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 h*tau* 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

h*tau* 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, immunochemical, 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 h*tau* 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-μm 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 h*tau* 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 samples were prepared from mitogen-stimulated splenocytes of transgenic rats. The biotin-16-dUTP-labelled *tau* cDNA clone in the pCXN2 vector[13] 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 h*tau* gene. Twenty-three out of the 45 rats had the h*tau* 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 h*tau* gene. On the other hand,

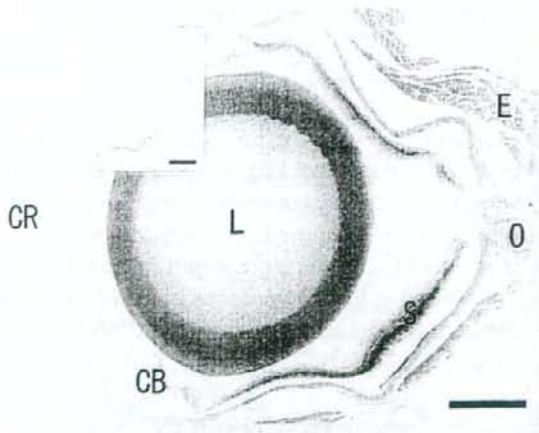
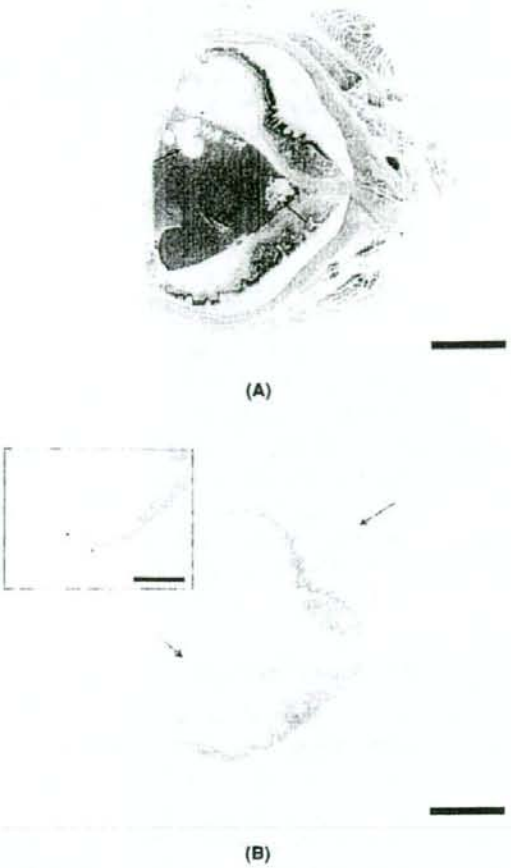


FIGURE 1 Ciliary body (CB), cornea (CR), extraocular muscle (E), lens (L), optic nerve (O), and sclera (S) from a rat not bearing the *tau* gene (H&E). Inset shows immunohistochemical stain, hematoxylin counterstain. Expression of *Tau* protein in the normal eye from a rat not bearing the *tau* gene.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

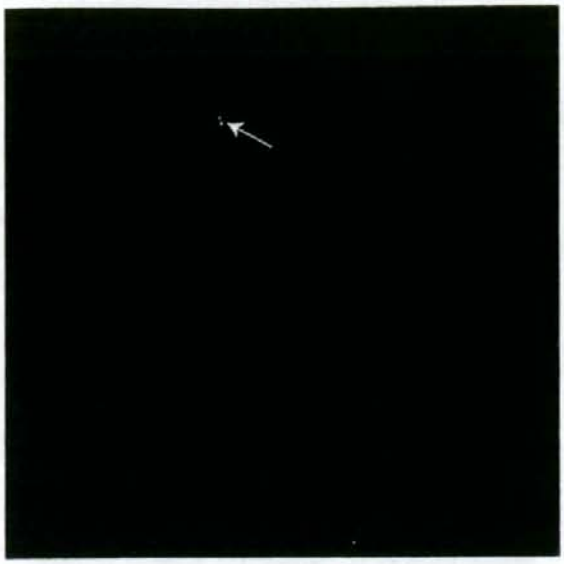


FIGURE 3 Chromosomal location of the human *tau* gene in a transgenic rat. The signal was visualized indirectly with FITC (arrow).

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

In this study, we obtained 23 transgenic rats carrying the h*tau* 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 h*tau* 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 h*tau* gene.

