Full title: Superior Segmental Optic Hypoplasia Found in the Eye Health Care Project in Tajimi

Running title: Superior Segmental Optic Hypoplasia in Tajimi

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Contents of manuscript

Title page	1 page
Abstract/key words	1 page
Text	7 pages
References	2 pages
Figures	1 figure
Tables	5 tables

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Abstract

Purpose: To investigate the prevalence and characteristics of superior segmental optic hypoplasia in Japanese.

Methods: We studied 14,779 subjects, aged 40 years or older, who underwent IMAGEnet fundus photography for a large-scale eye disease screening project conducted in Tajimi, Japan. A single researcher reviewed all of the photographs for the presence of ocular abnormality in the optic nerve head and retina, paying special attention to the presence of superior segmental optic hypoplasia.

Results: Fundus photographs of 28,396 eyes of 14,431 cases were successfully reviewed. We found superior segmental optic hypoplasia in 54 eyes of 37 cases (0.2% per eye and 0.3% per case). Of the 37 cases, 23 (0.2%) showed the corresponding visual field defect in at least one eye.

Conclusion: The prevalence of superior segmental optic hypoplasia is 0.3% in Japanese.

Key words: superior segmental optic hypoplasia, prevalence, optic disc anomaly, glaucomatous optic neuropathy

Introduction

Superior segmental optic hypoplasia is a congenital anomaly affecting the optic nerve head and the retina. This condition is ophthalmoscopically characterized by a relatively superior entrance of the central retinal artery, pallor of the superior optic disc, a superior peripapillary scleral halo, and thinning of the superior peripapillary nerve fiber layer.[1-8] Perimetry reveals inferior altitudinal defect or inferior sector defect connecting to the blind spot. Visual acuity is not affected in most cases. In an optical coherence tomographic study of this condition, Unoki et al. suggested the usefulness of optical coherence tomography for detecting mild cases of superior segmental optic hypoplasia.[1]

Superior segmental optic hypoplasia was originally reported as a kind of optic nerve hypoplasia. The term, superior segmental optic hypoplasia, was generally accepted after Kim et al. investigated an association of this condition with maternal type I diabetes mellitus.[2] Hoyt coined the term, topless optic disc,[3] to emphasize the appearance of the optic disc. Although the association with maternal diabetes is suspected, the etiology of this congenital disorder is not well understood. Unoki et al. reported familial cases of superior segmental optic hypoplasia and suggested the involvement of a genetic factor in this condition.[1]

Because thinning of the neuroretinal rim of the optic nerve head occurs in superior segmental optic hypoplasia, predominantly in the nasal superior region, differentiation of this condition from glaucomatous optic neuropathy is of clinical importance. In particular, normal-tension glaucoma resembles superior segmental optic hypoplasia in terms of its localized rim thinning and the lack of elevated intraocular pressure.

To investigate the basic features of superior segmental optic hypoplasia, especially its prevalence, we conducted the present study in a large-scale eye disease screening project.

Materials and Methods

The data used in the present study were obtained at the Eye Health Care Project in Tajimi and were provided by the Japan Glaucoma Society, which conducted the large-scale eye disease screening project. Our usage of the data was approved by the Japan Glaucoma Society, which has contracted with Tajimi City so that the society can use the data strictly for scientific purposes as long as subject anonymity is preserved. Additionally, informed consent was obtained from all participants before participating in the eye disease screening project and all of them gave the Japan Glaucoma Society permission to use the individual data for scientific research on condition of anonymity. The details of the Eye Health Care Project in Tajimi will be published elsewhere.[9] In short, the study was based on a large-scale eye disease screening project conducted in Tajimi City, Gifu, Japan between September 2000 and October 2001. The project was comprised of two study populations: one consisted of 4,000 randomly selected citizens aged 40 or older who underwent a detailed ophthalmological check-up, and the other consisted of a general screening for the general population aged 40 or older. In the latter, the following ophthalmological examinations were conducted for both eyes: visual acuity testing, refractometry with a refractometer (KP-8100PA, Topcon, Tokyo, Japan), corneal thickness measurement with an SP-2000P (Topcon, Tokyo, Japan), perimetry with an FDT (frequency doubling technology) screener (Humphrey Instruments, San Leandro, CA) with the C-20-1 screening program, 45-degree fundus photography with an IMAGEnet 6S (Topcon, Tokyo, Japan), applanation tonometry with a Goldmann tonometer, slit-lamp biomicroscopy, and van Herick testing. In addition, the participants were requested to fill out a questionnaire including their medical history, and their systemic blood pressure, body weight, and height were also measured. Since most of the participants were unfamiliar with FDT testing, the test was repeated after repeated full explanations of the testing and the second result was adopted if the first result was abnormal or unreliable. While the subject's

