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, and the cornea.

Research Activities

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

Neuro-ophthalmology
1. Leber hereditary optic neuropathy (LHON) is a maternally inherited optic neuropathy that leads to central loss of vision, predominantly in young males. Most LHON cases have one of three primary point mutations in mitochondrial DNA (mtDNA). The annual incidence and prevalence of LHON in Japan are not known. Thus, we estimated the annual incidence of molecularly confirmed LHON in Japan during 2014. Sequential questionnaires were sent to 1,397 facilities and we received 861 responses to the first questionnaire. Approximately 120 cases (95% confidence interval ranged from 81 to 153) of newly developed LHON were reported during 2014 in Japan, and 93.2% were males. For the second questionnaire, responses were received from 30 facilities, and 86.5% of cases possessed the mtDNA ND4/G11778A mutation.
2. We report a rare case of macular hypoplasia with retinal folds in a patient with septo-optic dysplasia (SOD). She had a history of hypoglycemia attacks and growth-hormone deficiency. Ophthalmoscopic examination revealed bilateral optic nerve hypoplasia and tortuous retinal vessels. Optical coherence tomography revealed foveal hypoplasia and retinal folds. Magnetic resonance imaging of the brain indicated atrophy of the bilateral optic nerves as well as atrophy of the optic chiasm and bilateral optic tracts. The pituitary

gland also exhibited atrophy. On the basis of genetic and environmental evidence, we hypothesize that a common factor causes both foveal hypoplasia and SOD.

Ocular oncology and histopathology

1. We reviewed the diagnosis of optic nerve sheath meningioma and optic pathway glioma of primary optic nerve tumors. We presented the features of the ocular fundus of melanocytoma on the optic disc and epipapillary capillary hemangioma (von Hippel-Lindau disease).
2. We lectured the clinical diagnosis including radiological findings for orbital mass lesions, and the indication and methods of surgery for orbital tumors.
3. We reported rare cases of intraorbital granular cell tumor with the inferior rectus muscle involvement, orbital tumor associated with chronic lymphocytic leukemia presenting spontaneous regression following biopsy and conjunctival squamous cell carcinoma in a young man.

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 are important until the advanced stage 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 and 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 be used to 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 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 TVS may effectively reduce operative times of select cases that do not require the full capability of conventional vitrectomy.
To evaluate clinical efficacy of 7mm 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.
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.
As a method of treatment for a dropped lens nucleus that occurred during cataract surgery, we removed the dropped lens nucleus through the corneal wound without using a pars plana vitrectomy (PPV).

Electrophysiology
We are recording electroretinograms to evaluate whether there are 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 has 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 PCV (Polypoidal choroidal vasculopathy) with recurrent or resistant retinal fluid and PED (pigment epithelial detachment) after multiple injections of intravitreal aflibercept.

Biochemistry
We examined the role of chemokines in a Abca4(−/−)Rdh8(−/−) mouse model of Stargardt disease and the 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 those disorders and successfully identified several novel pathogenic variants. In addition, among 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.

Publications

Itoh Y, Nakamoto K*[1,2]*, Horiguchi H, Ogawa S, Noro T, Sato M*[3]*, Nakano T, Tsuneoka H, Yasuda N*[4] *(*[1]Tokyo Metropolitan Police Hosp,*** [2]***Nippon Med Sch,*** [3]***Niizashiki Central General Hosp,*** [4]***Showa Univ).*** Twenty-Four-Hour Variation of Intraocular Pressure in Primary Open-Angle Glaucoma Treated with Triple Eye Drops. *J Ophthalmol.* 2017; **2017:** 4398494.

Kasai K, Kato N*[1,2]*, Konomi K*[1,3]*, Shinzawa M*[1]*, Shimazaki J*[1] *(*[1]Tokyo Dental College,*** [2]***Saitama Med Univ,*** [3]***Keio Univ).*** Flattening effect of corneal cross-linking depends on the preoperative severity of keratoconus. *Medicine. (Baltimore).* 2017; **96:** e8160.

Takashina H, Watanabe A, Tsuneoka H. Full-thickness Macular Hole Formation in the Postoperative Period After Initial Vitrectomy for Rhegmatogenous Retinal Detachment. *Case Rep Ophthalmol.* 2017; **8:** 595-601.

Takashina H, Watanabe A, Tsuneoka H. Perioperative changes of the intraocular pressure during the treatment of epiretinal membrane by using 25- or 27-gauge sutureless vitrectomy without gas tamponade. *Clin Ophthalmol.* 2017; **11:** 739-43.

Takahashi G, Demirel S*[1]*, Johnson CA*[2] *(*[1]Devers Eye Institute,*** [2]***University of Iowa Hospitals and Clinics).*** Predicting conversion to glaucoma using standard automated perimetry and frequency doubling technology. *Graefes Arch Clin Exp Ophthalmol.* 2017; **255:** 797-803.

Otori Y*[1]*, Takahashi G, Urashima M, Kuwayama Y*[2]; Quality of Life Improvement Committee (*[1]***National Hospital Organization Osaka National Hospital,*** [2]***Fukushima Eye Clinic).*** Evaluating the Quality of Life of Glaucoma Patients Using the State Trait Anxiety Inventory. *J Glaucoma.* 2017; **26:** 1025-9.

