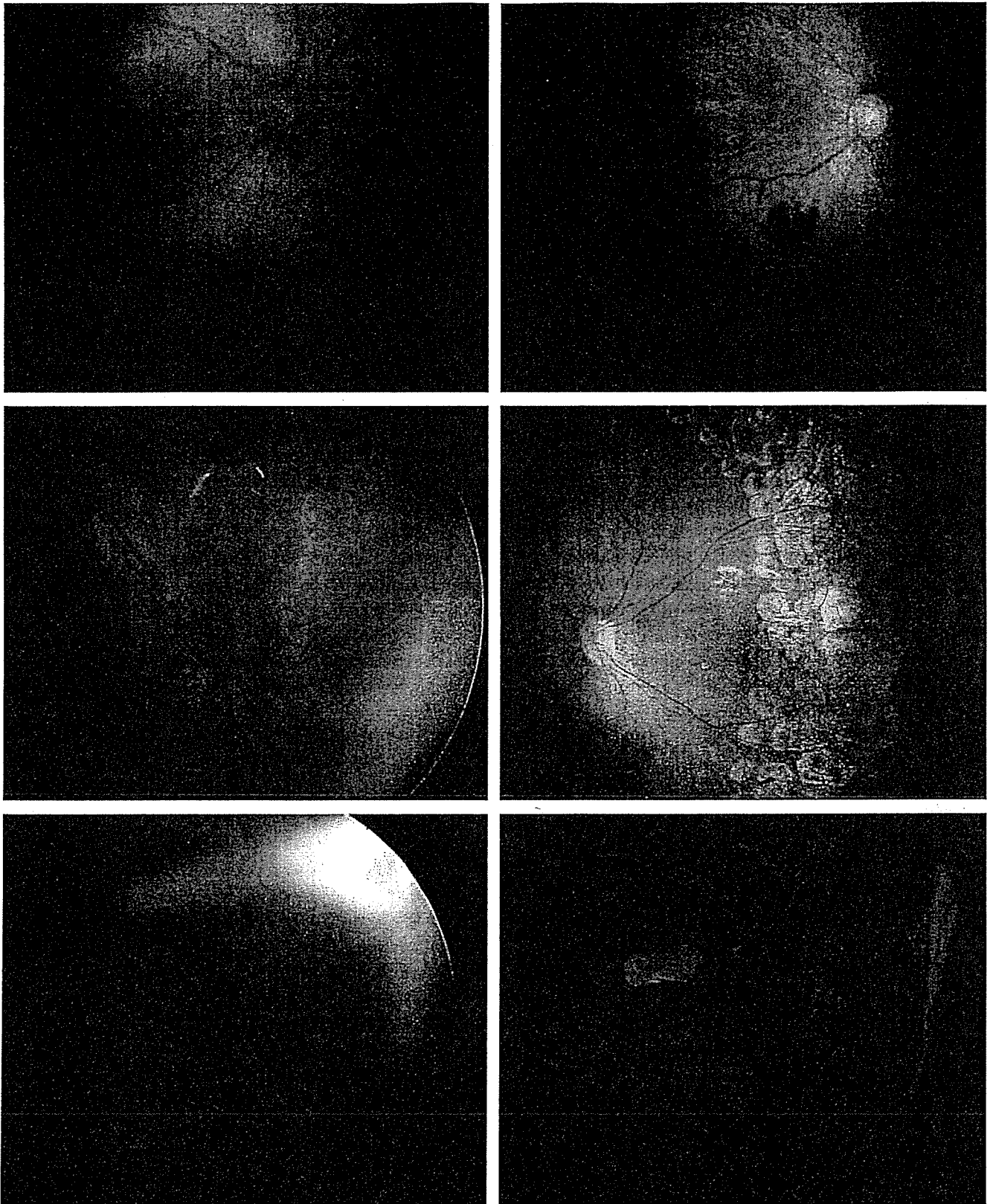


FIGURE 2. Preoperative and postoperative fundus images of aggressive posterior retinopathy of prematurity (ROP) in which early vitrectomy and lensectomy were performed. (Top row) The right eye of Patient 11 (gestational age 25 weeks; birth weight, 798 g). (Middle row) The left eye of Patient 13 (gestational age 26 weeks; birth weight 897 g). (Bottom row) The left eye of Patient 7 (gestational age 24 weeks; birth weight 526 g). (Left column) Preoperative fundus images. (Right column) Postoperative fundus images. Various configurations of retinal detachment and fibrovascular tissue (FT) in Stage 4 ROP may reflect the outcomes of vitreous surgery. Preoperatively, FT arises in the photocoagulation scars, reaches the posterior lens surface (Top left), extends toward the vitreous base (Middle left), and is attached to the ciliary body and peripheral retina at the vitreous base (Bottom left), under which a regional traction retinal detachment does (Stage 4B) (Middle left, Bottom left) or does not (Stage 4A) (Top left) affect the fovea. The retina has reattached with (Middle right, Bottom right) or without (Top right) residual retinal folds and dragging under the residual fibrous tissue. The dilation and tortuosity of the retinal vessels have decreased postoperatively, and there is little intraoperative and postoperative bleeding in each eye.

eyes; fibrovascular tissue did not extend to the vitreous base in two eyes, was attached to the ciliary body and peripheral retina at the vitreous base for less than 3 clock hours in three eyes and 3 clock hours or more in two eyes (Patients 7 and 8 in Table).

• **SURGICAL RESPONSE:** In six eyes in which a lens-sparing vitrectomy was performed, fibrovascular tissue (FT) continued to grow along the residual peripheral vitreous, resulting in substantial retinal detachments (Stage 5) (Figure 1, Bottom left). Another vitrectomy with lensectomy was performed one month later when the vascularization became quiet. Retinal reattachment was achieved in all six eyes, but there was substantial retinal degeneration (Figure 1, Bottom right). The visual function of the six eyes was light perception or hand motions.

In contrast, in the 16 eyes in which vitrectomy was easily performed to the vitreous base after lensectomy, complete retinal reattachment was achieved at the last follow-up examination. The retina was dragged around the scarring of the residual FTs in one (10%) of 10 eyes in which ROP had progressed to Stage 4A preoperatively, but in all six eyes in which ROP had progressed to Stage 4B, because the surgery failed to release the traction of the wide circumferential FT that was not dissected or removed (Figure 2, Middle and Bottom row). In three eyes in which an iatrogenic break developed, the retina also was reattached by fluid-air exchange and endophotocoagulation.

Slight vitreous bleeding occurred from the FT during vitrectomy in all eyes but was spontaneously absorbed within two to three weeks postoperatively. The fovea was well formed at the correct retinal position in nine (90%) of 10 eyes with preoperative Stage 4A ROP (Figure 2, Top row) and was mildly hypoplastic in one (10%) of 10 eyes with Stage 4A ROP and four (75%) of six eyes with Stage 4B (Figure 2, Middle row). All 14 eyes had steady central fixation (SCF). However, in two eyes with stage 4B ROP, in which wide circumferential FT was attached to the ciliary body and the peripheral retina at the vitreous base preoperatively, the retina had been dragged extensively, the fovea failed to form, and there was no SCF (Figure 2, Bottom row; Patients 7 and 8 in Table).

No eyes had additional vitreous bleeding, endophthalmitis, rhegmatogenous retinal detachment, or neovascular glaucoma. Two eyes had a transiently high intraocular pressure level that was managed with hypotensive medication. The characteristics of the 22 eyes are summarized in the Table.