ethnicity was not determined in the questionnaire, practically speaking, all of the participants were Japanese. The general screening targeted 50,165 citizens aged 40 or older. Of the 50,165 citizens, 14,779 participated in the screening, yielding a response rate of 29.5%. Additionally, we offered a second, voluntary definitive examination on another day to participants who were suspected to have any ocular diseases. At the definitive examination, visual field testing with a Humphrey Field Analyzer (HFA) using the 30-2 SITA Fast program was conducted for subjects with suspected optic disc abnormalities of any type.

In the present study, all of the 45-degree IMAGEnet fundus photographs of the above-mentioned 14,779 participants were reviewed for the presence of ocular abnormality in the optic nerve head and the retina of the posterior pole by one of the authors (TY), who was also one of the chief investigators for the Eye Health Care Project in Tajimi. The reviewer paid special attention to the presence of superior segmental optic hypoplasia. The subject information, except for the bilateral fundus photographs, was masked to the reviewer. The definition of superior segmental optic hypoplasia in the present study was: rim thinning of the optic nerve head most prominent in the superior nasal region with corresponding nerve fiber layer defects in the superior nasal region in at least one eye. In cases with superior segmental optic hypoplasia, visual function, *i.e.*, visual acuity, the FDT screener result, and the HFA result, if available, was reviewed after reading the fundus photographs. In addition, demographic and other ophthalmological data were reviewed. An FDT abnormality was defined as the presence of test points with a *p* value less than 5% in the probability map. An HFA abnormality was defined based on the criteria proposed by Anderson and Patella[10]: when the pattern standard deviation probability plot showed a cluster of three or more nonedge contiguous points having sensitivity with probability of less than 5%, with one of these having a probability of less than 1% in one hemifield, the hemifield was rated as abnormal. If the corresponding inferior defect in the FDT screening or the HFA testing was present, the eye was rated

as superior segmental optic hypoplasia definite; if not, it was rated as superior segmental optic hypoplasia suspect.

The data were analyzed using StatView® version 5.0 (SAS Institute Inc., Cary, USA) on a personal computer. Differences among the groups were evaluated using chi-square test when applicable.

Results

Of the 14,779 participants in the screening project, 45-degree IMAGEnet fundus photographs of 28,396 eyes of 14,431 cases were successfully reviewed. A total of 1,162 eyes of 814 cases were not used because the fundus photos were unavailable for 312 eyes and because the photos were of poor quality for 850 eyes. The age and gender distribution of the study population is shown in Table 1. Of the 14,431 cases reviewed, we found 54 eyes of 37 cases of superior segmental optic hypoplasia (0.2% per eye and 0.3% per case): 23 cases (0.2%) were superior segmental optic hypoplasia definite in at least 1 eye and the remaining 14 cases (0.1%) were suspect. Of the 23 definite cases, 5 were definite bilaterally, 5 were definite in 1 eye and suspect in the other eye, and 13 were unilateral. Of the 14 suspect cases, 7 were bilateral and 7 unilateral. The age and gender distribution of superior segmental optic hypoplasia found in the present study is shown in Table 2 (Table 2A for the overall cases and Table 2B for the definite cases). There was a statistically significant difference in the prevalence among age groups (p=0.0103 and p=0.0425, for overall and definite cases, respectively). No significant gender difference was found (p=0.1765 and p=0.8942, for overall and definite cases, respectively).

