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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 was 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. We edited the textbook entitled *Clinical Decisions in Neuro-Ophthalmologic Disorders* and wrote the book's chapters about optic disc edema being a medical emergency, optic neuritis in children, neuroretinitis, and papilledema.
2. The syndrome of transient headache and neurologic deficits with cerebrospinal fluid lymphocytosis is not extremely common but is listed in *The International Classification of Headache Disorders*. We reviewed clinical features of systemic conditions, laboratory tests, neuro-ophthalmological signs, the diagnosis, and treatment of this syndrome.
3. We reviewed drug-induced optic neuropathy caused by novel drugs, including targeted agents in cancer therapy, immunosuppressive agents, and biological agents.
4. Anti-aquaporin 4 antibody-positive optic neuritis, an intractable optic neuropathy, has recently been reported. We reproduced practical guidelines for this type of optic neuritis.

Ocular oncology and histopathology

1. Immunoglobulin (Ig) G4-related disease is a novel clinical entity characterized by infiltration of IgG4-immunopositive plasmacytes and an elevated concentration of serum IgG4 accompanied by various organs, including the lacrimal gland, salivary gland, and pancreas, that are enlarged and contain masses. Recent studies have clarified that conditions previously diagnosed as Mikulicz disease, as well as various types of lymphoplasmacytic infiltrative disorders of the ocular adnexa, are consistent with a diagnosis of IgG4-related disease. Against this background, the diagnostic criteria for IgG4-related ophthalmic disease have recently been established on the basis of the clinical and histopathologic features of the ocular lesions. This article reviews these new criteria with reference to the comprehensive diagnostic criteria for IgG4-related disease for all systemic conditions reported in 2012.

2. We reviewed the surgical approach for intraorbital tumors and stereotactic radiation therapy for optic nerve sheath meningioma.

Glaucoma

1. Analysis with the Markov model of the effects of a glaucoma examination program

Glaucoma produces an irreversible visual field loss and is the main cause of visual impairment in Japan. Early detection and treatment are important until the period of progression because symptoms are poor. We used the Markov model to analyze the effects of screening of adults for glaucoma. The early detection and early treatment of glaucoma are economically beneficial.

2. The purpose of treatment in patients with glaucoma is to maintain visual function and to reduce the intraocular pressure (IOP). 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 allowed detailed measurement of 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).

3. 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 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 on their ease of use in patients with glaucoma. We found that the daily long-acting carteolol hydrochloride

eyedrops improved compliance, were more convenient, and were equal to twice-daily eyedrops in lowering IOP.
4. 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, and the difference between them (ΔIOP 10 min) was 3.43 ± 1.8 mm Hg ($p < 0.05$). Sitting IOP and ΔIOP 10 min were significantly correlated ($r = 0.66$, $p < 0.0001$). The lower the sitting IOP was, the lower ΔIOP 10 min was.

Functional neuroimaging
Myelin is distributed in mainly the white matter of the brain. Yet in the gray matter, the myelin content depends on axonal projections respecting functional distribution. Some sensory, motor, and specifically associated cortices demonstrate higher myelin content than do adjacent cortical areas. Cortical myelination can be calculated with T1-weighted images divided from T2-weighted images as cortical myelin mapping with MRI. Detailed axonal projections to primary visual areas were examined with the cortical myelin mapping technique in patients with hemianopia who have altered optic radiation. Myelin mapping in these patients showed that myelin content was reduced in some areas, especially the posterior portion of the primary visual cortex, but was relatively conserved at the anterior portion, respecting their visual field defects. Cortical myelin mapping is also useful for estimating acquired axonal alteration reflecting detailed axonal projection to the cortex.

Developmental functional abnormality
Diffusion tensor imaging is a noninvasive technique to visualize axonal connectivity in the entire brain. Diffusion tensor images were acquired to evaluate axonal-axonal density by using fractional anisotropy on major white matter tracts to compare strabismic and control groups. The fractional anisotropy value of the strabismic group was reduced at the forceps major, which connects the occipital lobes via the splenium of the corpus callo-

sum. The reduction of fractional anisotropy at the forceps major of the strabismic group suggests that some morphological alterations exist for the axons connecting both occipital lobes.

Visual neuropsychology

1. Assessment of plasticity and stability in the visual cortex and the visual pathway in patients with a lesion of either cones or retinal ganglion cells

We assessed the degrees of plasticity and stability of the visual cortex and the visual pathways in a patient who had a central scotoma with lesions of either cones or retinal ganglion cells. In addition to using fMRI as we have in previous studies, we performed diffusion MRI, which allows us to quantify the visual pathway, which consists of white matter, on the basis of the free movements of water molecules. Ogawa et al. have reported the results of quantification of the visual pathway in patients with a lesion of either cones or retinal ganglion cells.

2. Identification of cortical area for visual awareness

Because the human temporoparietal junction is a very large cortical region that responds to many kinds of stimuli, it has not been precisely mapped. Here, using fMRI and a mixture of visual and auditory stimuli, we revealed a small visually responsive area in the right temporoparietal junction, which has previously been suggested to play a role in visual awareness.