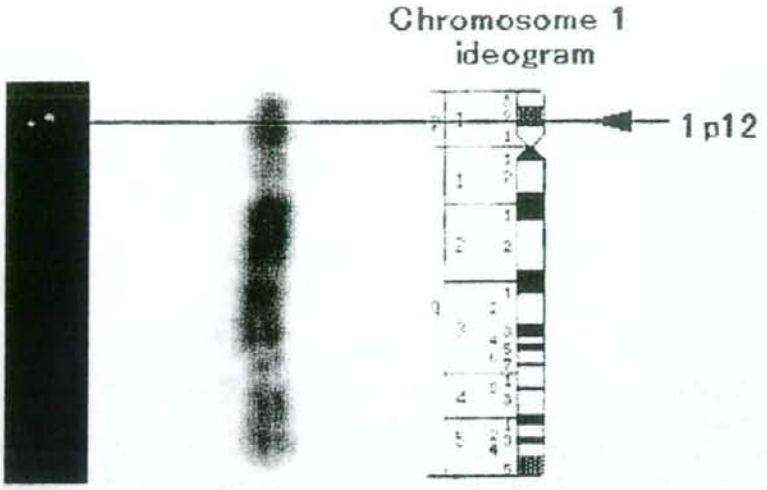


FIGURE 4 **Ideogram showing the cytogenetic location of *tau* in 1p12.**

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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東　　範行

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の占める比率は急に増加している（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．

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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[4)5)]．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[4)5)]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 neovasuclarization；図2B, C）．ここまでを活動期と呼ぶ．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

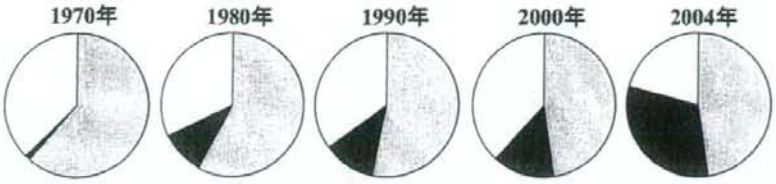

図1 小児の失明原因（盲学校統計[3] 3～5歳，6～12歳より作成）
灰色：先天異常，黒：未熟児網膜症．

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中途で停止し，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，aggressive 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，

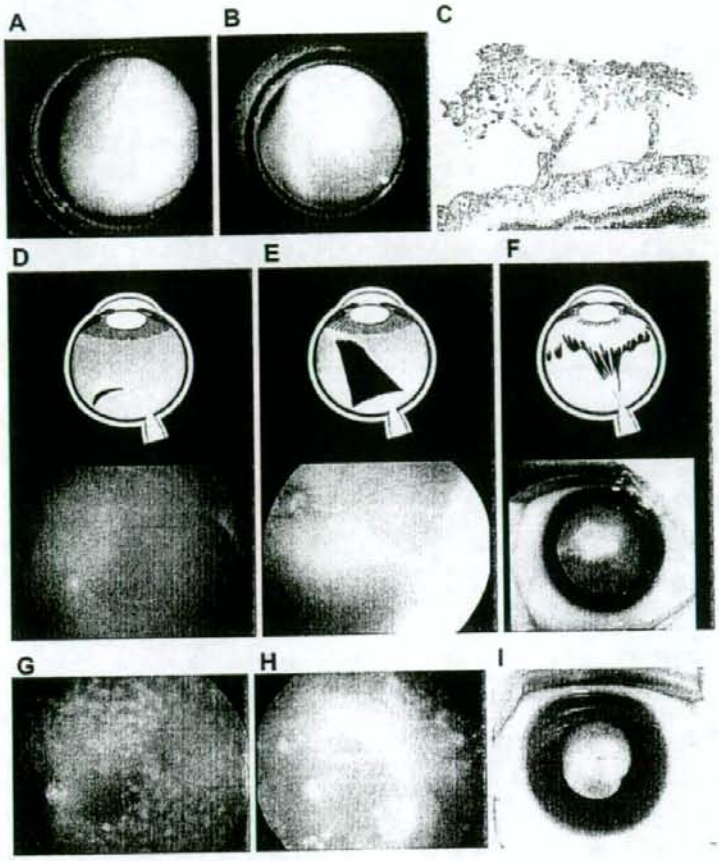

図2　未熟児網膜症の進行

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剝離（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剝離（厚生省分類4期，国際分類 stage 4B），F：網膜全剝離（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：網膜全剝離となり，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，無血管領域を広汎に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

