Department of Ophthalmology

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General Summary

The main research interest of our department is the pathophysiology of the visual processing system. The following topics are the subjects of basic and clinical studies: cataract, neuro-ophthalmology, ocular oncology and histopathology, biochemistry, functional magnetic resonance imaging (fMRI), glaucoma, electrophysiology, diabetes, vitreoretinal diseases, age-related macular degeneration, uveitis, color vision, and the cornea.

Research Activities

Cataract

The widespread use of ultrasound technology in cataract surgery and the introduction of foldable intraocular lenses (IOLs) have allowed cataract surgery and IOL implantation through incisions of 2.4 to 3.0 mm. Surgeons are now experimenting with even smaller incisions. We began to use a standard phacoemulsification and aspiration (PEA) device to perform bimanual PEA with a sleeveless phaco tip through incisions 1.2 to 1.4 mm wide. We used an irrigating hook through a side port to infuse the anterior chamber. After the lens was extracted, we were able to implant safely hydrophobic acrylic single-piece IOLs through a 1.8-mm incision. We can choose various premium IOLs, for example, multifocal IOLs, toric IOLs, and yellow IOLs. We implant these new IOLs and evaluate visual functions with them.

Neuro-ophthalmology

1. Neuromyelitis optica (NMO) is characterized by optic neuritis (ON) and acute myelitis. In 2004, an antibody specific for NMO was discovered. This antigen turned out to be aquaporin-4 (AQP4), a water channel predominantly expressed within the central nervous system. We described a patient with NMO in whom anti-AQP4 antibodies were present and myelitis developed 25 years after the onset of ON. This case fulfilled all 3 defining criteria for NMO. The present case also showed the longest documented period to date between the onset of ON and the subsequent development of myelitis. The length of the interval between these events may be irrelevant to the diagnostic criteria for NMO. When a patient who has ON and anti-AQP4 antibodies exhibits numbness and paralysis over the long term, ophthalmologists and neuro-ophthalmologists should recog-

nize the possibility of myelitis, even when the patient has no history of myelitis.
2. We started a randomized, parallel-group, multicenter clinical trial of treatment with topical unoprostone for acute nonarteritic anterior ischemic optic neuropathy. Criteria for eligibility included an age of 50 years or older, duration of symptoms less than 2 weeks, visual loss or visual field defects consistent with optic neuropathy, absence of pain, a relative afferent pupillary defect, and optic disc edema. The primary endpoint was the mean deviation on perimetry with the Humphrey field analyzer at 12 months.
3. In patients who had undergone temporal lobectomy for epilepsy, we assessed the correlation between degeneration along Meyer's loop and postoperative visual field defects by means of diffusion tensor imaging, which can be used to evaluate axonal integrity in the white matter. The probabilistic fiber tracking method demonstrated axonal disruption over the temporal horn of the lateral ventricle. Diffusion tensor imaging would be a useful method for delineating Meyer's loop.
4. We reported two cases of recurrent ON with panhypopituitarism caused by hypophysitis, anti-aquaporin 4 antibody-positive familial neuromyelitis optica in a mother and daughter, and an atypical case of papilledema in a patient with a jugular foramen tumor. These reports described etiologic relationships and were highly suggestive.

Ocular oncology and histopathology
1. Mixed tumors originating from both tubular epithelial cells and myoepithelial cells usually develop in the major lacrimal gland of the ocular adnexa. They rarely develop in the eyelid. Mixed tumors arising from Moll's glands are extremely rare. We reported a rare mixed tumor of Moll's gland origin in the margin of the lower eyelid. Histopathological examination showed a well-circumscribed nodular lesion in the dermis containing fibrous, hyaline, and myxoid elements. The tumor showed cords and nests of proliferating tubular epithelial cells and myoepithelial cells. Spindle-shaped myoepithelial cells were observed. The tumor was diagnosed as a mixed tumor. On immunohistochemical analysis the tumor cells were positive for S-100 protein, and proliferative lesions of tubular epithelial cell origin were strongly positive for gross cystic disease fluid protein- 15 (GCDFP- 15). Mixed tumors of the eyelid may arise from the accessory lacrimal glands of Krause and Wolfring, eccrine sweat glands, or apocrine (Moll's) sweat glands. This tumor was considered to be of Moll's gland origin because of its location, the features of the surrounding tissue, its composition of tubular epithelial cells, and its positive staining for GCDFP-15.
2. We reported rare cases of malignant solitary fibrous tumors of the eyelid in a patient with myotonic dystrophy, giant subretinal hematoma improved by vitreous hemorrhage with presumed vasoproliferative retinal tumor, and spontaneous regression of hemangioma in the optic disc. These reports described the etiologic relationships and were highly suggestive.

