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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: color vision, ocular oncology, histopathology, biochemistry, eye movement, neuro-ophthalmology, corneal and refractive surgery, cataract, glaucoma, electrophysiology, diabetes, vitreoretinal diseases, and uveitis.

Research Activities

Color-vision defects and inherited retinal diseases

Our research goals are to investigate clinical features and the genetic basis of color-vision defects and inherited retinal diseases and to clarify genotype and phenotype correlations. The Lanthony desaturated panel D-15 test consists of 16 caps, similar to those of the Farnsworth dichotomous test. The color caps of the Lanthony test are of lower chroma and higher value than those of the Farnsworth test. We evaluated the Lanthony test in anomalous trichromats with congenital red-green color-vision defects. We examined 162 anomalous trichromats (155 male and 7 female) identified with a Nagel type I anomaloscope. All subjects had passing results on the Farnsworth test, 1.0 or better of best-corrected visual acuity, and no ocular disease. Pass/fail results of Lanthony test were compared between protanomalous trichromats and deteranomalous trichromats by means of the chi-square test (with significance at $p<0.05$). Odds ratios (ORs) were calculated. The pass/fail results of the Lanthony test were compared between anomalous trichromats aged 7 to 10 years and those 11 years or older. Nineteen of the 54 (35.2%) protanomalous trichromats and 19 of the 108 (17.5%) deteranomalous trichromats had failing results on the Lanthony test. The difference was significant (OR, 2.50; 95% confidence interval, 1.1–5.7; $p=0.013$). The failure rate of anomalous trichromats aged 7 to 10 years was much higher than that of anomalous trichromats 11 years or older. The results suggest that failure on the Lanthony test is more likely for protanomalous trichromats than for deteranomalous trichromats and more likely for anomalous trichromats aged 7 to 10 years than for those 11 years or older.

Ocular oncology and histopathology

1. We reported 2 cases of conjunctival and corneal intraepithelial neoplasia treated by

topical fluorouracil and proposed the therapeutic regimen for this condition. We treated 2 patients with conjunctival and corneal intraepithelial neoplasia. One patient was a 73-year-old man, and the other patient was an 81-year-old woman. Both cases were unilateral. The diagnoses, by biopsy, were severe dysplasia and carcinoma *in situ*, respectively. After a trial period of treatment with 0.5% fluorouracil, the doses were changed to 1.0%, to be administered 4 times daily for 4 consecutive days. Treatment was repeated 6 times at intervals of 1 month. The lesions showed marked improvement in both cases. No corneal side effects developed. Pulsed treatment with topical fluorouracil is safe and effective for conjunctival and corneal intraepithelial neoplasia.

2. Malignant lymphoma in the eye consists of ocular adnexal lymphoma and intraocular lymphoma. A significantly increased incidence of malignant lymphoma in the ocular adnexa was found in our most recent series. An approach to the diagnosis of malignant lymphoma in the ocular region was reviewed.

Biochemistry

1. We investigated the protective effect of pigment epithelium-derived factor-loaded nanoparticles (PEDF-NPs) against photoreceptor degeneration in Royal College of Surgeons rats. Intravitreously administered PEDF-NPs showed significant protective effects, due to the targeting and the sustained release of PEDF *in situ*, against photoreceptor degeneration. The results of these studies suggest that the intravitreous injection of PEDF-NPs is a promising therapeutic strategy for rescue of photoreceptors and the retinal pigment epithelium.

2. Interleukin (IL)-31 is a newly discovered T-cell cytokine that, when overexpressed in mice, results in pruritus and skin dermatitis resembling human atopic dermatitis. Although IL-31 has been regarded as a factor in atopic dermatitis and bronchial asthma, its role in allergic conjunctivitis remains unknown. In this study, we investigated the effects of IL-31 on allergic conjunctivitis in a murine model of allergic conjunctivitis induced by Japanese cedar pollen allergen (Cry j 1). After sensitization with Japanese cedar pollen allergen (Cry j 1), IL-31 instillation stimulated conjunctival epithelial cells and activated macrophages in the conjunctiva. The (stimulated) epithelial cells produced such chemokines as thymus and activation-regulated cytokine and macrophage-derived chemokine, and recruited helper T type 2 cells into the conjunctiva. Finally, helper T type 2 cytokines induced eosinophil infiltration. In conclusion, the study revealed that IL-31 instillation following sensitization with Cry j 1 aggravates allergic conjunctivitis.