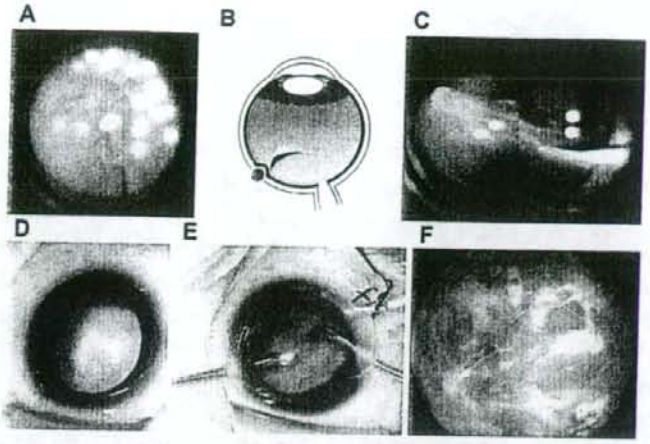

図3 未熟児網膜症の治療
A：光凝固，B，C：網膜部分剝離に対するバックリング治療（B：眼球シェーマ，C：眼底写真），D～F：網膜全剝離に対する硝子体手術（D：術前，E：術中，F：術後眼底所見で変性著明）．

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）[13]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）Study[14]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，部分的でないと効果がない．

（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は，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，網膜牽引や襞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

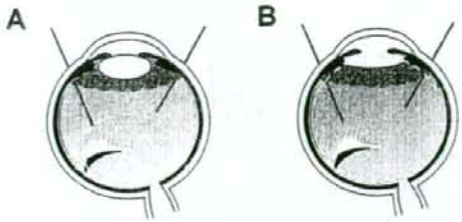

図4　水晶体温存あるいは除去した場合の硝子体手術
水晶体を温存した場合（A）より除去した場合（B）の方が，広い範囲（点線内）で手術操作ができる．

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[2)6)]．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[3)]．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剝離が生じ始めた早期に硝子体切除を行えば，網膜剝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剝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[4)]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，全例が高度の網膜剝離に進行した．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カ月待っ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眼で網膜剝離は全治癒した．既に網膜剝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．網膜が全部剝離してから（stage 5），増殖膜内の血管が枯れるのを待って行う従来の硝子体手術では，光か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[2)]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は網膜が全部剝がれていない部分剝離（厚生省分類4期，国際分類stage 4）であったが，網膜剝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，網膜剝離が黄斑に及ぶ国際分類stage 4Bでは網膜が復位しても，剝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