DISCUSSION

RETINAL PHOTOCOAGULATION OR CRYOPEXY IS SOMETIMES effective for stabilizing aggressive posterior ROP; however, it sometimes cannot stop the progression to retinal detachment, despite being performed early, densely,

and with early retreatment.^{19,20} When FT and traction retinal detachment occur 360° circumferentially in zone I, where aggressive posterior ROP usually occurs, scleral buckling is not only difficult to perform but also does not effectively release the traction, because the summit of the buckle cannot be positioned to counteract the direction of the fibrovascular growth.^{9,19} Another surgical procedure to remove or divide the encircling buckle then is needed to facilitate ocular growth.²⁷

When vitreous surgery is performed for ROP that progresses to Stage 5, postoperative visual outcomes are poor despite successful retinal reattachment.⁷⁻⁹ Furthermore, vitreous surgery sometimes cannot be performed when aggressive posterior ROP results in the development of corneal opacity, glaucoma, and phthisis soon after progression to Stage 5.^{16-18,20}

In the current study, we successfully treated aggressive posterior ROP by early surgical intervention with photocoagulation and vitreous surgery. The fovea was well formed in 56% of the treated eyes, and a good visual outcome was achieved in all but two eyes. These results indicate the great benefit of early surgery for aggressive posterior ROP, in comparison to the poor visual outcomes after vitreous surgery for Stage 5 ROP, despite surgical and anesthetic intervention on very small infants. Even though the vascularity was still active, it was suppressed considerably by retinal photocoagulation that was performed early, densely, and with early retreatment. We did not completely remove the FT but did remove the surrounding vitreous gel, even though there was still retinal traction. Thus, there was little intraoperative and postoperative bleeding.

Surgical removal of the vitreous framework might contribute not only to reduced tractional force of the fibrovascular tissue but also to suppressed growth of new vessels, which is activated by the traction.³⁻⁶ This is similar to outcomes of early vitreous surgery for diabetic retinopathy.^{28,29} In patients who are young and have more severe proliferative diabetic retinopathy, there is an obvious advantage to performing early vitrectomy, while no such advantage exists for patients with retinopathy consisting of minimal severe new vessels. Early vitrectomy for diabetic retinopathy is most suitable for eyes in which both fibrous proliferation and at least moderately severe new vessels are present and in those eyes in which extensive scatter photocoagulation has already been applied.²⁹

Lens preservation is important to prevent deprivation amblyopia and promote visual development.^{30,31} However, our experience with lens-sparing vitrectomy to treat aggressive posterior ROP did not stop the progression of retinal detachment compared with the group in which lensectomy was performed. Fibrovascular tissue arises from the posterior retina, reaches the posterior lens surface, then extends toward the vitreous base, where the vitreous framework is most condensed, and contracts.¹ The space in which the vitreous gel is removed by lens-sparing vitrec-

tomy is limited to the posterior portion of the vitreous cavity.^{10,31} Thus lensectomy is necessary to remove the vitreous gel from a wide area including the vitreous base.

There are various configurations of retinal detachment and fibrovascular tissue in Stage 4 ROP, which may predict the outcomes of vitreous surgery. When the fovea is involved in the retinal detachment, early vitreous surgery fails to obtain good foveal formation, probably because the fovea continues to develop after birth.³² When fibrovascular tissue reaches the posterior lens surface and does not extend toward the vitreous base, the vitreous gel around the FT is easily removed surgically, resulting in good outcomes. In contrast, when the FT extends and attaches to the ciliary body and the peripheral retina at the vitreous base, the retinal detachment usually progresses more and involves the fovea. In this case, cutting the FT and removing the vitreous gel from the vitreous base region are difficult and result in residual retinal folds or a dragged retina and no foveal formation. Thus vitreous surgery may be performed during the period when the FT grows to the posterior lens surface and has not extended toward the vitreous base.

The current study had some limitations in that it was not randomized, controlled, or prospective, the patients had various systemic conditions, and there were various types of retinal vasculature and retinal detachments. In eyes with much poorer retinal vasculature, in which vessels are present only near the optic disk, FTs likely grow on the retinal surface and along the trunk of the hyaloid vessels that arise from the optic disk. Retinopathy that has progressed further with more extensive retinal detachment also may be a contraindication to early vitrectomy, because new vessels secondarily invade and mature in the FT at an early phase of the regression of retinopathy.

Certain logistical problems also accompany early surgery for aggressive posterior ROP. Because aggressive posterior ROP rapidly progresses to Stage 5,¹⁶⁻¹⁸ and there are few surgeons who specialize in vitreous surgery for ROP, prompt transport of infants and preoperative systemic examination and management for anesthesia are necessary. If the surgery is delayed as little as a few days, ROP might progress to Stage 4B or 5, resulting in poor surgical outcomes. The surgery should be completed within a short time, because small premature babies cannot tolerate systemic anesthesia for a long period.³³ Additional anesthesia after a short period sometimes causes edema of the vocal cords or trachea or apnea after extubation that might result in respiratory insufficiency.^{33,34} Thus surgery that is performed on both eyes with simultaneous aggressive posterior ROP on the same day may be unavoidable in premature babies who cannot tolerate anesthesia again during the course of a few days. Lengthy surgical procedures also should be avoided, including application of additional photocoagulation, hemostasis, and repairing of iatrogenic breaks. Thus aggressive removal of the FT on the retina also might be contraindicated to avoid bleeding

and iatrogenic break formation. Early, wide, and dense application of photocoagulation before vitrectomy is important not only to delay progression of retinal detachment but also to stabilize vascularity of the retinopathy.

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Small Eye Phenotypes Observed in a Human *tau* Gene Transgenic Rat

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ABSTRACT We developed a rat line showing small eye from transgenic rats that were obtained by microinjection of a DNA segment containing the human (h)*tau* cDNA (GenBank: BC000558: 31-677,774-1180) expressed under control of CAG promoter, which is related to Alzheimer disease, into the pronuclei rat embryos. The rat line was established by selective brother-sister mating of rats showing small eyes. Of 11 offspring in the 11th generation, there were eight animals with microphthalmia and the transgene. The remaining three rats without transgene did not show the small eyes phenotype. The globes of affected rats were 1.2 mm in length compared with normal globes (3.5 mm), and all other ocular structures were normal. The expression of hTau protein was evident immunohistochemically in the ciliary body, extraocular muscle, lens epithelium, and pigment epithelium. Cytogenetic analysis suggested that the chromosome location of the transgene was chromosome 1 (1p12). This region may include genes related to lens development, such as *Cat5*.

KEYWORDS *Cat5*; cataract; rat; small eye; Tau

INTRODUCTION

It is reported that Parkinson disease is inherited as an autosomal dominant gene, and the gene is linked to chromosome 17q21-22.¹ Human (h)*tau* gene was located on the locus, and mutation of the gene was found in frontotemporal dementia with parkinsonism linked to chromosome 17 (FTDP-17). The neurofibrillary tangles composed of microtubule-associated protein Tau are related to not only the FTDP-17 but also to Alzheimer disease. The gene encoding microtubule-associated protein has been reported in rats as well, and the gene (*Map1a*) was linked to chromosome 3q36.² Many transgenic mouse lines that express hTau protein have been established to investigate the relationship between the hTau protein and tauopathy.³ Recently, we generated three transgenic rats (founder) carrying the *htau* gene, and they showed small eyes.

Mice and rats with ocular phenotypes, such as aniridia,⁴ cataract,⁵ microphthalmia,⁶ and small eyes,⁷ were reported, and a number of genes, including *Bld*,⁸ *Cat*,⁹ *Maf*,¹⁰ and *Pax*,¹¹ related to these abnormalities have been reported as well. In this study, we characterized the phenotype of transgenic rats with small eyes, and the candidate gene causing the phenotype was predicted.

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MATERIALS AND METHODS

Transgenic Constructs and Animals

htau cDNA (GenBank: BC000558: 31-677,774-1180) and rabbit β -globin polyA provided by Dr. Oyama (Department of Neuropathology, University of Tokyo)¹² were microinjected into the pronuclei of fertilized Jcl:SD rat (CLEA Japan Inc., Tokyo, Japan) embryos, and the embryos were transferred to the oviducts of pseudopregnant SD rats. Testing for the transgene in offspring was performed by polymerase chain reaction (PCR). The primers and conditions for the PCR are described below. In histopathological, immunohistochemical, and fluorescent *in situ* hybridization (FISH) analysis, four out of the 8 rats, aged 8 weeks, with small eyes were used. The rats were maintained in accordance with the Animal Care Guidelines of the Central Institute for Experimental Animals (Kanagawa, Japan).

