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 (MRI), glaucoma, electrophysiology, diabetes, vitreoretinal diseases, age-related macular degeneration, uveitis, color vision, cornea, and the oculoplastic.

Research Activities

Cataract
We are able to choose various premium intraocular lenses (IOLs), such as multifocal, toric, and yellow IOLs. We implant these new IOLs through microincisions and evaluate subsequent visual function.

Neuro-ophthalmology
1. We report an unusual case of spontaneous improvement of visual acuity in a boy with neuromyelitis optica spectrum disorder. Ophthalmic and MRI evaluations demonstrated the presence of unilateral optic neuritis. After serological tests showed positivity for anti-aquaporin 4 antibody, neuromyelitis optica spectrum disorder was diagnosed. Because the patient's unilateral optic neuritis was considered to reflect mild disease activity, only follow-up observations were performed. One week after the first examination, both visual acuity and central scotoma had improved. In the absence of any specific treatments, good visual acuity has remained for 20 months, with no relapse of optic neuritis.
2. We reviewed the differential diagnosis of visual impairment of sudden onset and the management of optic neuritis.
3. In a lecture on the pathophysiology of the clinical aspects of optic neuritis we reported on the polymorphism in the promoter region of aquaporin 4 associated with an increased risk of neuromyelitis optica in the Japanese population and on 2 cases of the coexistence of neuromyelitis optica and myasthenia gravis. We lectured on recent topics of drug-induced optic neuropathy caused by novel drugs, including targeted agents in cancer therapy, immunosuppressive agents, and biological agents.

4. We reported the characteristics of Japanese patients with Leber's hereditary optic neuropathy and a trial of the drug idebenone, a case of immunoglobulin G4-related infiltrative optic neuropathy with immunoglobulin G4-related sinusitis, and MRI findings of nontraumatic orbital subperiosteal hemorrhage.

Ocular oncology and histopathology

1. We reported on a case of orbital cavernous hemangioma removed using a navigation system and on 2 cases of lacrimal sac tumors found with lacrimal endoscopy.
2. We reported the visual and vital prognosis of 36 patients with optic glioma treated with chemotherapy alone. The overall 10-year survival rate was more than 90%. We reported cases misdiagnosed as optic glioma, i.e., infiltrating optic neuropathy with the recurrence of acute lymphocytic leukemia, hemangioma in the optic nerve with von Hippel-Lindau disease, and medulloepithelioma in the optic chiasma.

Glaucoma

Analysis with the Markov model of the effects of an examination program showed that glaucoma produces an irreversible visual field loss and the most common type of visual impairment in Japan. Early detection and treatment until the advanced stage are important because symptoms are poor. We used the Markov model to analyze the effects of screening for glaucoma in adults. The early detection and early treatment of glaucoma are economically beneficial.

Functional neuroimaging

Cortical myelination was calculated with T1-weighted images divided by T2-weighted images as cortical myelin mapping with clinical MRI. In patients with hemianopsia and altered optic radiation, myelin content was reduced, particularly in the posterior portion of the primary visual cortex, but was better conserved in the anterior portion, respecting their visual field defects.

Developmental functional abnormality

Diffusion tensor imaging was performed to evaluate axonal-axonal density by means of fractional anisotropy on major white-matter tracts to compare subjects with or without strabismus. The fractional anisotropy value of the subjects with strabismus was reduced at the forceps major, which connects the occipital lobes via the splenium of corpus callosum.

Visual neuropsychology

With the use of functional MRI or diffusion MRI or both, many eye diseases have been shown to change the visual cortex and the visual tract. We are now attempting to stabilize a scanning procedure for quantitative MRI and to apply it to a volunteer who has an eye disease. Quantitative MRI allows us to directly measure T1 values. By using T1 values, we can estimate cell compositions at a voxel, each of which is an array of elements in a brain image.

Low vision
We assessed the effect of rehabilitation for patients with visual field loss by using the active field analyzer, which can help clarify a visual search function that is a factor in the specificity of the visual field but not in visual acuity.

Vitreoretinal surgery
We have used a 23-, 25- and 27-gauge transconjunctival vitrectomy system for the treatment of 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 a 25- and 23-gauge transconjunctival vitrectomy system might effectively reduce operative times of select cases that do not require the full capability of conventional vitrectomy.
To evaluate the clinical efficacy of a 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® camera system (Oculus Optikgeräte GmbH).
We will 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 the nucleus through the corneal wound without using a pars plana vitrectomy.

Electrophysiology
We are recording electroretinograms to evaluate possible functional disorders at the retinal-cell level in hereditary retinopathy, retinal dystrophy, and macular disease. The electroretinographic 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.

Diabetic Retinopathy section
A group of vulnerable retina ganglion cells have been reported in patients with diabetes mellitus and in animal models of diabetes. We are recording electroretinograms to evaluate retinal function in patients with diabetes but without retinopathy, as shown with ophthalmoscopy.