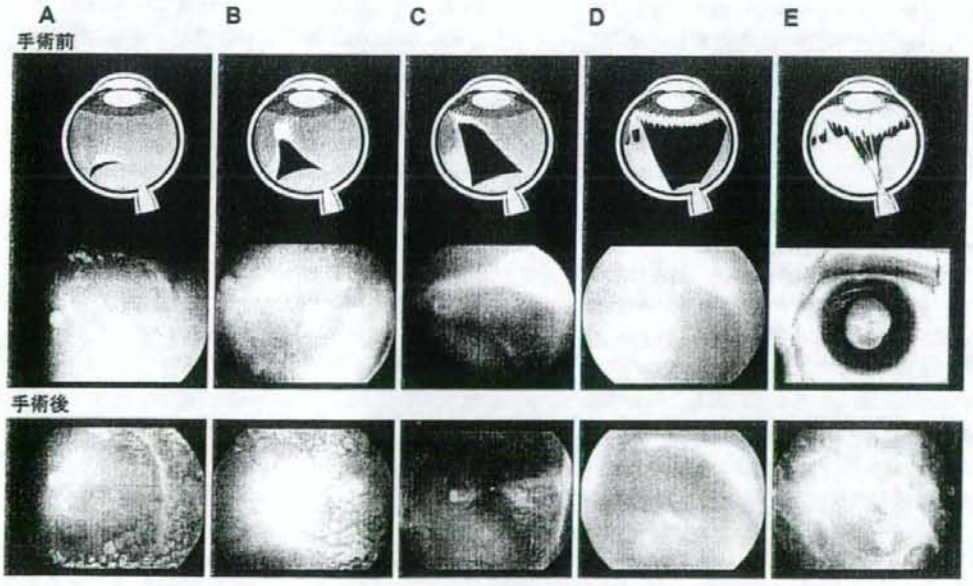

図5　II型/aggressive posterior ROPの進行と早期硝子体手術の結果
術前A：増殖組織の伸展と牽引網膜剝離の開始（国際分類stage 4A初期），B：網膜剝離は黄斑に及び始め（stage 4A後期〜stage 4B初期），線維組織は周辺部へ向う，C：Stage 4B，増殖線維組織の一部が硝子体基底部に接着，D：Stage 4B後期，線維組織が広汎に硝子体基底部に接着，E：網膜全剝離（stage 5）．早ければ1週間程でAからEへ進行する．術後，A，Bでは網膜は復位し，黄斑が形成されているが，Cでは一部網膜剝離を残して黄斑は形成されず，Dでは網膜剝離が治癒しない．Eは進行し過ぎており，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って手術するが，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，他眼が網膜剝離へ進んでも，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，早期手術を網膜剝離の発生初期（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．網膜剝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剝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，網膜剝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[12]，従来はII型/aggressive posterior ROPで網膜剝離に進行すれば，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[1,12]，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っ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が網膜剝離に進行すれば，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.

Discordance Between Subjective Perimetric Visual Fields and Objective Multifocal Visual Evoked Potential-Determined Visual Fields in Patients With Hemianopsia

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• PURPOSE: To investigate the concordance between subjectively and objectively acquired visual fields in patients with subjectively determined hemianopsia.
• DESIGN: Retrospective observational study.
• METHODS: Ten patients, six men and four women, ranging in age from 28 to 68 years, were studied. Goldmann or Humphrey perimeters were used to obtain the subjectively determined visual fields for up to 25 degrees of eccentricity, and the VERIS Scientific System (Electro-Diagnostic Imaging, San Francisco, California, USA) was used to record multifocal visual evoked potential [VEPs] (mfVEPs) to obtain the objective visual fields. Each of the 60 black-and-white segments of the checkerboard stimulus was alternated according to a binary m sequence. The first slices of the second-order kernels were extracted and analyzed.
• RESULTS: In five cases, the visual field loci where the mfVEPs were within normal limits corresponded to the scotomatous areas obtained by conventional perimetry. In these discordant cases, the lesions (e.g., arteriovenous malformation) were located in the occipital lobe. Two of these cases had a complete recovery of the subjective visual field. The lesions of the concordant cases were located outside the occipital lobe (e.g., pituitary adenoma). In these cases, no visual field improvement was seen. The temporal crescent syndrome was ruled out in patients with posterior lesions by computed tomography (CT) or magnetic resonance imaging (MRI) findings.
• CONCLUSIONS: In some patients with occipital lesions, the subjective and objective visual field results are discordant, and some of them will show a recovery of the visual field deficits. (Am J Ophthalmol 2007;143: 295–304. © 2007 by Elsevier Inc. All rights reserved.)

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VISUAL FIELDS OBTAINED BY THE GOLDMANN AND Humphrey perimeters have been the gold-standards for the evaluation of optic nerve diseases and pathologic changes in the visual pathways. These tests are used routinely, but, unfortunately, they are subjective tests. Several methods have been used to try to determine the visual fields objectively; for example, conventional flash and pattern visual-evoked potentials (VEPs),[1–5] vector VEPs,[6] pupillography,[7] scalp topography of VEPs,[8] positron emission tompgraphy,[9] multifocal VEPs (mfVEPs),[10–19] and functional magnetic resonance imaging (MRI).[20–22] However, none of these techniques is used routinely on patients.

The topographic map of the amplitudes of the mfVEPs has been reported to show good agreement or concordance with the results of conventional visual field tests if occipital bipolar electrodes are used.[15,16] Thus mfVEPs have been used on patients with glaucoma to evaluate the functional glaucomatous loss objectively.[19,23,24] In addition, the mfVEPs, summed within the four quadrants, have been used as an objective evaluator of the visual fields in patients with visual field loss.[16,17,19,23,24] However, we have found that the alterations of the topographic map of the mfVEPs are not always in good concordance with the subjectively determined visual fields in some cases with hemianopic field defects.

The purpose of this study was to determine whether the subjectively obtained visual fields and the objectively obtained visual fields were concordant in patients with hemianopsia. In addition, we examined whether the discordance of the subjective and objective visual fields was related to the location of the lesion giving rise to the hemianopsia.