Glaucoma
1. We evaluated the validity of the visual field index slope (VFIS) compared with the pattern standard deviation slope (PSDS) for assessing glaucomatous progression. In a large percentage of eyes examined, the VFIS and PSDS did not agree, and the results sug-

gest that VFIS may be more affected by central weighting of the index than is traditional PSDS.

2. We evaluated the effect of intraocular pressure (IOP) reduction and the safety of 0.0015% tafluprost ophthalmic solution in patients with normal-tension glaucoma with an IOP of 16 mm Hg or less. Tafluprost significantly reduced IOP without apparent safety concerns in these patients.

3. We compared the change in wavefront aberrations after simultaneous cataract surgery and trabeculectomy through the same wound under the scleral flap and through a separately created corneal incision. Wavefront aberration analysis was an effective method for evaluating ocular function after the operation, and the results suggest that differences in the incisions for combined surgery affect postoperative aberrations.

Functional Neuroimaging

Patients with glaucoma were examined to confirm several structural changes in the visual pathway by means voxel-based morphometry. The chiasm was evaluated with 3-dimensional T1-weighted images, and the structure of the optic radiation was evaluated with diffusion tensor images. Both types of images were acquired with a clinical MR scanner. Fifteen patients with glaucoma and 15 age-matched healthy volunteers were recruited. A significant decrease in signal strength was observed with voxel-based morphometry in areas corresponding to the optic chiasm and the optic radiation in patients with glaucoma. Thus, these results suggest that structural changes to the visual pathway occur in intracranial structures as well as in the eyes of patients with glaucoma.

Developmental functional abnormality

Binocular summation on the visual cortex was explored with fMRI in patients with postoperative strabismus and in healthy volunteers. Binocular summation was demonstrated to be less important for patients with strabismus at the foveal projection area and at a peripheral 2-degree projection area. This result suggests that abnormal cortical visual processing is present as cortical suppression of the prefoveal projection area in patients with strabismus.

Visual neuropsychology

1. Review articles on visual psychology and neuro-ophthalmology

We wrote review articles that summarized contemporary topics about visual information processing in the primary visual cortex (V1), plasticity in the visual cortex, photophobia, visual experience during dreaming, and cortical visual prosthesis.

2. Follow-up report for plasticity in adult human V1

We extended the measurement to subject with retinitis pigmentosa. Our results were same as in patients with macular degeneration; there is no large-scale remapping in the adult human V1. Our results support vision-restoring therapies that rely on the stability of the human V1.

3. Three papers published in international journals

Three of our studies previously reported here have been published: objective perimetry using fMRI (*Experimental Neurology*; impact factor=3.9); 2 temporal channels in human

V1 identified with fMRI (*NeuroImage*; impact factor=5.7); and evaluation of subjective color sense after cataract surgery from the super early state (15 minutes after removing an eye patch) (*Journal of the Optical Society of America*, impact factor=1.9).

Vitreoretinal diseases

We have used a 23-gauge and 25-gauge transconjunctival vitrectomy system for treating macular holes, epiretinal membrane, macular edema, and rhegmatogenous retinal detachment. The 25- and 23-gauge sutureless vitrectomy techniques decrease surgical trauma and improve patients' postoperative comfort. The 25- and 23-gauge instrumentation is effective for a variety of vitreoretinal surgical indications. Although the infusion and aspiration rates of the 25- and 23-gauge instruments are lower than those of the 20-gauge high-speed vitrectomy system, the use of 25- and 23-gauge transconjunctival vitrectomy systems may effectively reduce operative times for selected cases that do not require the full capability of conventional vitrectomy.

