

## 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: color vision, ocular oncology, histopathology, biochemistry, eye movement, neuroophthalmology, corneal and refractive surgery, cataract, glaucoma, electrophysiology, diabetes, and vitreoretinal diseases.

### Research Activities

#### *Color vision defects and inherited retinal diseases*

We evaluated the usefulness of the Waggoner Hardy-Rand-Rittler (HRR) pseudo-isochromatic plate as a screening test for anomalous trichromacy in patients with congenital red/green color vision deficiencies. The Richmond HRR and the Waggoner HRR tests were performed in 16 protanomals and 38 deuteranomals. Results of the Waggoner HRR test were statistically compared with those of the Richmond HRR test for each severity scaling. In addition, colorimetric measurements of the figure dots and the background dots of the HRR tests were made with a spectrophotometer and plotted on a CIE 1976 ( $L^*$ ,  $u^*$ ,  $v^*$ ) chromaticity diagram. Severity scale scores were identical on the Waggoner HRR and Richmond HRR tests in 87.5% of the protanomals and in 73.7% of the deuteranomals. No significant differences in severity scaling were seen between the tests. Subjects whose scale scores differed between the tests showed milder severity on the Waggoner HRR test than on the Richmond HRR test. Chromaticity differences between the figure and background dots were greater on the Waggoner HRR test. Our results suggest that the utility of the Waggoner HRR test may be equivalent to that of the Richmond HRR test for evaluating the severity of anomalous trichromacy. The differences in severity outcomes in some cases may be due to chromaticity differences of the figure and background dots between the tests.

#### *Ocular oncology and histopathology*

1. We demonstrated the pathological features of an extremely rare case of transitional cell carcinoma (TCC) of the bladder metastatic to the orbit and reviewed the literature on such cases. A man presenting with proptosis underwent transeptal anterior orbitotomy. Histopathological examination of the orbital lesion revealed nests of carcinomatous cells. Atypical pleomorphic cells with vacuolated cytoplasm were evident.

The cellular morphology of the orbital lesion was identical to that of the primary TCC. There have been 12 previously reported cases of TCC of the bladder metastatic to the orbit, with the time from onset of primary TCC to observation of ocular symptoms ranging from 3 weeks to 11 years. Mean survival after orbital metastasis is 3.0 months. This study presented a detailed description of the pathological features of TCC metastatic to the orbit. In such cases the prognosis is extremely poor.

2. We reported rare cases of optic neuropathy caused by an intraorbital tumor in a patient with von Hippel-Lindau disease and a schwannoma presenting with clinical features of lacrimal gland tumor.

### *Biochemistry*

Staphylococcal enterotoxin B (SEB) is a type of superantigen, which is delivered by bacteria, viruses, and mycoplasmas. Superantigens are powerful T-cell activators which are regarded as a leading cause of infectious etiology in autoimmune disease. We investigated the effects of SEB in experimental autoimmune uveoretinitis (EAU). SEB increased clinical and histological scores of EAU. Clinical were significantly higher scores in the SEB-treated group than in the control group on day 28. The invasion of T cells and the proliferation of Muller cells were increased in the SEB-treated group. Furthermore, SEB increased T-cell proliferation specific for interphotoreceptor retinoid-binding protein and increased interferon  $\gamma$  production. An antibody against V $\beta$ 8 showed significant anti-inflammatory and immunosuppressive effects in EAU. SEB may play a role in the development of EAU via T-cell receptor V $\beta$ 8.

### *Eye movement*

Binocular summation on the visual cortex was investigated by comparing cortical responses to binocular and monocular visual stimulation by means of functional magnetic resonance imaging (fMRI). Signal intensities were markedly higher with the binocular condition than with the monocular condition. We believe this result reflects the binocular summation process in the visual cortex.

### *Neuro-ophthalmology*

1. Hemianopia respecting the vertical meridian generally results from a disturbance in the optic chiasm or the postchiasmal visual pathway. We described 5 unusual patients with visual field defects respecting the vertical meridian that were not related to distinct chiasmal or postchiasmal lesions, as determined with MRI. Optic neuritis and the effects of the testing algorithm for perimetry were possible causes in 2 cases. The symptoms of 1 patient with homonymous hemianopia were a functional deficit. In the 2 other cases, the visual field defects may have been caused by optic disc abnormalities. Although visual field defects respecting the vertical meridian, and without any evidence of distinct disease, are uncommon, neurologists and neuro-ophthalmologists should consider the differential diagnosis if MRI does not show distinct lesions in the optic chiasm or the postchiasmal visual pathway.

2. Several advantages of kinetic perimetry in neuro-ophthalmology were reviewed.

3. We examined the association between a polymorphism of the endothelin-1 gene and

the occurrence of nonarteritic anterior ischemic optic neuropathy and found an increased prevalence of G/T polymorphism of the gene.

4. We evaluated the efficiency of long-term, low-dosage steroid therapy for ocular myasthenia gravis (MG). This therapy would be effective for reducing or eliminating symptoms in patients with ocular MG and may also prevent progression to generalized MG.

5. We reported rare cases of Gradenigo syndrome presenting with typical findings on MRI, midbrain ptosis caused mainly by a lesion in the periaqueductal gray matter, and reversible posterior leukoencephalopathy syndrome with bilateral visual impairment.

