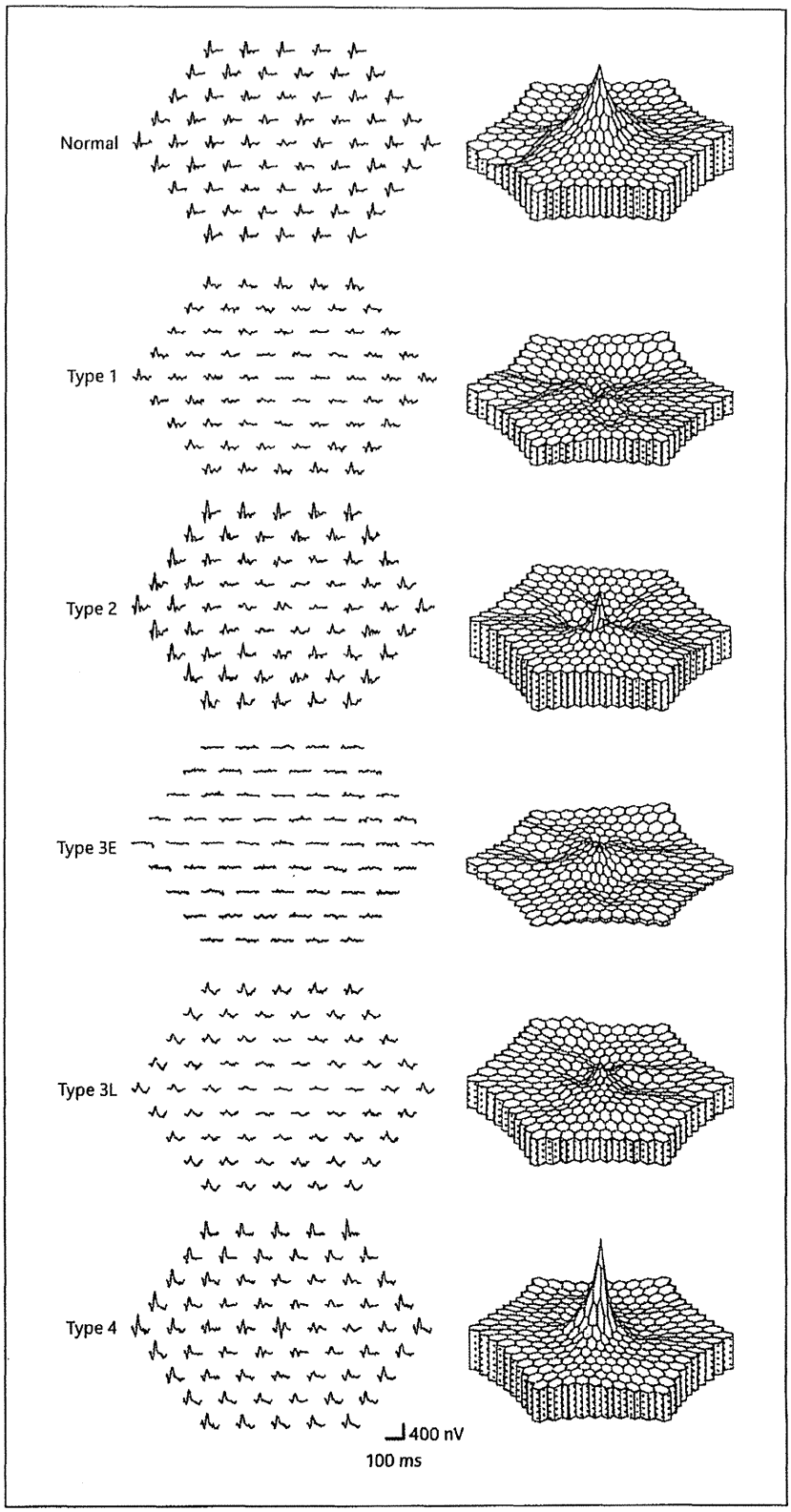

Fig. 3. Trace arrays of mfERGs (left) and 3D display of the amplitude densities of P1 (right) of a normal eye and of eyes with type 1 (patient 1), type 2 (patient 10), type 3E (patient 11), type 3L (patient 17), and type 4 SFF (patient 25). Type 3 was divided into two subtypes: early onset (3E) and late onset (3L).

