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Quantification and anatomic distribution of choroidal abnormalities in patients with type I neurofibromatosis

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Abstract *Background:* Choroidal abnormality manifesting as a bright patchy lesion under infrared monochromatic light has previously been described in neurofibromatosis type I patients in whom the choroid appears normal under conventional ophthalmoscopic examination or on the fluorescein angiogram. We investigated the correlation between patient age and the number of choroidal abnormalities, as well as the anatomic distribution of choroidal abnormalities in the fundus. *Methods:* We examined the fundus of 28 eyes in 14 patients with neurofibromatosis type I. Patients ranged in age from 2 to 38 years and were examined between April 2001 and April 2002 by confocal scanning laser ophthalmoscopy with infrared monochromatic light (780 nm wavelength). We divided the fundus into five regions (one within the retinal vascular arcade and those supero-temporal, infero-temporal, supero-nasal, and infero-nasal to it), and lesions on the border between regions were assigned to the region containing the greater part of the lesion. We studied the total number of choroidal abnormalities and the correlation between the total number and age. *Results:* A positive correlation was found between the total number of choroidal abnormalities and age (Spearman rank correlation coefficient, r=0.6209, P=0.0178). There was a significantly greater number of choroidal abnormalities in the arcade region than in the other four regions (ANOVA, P<0.001). *Conclusions:* Choroidal abnormalities tend to increase with age and are most often observed within the vascular arcade.

Keywords Choroid · Neurofibromatosis type 1 · Confocal scanning laser ophthalmoscopy · Infrared monochoromatic light

Introduction

Neurofibromatosis type I, also known as von Recklinghausen's disease, is an autosomal dominant disorder and one of the most common genetic diseases, affecting one in approximately 3000 persons [19]. Because its pathogenesis involves neural crest-derived melanocytes, Schwann cells, prevertebral ganglion and sympathetic neurons, it is considered a neurocristopathy [3, 12, 21]. Clinically, the disease is characterized by cafe-au-lait spots, freckle-like deposits in the skin, and neurofibroma. Ophthalmologic manifestations include Lisch nodules and optic nerve glioma [19]. Choroidal changes in the fundus have been reported [13, 18], but pathologic choroidal changes are difficult to detect by routine clinical examination under visible light [5]. Scanning laser ophthalmoscopy with near-infrared light is useful in detecting choroial changes. Near-infrared light penetrates more deeply into the choroid than visible light,

and the confocal nature of direct-mode of a scanning laser ophthalmoscopy provides better contrast than is possible with a fundus camera by eliminating scattered light from the choroid [5]. We reported previously that patients with neurofibromatosis type I have a high incidence of choroidal abnormalities detected by scanning laser ophthalmoscopy. These abnormalities appear as hypofluorescent patches in the early phase of indocyanine-green angiography and as bright patchy lesions under infrared monochromatic light; they are not seen in conventional ophthalmoscopic examination or by means of fluorescein angiography [22]. We studied choroidal abnormalities to determine whether a relation exists between age and the number of abnormalities. We also studied patterns of anatomic distribution in the fundus.

Materials and methods

We examined the fundus of 28 eyes in 14 patients with neurofibromatosis type I. Patients ranged in age from 2 to 38 years and were examined between April 2001 and April 2002 by confocal scanning laser ophthalmoscopy (Heidelberg Retinal Angiogram, Heidelberg, Germany) with infrared monochromatic light (780 nm wavelength) under mydriasis. The angle of photography was 30°. After the posterior fundus was photographed, the confocal scanning laser ophthalmoscope was adjusted to capture regions superior, supero-temporal, temporal, infero-temporal, inferior, infero-nasal, nasal, and supero-nasal to the posterior region within the retinal vascular arcade, in that order. After the images of each region were printed, the fundus was divided into five regions (a region within the arcade, and supero-temporal, infero-temporal, supero-nasal, and infero-nasal regions) (Fig. 1). Lesions on the border between regions were assigned to the region that contained the greater part of the lesion. The correlation between the total number of choroidal abnormalities and age and the patterns of anatomic distribution in the fundus were analyzed.