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TABLE 1. Demographics and Summary of the Findings of mfVEP and Diagnosis of the Patients

Patient No	Age	Gender	Visual Field Loss			Diagnosis	mfVEPs (Concordance or Not)
1	51	F	Btemp. h.	◐	◑	Pituitary adenoma	Yes
2	49	M	Btemp. h.	◔	◔	Pituitary adenoma	Yes
3	38	F	Rt. homo. h.	◑	◑	Skull base meningioma	Yes
4	60	F	Lt. homo. h.	◐	◐	Brain meta (rt. parieto-occipital)	Yes
5	49	M	Lt. homo. h.	◐	◐	Craniopharyngioma	Yes
6	46	M	Rt. homo. h.	◑	◑	Meningioma (lt. occipital)	No
7	28	M	Lt. homo. h.	◐	◐	AVM postoperatively (rt. occipital)	No
8	68	M	Lt. homo. h.	◐	◐	Glioma (rt. occipital)	No
9	35	M	Rt. homo. h.	◶	◶	Cavernous hemangioma (lt. occipital)	No
10	30	F	Lt. homo. h.	◴	◴	Subarachnoid hemorrhage postoperatively (rt. occipital)	No

mfVEP = multifocal visual evoked potentials; M = male; F = female; btemp. h = bitemporal hemianopsia; rt. homo. h = right homonymous hemianopsia; lt. = left; AVM = arteriovenous malformation.

Concordance or not: "yes" means that no mfVEP response was observed at the area of visual field deficit. "no" means that mfVEP response was observed at the area of visual field deficit.

METHODS

• SUBJECTS: All of the research procedures conformed to the guidelines of the Declaration of Helsinki, and an informed consent was obtained from all subjects after an explanation of the purpose and the procedures to be used in the experiments. The mfVEPs were recorded from 10 consecutive patients who had hemianopsia, either a complete hemianopsia or quadrantanopsia, which was documented by conventional perimetry. The examinations were performed between January 1999 and February 2004 at the Keio University Hospital. The patients consisted of six men and four women whose ages ranged from 28 to 68 years with a mean of 45.4 ± 12.8 years (± standard deviation [SD]; Table 1). Three of the patients had a right and five patients had a left homonymous hemianopsia. The two remaining patients had bitemporal hemianopsia. All patients had evidence of damage to the visual pathway by computed tomography (CT) or magnetic resonance imaging (MRI), or both, which could accounted for the visual field deficits. The causes of the visual impairment were brain tumors, cerebral infarctions, or postneurosurgery for either arteriovenous malformation or subarachnoid hemorrhage. The temporal crescent syndrome was ruled out in patients with posterior lesions by CT or MRI findings.

All patients had a routine ophthalmologic examination including slit-lamp biomicroscopy, ophthalmoscopy, and attenuation tonometry. All patients had a corrected visual acuity of 20/20 or better and a refractive error of less than −5.25 diopters in both eyes. There was no history of ophthalmologic abnormalities such as glaucoma or diabetic retinopathy that could affect the visual function especially the visual fields. The perimetric examinations and mfVEPs recordings were carried out during the same period. Normative data were collected from 10 healthy eyes except for refractive error, although the age did not match the patients (age range, 27 to 65; 35.6 ± 11.6).

Because the SDs of the amplitudes of the multifocal electroretinograms (mfERGs) were relatively large (see Supplemental Table 1 available at AJO.com) in normal subjects, the ratio of the amplitudes or implicit times from horizontally adjacent quadrants was calculated. For example, the ratio of the amplitude of the summed response from superior nasal quadrant was compared with that from the superior temporal quadrant, the SN/ST ratio. The ratios of the amplitudes of the mfVEPs in the inferior nasal to inferior temporal ratio (IN/IT) were calculated in the same way. The SN/ST and IN/IT ratios of the implicit times were also calculated for R1 and R2. It was reported,[16,24,25] and confirmed here, that the general shape of the summed responses of the temporal and nasal visual fields are very similar, whereas those of the superior and inferior visual fields differed in phase and amplitude in normal subjects.

• STIMULUS FOR MFVEPS: The stimulus was similar to that used in Klistner protocol, with a dartboard pattern consisting of 61 sectors that was created on a computer monitor (17 inch, high-resolution display, stimulation rate 75 Hz; Nanao, Ishikawa, Japan).[15] Each check was either white or black with a 92% contrast (white = 160 cd/m^2; black = 7 cd/m^2), and the luminance alternated pseudorandomly at 75 frames per second. The m binary sequence was repeated two times.[16]

The individual kernels of the responses were determined by cross-correlating the digitized output signal with the binary input sequences using a fast Walsh transform. As shown in the Supplemental Figures 1 and 2 (available at AJO.com), the size of each segment was cortically scaled with eccentricity to stimulate approximately equal areas of cortical (striate) surface.[15,18,26–29] The overall stimulus subtended approximately 25 degrees at the eye.