Uveitis
We reported on a patient with an atypical presentation of a phakic IOL who initially had vitelliform submaculopathy, a vitreous haze, and a peripheral retinal focus. We described

detailed enface imaging of swept-source optical coherence tomography findings for 3 patients with acute zonal occult outer retinopathy.

Macular degeneration
We reported the effects of photodynamic therapy plus intravitreal aflibercept with subtenon triamcinolone acetonide injections for treating aflibercept-resistant polypoidal choroidal vasculopathy. Triple therapy improved visual and anatomical outcomes in patients who had polypoidal choroidal vasculopathy with recurrent or resistant retinal fluid and pigment epithelial detachment after multiple injections of intravitreal aflibercept.

Biochemistry
We examined the role of chemokines in an ATP-binding cassette, sub-family A, member 4 (*Abca4*)$^{-/-}$ retinol dehydrogenase 8 (*Rdh8*)$^{-/-}$ mouse model of Stargardt disease and the MER proto-oncogene tyrosine kinase (Mertk)$^{-/-}$ mouse model of retinitis pigmentosa. Our results indicated that the chemokine (C-C motif) ligand 3 gene (*Ccl3*) plays 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. To identify pathogenic variants, we performed direct sequencing and whole-exome sequencing analysis for these disorders and successfully identified several novel pathogenic variants. In addition, among cases of congenital color blindness, we analyzed genetic variations for congenital achromatopsia, including congenital achromatopsia and blue cone monochromacy.

Cornea
We will assess the age and disease condition of patients with keratoconus and determine the most appropriate approach for improving vision and quality of life.

Oculoplastic
1. We reported the effect of fatty degeneration of the levator palpebrae superioris muscle on surgical outcomes for involutional blepharoptosis
2. We reported differences in surgical outcomes between anterior and posterior approaches for blepharoptosis repair
3. We lectured on utility in endonasal dacryocystorhinostomy using a navigation system

Publications

Shoji N*[1]*, Arakaki Y*[2]*, Nakamoto K*[3]*, Yamamoto T*[4]*, Kuwayama Y*[2]; Collaborative Bleb-related Infection Incidence and Treatment Study Group (Noro T) (*[1]*Kitasato Univ Hosp,* [2]*Univ the Ryukyus,* [3]*Tokyo Metropolitan Police Hosp,* [4]*Gifu Univ Graduate Sch Med,* [5]*Osaka Koseinenkin Hosp).*** Efficacy of predetermined therapeutic measures against bleb-related infection in the Collaborative Bleb-related Infection Incidence and Treatment Study. *Acta Ophthalmol.* 2018 Mar; **96:** e229-36.

Sasano H, Obana A*[1,2]*, Sharifzadeh M*[3]*, Bernstein PS*[3]*, Okazaki S*[2]*, Gohto Y*[1]*, Seto T*[1]*, Gellermann W*[3] *(*[1]*Seirei Hamamatsu Hosp,* [2]*Hama-

matsu Medical Univ, [3]***Utah Univ).*** Optical Detection of Macular Pigment Formation in Premature Infants. *Trans Vis Sci Tech.* 2018; **7:** 3.

Terauchi Y, Horiguchi H, Shiba T. The Pharmacological Mydriatic Pupil-to-Limbal Diameter Ratio as an Intuitive Predictor for the Risk of Intraoperative Floppy Iris Syndrome. *J Ophthalmol.* 2018 Dec 20; **2018:** 2837934.

Masuda Y, Iwaki H [1]***, Kato N, Watanabe A, Takada A, Okamoto T*** [2]***, Oki K*** [3]***, Nakano T, Tsuneoka H (*** [1]***Iwaki eye clinic,*** [2]***Nakamurabashi eye clinic,*** [3]***Oki eye surgery center).*** The safety and efficacy of phaco-sleeve irrigation-assisted hydrodissection during femtosecond laser-assisted cataract surgery. *Clin Ophthalmol.* 2018; **12:** 1829-35.

Yoshimine S, Ogawa S, Horiguchi H, Terao M [1]***, Miyazaki A*** [2]***, Matsumoto K*** [2]***, Tsuneoka H, Nakano T, Masuda Y, Pestilli F*** [3] ***(*** [1]***Yamaguchi Univ,*** [2]***Tamagawa Univ,*** [3]***Indiana Univ).*** Age-related macular degeneration affects the optic radiation white matter projecting to locations of retinal damage. *Brain Struct Funct.* 2018; **223:** 3889-900.

Kato N, Masuda Y, Oki K, Iwaki H [1]***, Tsuneoka H (*** [1]***Iwaki eye clinic).*** Influence of irrigation dynamic pressure assisted-hydrodissection on the intraocular pressure and the posterior chamber-anterior hyaloid membrane barrier during cataract surgery. *Jpn J Ophthalmol.* 2019; **63:** 221-8.