PCR Analysis

To select rats carrying the *htau* gene, PCR analysis was performed using the oligonucleotides, t1 (5'-AAG CTC GCA TGG TCA GTA AA-3') and t2 (5'-GAC TTG ACA TTC TTC AGG TC-3'), and *Taq* polymerase (Takara Shuzo, Co., Ltd., Shiga, Japan) according to the manufacturer's protocol.

Histopathology

The formalin-fixed materials were embedded in paraffin, and 5- μ m sections were stained by a standard method with hematoxylin and eosin (HE). The sections were examined under a light microscope to evaluate morphologic characteristics and pathologic changes. For detection of hTau protein in the tissues, all sections were stained by the dextran polymer-immunoperoxidase complex method (ENVISION kit, DakoCytomation, Kyoto, Japan) using anti-bovine Tau (mouse) serum (EMB Biosciences, Inc., San Diego, CA, USA) at 1:5000 dilution as the primary antibody and then counterstained with hematoxylin.

FISH Analysis

Determination of the chromosomal location of the *htau* gene in the transgenic rats was undertaken by FISH analysis, and closely linked genes associated with ophthalmopathy were screened using the rat genome database (<http://rgd.mcw.edu/>). The chromosome sam-

ples were prepared from mitogen-stimulated splenocytes of transgenic rats. The biotin-16-dUTP-labelled *tau* cDNA clone in the pCXN2 vector¹³ was used for hybridization. FISH analysis was performed essentially as described by Matsuda et al.¹⁴ Observations were carried out with a Leica Q550 system (Leica Microsystems K.K., Tokyo, Japan), and chromosomes with fluorescent signals were identified according to G-banding standards.

RESULTS

Forty-five rats in total were obtained from the founder male rat carrying the *htau* gene. Twenty-three out of the 45 rats had the *htau* gene, and 3 of 23 (2 males and one female) rats showed small eyes. F2 rats were obtained by mating between a rat with small eyes and a Jcl:SD rat, and the animals were maintained by selective breeding of a small-eye line and brother-sister mating. At the 11th generation, 11 offspring were obtained, and 8 of the 11 offspring showed small eyes.

Histopathological Analysis

The globes of affected rats were 1.2 mm in length compared with normal globes (3.5 mm), and all other ocular structures were normal (Figs. 1 and 2A). Vacuolation was observed in lens of the rats, but no lesions were observed in other tissues such as the cornea and iris. These abnormalities were observed only in rats of this line bearing the *htau* gene. On the other hand,

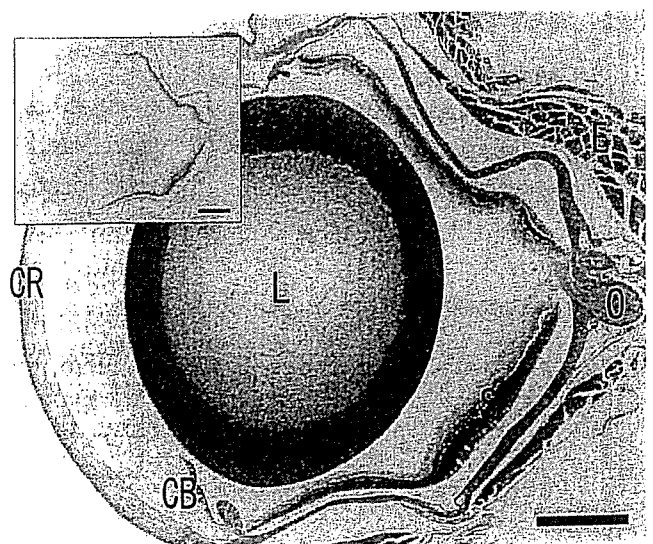
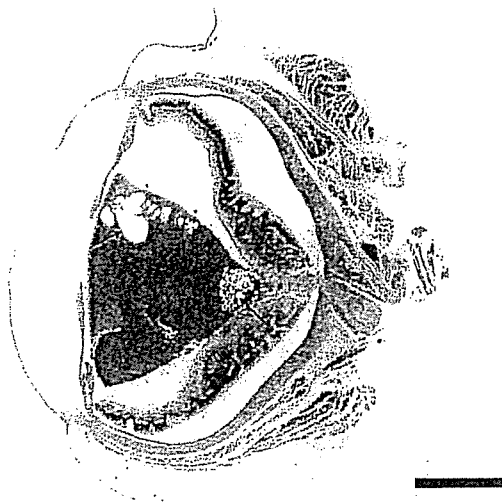
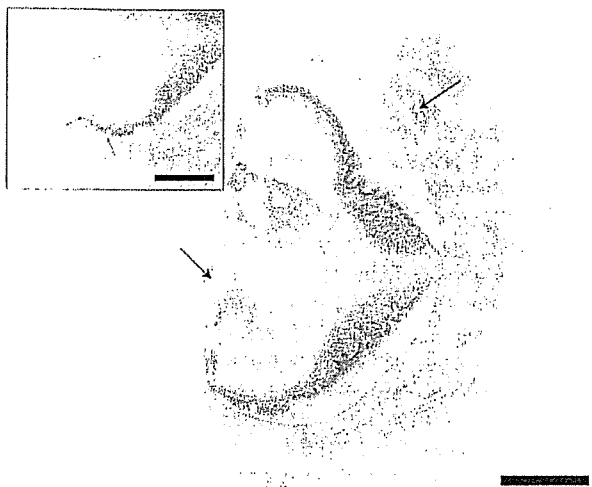


FIGURE 1 Ciliary body (CB), cornea (CR), extraocular muscle (E), lens (L), optic nerve (O), and sclera (S) from a rat not bearing the *tau* gene (H&E). Inset shows immunohistochemical stain, hematoxylin counterstain. Expression of *Tau* protein in the normal eye from a rat not bearing the *tau* gene. Bar = 1 mm.



(A)



(B)

FIGURE 2 (A) Small lens observed in human *tau* gene transgenic rats. Vacuolation is present in the lens (arrows) (H&E). Bar = 1 mm (B). Immunohistochemical stain, hematoxylin counterstain. Tau protein expression evident immunohistochemically in the ciliary body, extraocular muscle, lens epithelium, and pigment epithelium (arrow). Bar = 1 mm. Inset shows detail of ciliary body and pigment epithelium. Bar = 1 mm.

ophthalmic lesions were not observed in wild-type rats and rats from other rat lines carrying the gene (data not shown). Tau protein expression was evident immunohistochemically in the ciliary body, extraocular muscle, lens epithelium, and pigment epithelium (Fig. 2B).

Location of the *htau* gene was analyzed by the FISH method, and the gene was found to be located on chromosome 1p12 (Figs. 3 and 4).

DISCUSSION

Tau protein is a microtubule-associated protein. In Alzheimer disease, Pick disease, and corticobasal degeneration, typical mutations were found in the gene.