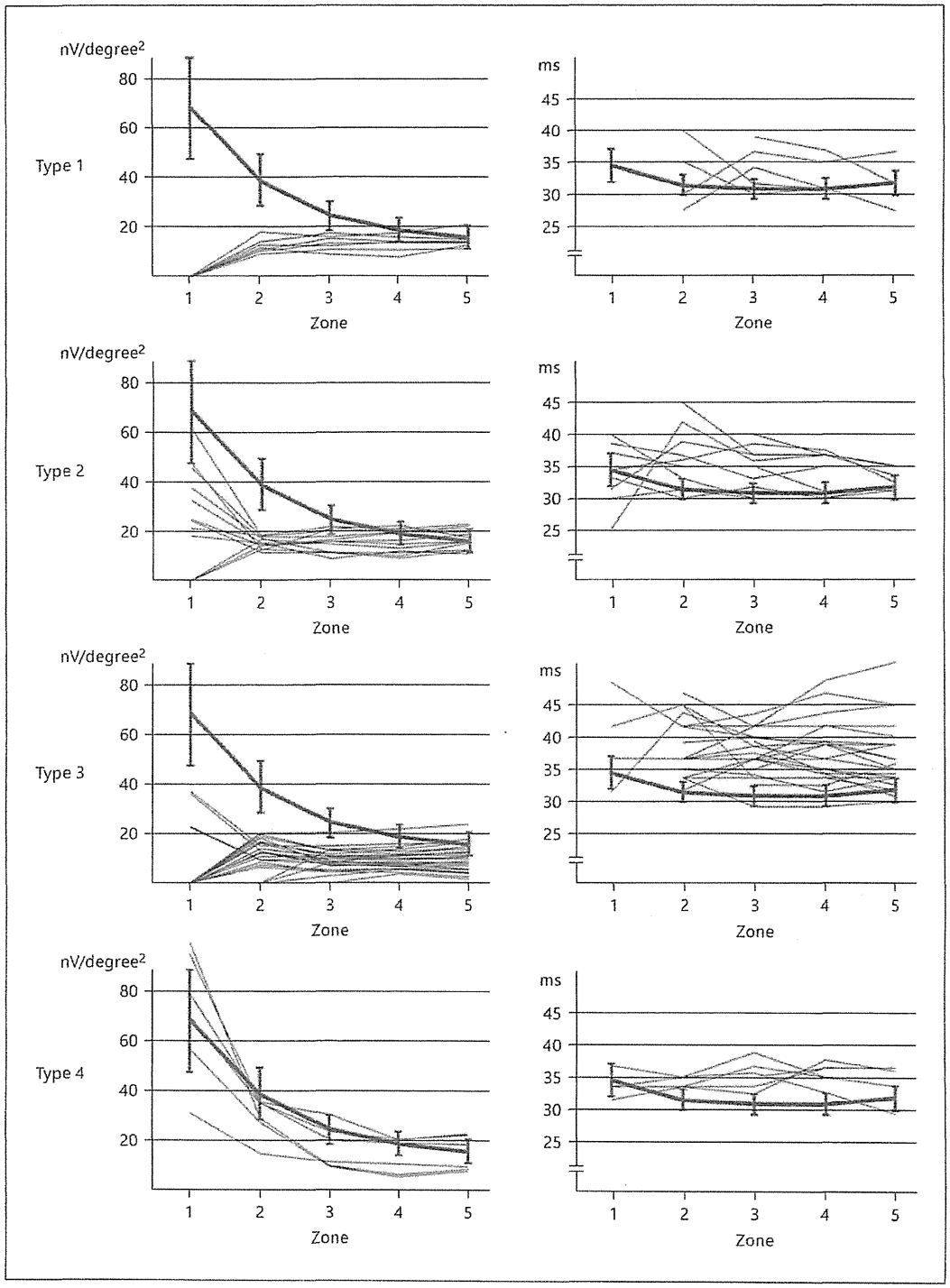

Fig. 4. Graphs of response density (left) and implicit time (right) of P1 in each zone. Thick lines with vertical bars: averages and standard deviations for normal subjects. Fine lines: individual values for eyes with SFF.

