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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 IOLs, and yellow IOLs. We implant these new IOLs and evaluate subsequent visual function.

Neuro-ophthalmology

1. We examined the relationship between nonarteritic anterior ischemic optic neuropathy (NAION) and genetic polymorphisms of enzymes influencing endothelial function. The genotype distribution of the G/T (Lys198Asn) polymorphism of the endothelin-1 (ET-1) gene varied significantly in patients with NAION. In persons with the TT genotype of the Lys198Asn polymorphism, NAION was more likely to develop than in persons with the GG genotype. We found an increased prevalence of a G/T polymorphism of the ET-1 gene in patients with NAION. Our data suggest that this polymorphism may be an important risk factor for NAION in the Japanese population.
2. A rare manifestation of a limited form of neuromyelitis optica (NMO) with a lesion of the trochlear nerve nucleus was demonstrated. Detection of anti-aquaporin 4 (AQP4) antibodies in patients with myelitis facilitates the diagnosis of a limited form of NMO in

cases without optic neuritis. The brain lesions of NMO predominantly involve the hypothalamus and areas of the brainstem surrounding the third and fourth ventricles. Ocular motor nerve palsy due to lesions of brainstem nuclei may manifest in NMO, although ophthalmoplegia is rarely reported.
3. The aim of the present study was to clarify the association of genetic variation of the AQP4 gene with susceptibility to anti-AQP4 antibody-positive NMO in a Japanese population. We found that an AQP4 promoter polymorphism, rs2075575, is significantly associated with an increased risk of anti-AQP4 antibody-positive NMO in our Japanese population. Our data suggest that the AQP4 polymorphism is an important risk factor for the development of NMO.
4. We reported a case of asymmetric papilledema with normal cerebrospinal fluid pressure and a case of acute disseminated encephalomyelitis presenting as papilledema followed by optic neuritis.
5. We reviewed traumatic optic neuropathy and ischemic optic neuropathy and lectured on the diagnosis and treatment of neuro-ophthalmologic disorders.

Ocular oncology and histopathology
1. Immunoglobulin (Ig) G4-related ophthalmic disease belongs to a category of ocular adnexal lymphoproliferative disorders, the most frequent group of orbital tumors and simulating lesions. The aim of this study was to clarify the number of IgG4-related diseases among orbital lymphoproliferative disorders and to correlate the age and sex of such patients from 18 centers in Japan. A total of 1014 patients with orbital lymphoproliferative disorders were enrolled in this study. All had lymphoproliferative disorders pathologically diagnosed with surgical samples of ocular adnexal tissue. Of the 1014 patients with orbital lymphoproliferative disorders, 404 (39.8%) had extranodal mucosa-associated lymphoid tissue (MALT) lymphoma, 156 (15.4%) had other malignant lymphomas, 191 (18.8%) had non-IgG4 orbital inflammation, 219 (21.6%) had IgG4-related orbital inflammation, and 44 (4.3%) had IgG4-positive MALT lymphoma. The median age of patients with IgG4-related orbital inflammation was 62 years and was significantly lower than that of patients with MALT lymphoma (66 years) and higher than that of patients with non-IgG4 orbital inflammation (57 years). The male:female ratio was 105:114 among patients with IgG4-related orbital inflammation. Nearly a quarter of orbital lymphoproliferative disorders in Japan are related to IgG4.
2. We reviewed the frequency of orbital tumors and pointed out some limitations of surveys of orbital tumors in Japan.

Glaucoma
1. Analysis with the Markov model of the Eeffects analysis of the a glaucoma examination program using the Markov model.
The Gglaucoma produces an irreversible visual field loss field of vision obstacle by the cause disease of the main visual impairment of this country, and it is said that Eearly detection and, treatment is are important until the progress period because subjective symptoms are poor. We used the Markov model to perform analyze the effects of analysis using the Markov model screening of adults for glaucomanow when glaucoma was

screened in adult eyes examination. The early detection and, early treatment in of the glaucoma is are also useful for 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 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 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, and the The difference between 10-minute supine IOP and sit-

ting IOPthem (ΔIOP 10 min) was 3.43 ± 1.8 mmHg ($p < 0.05$). 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 neuro-imaging

Diffusion tensor imaging is a noninvasive technique to visualize axonal construction. The optic chiasm cannot be visualized with conventional diffusion imaging caused by magnetic susceptibility artifact around the sphenoid sinus. Two novel methods were used to visualize crossed and uncrossed fibers of the optic chiasm with the diffusion tensor imaging technique. With the readout segmentation of long variable echo-trains (RESOLVE) technique, susceptibility artifacts can be reduced through a different method of scanning raw data. TOPUP, a part of brain analysis software distributed by University of Oxford, can also solve susceptibility artifacts by calculating the "real image" through paired distorted images with known differences in direction. These 2 methods could distinguish crossed and uncrossed fibers in the optic chiasm.

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

We tried to assessed how the degrees much a visual cortex and a visual pathway haveof plasticity and stability of the visual cortex and the visual pathways in in a patient who hads a central scotoma with a lesions on of either cones or retinal ganglion cells. BesidesIn addition to using fMRI as we have beenhave used forin the previous studies, we measured the performed patients with diffusion MRI, which allows us to quantify a the visual pathway, which that consists of white matters, based on the basis of on the free movements of water molecules. Ogawa et al. have reported the results for of quantification of the visual pathway in patients with a lesion on of either cones or retinal ganglion cells.