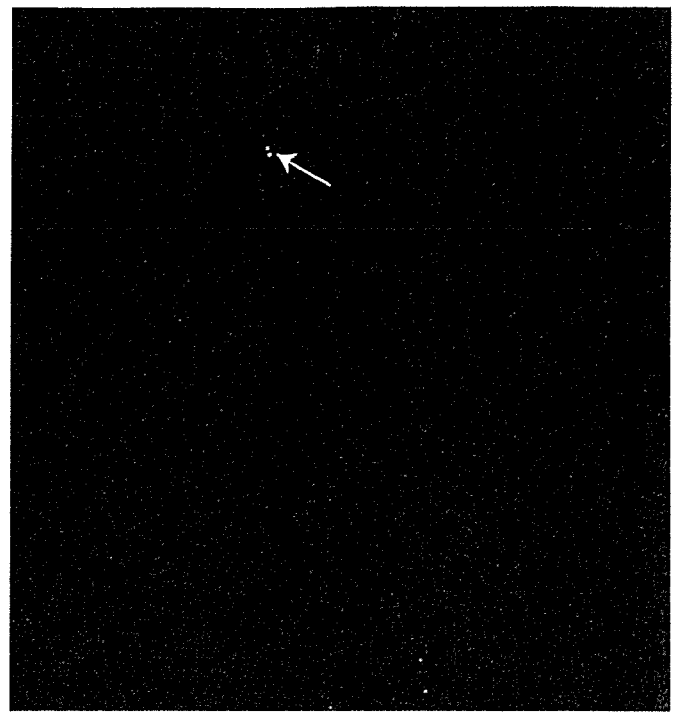


FIGURE 3 Chromosomal location of the human *tau* gene in a transgenic rat. The signal was visualized indirectly with FITC (arrow).

Mutations that affect exon 10 splicing cause frontotemporal dementia with parkinsonism.

In this study, we obtained 23 transgenic rats carrying the *htau* gene from one founder transgenic rat, and in three out of the 23 rats small eyes appeared. Histopathologically, the lens of the rats was small in size with vacuolation. Lens development is regulated by a variety of genes, such as *L-Maf*, *Pax6*, and *Sox2*. Microphthalmic rats and mice caused by mutation of these genes were reported previously,^{15,16} but all of them were not caused by the *tau* gene. Lewis et al. reported eye irritations in mice expressing mutant Tau protein but microphthalmia was not observed.¹⁷ Only three (2 males and one female) of these 23 transgenic rats showed small eyes, suggesting that small eyes observed in this study were not caused by *htau* gene. The human *Pax6* gene was first reported as a candidate gene for evolution of morphogenesis of the eye.^{18,19} In rats, the *Pax6* gene is located on chromosome 3q32-3q36. Because the transgene in the rats with small eyes was mapped to chromosomal 1p12, it was suggested that the *Pax6* gene was not related to abnormalities in this study. Based on the database analysis of the transgene locus (1p12) in rats, several genes have been mapped in the locus. In the locus, *Cat5* was mapped as a cataract-related gene.

In conclusion, we established a rat line, that shows small eyes from transgenic rats carrying *htau* gene.

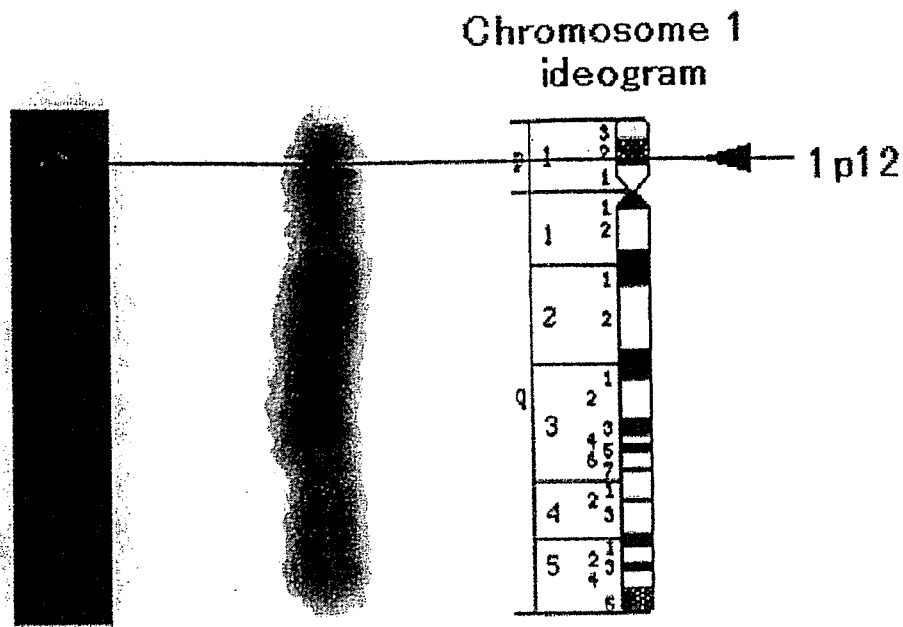


FIGURE 4 Ideogram showing the cytogenetic location of *tau* in 1p12.

Typical phenotypes were characterized by a small lens with vacuolations observed in the lens. The map location of the transgene suggested that the candidate gene causing small eye is located in 1p12.

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総 説

重症未熟児網膜症の治療

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要 旨

未熟児網膜症は網膜剝離に進行すれば失明に通ずるが、超低出生体重児の管理の進歩に伴ってより未熟な児の生存が可能になって、近年重症例が増加している。治療は、網膜症が中等度まで進行すれば、まず光凝固が行われる。網膜剝離に至れば、バックリングや硝子体手術が行われるが、有用な視力はなかなか得られない。ことに、II型/aggressive posterior ROPと呼ばれる劇症型は急速に進行することが特徴であり、光凝固が奏功せずに網膜剝離に至れば、予後がきわめて悪かった。これに対して早期硝子体手術を行えば、網膜剝離の進行が高率に予防され、良好な視反応が得られることが明らかとなった。重症未熟児網膜症の治療適応は、今後大きく変わると考えられる。

キーワード：未熟児網膜症，病期分類，光凝固，網膜剝離，硝子体手術

はじめに

未熟児網膜症 (retinopathy of prematurity, 以下ROP) は発達途上の網膜血管が増殖する疾患であり、在胎週数が短く出生体重が少ないほど網膜血管の未熟性が強く、発現頻度や程度が高い。近年は、新生児集中治療室での管理の進歩によって体重が極端に少ない超低出生体重児が救えるようになり、きわめて重症かつ非定型例のROPが多くみられるようになった¹⁾²⁾。盲学校の小児失明原因統計³⁾でもROPの占める比率は急増加している (図1)。

ROPがある程度まで進むと光凝固治療を行い、治癒すれば比較的良好な視力が得られる。しかし、進行を阻止できないと網膜剝離にいたって予後がきわめて悪くなる。従来は、網膜剝離にバックリングや硝子体手術を行っていたが、十分な効果が得られず、網膜障害が進んでしまえば、大部分は僅かな視力しか得られない。ことに、II型/aggressive posterior ROPと呼ばれる劇症型は、急速に網膜剝離に進み、失明に至ることが多い^{4)~7)}。

国立成育医療センターでは、この重症ROPに早期

硝子体手術を行い、きわめて良好な成果を得ている⁸⁾。本手術の導入によって、ROPの治療適応が大きく変わると思われるので、その概略を述べる。

ROPの進行と病期分類

(1) 段階的に進行するROP

わが国では1976~1983年に「未熟児網膜症厚生省分類」が作成された⁹⁾。その後、わが国を含むROP研究者が国際分類を作成し1984年⁹⁾、1987年¹⁰⁾に発表した⁹⁾が、2005年に改定された⁷⁾。厚生省分類と国際分類はいずれも5つの病期に分け、stage 1とstage 2の扱いが異なるが、書き換え可能である (表1)。国際分類では、眼底を3つのzoneに分けて病変の局在と範囲を示す、優れた記載法をとっている。

この段階的に進行するROPは、厚生省分類⁹⁾ではI型と呼ばれ、旧国際分類⁹⁾¹⁰⁾のstageもこれを表している。まず血管成長先端部の網膜内で血管芽細胞が増殖を始め、白い境界線 (demarcation line; 図2A) を形成する。次いで網膜内の血管芽細胞増殖は硝子体腔にむかって隆起し (ridge), 新生血管として硝子体腔内に発芽し、硝子体を構築するコラーゲン線維束に沿って伸びる (extraretinal neovascularization; 図2B, C)。ここまですべてを活動期と呼ぶ。やがて新生血管は退縮し、周囲に結合組織が産生されるが、以降を瘢痕期と呼ぶ。結

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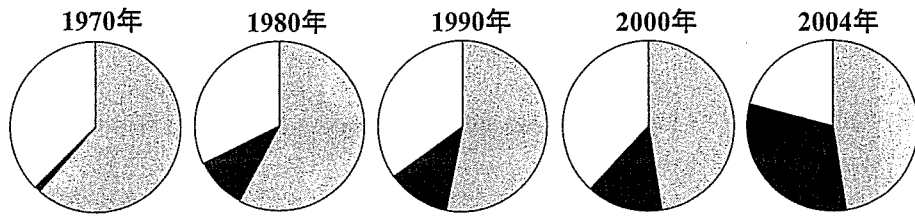


図1 小児の失明原因 (盲学校統計³⁾ 3~5歳, 6~12歳より作成)
 灰色: 先天異常, 黒: 未熟児網膜症.