The correlation between patient age and the total number of choroidal abnormalities was calculated by the Spearman rank correlation coefficient. Trends in the number of choroidal abnormalities and distribution by location within the fundus were evaluated by adding the choroidal abnormalities in both eyes in a given region and testing the data by two-way analysis of variance (ANOVA) and Scheffe's multiple comparisons test. Difference in the number of choroidal abnormalities between the left eye and the right

Table 1 Number of choroidal abnormalities per region

			Left eye region					Right eye region				
Patient	Age (y)	Sex	1	2	3	4	5	1	2	3	4	5
1	2	F	0	2	0	1	1	2	1	1	1	0
2	3	M	2	0	0	0	0	0	0	0	0	0
3	4	F	1	0	0	0	0	1	0	0	1	0
4	5	F	5	1	1	0	1	4	0	1	1	0
5	7	F	4	2	2	1	2	0	0	2	0	1
6	8	M	11	5	4	5	4	1	1	2	3	1
7	12	M	2	1	0	1	2	2	0	0	0	0
8	14	M	2	0	0	0	0	3	0	0	1	2
9	15	M	21	2	1	2	2	29	0	1	2	1
10	16	M	18	3	4	3	3	19	10	10	12	7
11	17	M	5	5	6	2	2	7	4	6	3	3
12	23	M	10	0	9	11	0	21	9	7	6	0
13	30	F	7	4	2	3	3	0	2	3	0	2
14	38	M	21	7	15	2	1	14	8	7	2	0

F=female; M=male
Region 1: within the retinal vascular arcade. Region 2: supero-temporal to the upper arcade. Region 3: infero-temporal to the lower arcade. Region 4: supero-nasal to the optic disc. Region 5: infero-nasal to the optic disc

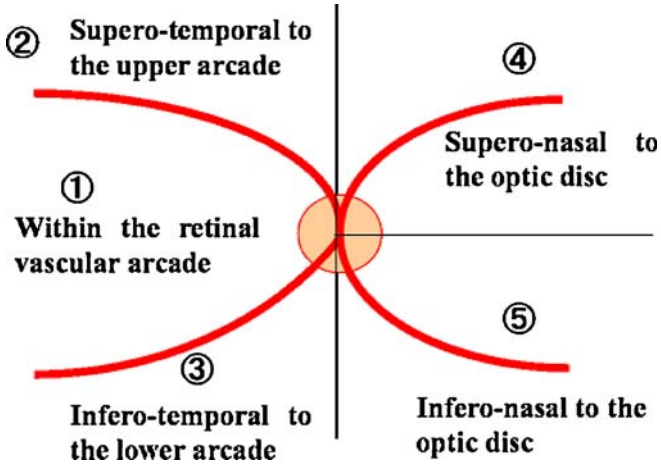

Fig. 1 Regions of the fundus, as defined in our study

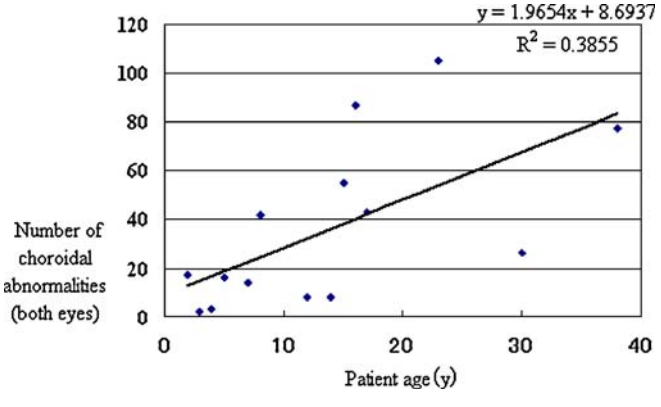

Fig. 2 Correlation between the number of choroidal abnormalities and patient age (r=0.6209, P=0.0178)

Table 2 Statistical analysis of the distribution of choroidal abnormalities

Region (total both eyes)	F value	P value
Region 1–Region 2	6.1108	0.000*
Region 1–Region 3	5.4086	0.000*
Region 1–Region 4	7.2883	0.000*
Region 1–Region 5	7.7340	0.000*
Region 2–Region 3	0.0214	0.9991
Region 2–Region 4	0.0518	0.9948
Region 2–Region 5	0.0955	0.9835
Region 3–Region 4	0.1399	0.9666
Region 3–Region 5	0.2074	0.9332
Region 4–Region 5	0.0066	0.9999

*$P<0.01$ by ANOVA and Scheffe's multiple comparisons test

eye was analyzed by the appropriate *t*-test. *P*-values of 0.05 or less were considered significant.

Results

The number of choroidal abnormalities per region for each of the 14 patients is shown in Table 1. The total number of choroidal abnormalities increased significantly with age, and there was a positive correlation (correlation coefficient, $r=0.6209$; $P=0.0178$) (Fig. 2). Choroidal abnormalities occurred significantly more often within the arcade region than in any of the other four regions (ANOVA, Scheffe's multiple comparisons test; $P<0.001$) (Table 2). There was no difference in the number of choroidal abnormalities between the left and right eyes (paired *t*-test; $P=0.1304$) (Figs 3 and 4).