Matsuda H, Shiba T, Takahashi Y*[1]*, Tsuneoka H (*[1]Aichi Med Univ).*** Relationship between the phenylephrine test and eyelid droop after aponeurotic repair with the use of an epinephrine-containing local anaesthetic. *Eye.* 2018; **32:** 93-8.

Matsuda H, Shiba T, Takahashi Y[1], Tsuneoka H ([1]Aichi Med Univ). Transcutaneous aponeurotic repair with small detachment of the levator aponeurosis for aponeurotic blepharoptosis in Japanese patients. *J Plast Reconstr Aesthet Surg.* 2018; **71:** 425–30.

Katagiri S, Negishi Y, Mizobuchi K, Urashima M, Nakano T, Hayashi T. ABCC6 Gene Analysis in 20 Japanese Patients with Angioid Streaks Revealing Four Frequent and Two Novel Variants and Pseudodominant Inheritance. *J Ophthalmol.* 2017; **2017:** 1079687.

Nakano T, Hayashi T[1], Nakagawa T[1], Honda T[1], Owada S[2], Endo H, Tatemichi M[2] ([1]Hitachi Health Care Center, [2]Tokai Univ). 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; **28:** 214–9. Epub 2017 Nov 25.

Komatsu K, Matsuda H, Takahashi Y[1], Nakano T ([1]Aichi Med Univ). Recurrent Lower Eyelid Ectropion After Graft Surgery Using Autogenous Palmaris Longus Tendon. *J Craniofac Surg.* 2018; **29:** e195–6. Epub 2017 Dec 7.

Akiyama G[1], Azuchi Y[2], Guo X[2], Noro T, Kimura A[2], Harada C[2], Namekata K[2], Harada T[2] ([1]Akiyama eye clinic, [2]Tokyo Metropolitan Institute of Medical Science). Edaravone prevents retinal degeneration in adult mice following optic nerve injury. *Invest Ophthalmol Vis Sci.* 2017; **58:** 4908–14.

Hayashi T, Sasano H, Katagiri S, Tsunoda K[1], Kameya S[2], Nakazawa M[3], Iwata T[1], Tsuneoka H ([1]National Hospital Organization Tokyo Medical Center, [2]Nippon Med Sch Chiba Hokusoh Hosp, [3]Hirosaki Univ). Heterozygous deletion of the OPA1 gene in patients with dominant optic atrophy. *Jpn J Ophthalmol.* 2017; **61:** 395–401.

Katagiri S, Hayashi T, Gekka T, Tsuneoka H. A novel homozygous CYP4V2 variant (p.S121Y) associated with a choroideremia-like phenotype. *Ophthalmic Genet.* 2017; **38:** 286–7.

Ueno S[1], Nakanishi A[1], Kominami T[1], Ito Y[1], Hayashi T, Tsunoda K[2], Iwata T[2], Terasaki H[1] ([1]Nagoya Univ, [2]Natl Hosp Organization Tokyo Medical Center). In vivo imaging of cone mosaic in patient with GNAT2 variant associated achromatopsia. *Jpn J Ophthalmol.* 2017; **61:** 92–8.

Katagiri S, Tanaka S[1], Yokoi T[2], Hayashi T, Matsuzaka E[2], Ueda K[1], Matsuzaka E[2], Yoshida-Uemura T[2], Arakawa A[1], Nishina S[2], Kadonosono K[1], Azuma N[2] ([1]Yokohama City University Medical Center, [2]National Center for Child Health and Development). Clinical features of a toddler with bilateral bullous retinoschisis with a novel RS1 mutation. *Am J Ophthalmol Case Rep.* 2017; **5:** 76–80.

Ishikawa K, Gekka T, Hayashi T, Kikuchi S[1], Kameya S[1], Tsuneoka H ([1]Nippon Medical Sch). Closure of a full-thickness macular hole without vitrectomy in choroideraemia. *Clin Exp Optom.* 2017; **100:** 294–5.

Matsushita I[1], Nagata T[1], Hayashi T, Kimoto K[2], Kubota T[2], Ohji M[3], Kusaka S[4], Kondo H[1] ([1]Univ Occupational and Environmental Health, [2]Oita Univ, [3]Shiga Univ, [4]Kindai Univ). Foveal hypoplasia in patients with Stickler syndrome. *Ophthalmology.* 2017; **124:** 896–902.

Ueno S[1], Nakanishi A[1], Akira S[1], Kominami T[1], Ito Y[1], Hayashi T, Tsunoda K[2], Iwata T[2], Terasaki H[1] ([1]Nagoya Univ, [2]National Hospital Organization Tokyo Medical Center). Differences of ocular findings in two siblings; one with complete and other with incomplete achromatopsia. *Doc Ophthalmol.* 2017; **134:** 141–7.

Reviews and Books

Hayashi T. Cone dysfunction syndrome in Japanese population. In: Prakash G, Iwata T, editors. Advances in Vision Research. Tokyo: Springer Japan, 2017. p.129–35.