表1 厚生省新分類と国際分類

厚生省分類		国際分類	
I 型			
1 期	網膜内血管新生		
2 期	境界線形成	←→	Stage 1 Demarcation line
3 期	硝子体内滲出・増殖期		
	初期	←→	Stage 2 Ridge
	中期 } 後期 }	←→	Stage 3 Ridge with extraretinal fibrovascular proliferation mild moderate severe
4 期	部分的網膜剝離	←→	Stage 4 Subtotal retinal detachment 4A Extrafoveal 4B Retinal detachment including fovea
5 期	網膜全剝離	←→	Stage 5 Total retinal detachment 重症兆候 Plus disease
II 型		←→	Aggressive posterior ROP

合組織は筋線維芽細胞を多く含むため、創傷治癒に類似して強く収縮する。これが網膜を強く牽引し、網膜剝離が起こる (図 2D)。網膜の層構造形成は途中で停止し、しかも脈絡膜からの酸素・栄養供給が絶たれるので、短期間で障害され変性する。増殖の範囲が狭ければ、網膜は限局的に牽引されるので、牽引乳頭や網膜襞のような部分的剝離にとどまり (図 2E)、日常生活ができる程度の視力は確保できる。しかし、高度の増殖が起これば網膜は全て剝離し、失明するか、得られても光や影しか分からない視力に止まる (図 2F)。

(2) 急速に進行する劇症型の II 型未熟児網膜症/aggressive posterior ROP

ROP には、わずか 1~2 週のうちに急速に網膜剝離に進む劇症型が存在する。厚生省分類では、活動期の順を追って進行する I 型に対し、II 型と名付けて注意を喚起している^{4)~6)}。旧国際分類では、この II 型と I 型が全く異なる病態の考えに理解が得られず、重症兆候として、眼底後方の網膜血管が拡張・蛇行する虚血所見に対し、stage 記載の後に + の文字を加えて plus disease と称するに止まった⁹⁾¹⁰⁾。しかしその後、欧米でもわが国の考えが認識され、2005 年に改訂された国際分類では、II 型の概念を全面的に取り入れて、ag-

gressive posterior ROP と規定した⁷⁾。これは、1) 眼底の後方で起こり、2) 網膜血管は顕著に拡張・蛇行し、シャントを形成、3) 通常の stage 1 から 3 への段階的な進行は示さず、急速に悪化して stage 5 の網膜剝離に至ることが特徴である。この II 型/aggressive posterior ROP はきわめて難治で、早期から光凝固を広汎かつ密に行っても、抵抗してしばしば網膜剝離に進行する (図 2G~I)。

ROP の悪化要因として、酸素投与、呼吸窮迫症候群、交換輸血、敗血症、脳室内出血、栄養・水分投与のアンバランス等が知られている。しかし、その発生に最も大きく関与する因子は網膜血管の未熟性であり、在胎週数が早いほど、出生時体重が少ないほど重篤である¹¹⁾¹²⁾。II 型/aggressive posterior ROP の発生では、網膜血管成長がごく僅かであることが第一条件なので、体重の極端に小さい超低出生体重児の生存率が向上している現在、急速に増加している²⁾。

眼底検査の開始時期

ROP に対する眼底検査の開始条件は、わが国の方が米国より厳しい。米国では、まず出生体重 1,300g 以下、

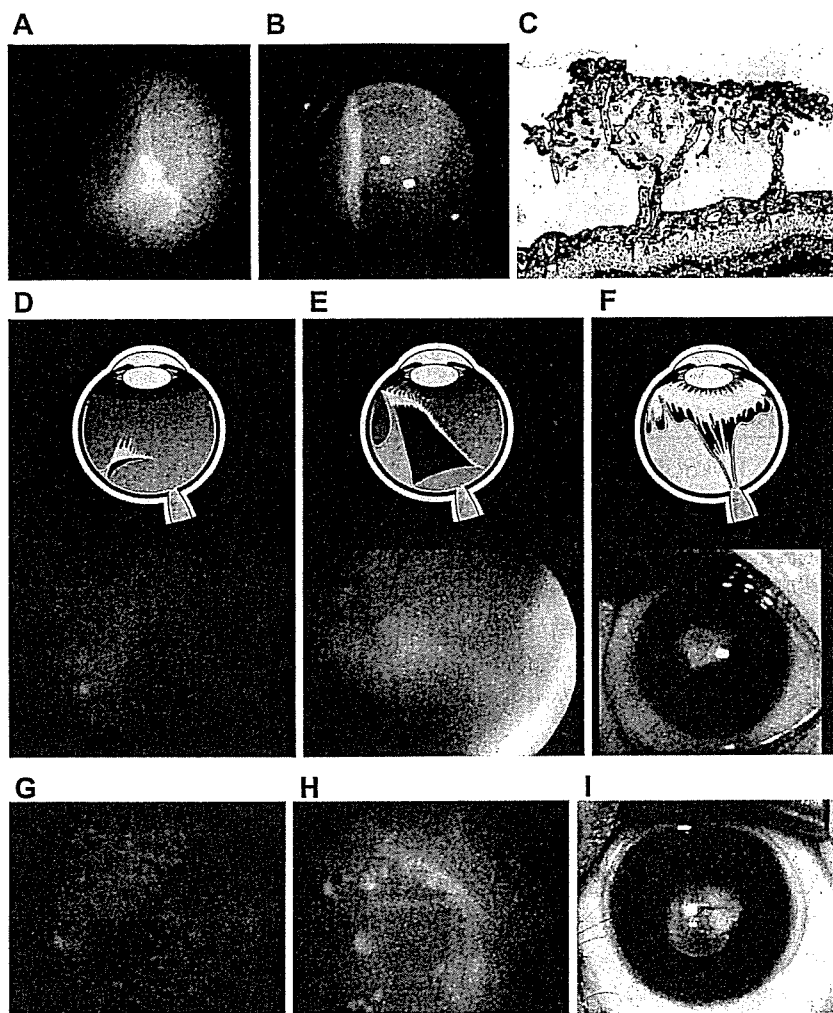


図2 未熟児網膜症の進行

A:境界線(厚生省分類2期, 国際分類 stage 1), B:網膜外血管増殖(厚生省分類3期, 国際分類 stage 3), C:その病理, D:黄斑に及んでいない網膜部分剥離(厚生省分類4期, 国際分類 stage 4A), E:黄斑に及び牽引網膜/乳頭となっている網膜部分剥離(厚生省分類4期, 国際分類 stage 4B), F:網膜全剥離(厚生省分類5期, 国際分類 stage 5). G~I: II型未熟児網膜症/aggressive posterior ROP, G:光凝固後, 網膜血管の拡張・蛇行著明, H:光凝固が奏功せず, 網膜外血管増殖が発生, I:網膜全剥離となり, 白色瞳孔を呈する。

