

Familial Cases with Age-Related Macular Degeneration

Ayako Yoshida, Motoaki Yoshida, Shigeo Yoshida, Satomi Shiose, Goro Hiroishi and Tatsuro Ishibashi

Department of Ophthalmology, Faculty of Medicine, Kyushu University, Fukuoka, Japan

Background: The pathogenesis of age-related macular degeneration (AMD) remains unknown. Genetic and environmental factors are thought to be associated with AMD. Although some studies have reported familial cases of AMD in the United States, as far as we know, familial cases of AMD have rarely been reported in Japan.

Cases: We describe three families with two members of each family affected with AMD and one family with three affected members.

Observations: In one family, two siblings were affected with AMD with choroidal neovascularization and two other siblings had retinal pigment epithelial abnormalities or drusen of the maculas, suggesting the heterogeneity of the maculas in the family. However, the other families did not show such heterogeneity of the fundus. Among the four families, six of nine affected individuals had a smoking habit, a risk factor for AMD.

Conclusions: These findings suggest that the development and progression of AMD might be associated with genetic factors and environmental factors. **Jpn J Ophthalmol 2000;44:290–295** © 2000 Japanese Ophthalmological Society

Key Words: Age-related macular degeneration, environmental factors, family, genetic factor, smoking.

Introduction

Age-related macular degeneration (AMD) is the major cause of severe visual impairment among persons over 50 years. The prevalence in Japan is expected to increase as the result of an increase in the proportion of the elderly in the population. In some classification systems, the diagnosis of AMD is confined to advanced forms of age-related maculopathy, with geographic atrophy or extensive maculopathy.¹ Only laser photocoagulation has been thought to be an effective treatment, but its use is confined to a small proportion of patients, and its benefits are limited.^{2–5}

The exact pathogenesis of AMD remains unknown. Genetic and environmental factors have been implicated in this disease. Support for genetic factors includes an increased family incidence of AMD,^{6–8} a strong concordance of AMD in monozygotic twins,⁹ and the results of segregation analysis. Some investigators suggested smoking^{10,11} and postmenopausal exogenous estrogen use¹¹ as environmental factors. In addition, a history of one or more cardiovascular diseases is thought to be a risk factor for AMD.⁶

Although familial cases of AMD have been reported in the United States,^{12,13} as far as we know, only one report exists of two siblings with AMD in Japan.¹⁴ A greater understanding of the familial cases of AMD would be useful to evaluate the pathogenesis of this disease. In this report, we describe macular findings in four families with more than one member affected with AMD.

Materials and Methods

The criteria for diagnosis of AMD included one or more of the following features, as described previously:¹ (1) delineated, roughly round or oval area of hypopigmentation or depigmentation or apparent absence of the retinal pigment epithelium; (2) retinal pigment epithelial detachment(s); (3) subreti-

Received: May 31, 1999

Correspondence and reprint requests to: Tatsuro ISHIBASHI, MD, PhD, Department of Ophthalmology, Faculty of Medicine, Kyushu University, Fukuoka 812-8582, Japan



Figure 1. Family pedigrees

nal or subretinal epithelial neovascular membrane(s); (4) epiretinal, intraretinal, subretinal, or subpigment epithelial scar/glial tissue or fibrin-like deposits; or (5) subretinal hemorrhages. None of the individuals with AMD had high myopia, intraocular inflammatory disease, or any hereditary diseases with macular degeneration, such as spinocerebellar ataxia and myopathy.

Case Reports

Family 1. The proband (II-1) (Figure 1) was found to have a scotoma in his right eye at the age of 65. At age 68, he was examined and was found to have a disciform scar of the right macula, and a subretinal hemorrhage, serous retinal detachment, and choroidal neovascularization of the left macula (Figure 2). There were no changes in the peripheral retina of both eyes. He had a history of angina pectoris and was the only family member with a smoking habit. Sibling II-3 noted a decline of central vision of her right eye at age 66 years, and was found to have a disciform scar of the right macula and some drusen and choroidal neovascularization of the left macula at age 67 years (Figure 3). Sibling II-4 had metamorphopsia of his left eye at age 55 years. He was found to have a retinal pigment epithelial detachment and choroidal neovascularization of the left macula and retinal pigment epithelial abnormalities of the right macular at age 65 years (Figure 4). Siblings II-3 and II-4 had no changes in their peripheral retinas and had no history of systemic disease. Both parents of the proband were deceased and had no history of ocular disease.

Family 2. The proband (II-3) was a 66-year-old man who reported that he had metamorphopsia of the left eye. He was found to have serous retinal detachment, soft drusen, and choroidal neovascularization of the left macula, and retinal pigment epithelial abnormalities and soft drusen of the right macula (Figure 5). He had a history of asthma and cholelithiasis. Both parents of the proband were deceased and had no known history of AMD or unexplained vision loss. Sibling II-1 complained of difficulty of

central vision of the right eye at the age of 73. Ophthalmoscopic examination showed subretinal hemorrhage, serous retinal detachment, and choroidal neovascularization in the right macula (Figure 6). His left fundus showed no change in the macula. He also had a history of cholelithiasis. Sibling II-4 was examined at age 65 years, and the findings included retinal pigment epithelial abnormalities of both maculas. Sibling II-6 was examined at age 60 years and had drusen of the left macula. Siblings II-1, II-3, II-4, and II-6 showed no change in the peripheral retina. All individuals, except siblings I-2 and II-5, had a smoking habit.