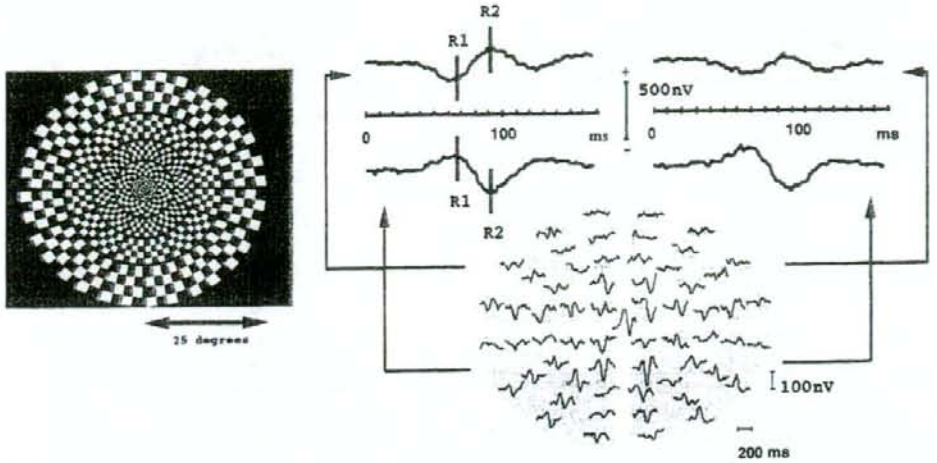

FIGURE 1. Stimulus for multifocal visual-evoked potentials. (Left) Stimulus was a dartboard pattern consisting of 61 sectors. (Right) Individual second-order kernels of the multifocal visual evoked potentials (mfVEPs) are plotted retinotopically in the lower half. The sums of the responses in each of the four quadrants are plotted in the sectors in the upper half except for the response from the very central sector.[16]

TABLE 2. The Ratio of the mfVEPs Parameters in All the Patients

Case	Conventional Left Eye	Visual Field Right Eye	Amplitude				R1 Latency				R2 Latency			
			Left Eye		Right Eye		Left Eye		Right Eye		Left Eye		Right Eye	
			SN/ST	IN/IT	SN/ST	IN/IT	SN/ST	IN/IT	SN/ST	IN/IT	SN/ST	IN/IT	SN/ST	IN/IT
			◰/◱	◳/◲	◰/◱	◳/◲	◰/◱	◳/◲	◰/◱	◳/◲	◰/◱	◳/◲	◰/◱	◳/◲
No.1	◐	◑	—	—	—	—	—	—	—	—	—	—	—	—
No.2	◔	◔	—	1.829	—	1.652	—	0.989	—	0.956	—	1.074	—	0.945
No.3	◑	◑	—	—	—	—	—	—	—	—	—	—	—	—
No.4	◐	◐	—	—	—	—	—	—	—	—	—	—	—	—
No.5	◐	◐	—	—	—	—	—	—	—	—	—	—	—	—
No.6	◑	◑	0.618	1.792	1.630	0.485	1.244	1.000	0.939	1.449 H	0.955	0.945	0.875 L	1.479 H
No.7	◐	◐	1.750	0.821	0.604	1.400	1.000	0.868 L	1.211	1.024	1.171 H	0.914	1.325 H	1.268 H
No.8	◐	◐	1.130	0.612	0.374	1.732	0.977	0.878 L	0.951	1.084	1.038	0.863 L	1.000	1.135 H
No.9	◔	◔	0.731	1.771	1.226	0.868	1.057	1.325 H	1.524 H	1.439 H	1.044	1.549 H	1.171 H	1.009
No.10	◴	◴	0.980	1.786	0.803	0.462	0.988	0.976	1.000	1.000	0.975	1.102	0.911 L	1.027

P1 amplitude = amplitude of the first positive component around 100 ms after stimulation; R1 latency = time interval between the stimulation and first negative component around 75 ms after stimulation; R2 latency = time interval between the stimulation and first positive component around 100 ms after stimulation; SN = superior nasal; ST = supealtemporal; IN = inferiornasal; IT = inferiortemporal.

The ratio of each mfVEPs parameters in the normal control subjects are shown in the Supplemental Table.

The mean ± 2* SD were defined as cut-off values. When the patient's ratio of any mfVEPs parameter was out of this range, it is indicated with H or L in this Table. H = the value is higher than the cut-off value; L = the value is lower than the cut-off value; — = the ratio could not be calculated because the response from the quadrant of conventional visual field defect was noise level.