あるいは1,800g以下で補助的酸素投与を行った低出生体重児にすべてスクリーニングを行うことを勧め、出生後7~9週に初回の検査を行えば重症にいたる前のROPを発見できると考えた¹³⁾。しかし、それでは遅過ぎるとして、最近のEarly Treatment for ROP (ETROP) Studyでは、在胎28週未満であれば修正在胎31週から、出生時在胎28週以上であれば生後4週に初回検査を行うよう勧めている¹⁴⁾。

我々は、軽度の網膜血管異常をも把握するため、在胎36週未満、出生体重が1,800g以下、あるいは高濃度酸素使用、手術を行った場合はすべて検査対象としている。II型/aggressive posterior ROPを発症する超低出生体重児では、発症を初期から把握するには早くの検査開始が重要である。出生時在胎26週未満なら修正

在胎29週から、出生時在胎26週以上なら生後3週には初回検査を行うのが適切である²⁾。

これまでのROP治療

(1) 光凝固

ROPが厚生省分類3期初期あるいは国際分類 stage 2までならば自然寛解し、視力予後もよい。さらに進行すれば光凝固を行う(図3A)。血管新生は、vascular endothelial growth factorなどの血管新生因子が網膜無血管領域から放出されて起こると考えられている¹⁶⁾。これに対し、無血管領域を広く凝固することで血管新生因子の産生を抑制し、新生血管の増殖の場をなくすことが目的である。光凝固はわが国で1968

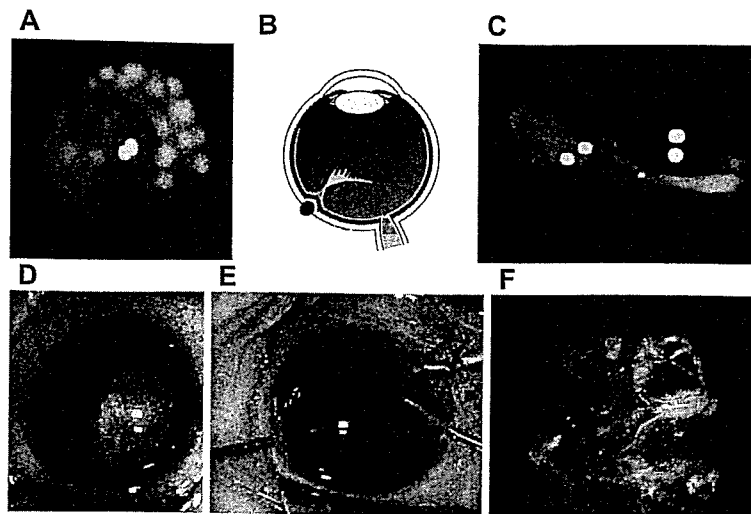


図3 未熟児網膜症の治療

A：光凝固，B，C：網膜部分剝離に対するバックリング治療（B：眼球シェーマ，C：眼底写真），D～F：網膜全剝離に対する硝子体手術（D：術前，E：術中，F：術後眼底所見で変性著明）。

年に世界に先駆けて行われ¹⁷⁾，以後広く行われるようになったが，米国ではずっと遅れて1988年に冷凍凝固に対する multicenter trial (CRYO-ROP Study)¹⁸⁾がまず行われ，ついで光凝固が一般化した。適応時期も，わが国では軽度の瘢痕をも防止して有用視力を得ることを目的として早めに行っていたが，欧米では失明予防を目的としており，治療開始がやや後期であった。しかし，良い視力を獲得できないことが判明し，Early Treatment for ROP (ETROP) Study¹⁴⁾が行われて治療開始が早期へ移ってきている。冷凍凝固は凝固能が強過ぎて眼球に障害を与え，無呼吸や徐脈，血圧低下など起こす危険性も高いので，最近はほとんど行われていない。

(2) 網膜部分剝離に対するバックリング手術

網膜症がさらに進行して網膜剝離になれば，重篤な視力障害にいたる。これに対し，まず強膜バックリング手術¹⁸⁾，次いで硝子体手術¹⁹⁾が行われる。バックリング¹⁸⁾は眼球の外にシリコンのスポンジやベルトを縫い付けて眼球壁を陥入し，牽引を軽減させて網膜剝離を治す方法である(図3B，C)。網膜剝離がまだ広がっておらず，部分的でない効果がない。

(3) 網膜全剝離に対する硝子体手術

網膜が全剝離に向かえば硝子体手術が行われる¹⁹⁾。これは，眼内に細い器具を挿入し，水晶体を除去してスペースを確保し，網膜を牽引している増殖膜(瘢痕化した新生血管由来組織)を除去する(図3D，E)。成人疾患と比べて，増殖膜と網膜の癒着が強く，網膜剝離の形態も複雑なので，成功率は高くない。しかも，剝離した網膜は高度に変性しており，治っても視力は

光や影の動きがわかる程度であることが多い(図3F)。手術時期は，網膜剝離を治し視力発達を促すことから，可及的速やかなことが望ましい。しかし，増殖膜内の血管の活動性が高ければ，術中に大出血を起こし失明に至るので，ROPでは硝子体手術を急ぐ方がむしろ危険と考えられている。増殖膜中の血管が十分に退縮してから手術した方が安全であるが，網膜剝離が起こってから1～2カ月待たねばならず，網膜障害が高度に進んでしまうので，決して良い視力は得られない²⁰⁾。

(4) 網膜部分剝離に対する水晶体温存硝子体手術

これに対して近年，より早期(厚生省分類4期，国際分類 stage 4)に水晶体を温存する硝子体手術(lens-sparing vitrectomy)⁹⁾が行われるようになった(図4A)²¹⁾。前もって光凝固を十分に行っておけば，出血も比較的少なく，良好な復位が得られ，良い視力が得られると報告されている。しかし，小児は眼球内で水晶体が占める比率が高く硝子体腔が狭いので，安全に操作できる範囲はごく狭い範囲に限られ，実際にはかなりの制約がある。

(5) II型/aggressive posterior ROPに対するこれまでの治療

劇症型のII型/aggressive posterior ROPは，診断がつき次第，直ちに光凝固を広汎かつ密に行わなければならない。何回かの追加凝固を要し，網膜牽引や膜の形成が残るにせよ，何とか抑えられることもある。しかし，効果なく網膜剝離へ進行すれば(図2G～I)，きわめて難治である。バックリング手術は，増殖組織と網膜剝離が眼球後方で広範囲にわたるので，手技が難しく，眼球壁圧迫による牽引解除の効果も僅かに過ぎ

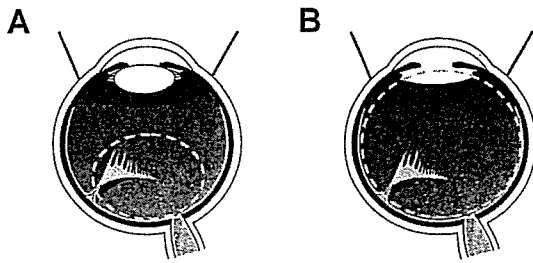


図4 水晶体温存あるいは除去した場合の硝子体手術
水晶体を温存した場合 (A) より除去した場合 (B)
の方が、広い範囲 (点線内) で手術操作ができる。

ない。硝子体手術は、増殖組織内の血管活動性がきわめて高く、退縮するまで時間がかかり、手術時期が非常に遅れる。手術が成功しても、既に網膜障害が顕著であり、視力予後も非常に悪い。さらに、広汎に生じた増殖組織は強く収縮して水晶体を前方に移動させ、早期に角膜混濁、緑内障あるいは眼球萎縮に至れば手術できなくなることも多い²⁶⁾。進んでしまえば、手をこまねいて見るに等しく、失明を覚悟するしかなかった。