Fiorentino A, Fujinami K, Arno G, Robson AG, Pontikos N, Armengol MA, Plagnol V, Hayashi T, Iwata T, Parker M, Fowler T, Rendon A, Gardner JC, Henderson RH, Cheetham ME, Webster AR, Michaelides M, Hardcastle AJ. Missense variants in the X-linked gene PRPS1 cause retinal degeneration in females. *Hum Mut.* 2018; **39:** 80-91.

Kominami A, Ueno S, Kominami T, Nakanishi A, Ito Y, Fujinami K, Tsunoda K, Hayashi T, Kikuchi S, Kameya S, Iwata T, Terasaki H. Case of cone dystrophy with normal fundus appearance associated with biallelic POC1B variants. *Ophthalmic Genet.* 2018; **39:** 255-62.

Omoto S, Hayashi T, Matsuno H, Higa H, Kameya S, Sengoku R, Takahashi-Fujigasaki J, Murayama S, Iguchi Y. Neuronal intranuclear hyaline inclusion disease presenting with chidhood onset night blindness associated with progressive retinal dystrophy. *J Neurol Sci.* 2018; **388:** 84-6.

Katagiri S, Hayashi T, Mizobuchi K, Yoshitake K, Iwata T, Nakano T. Autosomal dominant retinitis pigmentosa with macular involvement associated with a disease haplotype that included a novel PRPH2 variant (p.Cys250Gly). *Ophthalmic Genet.* 2018; **39:** 357-65.

Katagiri S, Hosono K, Hayashi T, Kurata K, Mizobuchi, Matsuura T, Yoshitake K, Iwata T, Nakano T, Hotta Y. Early onset flecked retinal dystrophy associated with new compound heterozygous RPE65 variants. *Mol Vis.* 2018; **24:** 286-96.

Hosono K, Nishina S, Yokoi T, Katagiri S, Saitsu H, Kurata K, Miyamichi D, Hikoya A, Mizobuchi K, Nakano T, Minoshima S, Fukami M, Kondo H, Sato M, Hayashi T, Azuma N, Hotta Y. Comprehensive molecular diagnosis of 34 families of Japanese Leber congenital amaurosis by targeted next generation sequencing. *Sci Rep.* 2018; **8:** 8279.

Katagiri S, Iwasa M, Hayashi T, Hosono K, Yamashita T, Kuniyoshi K, Ueno S, Kondo M, Ueyama H, Ogita H, Shichida Y, Inagaki H, Kurahashi H, Kondo H, Ohji M, Hotta Y, Nakano T. Genotype determination of the OPN1LW/OPN1MW genes: novel disease-causing mechanisms in Japanese patients with blue cone monochromacy. *Sci Rep.* 2018; **8:** 11507.

Katagiri S, Hayashi T, Yoshitake K, Murai N, Matsui Z, Kubo H, Satoh H, Matsufuji S, Takamura T, Yokoo T, Omori Y, Furukawa T, Iwata T, Nakano T. Compound heterozygous splice site variants in the SCLT1 gene highlight an additional candidate locus for Senior-Løken syndrome. *Sci Rep.* 2018; **8:** 16733.

Kondo H, Oku K, Katagiri S, Hayashi T, Nakano T, Iwata A, Kuniyoshi K, Kusaka S, Hiyoshi A, Uchio R, Kondo M, Oishi N, Kameya S, Mizota A, Naoi N, Ueno S, Terasaki H, Morimoto T, Iwaki M, Fujinami K, Tsunoda K, Shinoda K, Iwata T. Novel mutations in RS1 gene in Japanese patients with X-linked congenital retinoschisis. *Hum Genome Var.* 2019; **6:** 3.

Suzuki K, Gocho K, Akeo K, Kikuchi S, Kubota D, Katagiri S, Fujinami K, Tsunoda K, Iwata T, Yamaki K, Igarashi T, Nakano T, Takahashi H, Hayashi T, Kameya S. High-resolution retinal imaging reveals preserved cone photoreceptor density and choroidal thickness in female carriers of choroideremia. *Ophthalmic Surg Lasers Imaging Retina.* 2019; **50:** 76-85.

Nakano T, Hayashi T, Nakagawa T, Honda T, Owada S, Endo H, Tatemichi M. Increased Incidence of Visual Field Abnormalities as Determined by Frequency Doubling Technology Perimetry in High Computer Users Among Japanese Workers: A Retrospective Cohort Study. *J Epidemiol.* 2018 Apr 5; **28:** 214-9.

Matsuda H, Sakai T, Takahashi Y [1]***, Nakamura M, Nakano T (*** [1]***Aichi Med Univ).*** Influence of fatty deposits in the levator aponeurosis/levator palpebrae superioris muscle onoutcomes of aponeurotic repair in a Japanese population. *Eye (Lond).* 2018 Aug 16.