To evaluate the clinical efficacy of 7-mm IOLs (Eternity IOL, Santen Pharmaceutical Co., Ltd., Osaka) for combined pars plana vitrectomy, phacoemulsification, and IOL implantation, we examined the visibility of the retina during vitrectomy and measured the depth of the anterior chamber preoperatively and postoperatively with a tomographic scanner (Pentacam, Oculus Optikgeräte GmbH, Wetzlar, Germany).

We are planning to evaluate the changes in regular and irregular corneal astigmatism after 25-gauge and 23-gauge transconjunctival sutureless vitrectomy.

Electrophysiology

We are recording electroretinograms (ERGs) to evaluate whether functional disorders are present in retinal cell levels in hereditary retinopathy, retinal dystrophy, and macular disease. The ERG waveforms compound the responses from various retinal cells, such as ganglion, amacrine, bipolar, and photoreceptor cells, which are recorded as a single wave pattern. In addition, we perform examinations with 4 types of recording system: the Ganzfeld stimulator, multifocal stimulation, color stimulation, and focal macular stimulation. In Ganzfeld stimulation, we record separate responses from cone and rod cells of the retina according to an international protocol. The multifocal stimulator, which reflects cone function, can record the responses of each separate element in 61 areas of the central 30 degrees of the posterior pole. Furthermore, the results (objective examination) using the multifocal stimulator can be compared with those of the visual field tests (subjective examination). The color ERG records each response to separate long-, middle-, and short-wavelength cones. We have recently obtained a focal macular stimulator. This stimulator can record the retinal function of THE central 5, 10, and 15 degrees and can effectively search for unidentified conditions, such as occult macular dystrophy, causing visual disturbance.

In the future, we will evaluate the waveforms recorded from these ERG stimulators analyze them with personal-computer programs. Moreover, as we extract single waveforms from retinal cells of a specific type, we will be able to investigate retinal disorders at the cellular level.

Diabetic retinopathy section

We perform subtenon injections of triamcinolone acetonide for outpatients with diabetic macular edema. After injection, a decrease in macular retinal thickness can be observed with optical coherence tomography, but in some cases macular edema recurs 3 months after injection. For cases in which triamcinolone acetonide injection has no effect, we perform vitrectomy. Transconjunctival microincision vitrectomy is performed with a 23-gauge trocar system. The 23-gauge system is used to make a scleral incision that does not need to be sutured. The advantages of such small incisions include decreased postoperative inflammation and decreased surgical stress.

The vulnerability of retinal ganglion cells in diabetes mellitus has been observed in diabetic animal models and in patients. We are evaluating retinal function by recording ERGs in patients with diabetes in whom retinopathy is absent on ophthalmoscopy. We measured photopic negative responses (PhNRs) among wave patterns obtained in cone ERGs and examined the correlation between PhNRs and the duration of diabetes. We are measuring the thickness of the nerve fiber layer with optical coherence tomography and are investigating the correlation of nerve fiber layer thickness with PhNR amplitude and implicit time.

Uveitis

1. A novel therapy with a chimeric antibody against tumor necrois factor alpha for Behçet disease

Intravenous infliximab significantly decreased the frequency of ocular attacks and improved visual acuity. In addition, we believe that intraocular surgery can be performed effectively and safely to improve vision in patients receiving infliximab therapy for Behçet disease.

2. Cyclophosphamide pulse therapy for antineutrophil cytoplasmic antibody-associated scleritis

Antineutrophil cytoplasmic antibody (ANCA)-associated active scleritis tends to have more severe inflammation and requires more aggressive therapy. We reported a case of necrotizing scleritis positive for both cytoplasmic pattern ANCA and perinuclear staining pattern ANCA without underlying systemic vasculitis which was successfully treated with intravenous pulse cyclophosphamide therapy.

3. Cyclophosphamide pulse therapy for severe systemic lupus erythematosus retinopathy.

Any form of systemic lupus erythematosus retinopathy is more likely to be aggressive. We reported a case of severe systemic lupus erythematosus retinopathy that was successfully treated with intravenous pulse cyclophosphamide therapy.

Macular degeneration

1. Photodynamic therapy combined with intravitreal ranibizumab for neovascular age-related macular degeneration in Japanese patients.

We examined 3-month results of photodynamic therapy (PDT) with verteporfin combined with intravitreal ranibizumab for neovascular age-related macular degeneration (AMD). After 3 months PDT combined with intravitreal ranibizumab appeared to be

effective for Japanese patients with neovascular AMD.

