Department of Ophthalmology

Hiroshi Tsuneoka, *Professor*
Keigo Shikishima, *Professor*
Genichiro Takahashi, *Associate Professor*
Kazushige Toda, *Associate Professor*
Tadashi Nakano, *Assistant Professor*
Tsutomu Sakai, *Assistant Professor*
Katsuya Mitooka, *Assistant Professor*
Koichi Kumegawa, *Assistant Professor*
Osamu Taniuchi, *Professor*
Hisato Gunji, *Associate Professor*
Satoshi Nakadomari, *Associate Professor*
Masaki Yoshida, *Assistant Professor*
Akira Watanabe, *Assistant Professor*
Takaaki Hayashi, *Assistant Professor*
Takuya Shiba, *Assistant Professor*
Yoichiro Masuda, *Assistant Professor*

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 provided optimized protocols for examining the rat optic nerve using high-field and high-resolution MRI. The results would be useful for evaluating optic neuropathy in experimental animal models.
2. Ten Japanese patients with the anti-aquaporin-4 (AQP4) antibody-positive neuromyelitis optica (NMO) and 255 healthy control subjects were recruited to examine the association of genetic variation of the AQP4 gene with the susceptibility to NMO in a Japanese population. We found that the AQP4 promoter polymorphism is significantly associated with an increased risk of NMO.
3. We identified 2 Japanese families with dominant optic atrophy in whom 2 mutations of the OPA1 gene (IVS20+1 G>A and V942fsX966) were detected in affected patients. Mutations in the OPA1 gene may be a major cause of dominant optic atrophy

in Japanese patients.
4. Diffusion tensor MRI is a powerful tool to visualize the optic radiation. Probabilistic tractography was used to visualize the construction of the optic radiation, especially Meyer's loop, in great detail. Recently developed methods of phase imaging and multishot diffusion-weighted imaging were also used to evaluate the visual pathway in patients and healthy control subjects.
5. On the basis of recent evidence-based medicine and guidelines, we reviewed medical treatment for neuro-ophthalmic disorders, including optic neuritis, neuromyelitis optica, chronic relapsing inflammatory optic neuropathy due to autoimmune optic neuropathy, optic nerve involvement in sarcoidosis, traumatic optic neuropathy, ischemic optic neuropathy, and relapsing orbital myositis. Additionally, we began a multicenter, randomized controlled trial for nonarteritic anterior ischemic optic neuropathy and a study in our department of the efficacy of long-term, low-dosage steroid therapy for ocular myasthenia gravis.
6. We reported clinical features and evaluation using 3-dimensional true fast imaging with steady-state precession and 3-dimensional time-of-flight magnetic resonance angiography in superior oblique myokymia.
7. We reviewed the contraindications for steroid pulse therapy in traumatic optic neuropathy, the clinical features of scintillating scotoma and photophobia, and emergencies in oculomotor disorders.
8. We reported atypical cases of Leber's hereditary optic neuropathy preceded by bilateral idiopathic optic neuritis, unilateral papilledema with normal cerebrospinal fluid pressure, a limited form of neuromyelitis optica with a lesion of the trochlear nerve nucleus, and optic neuritis with hypophysitis. These reports described the etiologic relationship and were highly suggestive.

Ocular oncology and histopathology
1. Rosai-Dorfman disease is a rare disorder characterized by benign and reactive proliferation of distinctive histiocytes and manifests as chronic painless cervical lymphadenopathy, also known as sinus histiocytosis with massive lymphadenopathy. Several patients have extranodal manifestations. We reported a rare case of orbital involvement of Rosai-Dorfman disease. Pathological analysis revealed lymphophagocytosis (emperipolesis), which is characterized by histiocytes showing phagocytosed viable lymphocytes.
2. We lectured on the precise anatomy of the orbit; diagnostic approaches based on demographics, frequency, clinical features, and radiological imaging aspects; and therapeutic strategies, including detailed surgical techniques, in orbital inflammation and orbital tumors.

Glaucoma
1. 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, exac-

erbates 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).

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 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 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.

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 mmHg 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 mmHg and 13.7 ± 4.5 mmHg, respectively. The difference between 10-minute supine IOP and sitting IOP (ΔIOP_{10min}) was 3.43 ± 1.8 mmHg ($p < 0.05$). 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

A study of visual cortex function in patients with retinal degeneration

We used fMRI to compare responses in the primary visual cortex (V1) in patients with congenital or acquired retinal degeneration. In patients with congenital retinal degeneration, we observed task-independent responses in the V1 lesion projection zone (V1-LPZ) due to reorganization that had occurred in the plastic critical period. However, in patients with acquired retinal degeneration, the V1-LPZ response depended on the task. This finding suggest that in the stable cortex, the cortical circuit is not reorganized.

Low vision

On the basis of results of our questionnaire survey we developed a software program, "First Step," for supporting persons with visual disabilities. This study was supported by a grant from the Ministry of Health, Labour and Welfare (The comprehensive research for disabilities [sensory disability], H22-Sensory-general-005). The theme was the development of a comprehensive rehabilitation system program for vision. We also proposed "intermediate outreach support" as a model of how to support persons with visual disabilities in the next generation. The data showed that the activities of daily living and quality of life depend on the visual field, rather than on visual acuity.

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 in 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 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 to evaluate 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 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.

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 500,568 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 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.

Publications

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