2. Identification of cortical area for visual awareness

The Because the human temporo-parietal junction (TPJ) is a very large cortical region and that responds to many kinds of stimuli, so the precise mapping init has not been precisely mapped TPJ is still unclear. Here, using functional fMRI and a mixture of visual and auditory stimuli, we revealed a small visually responsive area in the right temporoparietal junctionTPJ (vTPJ), which has. Our results and previously been literature suggested that vTPJto may 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 which 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-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.

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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).

To evaluate clinical efficacy of 7 mm intraocular lens (ETERNITY® Santen Pharmaceutical Co. Ltd.) for combined pars plana vitrectomy, phacoemulsification and intraocular lens implantation, we observed the visibility of the retina during vitrectomy and measured the depth of anterior chamber preoperatively and postoperatively with the PENTACAM®.

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

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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 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 vulnerable of retina ganglion cells 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 evaluated the changes in health- and vision-related quality of life (HR-QOL and VR-QOL) in patients with Behçet uveitis receiving infliximab therapy. In We found that infliximab therapy conclusion, relievedf of episodes of uveitis attacks and extraocular manifestations byand infliximab therapy significantly improved the HR-QOL and VR-QOLboth health- and vision-related quality of life in patients with Behçet uveitis.

2. We studied choroidal thickness (CT) and circulation (CC) before and after immunosuppressive therapy in Vogt-Koyanagi-Harada disease (VKH). In conclusion, we found that evaluation of the choroidal status by with spectral domain (SD)-OCT and indocyanine green angiography ICGA was helpful to for monitoring the therapeutic response in VKH. Furthermore, indocyanine green angiography ICGA was superior to SD-OCT in the follow-up evaluation of this study.
3. We described a patient with Behçet disease in BD whom developed MSmultiple sclerosis—like lesions developed in the CNS central nervous system and spinal cord.
This case indicates that clinicians should pay attention to the development of MS-like lesions in the CNS and spinal cord of a patient with BD.
4. We investigated the relationship between serum levels of interleukin IL-6 and disease activity in patients with Behçet diseaseBD and concluded that levels of interleukin 6 might be a marker of disease activity in Behçet disease. In conclusion, circulating IL-6 may be a marker of BD activity.

Macular degeneration
1. We reported a case of macular hole because of prolonged viewing of a plasma flash by a femtosecond laser that was followed up with spectral domain optical coherence tomography (SD-OCT).
2. We evaluated the efficacy of reduced-fluence photodynamic therapy (RFPDT) for central serous chorioretinopathy (CSC). In conclusion, we found that RFPDT appears to be an effective treatment method for CSC. Outer nuclear layer ONL thickness is an important visual predictive factor of for the effect of RFPDT for CSC.
3. We described findings in spectral-domain optical coherence tomography (SD-OCT) findings forfrom four 4 patients with acute foveal photoreceptor damage. Lesions exhibiting orange-yellow foveal granularity characteristic of these four 4 cases corresponded to hyperreflective localized photoreceptor lesions on SD-OCT. Spectral-domain optical coherence tomographySD-OCT was useful for detecting an acute disruption and a resolution of the photoreceptor layer in the fovea.
4. We described a patient with spontaneous resolution of serous foveal detachment SFD in a dome-shaped macula DSM documented bywith serial spectral domain optical coherence tomography (SD-OCT).
5. We investigated the involvement of TNFtumor necrosis factor-α and monocyte chemoattractant protein MCP-1 in the serum and peripheral blood in of patients with neovascular age-related macular degenerationAMD (nAMD). In conclusion, Wwe found a close relationship between the cell-associated of tumor necrosis factor α and monocyte chemoattractant protein 1 TNF-α and MCP-1 and neovascular age-related macular degenerationnAMD.

Biochemistry
1. The therapeutic effects of cyclosporine A encapsulated in biocompatible and biodegradable blended nanoparticles of poly (lactic acid) (PLA) homopolymers and PEGpolyethylene glycol-block—poly (lactic acid) PLA copolymers (stealth nanocyclosporine) were examined in an experimental autoimmune uveoretinitis (EAU) model in Lewis

rats. The strong therapeutic benefit of stealth nanocyclosporine on in experimental autoimmune uveoretinitis EAU obtained with the stealth nanocyclosporine may have been due to sustained release in situ, prolonged blood circulation, and targeting to of the inflamed uvea and retina, in addition to sustained release in situ.

2. We report microglial/macrophage activation in a mouse model of both a Stargardt disease and age-related macular degeneration mouse model caused by delayed clearance of all-trans-retinal from the retina, and in a mouse model of retinitis pigmentosa mouse model with impaired retinal pigment epithelium (RPE) phagocytosis. This study demonstrates an important contribution of Toll-like receptor TLR4—mediated microglial activation by endogenous photoreceptor proteins in retinal inflammation that aggravates exacerbates retinal cell death. This pathway is likely to represent an underlying common pathology in degenerative retinal disorders.

Color vision defects and genetic analysis of retinal diseases

1. Retinitis pigmentosa and its allied disorders have genetic heterogeneity. In other words, there are lots ofmany causative genes in among those these disorders. Although direct sequencing analysis for several causative genes ishas generally been performed, there are few cases to identify causative gene mutations. So therefore, we have performed chose whole-exome sequencing analysis to identify gene mutations. With this method, we 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 cone dystrophies. We identified causative mutations in those these diseases. To clarify disease haplotypes, the results of haplotype analysis with mutations was 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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