To rule out cross-talk, half of the dartboard stimulus field was covered and the mfVEPs were recorded as usual. The mfVEPs usually elicited from the covered loci were completely flat.[30]

• RECORDING MFVEPS: Patients were preadapted to standard room lighting, and all recordings were performed under dim room lights. The pupils were fully dilated with 0.5% tropicamide and 0.5% phenylephrine hydrochloride. A small red fixation light was present in the center of the stimulus display, and the subjects were instructed to fixate on the red light and to try not to blink. The subjects wore their best refractive correction, and all recordings were monocular. One of the recording electrodes was placed 2.0 cm inferior to

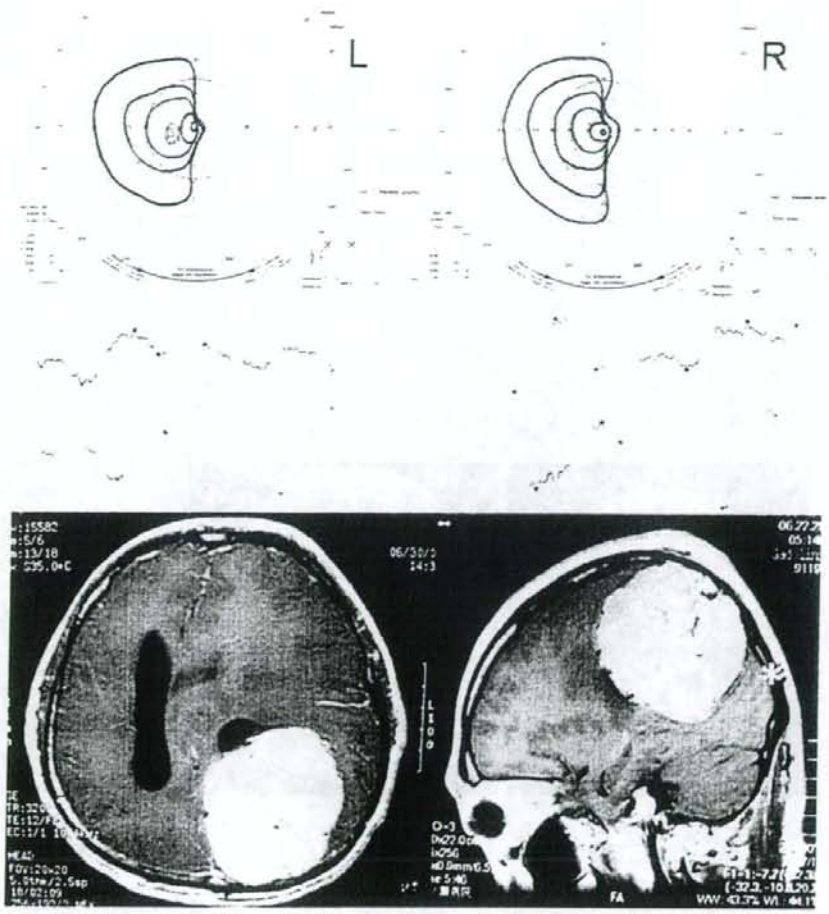

FIGURE 2. Findings in a 46-year-old man (Case 6) with right homonymous hemianopsia due to a meningioma extending from the left parietal lobe to the occipital lobe. (Top) Goldmann perimetric fields showing a left homonymous hemianopsia. (Middle) The multifocal visual evoked potentials (mfVEPs) are presented so that the average waveforms are seen in each of the quadrants where each waveform originates. The mfVEPs are not extinguished in the temporal fields of the right eye and the nasal fields of the left eye. (Bottom) An axial plane (left) and sagittal plane (right) of the magnetic resonance imaging (MRI) scan show a meningioma extending from the left parietal lobe to occipital lobe. Most of the lesion was primarily outside of primary visual cortex and in a more distal area.

(negative electrode) and the other 2.0 cm superior to (positive electrode) the inion.[15,16,32] The ground electrode was placed on the earlobe.

The mfVEPs were recorded with the VERIS II system (Tomey Co, Nagoya, Japan). Signals were amplified 50,000 times and bandpass filtered from 0.5 to 100 Hz. The sampling rate was 75 Hz, and the m-15 binary stimulation sequence was divided into 32 slightly overlapping segments. Each run was divided into eight equal segments with a total recording time of about seven minutes.

• ANALYSES: All of the mfERG data were analyzed using VERIS Science 3.01 software (Tomey Co, Nagoya, Japan).[16] The first slice of the second-order kernel was extracted and the 60 responses (omitting the central response) were divided into four quadrants and summed. Each mfVEP consisted of the R1 and R2 components that probably correspond to the N70 and P100 components of conventional VEPs (Figure 1). The implicit times and amplitudes (R2 peak − R1 peak) of R1 and R2 were calculated.