On the other hand, the eyes with type 2 or type 4 SFF had milder retinal impairments than the type 3 eyes. The full-field ERG photopic and scotopic b-waves in the eyes with type 2 or type 4 SFF were normal in most cases (table 1), and the mfERGs were normal in the mid-periphery (fig. 4). The averaged response density of P1 of the mfERGs was reduced in 7 of 10 eyes with type 2 SFF and in 3 of the 6 eyes with type 4 SFF. The response densities were >60% of the lower limit for normal subjects (table 1); however, the delayed implicit times in the eyes with type 2 or type 4 SFF suggest a mild and diffuse dysfunction of the middle retinal layers including signal transmission.

Recently, it was found that foveal sparing observed by ophthalmoscopy and/or fundus autofluorescence imaging resulted in relatively well-preserved visual acuity in patients with SFF [11, 13, 14]. Westeneng-van Haaften et al. [11] reported that all their SFF patients with foveal sparing had normal mfERG response densities in the foveal area. In our study, 8 of the 12 eyes with type 2 SFF and all eyes with type 4 SFF showed a recordable mfERG response in zone 1 (table 1; fig. 4), and some had a vision of 20/20 with sparing of the fovea. These patients had dark-red foveal pigmentation (types 2 and 4 in fig. 1); however, we did not perform fundus autofluorescence imaging on these patients. During fluorescein angiography, choroidal silence was seen diffusely in 18 patients, and at the posterior pole in 5 patients (table 1), but we did not find any significant relationship between the area of choroidal silence and the depression of mfERG responses.

SFF is slowly progressive, and one stage of the disease could progress to another stage [7]. Suzuki and Hirose [8] reported a 9-year-old boy who had a typical fundus appearance of SFF with relatively good full-field ERG responses at the initial visit; however, 17 years later, he was found to have the typical fundus appearance of retinitis pigmentosa with nonrecordable full-field ERGs.

Lois et al. [9] classified the retinal dysfunctions in patients with SFF into three types, namely, macular-localized dysfunction, diffuse cone dysfunction, and diffuse cone and rod dysfunction. Based on this classification, Fujinami et al. [15] reported that the retinal dysfunction localized in the macula can progress to diffuse cone dysfunction, and the diffuse cone dysfunction can progress to diffuse cone and rod dysfunction, during a longitudinal clinical follow-up. Thus, the classification of SFF based on the fundus appearance is clinically useful but does not always represent the true nature of this disease.

Limitations of this study are the small number of eyes, especially with type 1 and type 4 SFF, the absence of longitudinal observations of the cases, and the lack of genetic analysis. Visual fixation during the mfERG recordings also matters with patients with a large central scotoma. Genetic studies are important to determine the type of retinal degeneration, but they have not been established as routine clinical tests at the present time for SFF.

In conclusion, the mfERG findings indicate that each subtype of SFF has unique characteristics corresponding to the abnormal retinal functions. mfERGs will be helpful in evaluating the efficacy of newly developed experimental treatments for this disease, such as stem cell [30] or induced pluripotent stem cell [31] transplants.

Acknowledgements

We thank Mr. Hidetaka Kudo, Mayo Corporation, Aichi, Japan, who supported us technically during our research, and Mrs. Elizabeth Park and Ms. Charlene Skladzien for their technical assistance.

Disclosure Statement

None of the authors has a financial conflict of interest regarding any of the products, devices, or drugs used in this study.

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Clinical Ophthalmology

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CASE REPORT

Optical coherence tomographic findings at the fixation point in a case of bilateral congenital macular coloboma

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Background: Congenital macular coloboma is a rare ocular disease that consists of atrophic lesions in the macula with well-circumscribed borders. We report the findings of spectral domain optical coherence tomography (SD-OCT) at the fixation point in a case of bilateral macular coloboma.