Tables 1A & 1B, Tables 2A & 2B

The data for the 37 superior segmental optic hypoplasia cases found in the present study are summarized in Table 3 and example fundus photos are shown in Fig 1. Of the 37 superior segmental optic hypoplasia cases, 10 were male and the remaining 27 were female. The age was 53.1 ± 10.3 years (mean ± standard deviation) and ranged from 40 to 76 years. The visual acuity was better than or equal to 20/20 in 40 eyes (74%) and worse than 20/25 in 2 eyes (4%) of the 54 eyes with superior segmental optic hypoplasia. When the left eyes were selected in bilateral cases and the affected eyes were selected for unilateral cases, the refractive error in spherical equivalent was -1.54 ± 2.72 D (mean ± standard deviation) and ranged from -8.25D to +1.88D; the intraocular pressure was 14.2 ± 2.5 mmHg (mean ± standard deviation) and ranged from 9 mmHg to 19 mmHg. Maternal diabetes was not identified because the medical questionnaire did not address this issue. One case of superior segmental optic hypoplasia was reported to have diabetes mellitus but the remaining 36 cases were not.

Table 3 and Figure 1

Discussion

The definition of superior segmental optic hypoplasia employed in the present study was partly different from others. Originally, this anomaly is characterized by a relatively superior entrance of the central retinal artery, pallor of the superior optic disc, a superior peripapillary scleral halo, and thinning of the superior peripapillary nerve fiber layer.[1-8] However, optic disc pallor and superior peripapillary scleral halo are not necessarily seen in all patients, at least in Japanese. According to

Unoki et al.[1] superior scleral halo was not seen in 5 of 7 affected eyes in Japanese. In a study subjected four Japanese cases by Hashimoto et al.[7] only one eye showed superior scleral halo and disc pallor. Additionally, optic disc pallor was not found in Japanese cases with highly suspected superior segmental optic hypoplasia.[11,12]

The present study revealed that the prevalence of superior segmental optic hypoplasia is 0.3% in Japanese. This is the first report on the prevalence of superior segmental optic hypoplasia based on a large-scale eye disease screening. About two-thirds of the cases had the corresponding visual field defect. Because a diagnosis of superior segmental optic hypoplasia is based on optic disc appearance and the corresponding visual field, diagnostic measures including IMAGEnet fundus photography and an FDT screener seem to be appropriate for the detection of this disease. It should be emphasized that, in contradistinction to an epidemiological study, the present study was based on a large-scale screening and, thus, the 0.3% prevalence rate needs further validation. Additionally, the reason for age difference found in the present study should be sought though we cannot explain it at this moment.

Superior segmental optic hypoplasia resembles glaucomatous optic neuropathy in terms of localized rim thinning when the optic disc has a cupping. In glaucoma cases with normal intraocular pressure, *i.e.*, normal-tension glaucoma, differentiation with superior segmental optic hypoplasia is important since both conditions lack elevated intraocular pressure. The key point of differentiation is the localization of the rim thinning and the characteristic visual field changes: inferior altitudinal defect or inferior sector defect connecting to the blind spot. Since the 0.3% prevalence of superior segmental optic hypoplasia is substantial and represents about one-tenth of that of normal-tension glaucoma in Japanese,[9,13] awareness of this condition should increase in clinical practice.

In conclusion, we found that the prevalence of superior segmental optic hypoplasia is 0.3% in Japanese based on data from a large-scale eye disease screening.

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References

1. Unoki K, Ohba N, Hoyt WF. Optical coherence tomography of superior segmental optic hypoplasia. Br J Ophthalmol 2002;86:910-914.

2. Kim RY, Hoyt WF, Lessell S, Narahara MH. Superior segmental optic hypoplasia. A sign of maternal diabetes mellitus. Am J Ophthalmol 1989;107:1312-1315.

3. Landau K, Djahanshahi-Bajka J, Kirchschläger BM. Topless optic disks in children of mothers with type I diabetes mellitus. Am J Ophthalmol 1998;125:605-611.

4. Nelson M, Lessell S, Sadun AA. Optic nerve hypoplasia and maternal diabetes mellitus. Arch Neurol 1986;43:20-25.

5. Petersen RA, Walton DS. Optic nerve hypoplasia with good visual acuity and visual field defects. Arch Ophthalmol 1997;95:254-258.

6. Bjork A, Laurell CG, Laurell U. Bilateral optic nerve hypoplasia with good visual acuity. Am J Ophthalmol 1978;86:524-529.

7. Hashimoto M, Ohtsuka K, Nakagawa T, Hoyt WF. Topless optic disk syndrome without maternal diabetes mellitus. Am J Ophthalmol 1999;128:111-112.