Discussion

Among the National Institutes of Health diagnostic criteria of neurofibromatosis type I, features known to increase in number with age are neurofibromas [9] and Lisch nodules [10]. Although café-au-lait lesions and axillary or inguinal freckling have been confirmed to increase with age, such changes cannot be verified in geriatric patients because they become hidden by neurofibromas [9]. As with the Lisch nodules, unidentified bright objects seen on magnetic resonance images and thought to be hamartomas are seen in 60–90% of pediatric patients [1, 4, 7, 11]. However, there are no reports that the number of unidentified bright objects increases with age [4, 7], and, in fact, unidentified

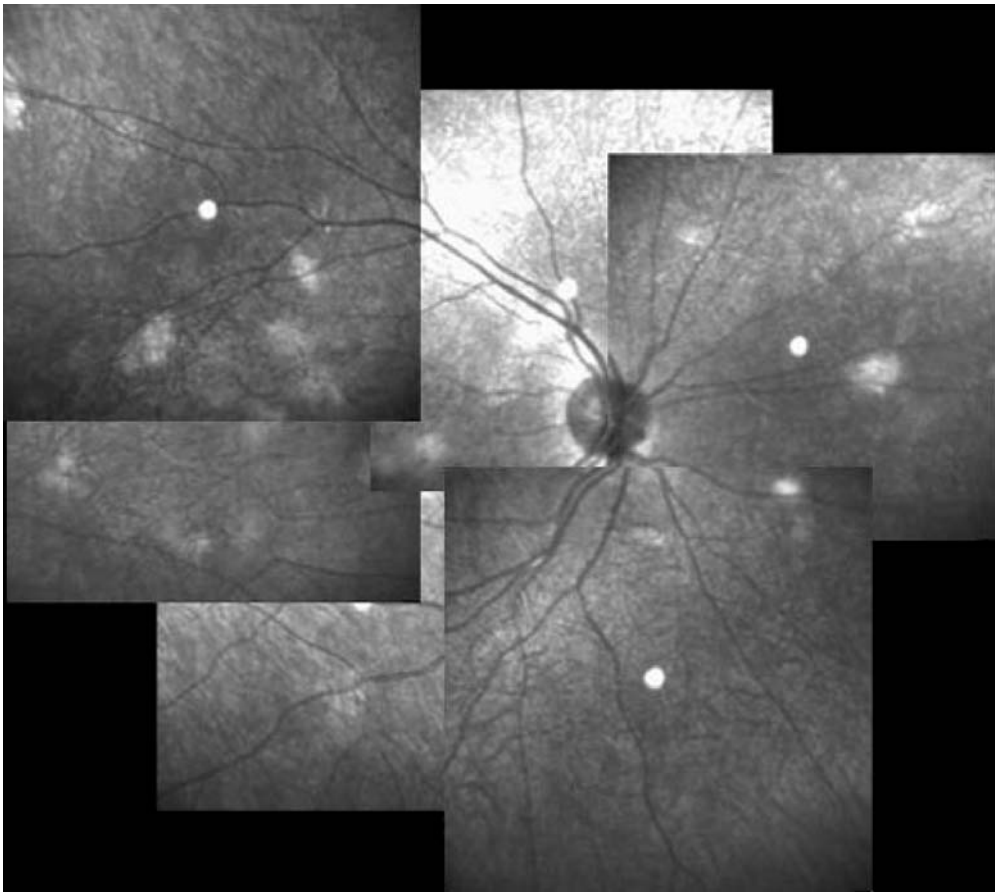

Fig. 3 Photographs obtained of patient 1, a 2-year-old child, during infrared-laser examination with a confocal scanning laser ophthalmoscope. Choroidal abnormalities are seen as bright patchy regions