Case report: The subject is a 4-year-old boy. He visited our hospital at age 1 year and 4 months for the evaluation of strabismus. The fundus examination of both eyes showed round-shaped sharply-demarcated atrophic lesions involving the macula with large choroidal vessels and bared sclera at the base. Immunologic tests including toxoplasmosis, rubella, varicella, herpes virus, and human T-cell leukemia virus were all negative. At age 4 years and 1 month, cycloplegic refraction showed insignificant refractive errors and his best corrected visual acuity was 0.6 bilaterally. The SD-OCT showed a crater-like depression accompanying atrophic neurosensory retina, and the absence of retinal pigment epithelium and choroid. Examination of the fixation behavior by visuscope showed steady fixation with an area 0.5° nasal to the nasal edge of the atrophic lesion bilaterally. The SD-OCT findings at fixation area showed remaining normal retinal structures involving inner segment-outer segment (IS/OS) junction line.

Conclusion: The findings of SD-OCT have been shown to be useful in the diagnosis of macular coloboma. In the fixation point, the structure of retina and choroid were well preserved.

Keywords: pediatric macular disease, macular structure, strabismus

Introduction

Congenital macular coloboma appears as atrophic lesions with well-circumscribed borders unilaterally or bilaterally, which result in a nonprogressive decrease in visual acuity. These findings are also seen in patients with intrauterine infection, especially toxoplasmosis. Spectral domain (SD) optical coherence tomography (OCT) is a beneficial tool to make a diagnosis of macular coloboma. We report on the SD-OCT findings in a patient with bilateral macular coloboma. Furthermore, we show the retinal structures at the fixation point.

Case report

The subject was a 4-year-old boy. He visited our hospital at age 1 year and 4 months for the evaluation of strabismus. He had medical history of ventricular septal defect. The anterior segments were normal. The Hirschberg test revealed an exotropia of 10°. The fundus examination of both eyes showed round-shaped sharply-demarcated atrophic lesions involving the macula with large choroidal vessels and the bared sclera at the base (Figure 1). The atrophic lesion was approximately 1 disc diameter (DD) in height and 1.2 DD in width in the right eye, and 1.2 DD in height and 1.5 DD in width

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http://dx.doi.org/10.2147/OPTH.S63595

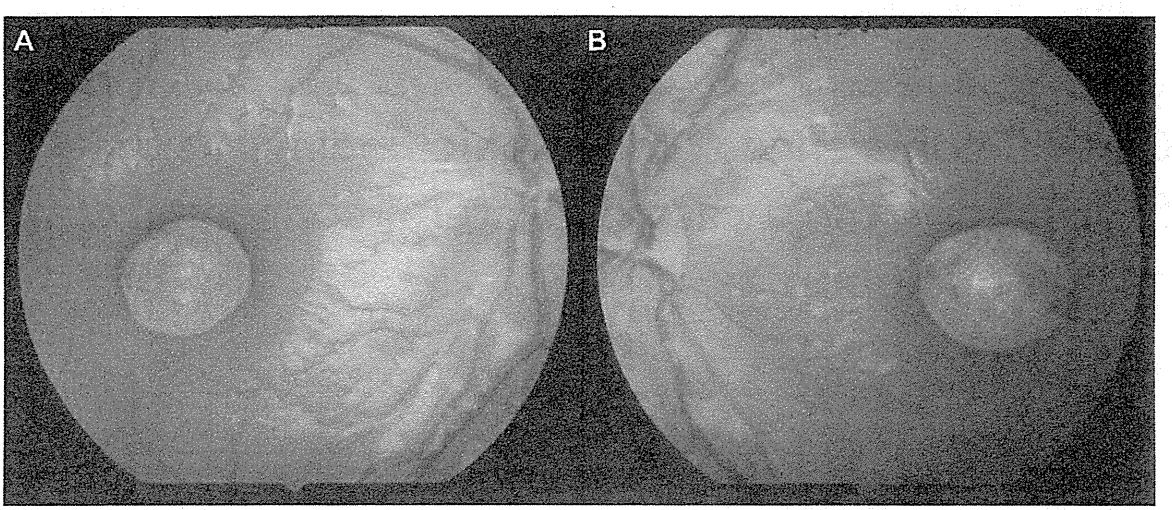

Figure 1 Fundus photographs taken at age 1 year and 4 months.
Notes: (**A**) Right eye. (**B**) Left eye.

