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 device to perform bimanual phacoemulsification and aspiration with a sleeveless phaco tip through an incision 1.2 to 1.4 mm wide. We used an irrigating hook through a side port to infuse the anterior chamber. After the lens had been extracted, we were able to safely implant hydrophobic acrylic single-piece IOLs through a 1.8-mm incision. We are able to choose various premium IOLs, for example, multifocal IOLs, toric IOL, and yellow IOLs. We implant these new IOLs and evaluate subsequent visual function.

Neuro-ophthalmology

1. Cases of anti-aquaporin (AQP)-4 antibody-positive familial neuromyelitis optica (NMO) in mothers and daughters are described. The demographic, clinical, neuroimaging findings and the anti-AQP-4 antibody status were investigated in 4 patients from 2 Asian families with anti-AQP-4 antibody-positive NMO. NMO was diagnosed with the latest diagnostic criteria in both mothers and daughters. All patients were anti-AQP-4 antibody-positive. Disease onset occurred at different ages, even within the same family. These cases will enhance our understanding of the genetic contribution to NMO. Our findings suggest that familial history must be carefully examined in patients with NMO.
2. We presented the results of research on OPA1 and OPA3 gene mutations in 5 families with autosomal dominant optic atrophy, the estimation of Meyers' loop with diffusion

tensor imaging in a patient who had undergone temporal lobectomy, the imaging of the optic radiation with 3-T MRI in patients and healthy control subjects, and the clinical features and evaluation with 3-dimensional true fast imaging with steady-state precession and 3-dimensional time-of-flight MR angiography in patients with superior oblique myokymia.

1) Clinical features were reviewed in a textbook for residents of ophthalmology on trauma of the optic nerve, optic nerve sheath meningioma, sphenoid meningioma, and the visual sensory system in aging.

2) We lectured at a symposium on medical treatments for neuro-ophthalmic disorders.

3) We reported cases of atypical Leber's hereditary optic neuropathy associated with systemic vasculitis and lymphadenopathy, Leber's hereditary optic neuropathy preceded by bilateral idiopathic optic neuritis, unilateral papilledema with normal cerebrospinal fluid pressure, a limited form of NMO with a lesion of the trochlear nerve nucleus, and papilledema in a child. These reports described the etiologic relationship and were highly suggestive of pathogenesis.

Ocular oncology and histopathology

1. Orbital tumors metastatic from prostate carcinoma are common in Western countries but have a frequency of only 3.1% in Japan. Radiological findings and clinical course in a case of orbital metastasis from prostate carcinoma showing deterioration after improvement of hormonal therapy was reported. Malignant lymphomas are important in ocular oncology. However, natural killer (NK)/T-cell lymphomas constitute an extremely small fraction of ocular adnexal lymphomas. We reported 2 cases of NK/T-cell lymphoma in the ocular adnexa. Both cases had an aggressive clinical course, even with radiation and chemotherapy, and had a poor outcomes with multiple recurrences. The clinical course of NK/T-cell lymphomas in the ocular adnexa differs from that of mucosa-associated lymphoid tissue lymphomas. These cases provide insight about the clinical and pathological varieties of ocular adnexal lymphomas, and each subtype of malignant lymphoma requires prompt treatment.
2. The clinical and pathologic features of retinal hemangioma, tumors of the retinal pigment epithelium, retinal hamartoma, and tumors of the optic nerve were reviewed in a textbook for residents of ophthalmology.
3. We lectured at a symposium on the status and problem in surveys of ocular tumors and the significance of multicenter studies.

Glaucoma

1. The purpose of the treatment of glaucoma is to maintain visual function, and the lower intraocular pressure. We have used eyedrops as a medical treatment and usually pursue an operative treatment only when glaucoma is refractory to eyedrops. On the other hand, surgery for glaucoma changes the shape of the cornea, exacerbates astigmatism, and decreases visual acuity. Astigmatism can be divided into cases that can and cannot be corrected with lenses. Therefore, it is most important to examine what type of astigmatism is increasing. Recently, a device for analyzing the shape of the cornea was developed and has made possible detailed measurement of the astigmatic quality. We

are performing examinations with Orbscan (Bausch & Lomb Surgical, Rochester, NY, USA) and the OPD Scan corneal analyzer (Nidek Co., Ltd., Gamagori, Japan).

2. Because eyedrops are needed for the long-term treatment of glaucoma, patient compliance is important. For drug therapy, β-adrenergic receptor antagonist eyedrops have been used. Twice-daily administration was necessary, but several kinds of eyedrops that can decrease intraocular pressure (IOP) for 24 hours with once-daily administration have recently become available. However, eye stimulation and foggy vision are a problem, because the eyedrops are a gel. However, when alginic acid is used as an agent, there are fewer side effects (stimulation and foggy vision); the same is true for long-acting carteolol hydrochloride eyedrops (Mikelan LA, Otsuka Pharmaceutical Co., Ltd., Tokyo). Therefore, we examined the effect of a change from twice-daily carteolol hydrochloride eyedrops to once-daily long-acting carteolol hydrochloride eyedrops on decreases in IOP and ease of use in a patient with glaucoma. We found that the daily long-acting carteolol hydrochloride eyedrops improved compliance and were more convenient, and were equal to twice-daily eyedrops in lowering IOP.