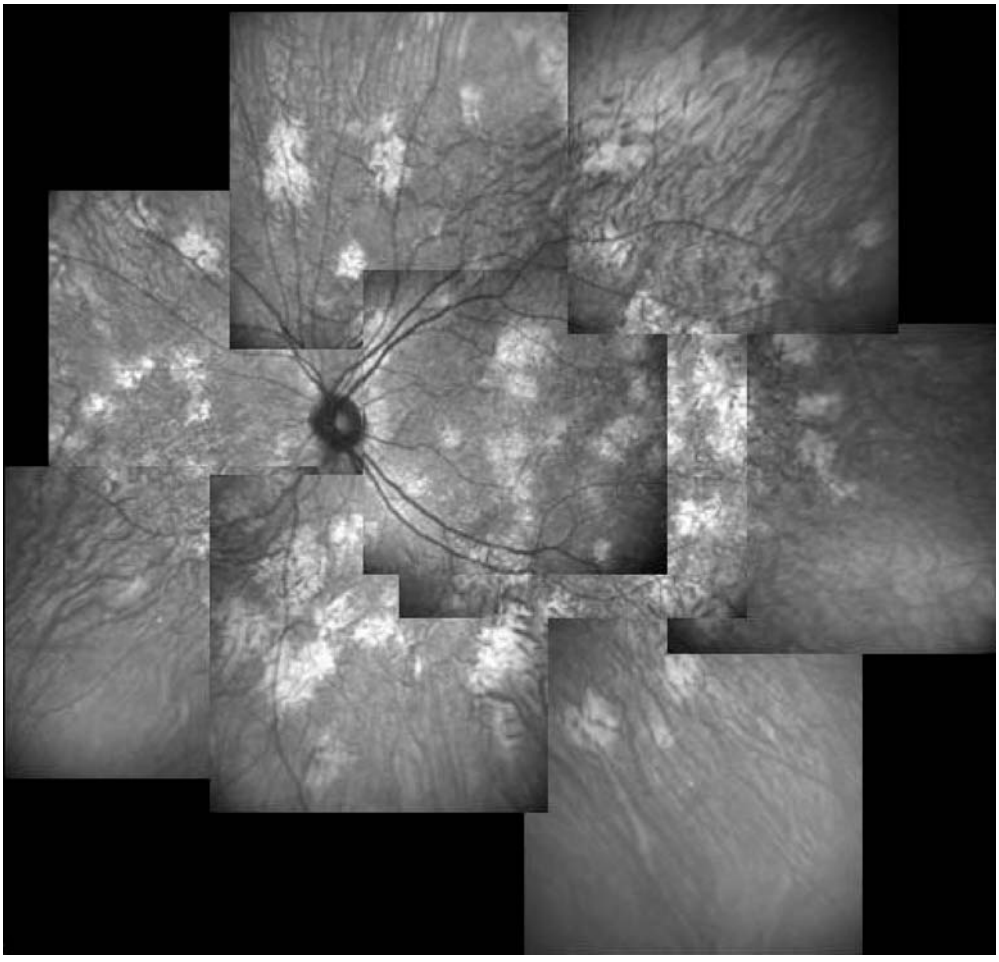

Fig. 4 Photographs obtained of patient 12, a 23-year-old man, during infrared-laser examination with a confocal scanning laser ophthalmoscope. Many bright patchy regions are seen

bright objects disappear in patients by the age of 20–30 years [11]. What is the basis for the age-related increase in the neurofibromas, Lisch nodules, and similarly in the choroidal abnormalities? It has been proposed that ultraviolet (UV) light is involved in the formation of Lisch nodules [14], which are proliferating melanocytic tissues. In the patient reported by Nichols et al., with a plexiform neurofibroma of one eye associated with complete ptosis, there was left-right asymmetry in the formation of Lisch nodules: only one was seen in the eye with complete ptosis, but 32 were seen in the unaffected eye [15]. The authors postulated that UV light, which is a melanocyte mitogen, was the underlying cause. Similarly, Nicolas et al. studied the distribution of Lisch nodules in the irises of 369 patients with neurofibromatosis type I and found that in 80% of cases, the nodules were located in the lower portion of the iris, where exposure to UV light is greater [16]. However, with regard to the location and development of choroidal abnormalities, UV light of 100–400 nm wavelength is essentially absorbed by the cornea, lens, and vitreous and thus does not reach the retina [2], so involvement of UV is unlikely. In neurofibromatosis type I patients, the choroid shows a proliferation of neural crest-derived melanocytes and neural cells, thickening the posterior fundus [14]. Of the two proliferating cell types, neural cells and melanocytes, melanocytes are rich in melanin, which absorbs near-infrared lights and at the same time causes the near-infrared light to be strongly backscattered due to Mie scattering from melanosomes [17]. Melanin in human skin is reported to provide strong contrast by the increased backscattering of infrared light such that the cytoplasm in heavily pigmented cells images brightly under confocal scanning laser microscopy [17]. Similarly, the densely packed, proliferating melanocytes in the choroid may appear as bright patchy lesions due to strong backscattering of the 780-nm wavelength near infrared light from melanosomes under confocal scanning laser ophthalmoscopy.

In the choroidal lesions of densely packed, proliferated neural cells and melanocytes, there might be a decrease in the volumetric percentage of blood components including hemoglobin, oxygenated hemoglobin, and water. Because these three blood components can absorb scattered near-infrared light [5], the relative decrease of the absorbers might cause the choroidal lesions to appear brighter than the surrounding choroid.