in the left eye. Some retinal vessels were disturbed at the margin. Immunologic tests including toxoplasmosis, rubella, varicella, herpes virus, and human T-cell leukemia virus were all negative. Anti-toxoplasma antibody was also negative in his mother. At age 4 year and 1 month, cycloplegic refraction showed insignificant refractive errors and his best corrected visual acuity was 0.6 bilaterally. No stereoacuity was detected with TNO stereo test and Titmus Stereo Test. The fundus examination showed no significant changes except for some pigmentation in the atrophic lesions (Figure 2). Examination of fixation behavior by visuscope showed steady fixation in the normal area close to the nasal edge of the atrophic lesion bilaterally (Figure 2). The SD-OCT (Cirrus HD-OCT; Carl Zeiss Meditec AG, Jena, Germany) showed a crater-like depression accompanying atrophic neurosensory retina, and the absence of the retinal pigment epithelium and choroid (Figure 3). The retinal structures of the fixation area were normal involving IS/OS junction line (Figure 3). In addition, it was not difficult to get the SD-OCT images on him with dilated pupil and without any anesthesia. At age 5 years and 3 months, his best corrected visual acuity was 1.0 OD and 0.8 OS.

Discussion

Congenital macular coloboma is thought to result from incomplete differentiation of the arcuate bundles along the horizontal raphe during development.[1] However, its morphology of the macular lesion is very similar to that of postinflammatory congenital macular scars resulting from ocular toxoplasmosis. Differentiation between macular coloboma

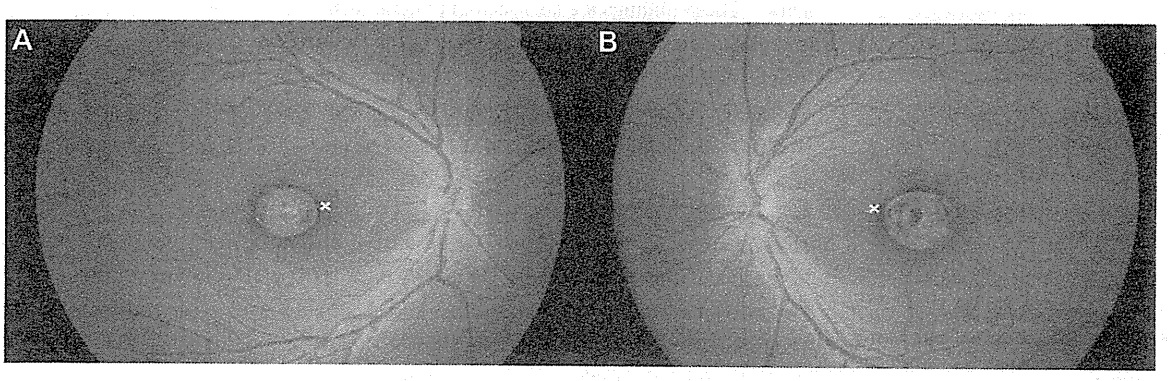

Figure 2 Fundus photographs taken at age 4 years and 1 month.
Notes: (**A**) Right eye. (**B**) Left eye. The white crosses show the fixation points.