II型/aggressive posterior ROPに対する早期手術

成人の重症糖尿病網膜症では、広範囲に光凝固が行われていれば、早期硝子体手術によって進行が防止できる²²⁾。これは、硝子体を構築するコラーゲン線維網を除去して新生血管成長の足場を無くし、血管新生を助長する硝子体の牽引を無くすことが機序と考えられている。従来のII型/aggressive posterior ROPの治療予後はあまりに悪いので、糖尿病網膜症のように、増殖組織が立ち上り網膜剥離が生じ始めた早期に硝子体切除を行えば、網膜剥離の重症化を軽減できるのではないかと考えて、国立成育医療センターでは2004年後半より早期硝子体手術を開始した。手術時の患児体重は1,500~2,000g程度で眼球も小さく、25Gのように繊細で、網膜を傷つけない安全な手術機器が開発されたことも、この手術に踏み切ることができた一因である。いずれも十分に光凝固したにもかかわらず、増殖組織が広く立ち上がって牽引網膜剥離を起こし始めた段階で手術を行った。術式の詳細は原著⁹⁾に譲るが、既に18例25眼 [出生時在胎22~30 (平均24) 週, 出生体重466~1,676 (平均773) g, 手術時修正在胎35~41 (平均37) 週, 体重1,560~2,602 (平均2,019) g] で手術を行い、予想をはるかに超える良好な成果が得られている。

最初の4例6眼では水晶体温存硝子体手術 (図4A) を行った。しかし、後方の限局的な部位でしか硝子体を切除できず、水晶体後面や周辺部が残って、ここに

増殖組織が進展し、全例が高度の網膜剥離に進行した。その後、従来のように増殖組織内の血管活動性が鎮静化するまで1~2カ月待つて再手術を行ったが、網膜の復位が得られたものの、既に高度な網膜変性が起こっており、いずれも視反応は光覚にとどまった (図5E)。

そこで以後は、水晶体を除去し、広汎に硝子体を切除した (図4B)。術中出血を恐れ、硝子体線維構築の除去にとどめ、血管を含む増殖組織は極力手をつけなかった。現在までに行った21眼 (国際分類 stage 4A: 12眼; stage 4B: 9眼) のうち、19眼で網膜剥離は全治癒した。既に網膜剥離が広く進んでいた2眼は、部分治癒にとどまった。そして、全治癒した19眼中、11眼 (58%) で明瞭な、6眼 (32%) でやや低形成ながら黄斑が形成され、これら全てで良好な視反応が確認された。網膜が全部剥離してから (stage 5)、増殖膜内の血管が枯れるのを待つて行う従来の硝子体手術では、光が影がわかる程度の視覚しか得られなかったのに比べ、きわめて良好な結果である。重症未熟児網膜症を起こす超低出生/極低出生体重児は中枢神経合併症等で視力が得られないこともあるが、網膜症の観点からは、この早期手術が奏功すれば、患児は盲学校ではなく普通学校へ行ける可能性が開けたことになる。

水晶体を失うことは視力発育において大きな問題である²²⁾が、予後に明確な差がある以上、II型/aggressive posterior ROPの硝子体手術において水晶体を除去するのはやむを得ない。水晶体を失えば、術後に眼鏡やコンタクトレンズによる屈折矯正、視能訓練を行う必要があるが、得られる恩恵は大きい。手術の合併症については、かなりの出血が起こることを予測していたが、ごく僅かに過ぎなかった。光凝固が十分に行われていたので、増殖の初期では、活動期と瘢痕期が混在しており、血管成分が比較的少ないと思われる。後に線維組織が伸展するにつれ、新生血管が成熟し太くなるか、二次的に血管侵入が起こると推測される。したがって本手術では、かなり進行した網膜症でない限り、術中出血はほとんど障害にならない。ただし、光凝固が不十分であれば、依然として危険を伴う。

II型/aggressive posterior ROP 早期手術の適応時期はごく短期に限られる

今回手術を行ったROPは網膜が全部剥がれていない部分剥離 (厚生省分類4期, 国際分類 stage 4) であったが、網膜剥離や増殖組織の形態によって手術予後に大きな差が生ずる。視力に関わる網膜黄斑部の形成は満期出生後でも3~4カ月まで続くので、網膜剥離が黄斑に及ぶ国際分類 stage 4Bでは網膜が復位しても、剥離が黄斑に及んでいない stage 4Aより術後の黄斑形

成が不良で、視力予後も悪い。

しかし、手術の成否は、線維組織の進展度とその方向に強く左右される。一般に、網膜から立ち上がった増殖組織は、硝子体線維の走行に沿って、まず水晶体後面に向かう。この段階で、増殖組織下の網膜は既に剝離し始めている(図5A)。その後、増殖は硝子体密度が最も高い周辺部(硝子体基底部)へ向かうので、線維組織と剝離網膜の先端はこの部位へ倒れ込む(図5B)。増殖組織の先端が対側組織に接着すれば、把持部を得て牽引力が非常に強くなり、網膜剝離は急速に進行する(図5C)。したがって、手術では水晶体後面と硝子体基底部の硝子体線維構築を除去し、この接続を断つことが重要である。ひとたび増殖組織が硝子体基底部に強く接着してしまえば、これを切開することはきわめて難しい(図5D)。血管の二次侵入のため出血が多く、組織が硬く癒着も強く、奥で網膜が複雑に剝がれていて傷つける危険性が高い。したがって、早期硝子体手術は、増殖組織が周辺部に接着していない前の段階で行うべきと考える(図5A, B)。II型/aggressive posterior ROPは急速に進むので、この手術が有効な時期は、増殖組織の立ち上がりと網膜剝離が起こり始

めてから、1週間程度に過ぎない。

早期手術を行う上での時間的制約

この手術には、他にもさまざまな時間的制約がある。まず、網膜症は数日の遅れであっても、増殖組織が周辺部に広く接着し、網膜剝離が急速に進行する恐れがある。ROPの硝子体手術を専門とする施設は限られているので、患児の迅速な移送が必要となる。新生児科医が付き添って、比較的近隣なら救急車のみでも可能だが、遠方であれば飛行機・救急車や新幹線・救急車の連携、あるいはヘリコプターによる移送を考えねばならない。ヘリコプターなら日本全国からの移送が可能で、国立成育医療センターではこれを採用しているが、費用や医師・看護師の付き添い、患児の全身状態等の十分な検討が必要である。移送するとなれば準備を含めて2~3日はかかる上に、転院後も全身麻酔の術前評価のために最低1日は要する。上述のように、手術を行って良好な視力が期待できる期間はごく僅かに限られ、II型/aggressive posterior ROPで十分な光凝固を行ったにもかかわらず増殖が始まった場合は、お