6. Conventional MRI 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 conservation of axonal fibers in the white matter. fMRI and DTI were simultaneously performed to explore the trajectory of the optic radiation and cortical activation in a patient with a right-sided hemianopia and a temporal lobe lesion. Although the left occipital cortex was anatomically preserved, 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. fMRI and DTI were useful for clinical evaluation of cerebral visual disability.

#### *Cornea and refractive surgery*

Automated lamellar therapeutic keratectomy, in which a microkeratome is used to make a lamellar flap, was performed in several cases of corneal opacity. We found that automated lamellar therapeutic keratectomy enables earlier suture removal and induces less astigmatism than does conventional lamellar keratoplasty.

We studied the clinical outcomes of secondary implantation of the 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 evaluated the Glaucoma Progression Analysis, which is a new event-type method of judging the progression of early glaucoma, in 152 eyes of 76 outpatients. The results suggest that detection with Glaucoma Progression Analysis was more sensitive than that with the MD slope, which is an analytical method of the trend type.

2. Studies in Europe and the United States have shown a high prevalence of glaucoma in patients with sleep apnea syndrome (SAS). However, a detailed examination of this relation has not been performed in Japan. Therefore, we examined the relationship between SAS and frequency-doubling technology (FDT) visual field abnormality in 182 outpatients attending the sleep clinic of The Jikei University School of Medicine. We found that the prevalence of FDT visual field abnormalities was high in patients with SAS, suggesting a relation between SAS and glaucoma.

3. We evaluated a stimuli of FDT perimetry by using fMRI. The results suggested

that the FDT stimuli detected the response of the subtype (My cell) of the M cell.

4. We examined the detection precision of an FDT screening program and compared it with Humphrey Matrix perimetry, which is considered a second-generation FDT, in terms of sensitivity, specificity, and inspection time.

5. We determined the diagnostic value of FDT for glaucoma by comparison of fundus photograph and intraocular pressure (IOP) measurement by non-contact tonometer. In conclusion, the FDT and fundus photograph had high sensitivity to detect glaucoma. In contrast, the IOP measurement had low sensitivity.

### *Electrophysiology*

We recorded electroretinograms in patients with hereditary retinal degenerative diseases. We follow international standards and record cones and rods separately. In addition, we use a colored light-emitting diode built in to the contact electrode, which can separate long- and middle-wavelength cones from short-wavelength cones. Such separation can be effective for recording rare cases, such as enhanced s-cone syndrome. In addition, we placed rats in a box made from materials similar to a colored intraocular lens (yellow lens) and created a light-damage model of the rat retina. We plan to record electroretinograms in these rats.

### *Diabetes and vitreoretinal diseases*

We have used 23-gauge and 25-gauge transconjunctival vitrectomy systems to treat 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 for the 20-gauge high-speed vitrectomy system, the use of 25- and 23-gauge transconjunctival vitrectomy systems may effectively reduce operative times of selected patients who do not require the full capability of conventional vitrectomy techniques.

### *Visual neuropsychology*

#### 1. Neuropsychology

Data from 3 patients with focal lesions suggest a relationship between the recognition of Mooney faces and the lateral surface of the right occipital lobe. We reported on patients with polyopia or metamorphopsia caused by cortical damage. We reported on 3 patients without vection perception. We commented on the neuroscientific theory proposed by Zeki.

#### 2. fMRI study

We developed a software program for perimetry analysis, mrFA, and we reported on visual stimuli and analysis methods to estimate the hemodynamic delay. The mrFA can be used as an objective method of perimetry and a decoder of brain activity, and we reported its practicality. We observed the selective activation of the magnocellular pathway associated with simple flickering visual stimuli. We observed activation during the pseudoisochromatic test and the color arrangement test; activation during the

latter test was correlated with activation in the more anterior region of the ventral occipital lobe. We observed nonhomogeneous responses in area V1 even with homogeneous stimuli with Ganzfeld. We assumed that these responses were due to the distribution of retinal ganglion cells. We could not detect activation in the foveal projection cortical region of patients with macular degeneration. We summarized studies of binocular visual function with fMRI. We commented on the loci of visual area maps on ordinary MR images based on visual area mapping with the recent fMRI technique. 3. We evaluated cyanopsia by means of achromatic-point settings before and after intraocular lens implantation for cataracts; we then found a large shift of the achromatic point observed within 1 hour after eyepatch removal.

#### *Low vision (poor visual acuity)*

We performed stabilometry for 40 patients with low vision and found that tunnel vision might contribute to decreased control of posture in patients. We found that patients with oscillopsia have poor visual short-term memory. We measured the reading profiles of patients with oscillopsia and found that severe oscillopsia does not contribute to visual acuity loss but does cause severe deterioration of maximal reading speed; therefore, we reported that such patients read more easily when the text size is larger. We introduced the activities of the Kanagawa Low Vision Network, which was established to improve the quality of low-vision care in Kanagawa Prefecture. We tried short-term admissions for the rehabilitation of patients with low vision and evaluated outcomes with the 25-Item Visual Function Questionnaire. We summarized dos and don'ts of perimetry for patients with unilateral spatial inattention and introduced the quantitative measurement of visual extinction. We showed in patients with brain damage that testing with Teller Acuity Cards showed significantly higher visual acuity than did ordinary visual acuity testing with Landolt rings. We reported on trends in the study of artificial eyes.

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