Family 3: The proband (II-3) was a 77-year-old man who reported that he had a decrease of vision in his left eye. At age 87 years, he noted difficulty with central vision of his right eye and was found to have subretinal hemorrhage, soft drusen, choroidal neovascularization in the right macula, and a disciform scar and atrophy in the left macula. There was no change in either peripheral retina. He had a history of cardiac disease and was the only member of the Ist and IInd generation who had a smoking habit. Sibling II-1 was found to have a disciform scar and pigmentary changes in the right macula, and serous retinal detachment, subretinal fibrosis, and pigmentary changes in the left macula at age 91. She had peripheral pigmentary change in the retina of both eyes. Both parents of the proband were deceased, and neither had a known history of AMD or unexplained vision loss. The proband has three sons, one of whom (III-1) was examined at age 60 and was found to have no change in either macula. He did not have a smoking habit, but III-2 and III-3 did.



Figure 2. Fundus of proband (II-1) of family 1. Disciform scar in right macula (left) and subretinal hemorrhage, serous retinal detachment, and choroidal neovascularization are observed in left macula (right).



Figure 3. Fundus of sibling II-3 of family 1. Disciform scar is seen in right macula (left) and some drusen and choroidal neovascularization in left macula (right).

Family 4. The proband (I-1) was a man who had metamorphopsia of both eyes at age 66 years. He was examined when 84 years old and was found to have a disciform scar and atrophy of both maculas without any change in the peripheral retina. He had a history of hypertension, arrhythmia, and brain infarction. II-2 was examined at age 49 years, and the findings included subretinal hemorrhage in the left macula. He also had a history of hypertension. They both had a smoking habit.

Discussion

Although AMD is thought to be associated with genetic and environmental factors, the pathogenesis of this disease remains unknown. In Japan, many people are affected with AMD, but we could find only one familial case with two siblings with AMD reported by Seguchi et al.¹⁴ In our report, we describe four families that included two or three individuals with AMD in each family. These findings support the importance of heredity in AMD. The prevalence of age-related maculopathy among firstdegree relatives of subjects with this disease, particularly with exudative disease, is greater than among first-degree relatives of subjects without this disease.⁸ Significant correlation of the signs of agerelated maculopathy exists among siblings.¹⁵ In a case-control study, a family history of AMD was shown to be a risk factor for AMD.⁶ In addition to these findings, reports of concordance for AMD in monozygotic twins9 and other family studies8,16 suggest the role of genetic factors in AMD.

However, there are environmental factors associ-



Figure 4. Fundus of sibling II-4 of family 1. Right eye has retinal pigment epithelial abnormalities of macula (left) and left eye has retinal pigment epithelial detachment (arrow) and choroidal neovascularization of macula (right).



Figure 5. Fundus of proband (II-3) of family 2. Retinal pigment epithelial abnormalities and soft drusen in right macula (left), and serous retinal detachment, soft drusen, and choroidal neovascularization in left macula (right) can be seen.

ated with AMD that are shared more often among siblings than among unrelated individuals. These include dietary intake and smoking habit.

Gene-environmental interactions might play a role.⁸ Smoking is thought to be a risk factor for AMD. One study reported that 71% of individuals with AMD had a smoking habit, while 59% of individuals without AMD had this habit.¹¹ Among the families in this study, six of nine individuals with AMD had a smoking habit.

It is well-known that the macular findings of agerelated maculopathy are heterogeneous. De la Paz et al¹² described the heterogeneity of the fundus in eight families with AMD. In family 2 in this study, two siblings were affected with AMD with choroidal neovascularization and two other siblings had retinal pigment epithelial abnormalities or drusen in the maculas, suggesting the heterogeneity of the maculas in the family. However, the other families did not show such heterogeneity of the fundus. One of the reasons for the low variability of phenotype might be that the number of relatives of affected individuals examined was small, which would limit the analysis. No information was found to suggest AMD in unexamined relatives in the families. However, Hyman et al⁶ demonstrated that the rate of underreporting by relatives as compared with examiners was about 30%. If we can examine more relatives of affected individuals, we may find more variable phenotypes of age-related maculopathy.

Analysis of heredity in AMD is limited because this disorder is associated with aging, frequently causing its most significant phenotypic manifestations in the later years of life.¹² Many individuals in the family are young, and have not yet reached the age of risk, and many of the older family members have died. Therefore, acquiring reliable information from several generations for genetic studies is difficult. Recently, mutations in the Stargardt disease gene, ABCR gene, at chromosome 1q21 were shown to be frequent in patients with AMD compared with control subjects.¹⁷ However, some investigators showed no correlation between this gene and AMD, suggesting further studies of genes associated with AMD are needed.

In summary, we have described four families with two or three individuals with AMD in each family. Genetic and environmental factors might contribute to the origin of their disease. A combined approach of genetics and epidemiology is needed to clarify the



Figure 6. Fundus of sibling II-1 of family 2. Right eye has subretinal hemorrhage, serous retinal detachment, and choroidal neovascularization.

relative contribution of each potential mechanism in the development and progression of this complex disease. More understanding of the pathogenesis would help to prevent or treat this disease.

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