8. Brodsky MC, Shroeder GT, Ford R. Superior segmental optic hypoplasia in identical twins. J Clin Neuro-ophthalmol 1993;13:152-154.

9. Iwase A, Suzuki Y, Araie M, et al. The prevalence and intraocular pressure of primary open-angle glaucoma in Japanese. The Tajimi Study. Ophthalmology *in press*

10. Anderson DR, Patella VM. Automated Static Perimetry, 2nd ed. St. Louis: Mosby; 1999.

11. Namba T, Wakakura M, Shirakawa S, Ishikawa S. Sectorial hypoplasia of the optic nerve. Neuro-ophthalmol Jpn 1987;4:444-450.

12. Okazaki S, Miyazawa H, Sekiya Y, et al. Partial hypoplasia of the optic nerve.

Neuro-ophthalmol Jpn 1987;4:438-443.

13. Shiose Y, Kitazawa Y, Tsukahara S, et al. Epidemiology of glaucoma in Japan. A nationwide glaucoma survey. Jpn J Ophthalmol. 1991;35:133-155.

Table 1. The age and gender distribution of the study population

A. Population targeted and actually screened

age (yrs.)	male	female	total
40-49	996/7,024	2,024/7,143	3,020/14,167
50-59	1,531/7,931	3,131/7,880	4,662/15,811
60-69	1,895/5,287	2,486/5,279	4,381/10,566
70-	1,162/3,822	1,554/5,799	2,716/9,621
total	5,584/24,064	9,195/26,101	14,779/50,165

Population actually screened / population targeted

Table 1. Continued

B. Population whose fundus photos were examined and subjected in the present study

age (yrs.)	male	female	total
40-49	985	2,009	2,994
50-59	1,513	3,101	4,614
60-69	1,861	2,427	4,288
70-	1,094	1,441	2,535
total	5,453	8,978	14,431

Table 2. The age and gender distribution of superior segmental optic hypoplasia found

A. Overall cases

age (yrs.)	male		female		total	
40-49	4/985	(0.4)	11/2,009	(0.5)	15/2,994	(0.5)
50-59	3/1,513	(0.2)	10/3,101	(0.3)	13/4,614	(0.3)
60-69	1/1,861	(0.1)	5/2,427	(0.2)	6/4,288	(0.1)
70-	2/1,094	(0.2)	1/1,441	(0.1)	3/2,535	(0.1)
total	10/5,453	(0.2)	27/8,978	(0.3)	37/14,431	(0.3)

Number of cases / population studied (prevalence in percent)

p=0.0103 for age and p=0.1765 for gender (chi-square test)

Table 2. Continued

B. Definite cases only

age (yrs.)	male		female		total	
40-49	3/985	(0.3)	7/2,009	(0.3)	10/2,994	(0.3)
50-59	3/1,513	(0.2)	4/3,101	(0.1)	7/4,614	(0.2)
60-69	1/1,861	(0.1)	2/2,427	(0.1)	3/4,288	(0.1)
70-	2/1,094	(0.2)	1/1,441	(0.1)	3/2,535	(0.1)
total	9/5,453	(0.2)	14/8,978	(0.2)	23/14,431	(0.2)

Number of cases / population studied (prevalence in percent)

p=0.0425 for age and p=0.8942 for gender (chi-square test)

Table 3. Superior segmental optic hypoplasia found in the present study.

Refractive error is expressed in spherical equivalent. The right eye of case 28 was rated as optic hypoplasia rather than superior segmental optic hypoplasia.

Abbreviations: FDT: frequency doubling technology screener, HFA: Humphrey Field Analyzer, D: diopter, SSOH: superior segmental optic hypoplasia, IOP: intraocular pressure, DM: history of diabetes mellitus, RE: right eye, LE: left eye, f: female, m: male, I: inferior defects; the number represents the number of defects, S: superior defects, ITD: inferior temporal defect, IAD: inferior altitudinal defect, GD: generalized depression, NA: not available, D: definite, S: suspect.