Eye movement

Binocular summation in the visual cortex was examined by comparing cortical responses of binocular and monocular visual stimulation by means of functional magnetic resonance imaging (fMRI). Two different checkerboard stimuli were used. The binocular condition demonstrated markedly greater signal intensities than did the monocular condition. Two stimuli demonstrated different binocular summation ratios and different increasing signal intensities. These results suggest that the binocular summation processes of these two visual stimuli differ in the visual cortex.

Neuro-ophthalmology

1. We examined performance characteristics of frequency-doubling perimetry (FDP) in comparison with standard automated perimetry (SAP) in patients with resolved optic neuritis. The Swedish interactive thresholding algorithm 30–2 program was used for SAP, and a full-threshold 30–2 program was used for FDP. Comparisons were made of the mean deviation, pattern standard deviation, and the percentage of abnormal points significantly depressed $<0.5\%$ in the total deviation probability plot. Defects detected with FDP were larger than those detected with SAP. The sensitivity of FDP for visual field defects in resolved optic neuritis is equal to and potentially greater than that of SAP. This short-term follow-up study in patients with resolved optic neuritis suggests that FDP detects characteristics of slower recovery in the fovea and in extrafoveal areas more effectively than does SAP. These properties may allow more accurate detection of visual field defects and may prove advantageous for monitoring patients with resolved optic neuritis.
2. We examined the association between the polymorphisms of the endothelial nitric oxide synthase (eNOS) gene and the occurrence of nonarteritic anterior ischemic optic neuropathy (NAION). There was no significant difference in the genotype distribution of the Glu298Asp polymorphism of exon 7 between patients with NAION and control subjects, whereas the genotype distribution of the T (-786) C polymorphism of the promoter region differed significantly. Subjects with the CC genotype of the T (-786) C polymorphism were more likely to have NAION than were subjects with the TT genotype. We found an increased prevalence of the T (-786) C polymorphism of the eNOS gene in patients with NAION. Our data suggest that the T (-786) C polymorphism of the eNOS gene is an important risk factor for NAION in Japanese subjects.
3. Pupillary abnormalities and the differential diagnosis of anisocoria were described in a textbook.
4. We reported a case of McCune-Albright syndrome presenting as acute compressive optic neuropathy.
5. Conventional magnetic resonance imaging cannot directly visualize wallerian degeneration of the optic radiation resulting from proximal axonal injury such as that caused by temporal lobe lesions. A new technique, diffusion tensor imaging (DTI), can show the extent of axonal conservation in the white matter. We performed fMRI and DTI simultaneously to explore the trajectory of the optic radiation and cortical activation in a patient with right-sided hemianopia and a temporal lobe lesion. Although the left occipital cortex was anatomically conserved, fMRI showed weaker cortical activation on the left side than on the right side. DTI tractography showed that the left optic radiation did not reach the occipital pole.
Our technique suggests that the hemianopia in this patient was caused by wallerian degeneration of the optic radiation. Both fMRI and DTI are useful for the clinical evaluation of cerebral visual disability.

Cornea and refractive surgery

The cornea group at The Jikei University chooses the most appropriate method of corneal surgery by discussing the various options with each patient. We replace only

those corneal components that are damaged. Photorefractive keratectomy (PTK) is effective for cases of surface corneal opacity, and automated lamellar therapeutic keratoplasty (ALTK) is also effective for cases of corneal stroma opacity. We also perform Descemet's stripping automated endothelial keratoplasty for corneal endothelium dysfunction.

We have adapted several new treatments for all corneal diseases, for example, xerophthalmia, corneal infection, corneal injury, hereditary corneal disease, allergic corneal disease, and keratoconus. ALTK, in which a microkeratome is used to create a lamellar flap, was performed in several cases of corneal opacity. We found that ALTK enables earlier suture removal and induces less astigmatism than does conventional lamellar keratoplasty.

We studied the clinical outcomes of secondary implantation of iris-clip intraocular lens for aphakic eyes 5 years postoperatively. Clinically significant complications were not found with specular microscopy or laser flaremetry.