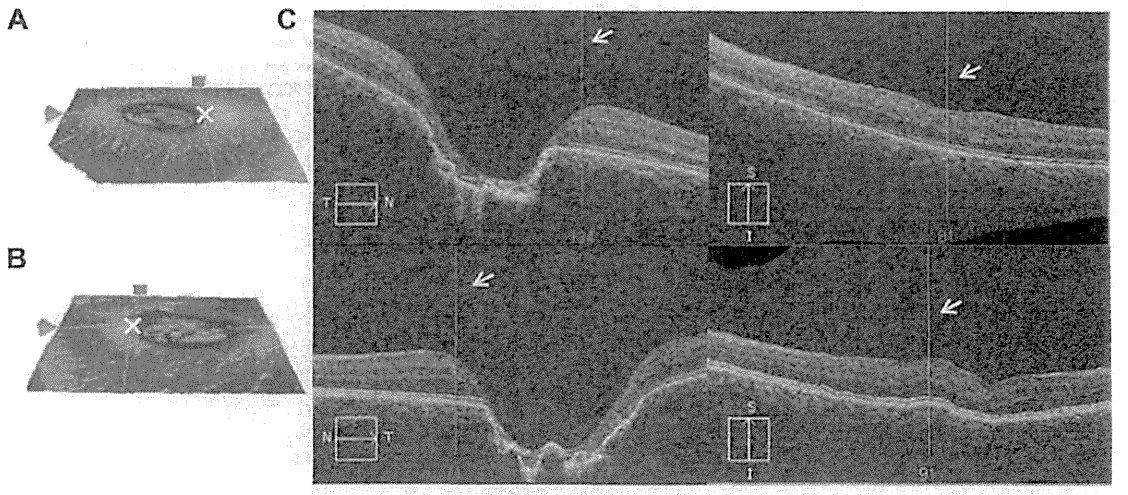

Figure 3 SD-OCT images at age 4 years and 1 month.
Notes: (**A**) Right eye. (**B**) Left eye. (**A** and **B**) ILM-RPE map on the macular cube 200×200. Cross points of vertical and horizontal lines show fixation points (white crosses). (**C**) B-scans. The bars show the fixation points (white arrows).
Abbreviations: ILM-RPE, internal limiting membrane – retinal pigment epithelium; SD-OCT, spectral domain optical coherence tomography.

and postinflammatory scarring is important to decide the course of treatment. SD-OCT is a beneficial tool in making a differential diagnosis of macular degeneration.[2]

The OCT findings of this case showed absence of the retina and choroid. This structure conformed well to the findings of previous reports.[2–5] On the other hand, the OCT features of congenital toxoplasmosis macular scars are retinal thinning, retinal pigment epithelium hyper-reflectivity, excavation, intraretinal cysts, and fibrosis.[6,7] Added to the results of immunologic test, the OCT findings showed that the diagnosis of this patient was congenital macular coloboma.

The fixation points of the patient were located close to the nasal edge of the atrophic lesion. The OCT findings suggested that the retinal structures of the fixation points were well conserved involving IS/OS junction line. It was thought that the patient made adaptation to reflect the image on the comparatively healthy peripheral retina. This phenomenon is known as eccentric viewing.[8,9] There have been no reports on the structure of the fixation point, although the retinal structure of the fixation point influences the visual acuity and binocularity of patients.

The visual acuity from previous reports[1–4,10–12] ranged from light perception to 0.8. However, the atrophic lesions of this case were comparatively smaller than other cases and the conserved normal retinal structures near the fovea resulted in the patient having better visual acuity than those of other cases, although he had exotropia and no stereoacuity. When his dominant eye perceived an image on the fixation point, the fellow eye perceived the image on the atrophic lesion, but the image on the atrophic lesion did not reach the visual cortex. This suggests that his monofixation is not caused by suppression.

Conclusion

The SD-OCT imaging is helpful in making a diagnosis and determining the course of treatments. Furthermore, the structure of the fixation point has a critical influence on the visual acuity and prognosis of congenital macular coloboma.

Disclosure

The authors report no conflicts of interest in this work.

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Novel nonsense and splice site mutations in CRB1 *gene in two Japanese patients with early-onset retinal dystrophy*

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Documenta Ophthalmologica
The Journal of Clinical Electrophysiology and Vision - The Official Journal of the International Society for Clinical Electrophysiology and Vision

ISSN 0012-4486
Volume 130
Number 1

Doc Ophthalmol (2015) 130:49-55
DOI 10.1007/s10633-014-9464-8

Springer