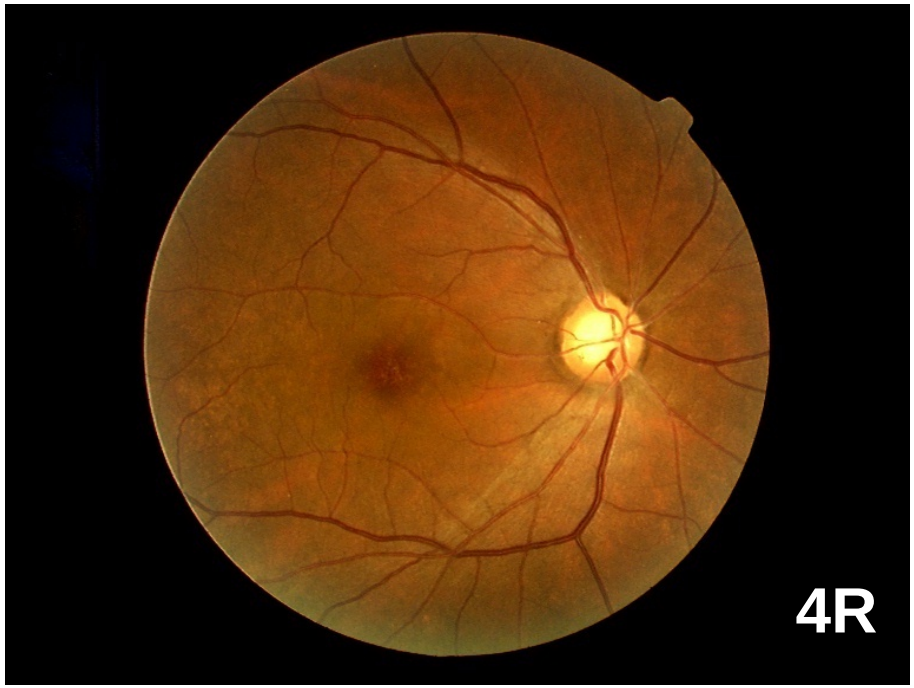
See attached sheet.

Figure legends

Fig. 1. Fundus photographs of superior segmental optic hypoplasia. Upper left: the right eye of case 4; upper right: the left eye of case 12; lower left: the left eye of case 18; lower right: the right eye of case 34.