If the response of the mfVEPs was reduced in the area where an absolute scotoma was detected by conventional visual field testing, this case was considered to have a concordance between the subjective and objective visual fields. To judge whether the amplitude from the quadrant was normal, we used a criterion of <2 SDs from the same region in normal subjects (see Supplemental Table 2 available at AJO.com).

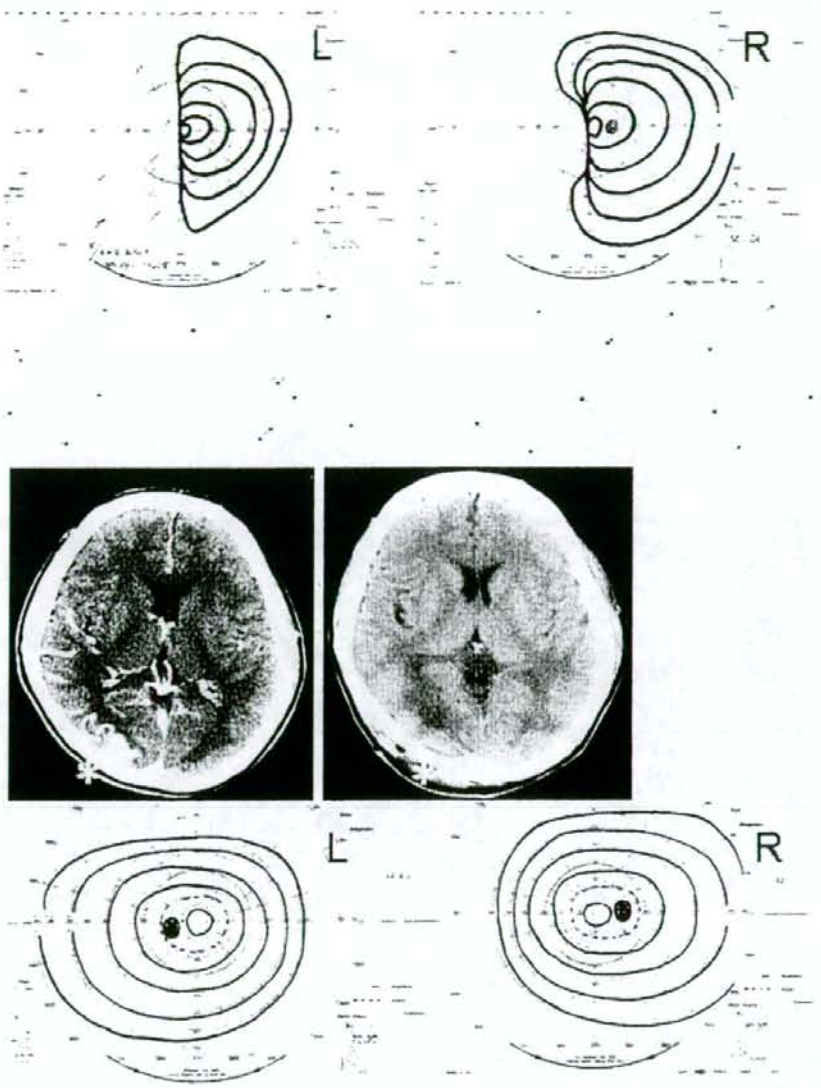

FIGURE 3. Findings in a 28-year-old man (Case 7) who underwent neurosurgery for an arteriovenous malformation in the right occipital lobe. (Top) Goldmann visual fields showing a left homonymous hemianopsia. (Second row) The multifocal visual evoked potentials (mfVEPs) are presented so that the average waveforms are seen in each of the quadrants where in the visual field each waveform originates. The mfVEPs were not extinguished in the temporal fields of the left eye and the nasal fields of the right eye. (Third row, left) Computed tomographic (CT) image showing an arteriovenous malformation in the right occipital lobe. (Third row, right) CT image showing a low-density area indicating postoperative edema in the right occipital region. (Bottom) Goldmann perimetric fields showing complete recovery of visual fields three months later.

RESULTS

THE SHAPES OF THE SUMMED MFVEPS IN THE UPPER visual field were approximately a mirror image of those in the lower field in normal subjects. This was also true for the mfVEPs elicited from the nonaffected quadrants of the patients.[16] The ratio of the mfVEPs parameters in all the patients are shown in Table 1. In some cases, the ratio could not be calculated because the mfVEP was at noise level.

A summary of our findings in the 10 cases is presented in Table 2. Five of 10 patients showed good concordance between the subjective and the objective visual fields. Thus the amplitudes of the mfVEPs were within