2. Single-session PDT combined with intravitreal bevacizumab and subtenon triamcinolone acetonide for polypoidal choroidal vasculopathy

We evaluated the efficacy of triple therapy consisting of a single session of PDT, intravitreal bevacizumab, and subtenon triamcinolone acetonide as the initial therapy for polypoidal choroidal vasculopathy (PCV). The present study showed that initial therapy consisting of a single session of PDT, intravitreal bevacizumab, and subtenon triamcinolone acetonide improves vision and reduces central macular thickness in PCV.

3. We reported a case delayed radiation maculopathy and papillopathy treated with intravitreal bevacizumab after irradiation for maxillary sinus cancer.

4. Cataract surgery and typical AMD

We compared background factors of the 2 predominant subtypes of exudative AMD in the Japanese population: typical AMD and PCV. A history of cataract surgery and a history of central serous chorioretinopathy are more frequent in typical AMD and in PCV, respectively.

Biochemistry

1. The peroxisome proliferator-activated receptor-α agonist fenofibrate has been shown to have anti-inflammatory activity and to suppress the development of experimental autoimmune encephalomyelitis. We investigated the effects of fenofibrate in experimental autoimmune uveoretinitis (EAU). The present results suggest that fenofibrate modulates the development of EAU and suppresses intraocular inflammation by decreasing the production of inflammatory cytokines.

2. Inhibition of extracellular signal-regulated kinase (ERK)/mitogen-activated protein kinase suppresses interleukin (IL)-23- and IL-1-driven IL-17 production and attenuates autoimmune disease. We investigated the effects of an ERK inhibitor (PD98059 or U0126) on EAU. The ERK inhibitor exhibited significant anti-inflammatory and immunosuppressive effects in EAU. The ERK inhibitor is a promising therapeutic modality for autoimmune uveitis.

Color vision defects and genetic analysis of retinal diseases

1. We performed genetic testing of a woman with X-linked red-green color vision deficiency diagnosed with deuteranomalous trichromacy. A 22-year-old woman (proband) and her parents were included in this study. A red-green color vision defect was diagnosed with a Nagel type I anomaloscope. Whether the color vision defects were of a mild or severe form was determined with the Farnsworth Panel D-15 test. Genotypes of L and M visual pigment genes were determined with the polymerase chain reaction. The difference in peak absorbance between the first 2 visual pigment genes was calculated. The proband and her father were found to have deuteranomalous trichromacy (mild form). Her mother was an obligate carrier of deuteranomaly because she had normal color vision. Molecular genetic analysis revealed that the proband had 2 distinct M-L hybrid genes. The first 2 expressed pigments from each X-chromosome gene array which differed in peak absorbance by 4 nm and 8 nm, respectively. Our results suggest that the genotype of a female proband with deuteranomaly can be determined when both

genetic and color vision testing are performed in family members.
2. We performed clinical and molecular genetic analysis of various inherited retinal diseases, such as retinitis pigmentosa and macular and cone dystrophies. We identified causative mutations in these diseases. To clarify disease haplotypes, haplotype analysis with mutations was compared between family members and controls.
3. We investigated the involvement of various genetic factors in Japanese patients with AMD, which is a common cause of blindness in elderly persons in industrialized countries. More than 500,5688 single nucleotide polymorphisms of the whole genome were genotyped with Affymetrix Human Mapping Arrays (Affymetrix, Santa Clara, CA, USA) and the TaqMan assay (Applied Biosystems, Inc., Carlsbad, CA, USA). We are now analyzing candidate single nucleotide polymorphisms involved in Japanese patients with AMD.

Cornea

The cornea group at The Jikei University selects the most-appropriate corneal surgery by discussing the various options with each patient. Automated lamellar therapeutic keratectomy, in which a microkeratome is used to make a lamellar flap, was performed in several cases of corneal opacity. We found that automated lamellar therapeutic keratectomy enables earlier suture removal and induces less astigmatism than does conventional lamellar keratoplasty.
We studied the clinical outcomes of secondary implantation of iris-clip IOLs for aphakic eyes 5 years postoperatively. Clinically significant complications were not found with specular microscopy or laser flaremetry.

Publications

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