Table 3

				visual acuity		FDT defects		HFA defects		refractive error (D)		IOP (mmHg)		type of SSOH	
case	sex	age (years)	DM	RE	LE	RE	LE	RE	LE	RE	LE	RE	LE	RE	LE
1	f	58	−	20/20	20/20	I−1 S−2	I−1	NA	NA	−0.25	−0.38	13	13	D	D
2	f	65	−	20/15	20/15	0	0	NA	NA	1.63	1.75	13	13	S	S
3	m	73	−	20/30	20/20	0	I−2	NA	NA	0.00	0.25	12	12	−	D
4	f	54	−	20/15	20/15	0	0	ITD	normal	−1.00	−1.00	14	15	D	−
5	m	58	−	20/25	20/15	0	0	NA	NA	0.88	0.63	17	17	S	S
6	m	56	+	20/15	20/15	I−1	0	NA	NA	0.13	−0.38	15	15	D	−
7	f	51	−	20/40	20/50	0	0	NA	NA	−6.63	−9.00	17	17	S	−
8	f	68	−	20/20	20/25	0	0	NA	NA	−7.38	−8.25	15	15	S	S
9	f	50	−	20/15	20/15	0	0	NA	NA	−0.75	−0.63	12	12	−	S
10	f	42	−	20/20	20/15	0	0	NA	NA	−2.38	−2.50	11	12	S	−
11	f	64	−	20/20	20/20	0	0	NA	NA	1.88	3.00	18	17	S	−
12	f	47	−	20/15	20/15	0	I−1	NA	NA	−3.25	−3.00	15	15	S	D
13	f	50	−	20/20	20/15	I−2	S−1	ITD	normal	−3.50	−4.00	16	16	D	−
14	f	42	−	20/20	20/20	0	0	NA	NA	−4.50	−5.50	15	15	S	S
15	m	46	−	20/15	20/20	0	0	ITD	normal	−1.50	−1.38	13	14	D	−
16	f	42	−	20/20	20/25	0	0	NA	NA	−3.25	−2.50	13	13	−	S
17	f	42	−	20/20	20/20	I−1	0	NA	NA	−3.63	−3.25	16	14	D	S
18	m	42	−	20/15	20/15	0	I−1	NA	NA	−0.13	−0.50	14	14	S	D
19	f	40	−	20/15	20/15	0	I−3	NA	NA	−1.38	−0.50	15	15	−	D
20	f	51	−	20/15	20/15	0	0	ITD	normal	−0.38	−0.13	13	12	D	−