3. Numerous studies have shown that human IOP in the sitting position is high in the morning and low in the afternoon and evening. When the subject is lying flat IOP increases by as much as 2 to 6 mm Hg in both healthy persons and in patients with glaucoma. Recent data incorporating the concept of the habitual body position—sitting during waking hours and supine during sleeping hours—have demonstrated that peak IOP is most likely to occur at night while the patient is supine. The progression of visual field damage in normal-tension glaucoma is associated with IOP in the supine position and the magnitude of IOP elevation accompanying postural changes. It would be beneficial if treatment options were available that could specifically decrease the supine IOP, resulting in a reduction in the magnitude of IOP fluctuation caused by postural change. However, treatment with timolol maleate, latanoprost, or brinzolamide lowers IOP in both the sitting and supine positions but does not alter the response of IOP to postural change. The postural response is also reportedly unaffected by trabeculectomy without mitomycin C and argon laser trabeculoplasty. In patients with primary open-angle glaucoma or normal-tension glaucoma, we evaluated the postural change in IOP following trabeculectomy with mitomycin C. The IOP was measured with a pneumatonometer after 5 minutes with the subject in the sitting position and after 10 minutes with the subject in the supine position. Sitting IOP and 10-minute supine IOP were 10.2±3.3 mm Hg and 13.7±4.5 mm Hg, respectively. The difference between 10-minute supine IOP and sitting IOP (ΔIOP_{10min}) was 3.43±1.8 mm Hg ($p<0.05$). Sitting IOP and ΔIOP_{10min} were significantly correlated ($r=0.66$, $p<0.0001$). The lower the sitting IOP was, the lower ΔIOP_{10min} was.

Functional neuroimaging

Patients with glaucoma were examined with voxel-based morphometry to confirm several structural changes in the visual pathway. 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 image were acquired with a clinical MR scanner. Fifteen patients with glaucoma and 15 age-matched healthy volunteers were

recruited. A significant signal decrease was observed with voxel-based morphometry in parts corresponding to the optic chiasm and the optic radiation in patients with glaucoma. Thus, these findings suggest that in glaucoma structural changes of the visual pathway occur in intracranial structures as well as in the eyeball.

Developmental functional abnormality

Binocular summation on the visual cortex was explored with fMRI in patients with postoperative strabismus and in healthy volunteers. For patients with strabismus, binocular summation was less important at the foveal projection area and at the peripheral 2-degree projection area. This result suggests that abnormal cortical visual processing causes cortical suppression of the prefoveal projection area in patients with strabismus.

Visual neuropsychology

1. Review papers for visual psychology and neuro-ophthalmology

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

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

To gather more information, we extended our measurements to subjects with retinitis pigmentosa. Our results were the same as in 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. Publishing 3 papers in international journals

Three of our research studies we reported previously here have been published: 1) Objective perimetry using fMRI (*Experimental Neurology*; impact factor=3.9); 2) Two temporal channels in human V1 identified using fMRI (*NeuroImage*; impact factor=5.7), and 3) 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 23-gauge and 25-gauge transconjunctival vitrectomy systems for treating macular hole, 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 of select cases that do not require the full capability of conventional vitrectomy.

To evaluate the clinical efficacy of the 7-mm IOL (Eternity®, Santen Pharmaceutical Co. Ltd., Osaka, Japan) for combined pars plana vitrectomy, phacoemulsification, and IOL implantation, we observed the visibility of the retina during vitrectomy and measured the depth of the anterior chamber preoperatively and postoperatively with the Pentacam®

scanner (Oculus Optikgeräte GmbH, Wetzlar, Germany).
We are planning to evaluate changes in regular and irregular corneal astigmatism after 25-gauge and 23-gauge transconjunctival sutureless vitrectomy.
We investigated changes in corneal thickness following vitreous surgery and determined whether such changes can be used as a criterion for evaluating the invasiveness of vitrectomy.

Electrophysiology
We are recording electroretinograms (ERGs) to evaluate whether there is functional disorder retinal dystrophy, or macular disease. The ERG waveforms are compounded from the responses of various retinal cells, such as ganglion, amacrine, bipolar, and photoreceptor cells, which are recorded as a single wave pattern. In addition, we performed examinations with 4 kinds of recording system, such as the Ganzfeld stimulator, multifocal stimulation, color stimulation, and focal macular stimulation. In Ganzfeld stimulation, we recorded the responses separately from cone and rod cells from the retina according to international protocols. The multifocal stimulator, which reflects cone function, can record the responses separately from each element in 61 areas in the central 30 degrees around the posterior pole. Furthermore, the stimulator can compare with visual field examination and is evaluated between subjective visual field examinations and objective ERGs. The color ERG records each response to separate long-, middle-, and short-wavelength cones. Recently, we have acquired a focal macular stimulator. This stimulator can record the retinal function of the central 5, 10, and 15 degrees and is effective for searching for conditions, such as occult macular dystrophy, causing unidentified visual disturbance.
In the future, we will evaluate waveforms recorded from these ERG stimulators and analyze them with personal computer programs. Moreover, as we extract 1 waveform from 1 type of retinal cell, we will attempt to detect retinal disorders at a cellular level.