Glaucoma

1. We compared the effectiveness of Humphrey matrix perimetry, scanning laser polarimetry (GDx-VCC polarimeter, Carl Zeiss), and optical coherence tomography (OCT3000) for early detection of glaucoma. We found that the detection precision of Humphrey Matrix perimetry was equal to that of these optical imaging devices and that the pattern standard deviation was the most effective variable.
2. We evaluated from various aspects the shape and structure of blebs after trabeculectomy. We examined risk factors causing leaking blebs and overhanging blebs on the basis of operative method and postoperative management.
3. We investigated the effects of ocular optical system aberrations in perimetry, especially for peripheral vision measurement. In peripheral vision, there were astigmatism and coma aberrations, and the point images that were projected onto the retina differed depending on the measurement sites. These results suggest that the aberration affects the results of threshold measurements in the peripheral vision.

Electrophysiology

We are recording electroretinograms (ERGs) to evaluate retinal functional disorders in hereditary retinal degenerative diseases.

ERG waveforms are recorded as the responses of retinal cells, such as ganglion, amacrine, bipolar, and photoreceptor cells. For ERG recording, we use 3 types of machine: full-field, multifocal, and color. The full-field ERGs are recorded according to an international standard, and we record the responses from cones and rod cells separately. Multifocal ERGs are obtained from the central 30-degree area of the retina, reflect mainly cone function, and can record from 61 elements. Color ERG sseparately record responses to long-, middle-, and short-wavelength cones.

We plan to evaluate and analyze waveforms recorded from full-field ERGs. Moreover, as we extract 1 waveform from 1 type of retinal cell, we will attempt to detect retinal disorders at more minute levels.

Diabetes and vitreoretinal diseases

We have used 23-gauge and 25-gauge transconjunctival vitrectomy systems to treat macular holes, the epiretinal membrane, macular edema, and rhegmatogenous retinal detachment. The 25- and 23-gauge sutureless vitrectomy techniques decrease surgical trauma and increase 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 for select cases that do not require the full capability of conventional vitrectomy. We plan to evaluate changes in regular and irregular corneal astigmatism after 25-gauge and 23-gauge transconjunctival sutureless vitrectomy.

Uveitis

1. A novel therapy with infliximab, a chimeric antibody against tumor necrosis factor α, in Behçet disease.

Intravenous infliximab significantly decreased the frequency of ocular attacks and improved visual acuity.

2. We identified bacterial and fungal pathogens in the intraocular fluid in endophthalmitis by means of DNA microarray analysis. The novel molecular approach can be performed, from pathogen isolation to species identification, within 12 hours in a research laboratory. We suggest that DNA microarray analysis is a useful tool for rapid identification of bacterial and fungal pathogens in the intraocular fluid in endophthalmitis.

3. We reported the clinical course of a patient with atypical Cogan's syndrome and posterior scleritis.

Visual neuropsychology

1. Two temporal channels in human V1 identified with fMRI

We measured the responses to spatial uniform (Ganzfeld) luminance changes in the human visual cortex using fMRI. We presented various temporal modulation stimuli without spatial contrast patterns and found that the BOLD signal consisted of transient and sustained channel responses reported in previous psychophysical studies. We identified these 2 independent channels with linear model analysis and revealed that the relative contribution of these channels varies with eccentricities across V1.

2. The objective visual field map with fMRI

We developed a software program to analyze visual field maps with fMRI. To evaluate the usefulness of this program, we planned an experiment with hemifield visual stimuli and succeeded in drawing a pseudohemianopsic visual field map.

3. Neural plasticity of area V1

We used fMRI to assess abnormal V1 signals in patients with juvenile macular degeneration. These signals have been interpreted as indicating cortical plasticity. Subjects viewed a stimulus passively or performed a stimulus-judgment task. During passive viewing, there were large unresponsive V1 regions, which we refer to as lesion projection

zones (LPZs). In patients with juvenile macular degeneration, we observed highly significant responses in the LPZ as they performed a task. These task-dependent signals can be explained with hypotheses that have very different implications for V1 plasticity. We propose that these responses were driven by feedback signals by the task demands. Deletion of the retinal feed-forward input may unmask pre-existing task-dependent feedback signals that are ordinarily suppressed.

Low vision

We compared the visual acuity of patients with both low vision and brain injury by means of 2 methods of measurement and examined the degree of divergence. Each eye's visual acuity was measured with both Teller acuity cards and Landolt rings. We also examined the degree of visual field loss. The visual acuity measured with Teller acuity cards was significantly better than that measured with Landolt rings in patients with brain injury and eccentric viewing.

We reported on children of school age who visited the low-vision clinic of the Kanagawa Rehabilitation Hospital who were supported by a home for visual disabilities in another paper.

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