Anatomically, the choroid in the posterior region of the fundus is 0.22 mm thick; in the peripheral regions, it is only 0.10–0.15 mm thick [6, 8, 20]. There are numerous branches of short ciliary nerves and abundant melanocytes in the choroid of the posterior region. It is for these reasons that we believe these choroidal abnormalities are seen more frequently in the arcade region.

Conclusion

The choroidal abnormalities that are specific to neurofibromatosis type I appear to increase significantly with age and are most frequently observed within the vascular arcade.

References

1. Aoki S, Barkovich AJ, Nishimura K, Kjos BO, Machida T, Cogen P, Edwards M, Norman D (1989) Neurofibromatosis type 1 and 2: cranial MR findings. Radiology 172:527–534
2. Boettner EA, Wolter JR (1962) Transmission of the ocular media. Invest Ophthalmol Vis Sci 1:776–783
3. Bolande RP (1974) Neurocristopathies: a unifying concept of disease arising in neural crest maldevelopment. Hum Pathol 5:409–429
4. Duffner PK, Cohen ME, Seidel FG, Shucard DW (1989) The significance of MRI abnormalities in children with neurofibromatosis. Neurology 39:373–378
5. Elsner AE, Burns SA, Weiter JJ, Delori FC (1996) Infrared imaging of sub-retinal structures in the human ocular fundus. Vis Res 36:191–205
6. Green WR (1986) The choroid. In Spencer WH (ed) Ophthalmic pathology: an atlas and text book, 3rd edn. Saunders, Philadelphia
7. Griffiths PD, Blaser S, Mukonoweshuro W, Armstrong D, Milo-Manson G, Cheung S (1999) Neurofibromatosis bright objects in children with neurofibromatosis type 1: a proliferative potential? Pediatrics 104:e49
8. Hogan MJ, Alvarado JA, Weddell JE (1971) Histology of the human eye: an atlas and textbook. Saunders, Philadelphia
9. Huson SM, Harper PS, Compston DA (1988) Von Recklinghausen neurofibromatosis. A clinical and population study in south-east Wales. Brain 111:1355–1381
10. Hunson S, Jones D, Beck L (1987) Ophthalmic manifestations of neurofibromatosis. Br J Ophthalmol 71:235–238
11. Itoh T, Magnaldi S, White RM, Denckla MB, Hofman K, Naidu S, Bryan RN (1994) Neurofibromatosis type 1: the evolution of deep gray and white matter MR abnormalities. Am J Neuroradiol 15:1513–1519
12. Kissel P, Andre JM, Jacquire A (1981) The neurocristopathies. Masson, New York, pp 223–232
13. Klein RM, Glassman L (1985) Neurofibromatosis of the choroid. Am J Ophthalmol 99:367–368
14. Lee WR (2002) Ophthalmic Histopathology, 2nd edn. Springer-Verlag, London, pp 260–261
15. Nichols JC, Amato JE, Chung SM (2003) Lisch nodule asymmetry in a patient with neurofibromatosis type 1. J Pediatr Ophthalmol Strabismus 40:243–244
16. Nichols JC, Amato JE, Chung SM (2003) Characteristics of Lisch nodules in patients with neurofibromatosis type 1. J Pediatr Ophthalmol Strabismus 40:293–296
17. Rajadhyaksha M, Grossman M, Esterowitz D, Webb RH, Anderson RR (1995) In vivo confocal scanning laser microscopy of human skin: melanin provides strong contrast. J Invest Dermatol 104:946–952
18. Rescaldani C, Nicolini P, Fatigati G, Bottini FG (1998) Clinical application of digital indocyanine green angiography in choroidal neurofibromatosis. Ophthalmologica 212:99–104
19. Stumpf DA, Alksne JE, Annegers JF (1988) Neurofibromatosis: conference statement. National Institutes of Health Consensus Development Conference. Arch Neurol 45:575–578
20. Salzmann M (1912) The anatomy and histology of the human eyeball in the normal state (translated by EVL Brown). University of Chicago Press, Chicago
21. Warwar RE, Bullock JD, Shields JA, Eagle RC Jr (1998) Coexistence of 3 tumors of neural crest origin: neurofibroma, meningioma and uveal malignant melanoma. Arch Ophthalmol 116:1241–1243
22. Yasunari T, Shiraki K, Hattori H, Miki T (2000) Frequency of choroidal abnormalities in neurofibromatosis type 1. Lancet 356:988–992