Low vision

On the basis of the results of our questionnaire survey (The comprehensive research for disabilities [sensory disability], H22-Sensory-general-005 by the Ministry of Health, Labour and Welfare), we created a software program, "First Step," and an Internet homepage, "Knowledge Bank," supporting persons with visual disabilities. We developed a new perimeter, "Active Field Analyzer," which can measure a visual search function that is a factor in the specificity of visual field, but not in the specificity of visual acuity, as revealed by a previous report (Practical verification of a next-generation supporting system for persons with visual impairment [sensory disability], H22-Sensory-general-005 by the Ministry of Health, Labour and Welfare).

Vitreoretinal diseases

We have used 23-, 25-, and 27-gauge transconjunctival vitrectomy system for macular hole, epiretinal membrane, macular edema and rhegmatogenous retinal detachment. The 25- and 23-gauge sutureless vitrectomy techniques decrease the 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 for the 20-gauge high-speed vitrectomy system, the use of 25- and 23-gauge transconjunctival vitrectomy systema 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 the 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 criteria for evaluating the invasiveness of vitrectomy.
To treat a lens nucleus that dropped during cataract surgery, we removed it through the corneal wound without using a pars plana vitrectomy.

Electrophysiology
We are recording electroretinograms (ERGs) to evaluate whether there are functional disorders at the retinal-cell level in hereditary retinopathy, retinal dystrophy, and 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 of 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, stimulator results can be compared with visual field examination results and 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 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.

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 after 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.
A group of vulnerable retina ganglion cells have been reported in patients with diabetes mellitus 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 reported the first case of toxoplasmic central retinal artery occlusion and diffuse retinal vasculitis.
2. We reported a case of type 2 paracentral acute middle maculopathy.
3. We described detailed spectral domain optical coherence tomographic findings for 2 patients with focal choroidal excavation (FCE) associated with focal retinochoroiditis. The FCE can be seen as a tomographic phenotype after the treatment of focal retinochoroiditis. Spectral domain optical coherence tomography was useful for detecting the development of FCE after treatment and for observing the regression of FCE.
4. We reported a case of Behçet's disease with parafoveal macular ischemia associated with retinal vasculitis under low-dose oral contraceptives.

Macular degeneration

1. Dome-shaped macula was described by Gaucher and associates as a convex protrusion of macula within a staphyloma in highly myopic eyes which causes visual impairment associated with serous foveal detachment. We described a patient with spontaneous resolution of serous foveal detachment in a dome-shaped macula documented with serial spectral domain optical coherence tomography.
2. We compared the 3-year visual outcome after double therapy of photodynamic therapy (PDT) with intravitreal bevacizumab and the triple therapy of PDT combined with intravitreal bevacizumab and subtenon triamcinolone acetonide (STTA) injections for polypoidal choroidal vasculopathy (PCV). Initial therapy consisting of a single session of PDT combined with intravitreal bevacizumab and STTA improves vision in patients with treatment-naïve subfoveal PCV. Compared with double therapy, this triple therapy may be more effective for PCV.
3. We performed proteomic analysis to identify potentially specific biomarkers of exudative age-related macular degeneration. Prostaglandin H2 D-isomerase was identified in 10 cases. Because oxidative stress and chronic inflammation are involved in the development and progression of age-related macular degeneration, the identification of prostaglandin H2 D-isomerase is an intriguing finding.

Biochemistry

1. The therapeutic effects of cyclosporine A encapsulated in biocompatible and biodegradable blended nanoparticles of poly (lactic acid) homopolymers and polyethyleneglycol-block-poly (lactic acid) copolymers (stealth nanocyclosporine) were examined in an experimental autoimmune uveoretinitis model in Lewis rats. The strong therapeutic benefit on the model obtained with the stealth nanocyclosporine may have been due to prolonged blood circulation and targeting to the inflamed uvea and retina, in addition to sustained release in situ.
2. Many degenerative retinal diseases illustrate retinal inflammatory changes that include infiltration of microglia and macrophages into the subretinal space. We examined the role of chemokines in the Abca4(−/−)Rdh8(−/−) mouse model of Stargardt disease and

the Mertk(−/−) mouse model of retinitis pigmentosa. Our results indicated that chemokine (C-C motif) ligand 3 has an essential role in regulating the severity of retinal inflammation and degeneration in these mouse models.

Color vision defects and genetic analysis of retinal diseases

1. Retinitis pigmentosa and its allied disorders have genetic heterogeneity. In other words, there are many causative genes among these disorders. Although direct sequencing analysis for several causative genes is generally performed, there are few cases to identify causative gene mutations. Therefore, we have chosen whole-exome sequencing analysis to identify gene mutations. In fact, we have successfully identified several novel gene mutations.
2. We performed clinical and molecular genetic analysis of various inherited retinal diseases, such as retinitis pigmentosa and macular and conic dystrophies. We identified causative mutations in these diseases. To clarify disease haplotypes, the results of haplotype analysis with mutations were compared between family members and control subjects.

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 donor corneas can be performed 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.

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