21	f	76	−	20/40	20/50	I−4	0	IAD	normal	1.88	1.75	14	14	D	−
22	f	47	−	20/20	20/20	I−1	0	NA	NA	−1.00	−2.00	18	18	D	−
23	f	66	−	20/25	20/25	I−1	0	ITD	ITD	1.13	0.50	12	12	D	D
24	f	47	−	20/20	20/20	0	0	NA	NA	−2.63	−3.13	18	18	S	S
25	m	45	−	20/15	20/20	0	0	NA	NA	0.38	0.38	16	16	S	S
26	f	40	−	20/20	20/20	0	I−2	normal	IAD	−6.63	−7.00	12	12	−	D
27	f	52	−	20/15	20/15	0	S−4	NA	NA	0.00	0.88	11	10	−	S
28	m	57	−	20/15	20/15	I−1	I−4 S−2	GD	IAD	−5.38	−6.63	16	18	−	D
29	f	50	−	20/15	20/15	0	0	NA	NA	0.00	0.38	13	13	−	S
30	f	56	−	20/25	20/25	0	0	NA	NA	−4.69	−5.24	15	14	S	S
31	m	74	−	20/25	20/25	0	I−2	NA	NA	0.63	1.00	14	14	S	D
32	f	68	−	20/25	20/20	0	0	ITD	ITD	1.38	1.25	10	9	D	D
33	f	43	−	20/15	20/15	0	0	normal	ITD	0.13	0.25	14	14	−	D
34	m	61	−	20/20	20/25	I−1	0	NA	NA	0.50	0.75	13	11	D	S
35	f	46	−	20/15	20/20	0	S−2	ITD	ITD	−1.50	−0.75	19	19	D	D
36	f	50	−	20/25	20/20	I−1 S−1	S−2	NA	NA	−1.75	−1.50	17	17	D	−
37	m	47	−	20/15	20/15	0	I−2	ITD	IAD	−5.13	−3.63	11	11	D	D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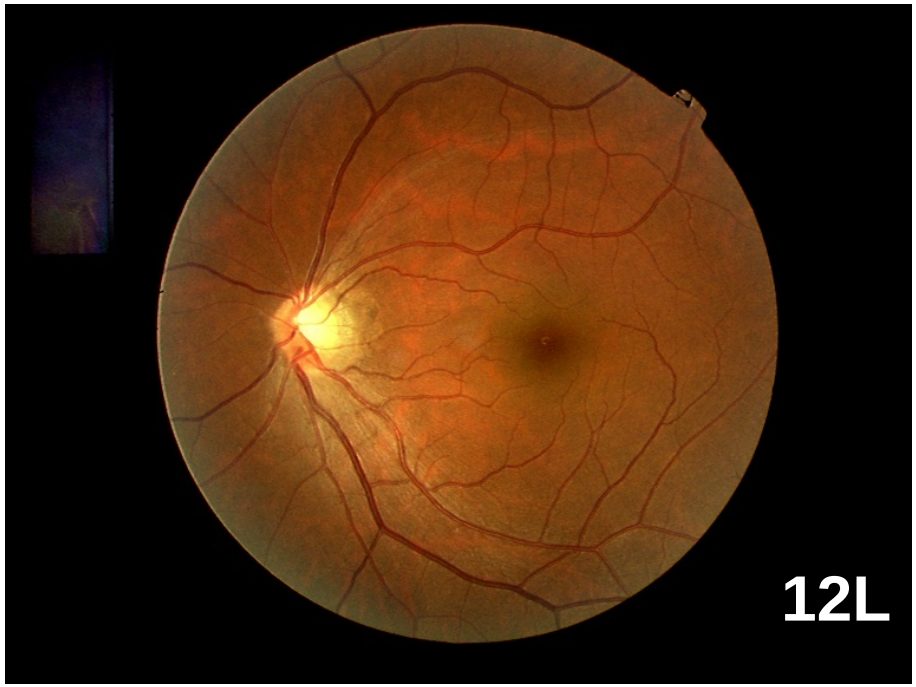
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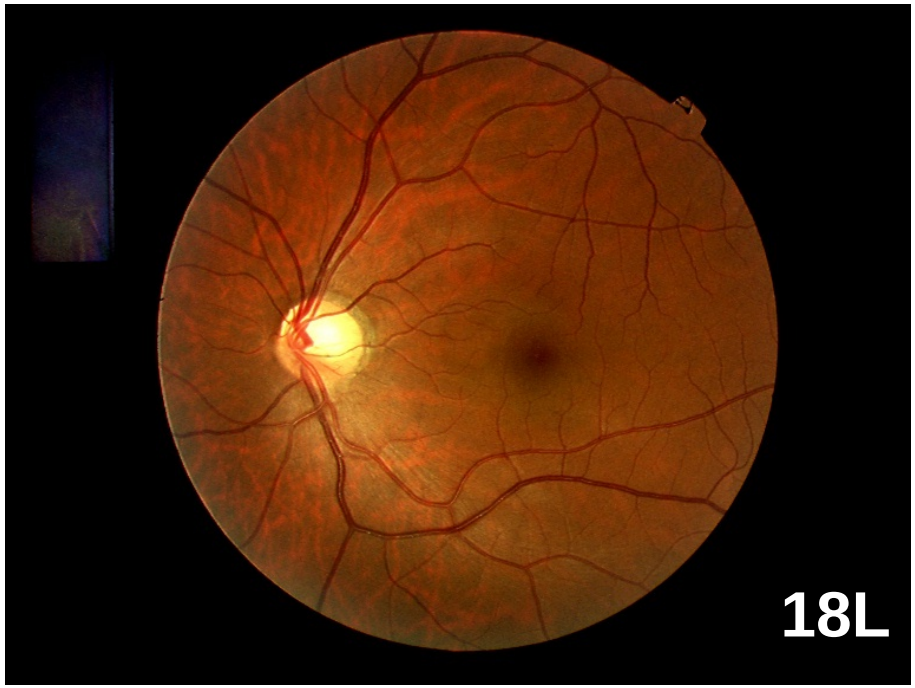
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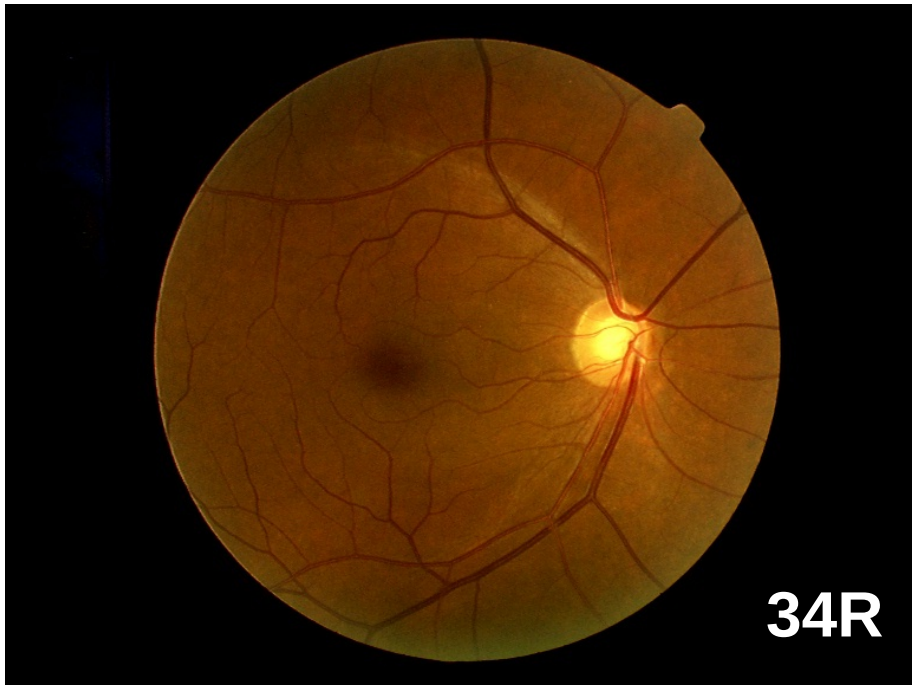
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