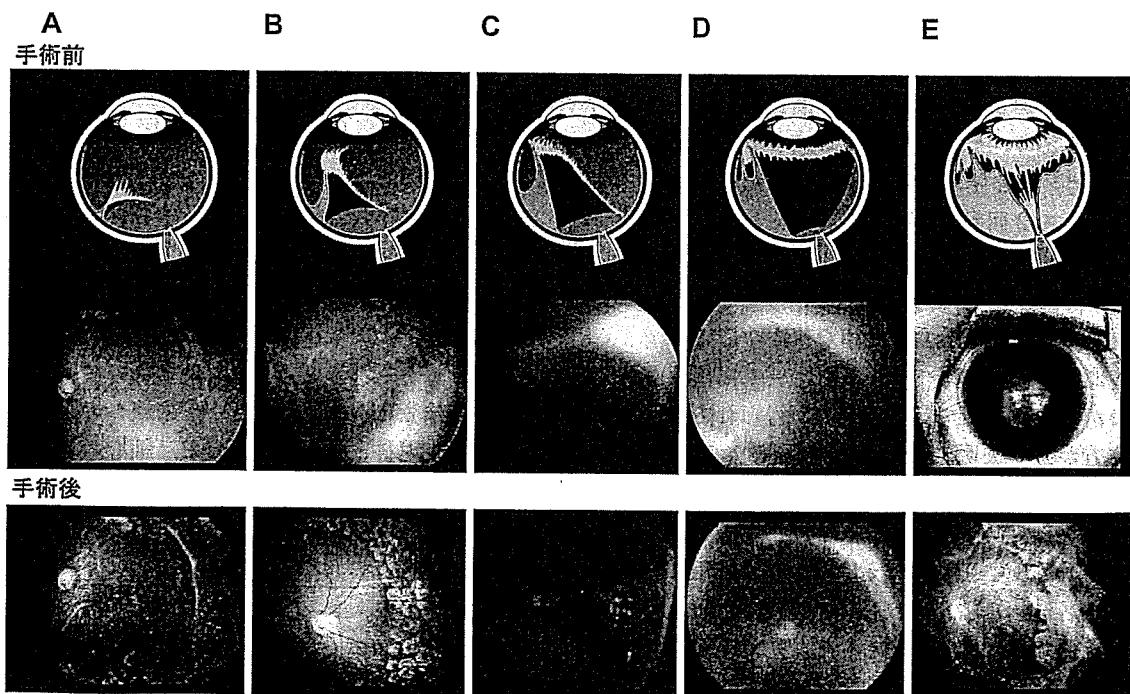


図5 II型/aggressive posterior ROPの進行と早期硝子体手術の結果

術前 A: 増殖組織の伸展と牽引網膜剝離の開始(国際分類 stage 4A 初期), B: 網膜剝離は黄斑に及び始め(stage 4A 後期~ stage 4B 初期), 線維組織は周辺部へ向う, C: Stage 4B, 増殖線維組織の一部が硝子体基底部に接着, D: Stage 4B 後期, 線維組織が広汎に硝子体基底部に接着, E: 網膜全剝離(stage 5). 早ければ1週間程で A から E へ進行する。術後, A, B では網膜は復位し, 黄斑が形成されているが, C では一部網膜剝離を残して黄斑は形成されず, D では網膜剝離が治癒しない, E は進行し過ぎており, もはや早期硝子体手術の適応ではない。従来通り血管の退縮を待つて手術するが, 網膜変性が進んでしまう。

おむね1週間も猶予がないと考えるのが安全である。

手術自体にも時間制限があり、超低出生/極低出生体重児はストレス障害に陥りやすいので可及的短時間で行う必要がある²⁴⁾。国立成育医療センターでは、全身合併症の有無にもよるが、通常は手術時体重が2,000gなら2時間、1,500gなら1時間半を手術時間の目安としている。抜管後に声帯や気管の浮腫、無呼吸を生じやすいため、短期間の繰り返し麻酔は極力避けたいので、両眼で網膜症が急速に進行する可能性がある場合には、両眼同時手術を行うこともやむを得ない。体重1,500gの両眼網膜症では、片眼45分で手術を終える必要がある。したがって、無駄な手術操作を極力排し、術中合併症を起こさないようにすることに努めている。

手術眼の選択と家族への説明

II型/aggressive posterior ROPは大部分が両眼に起こる。両眼とも早期手術の適応で、全身状態が短期間の繰り返し麻酔を許さなければ、両眼同時に手術を行うことが多い。全身状態が急変して手術を早めに切り上げねばならない場合や、出血などの処置で手術が長引いて麻酔の許容時間を使い果たす場合があるので、網膜症が軽度で視力予後が期待できる方の眼を先に行う。同様に、2回に分けて手術を計画する時も軽度な方を優先している。初回は悪い方を2回目に良い方を手術する選択もあり、悪い方が手遅れになることはなく、両眼にチャンスを与えることができる。しかし、全身状態が急変して2回目の手術ができなくなれば、両眼とも視力不良に終わる。いずれも、状態の良い片眼だけでも救うことが目的である。

片眼が光凝固で既に落ち着き、有用な視力が期待できる場合は、他眼が網膜剥離へ進んでも、従来は積極的に治療しなかった。手術で僅かな視力が得られても使わず、良い方が万一失明した場合の spare eye に過ぎない。多くは小眼球となり、整容目的でコンタクト義眼を装用するからである。しかし、早期手術を網膜剥離の発生初期(図5A, B)に行えば、かなり有用な視力が期待でき、目立つ程の小眼球にはならないので、積極的に手術を勧めるべきと考える。網膜剥離がやや進行しても(図5C)、失明することに比べれば、手術を考慮して良いと思う。一方、かなり進んでしまった場合は(図5D)、再手術を前提に、状態を良くする目的で手術する選択もあるが、慎重さが必要である。

いずれも、手術をどの位の時間・回数で行えるか、全身状態が優先する。インフォームドコンセントは重要で、新生児科医・麻酔科医とともに、保護者に眼と全身の状態を説明し、発展途上の治療法であること、手術にともなう危険性と利点について十分な理解を得

た上で、治療の選択を委ねている。

早期手術についての今後の展望

この早期手術は開始したばかりで、まだ安易に喧伝すべきでないと思う。無作為化比較試験を行うことは難しく、今後さらに症例を集積して適応や術式を検討し、視力を含めた長期予後を追跡しなければならない。晩期合併症の緑内障や裂孔原性網膜剥離にも注意が必要である。

もっと重症例、例えば網膜血管の成長が極端に悪い症例や、光凝固が不十分で血管活動性が非常に高い症例、網膜剥離が高度に進行した症例(図5E)では、本手術は効を奏さない。一方で、さほど進行せず軽微な瘢痕に止まる症例に誤って手術するのも厳に戒めるべきである。

さらに、この早期手術の導入によって治療適応が大きく変われば、懸念すべき社会的問題も多く生ずることが危惧される。これまでに未熟児網膜症では数多くの訴訟が起こされてきたが²²⁾、従来はII型/aggressive posterior ROPで網膜剥離に進行すれば、失明に至ってもやむを得ないとされていた。しかし、有用視力が得られる可能性があるとなれば、考え方はまったく変わる。多くの新生児集中治療室でII型/aggressive posterior ROPを起こす可能性がある超低出生/極低出生体重児が管理されているが²²⁾、一方で、ROP診療に関する教育がなかなか受けにくく、十分に対応できる眼科医が少ないことは大きな問題である。しかも、本早期手術は効果が非常に大きいにもかかわらず、多くの時間的制約があつて奏功するのは経過のごく短期間に過ぎず、少しでも遅れば予後が非常に悪くなるのが、最も懸念される点である。いずれにせよ、この時期の眼底検査と治療適応の判断、家族への説明には、小児・新生児科と眼科が連携して、細心の注意を払う必要がある。

おわりに

重症のII型/aggressive posterior ROPが網膜剥離に進行すれば、従来は失明に至ることを覚悟するしかなかった。しかし、早期硝子体手術で進行が抑えられ、良好な予後が得られることが明らかになった。重症未熟児網膜症の治療適応は大きく変わり、糖尿病網膜症と同じく、光凝固を十分に行っても功を奏さなければ、硝子体手術で治る時代になるとと思われる。このように治療適応が変わる一方で、重症網膜症がさらに増加することが危惧される状況では、小児・新生児科と眼科の連携はさらに重要になると考える。

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Treatments for Severe Type of Retinopathy of Prematurity

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Patients with severe type of retinopathy of prematurity (ROP) that often results in blindness, when progresses to retinal detachment, recently increase, because extremely-low-birth-weight infants are able to survive. When ROP progresses to stage 3, retinal photocoagulation is performed as an initial treatment. Scleral buckling or vitreous surgery may treat retinal detachment, but often fails to provide useful vision. Type II ROP designated by the Japanese Diagnostic and Therapeutic Criteria for ROP or aggressive posterior ROP by the International Classification of ROP rapidly progresses to a total retinal detachment within 1 to 2 weeks if left untreated. However, recent advance of early intervention with photocoagulation and vitreous surgery successfully treat retinal detachment in such severe forms of ROP.