Diabetic Retinopathy section
We perform subtenon triamcinolone acetonide injection for diabetic macular edema at our outpatient clinic. After injection, decreases in macular retinal thickness are evident with optical coherence tomography (OCT), but macular edema recurs in some cases 3 months of injection. For cases of diabetic macular edema refractory to triamcinolone acetonide injection, we perform transconjunctival microincision vitrectomy with a 23-G trocar system. With this system, the scleral incision is small and can be closed without sutures. Other advantages are the decreased postoperative inflammation and surgical stress.
The vulnerability of RGCs in diabetes mellitus has been reported in patients and in animal models of diabetes. We are recording ERGs to evaluate retinal function in patients with diabetes but without retinopathy, as shown with ophthalmoscopy. We measured the photopic negative response (PhNR) among wave patterns obtained with cone ERGs and examined the correlation between the PhNR and the duration of diabetes. We are measuring the thickness of the nerve fiber layer with OCT and are disordering the correlation of nerve fiber layer thickness with the PhNR amplitude or implicit time or both.

Uveitis

1. We reviewed findings of spectral domain OCT, fluorescein angiography, and indocyanine green angiography in patients with multifocal posterior pigment epitheliopathy treated with low-fluence photodynamic therapy (PDT). Early application of low-fluence PDT for multifocal posterior pigment epitheliopathy led to restoration of photoreceptor integrity with improvement of choroidal thickness and circulation.
2. We reported the findings of angiography and OCT evaluation of steroid-associated central serous chorioretinopathy in a patient with Vogt-Koyanagi-Harada disease. Accurate understanding of angiography findings is important for establishing diagnoses, although the noninvasive OCT provides helpful information.
3. We reported a case of refractory uveitis with bilateral optic disc swelling and retinal vasculitis that was suspected to be associated with idiopathic retinal vasculitis, aneurysms, and neuroretinitis.
4. We reported the outcomes of combined phacoemulsification and pars plana vitrectomy for restoring visual acuity in patients with cataract and posterior segment involvement due to ocular tuberculosis. Results indicate that combined phacoemulsification and pars plana vitrectomy can be used to remove cataracts and pathologic vitreous in the eyes of such patients. Although the exact role of vitrectomy remains to be determined, the combined surgery successfully restored useful vision in all cases.

Macular degeneration

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

We evaluated the efficacy of triple therapy consisting of single-session PDT, intravitreal bevacizumab, and subtenon triamcinolone acetonide as the initial therapy for polypoidal choroidal vasculopathy. We found that this triple therapy improves vision and reduces central macular thickness in polypoidal choroidal vasculopathy.
2. We described findings in spectral-domain OCT for 4 patients with acute foveal photoreceptor damage. These 4 cases of acute foveal photoreceptor damage may represent a novel clinical entity. As more cases are recognized, the characteristic features of the disease spectrum and etiology may become clearer.

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 results suggest that fenofibrate modulates the development of EAU and suppress intraocular inflammation by decreasing the production of inflammatory cytokines.
2. Inhibition of extracellular signal regulated kinase (ERK) mitogen-activated protein kinase suppresses interleukin (IL)-17 production driven by IL-23- and IL-1 and attenuates autoimmune disease. We investigated the effects of the ERK inhibitors PD98059 and U0126 on EAU. The ERK inhibitors exhibited significant anti-inflammatory and immunosuppressive effects in EAU. Such ERK inhibitors are promising treatments for

autoimmune uveitis.

Color vision defects and genetic analysis of retinal diseases

1. We investigated differences in color discrimination between the fellow eye and the affected eye successfully treated for unilateral age-related macular degeneration in a 69-year-old man with protanopia (a type of dichromacy in congenital color vision defects).
2. We performed clinical and molecular genetic analyses 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, results of haplotype analysis of mutations were compared between family members and control subjects.
3. We investigated the involvement of various genetic factors in Japanese patients with age-related macular degeneration, a common cause of blindness in industrialized countries. More than 500,5688 single-nucleotide polymorphisms of the whole genome were genotyped with Affymetrix Human Mapping Arrays and the TaqMan assay (Affymetrix Inc., Santa Clara, CA, USA). We are now analyzing candidate single-nucleotide polymorphisms involved in Japanese patients with age-related macular degeneration.

Cornea

The cornea group at The Jikei University chooses the ideal corneal surgery by discussing the various options with each patient.

Corneal transplantation has developed rapidly in recent years. Penetrating keratoplasty, a procedure consisting of full-thickness replacement of the cornea, has been the dominant procedure. Recently, lamellar transplantation surgery, which selectively replaces only diseased layers of the cornea, has becoming a standard procedure. A variety of corneal transplantation procedures with an imported donor cornea can be used according to the condition of the disease. We have performed Descemet's stripping automated endothelial keratoplasty for more than 30 patients and have obtained good postoperative results.

Publications

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