Epidemiology of Age-related Maculopathy

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INTRODUCTION

Age-related maculopathy, also referred to as senile or age-related macular degeneration, is the leading cause of permanent visual impairment among the elderly in western countries (1–4). Loss of vision results from the degeneration of the photoreceptors in the macular area; this occurs when the retinal pigment epithelium cells with which they are associated deteriorate and die. Useful intervention is limited to only a minority of patients (5, 6). Since the previous review of the epidemiology of age-related maculopathy by Ferris in 1983 (7), many investigations have focussed on this disease in an attempt to find additional etiologic clues. In this presentation we will review the current epidemiologic knowledge concerning age-related maculopathy and discuss diagnosis, frequency, risk factors, and prognosis.

DIAGNOSIS

Diagnostic criteria

Age-related maculopathy affects the center of the retina and choroid in the posterior pole of the eye. Generally, it is considered to be present when one or more of the following changes are visible in the macular area: 1) large drusen (yellow deposits below the retinal pigment epithelial cells); 2) hyper- and hypopigmentary changes of the retinal pigment epithelium; 3) atrophic macular degeneration, also known as geographic atrophy (well-defined areas of atrophy of the retinal pigment epithelium and choriocapillaris); and 4) neovascular macular degeneration (serous or hemorrhagic detachment of the pigment epithelium, choroidal neovascularization, and subsequent scarring of the macular area). Although these changes are all manifestations of the disease and are associated with increasing age, the range of variance is large, and for years this has been an obstacle to the development of a uniform definition and classification system. In addition, early epidemiologic studies have included decreased central visual acuity as one of the diagnostic criteria.

Recently, however, three grading systems have been developed to classify age-related maculopathy by means of color photographs of the macula lutea, without implication of visual acuity (8–10). The definitions of these grading systems are summarized in table 1. In brief, the system of Bressler et al. (8) consists of four categories, and at each step, from category one to category four, the system leaves out less severe abnormalities. The Wisconsin Age-related Maculopathy Grading System (9) provides a detailed grading of each abnormality with respect to size, area, and location. It defines early and late stages of age-related maculopathy (11). Presently, an international study group (10) has developed a classification system to facilitate comparison of data between the various epidemiologic studies. This system defines age-related maculopathy as all manifestations of this disorder and age-related macular degeneration as the late stages (atrophic or neovascular macular degeneration). For purposes of this review, we will maintain the terminology of the international system.

Differential diagnosis

Drusen must be differentiated from other conditions which have white spots in the macula, such as hard exudates, cotton wool spots, and retinal pigment epithelium hypopigmentations as found in fundus flavomaculatus and fundus albipunctatus. Pigmentary changes can also be seen in combination with other abnormal processes in the macular area which are not directly related to age-related maculopathy, such as those accompanying choriotreal scars due to choriotrealitis, trauma, or laser photocoagulation.
TABLE 1. Classification of age-related maculopathy

<table>
<thead>
<tr>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
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<tbody>
<tr>
<td>Presence of grade 4, 3, or 2, or eyes with at least five small drusen within 1,500 μm of the foveal center, or at least ten small drusen between 1,500 and 3,000 μm from the foveal center</td>
<td>Presence of grade 4 or 3, or eyes with ≥20 small drusen within 1,500 μm of the foveal center</td>
<td>Presence of grade 4, or eyes with large or confluent drusen, or eyes with local hyperpigmentation of the retinal pigment epithelium</td>
<td>Geographic atrophy of the retinal pigment epithelium or exudative changes (e.g., choroidal neovascularization, detachment of the retinal pigment epithelium, and disciform scarring)</td>
</tr>
<tr>
<td>Wisconsin Age-related Maculopathy Grading System (9)</td>
<td>Early age-related maculopathy: soft indistinct or reticular drusen or any drusen type except hard, indistinct, with retinal pigment epithelium degeneration or increased retinal pigment in the macular area and the absence of late age-related maculopathy</td>
<td>Late age-related maculopathy: signs of exudative age-related maculopathy or geographic atrophy</td>
<td>Age-related macular degeneration: the end stages of age-related maculopathy subdivided in dry or geographic and wet or neovascular macular degeneration</td>
</tr>
<tr>
<td>The International Age-related Maculopathy Study Group (10)</td>
<td>Age-related maculopathy: all stages of the disease; within this definition drusen and pigmentedary changes are subdivided by aspect, number, and size</td>
<td></td>
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</tr>
</tbody>
</table>

Any chorioretinal inflammation or scar may result in the growth of a subretinal neovascular membrane. Therefore, neovascular macular degeneration sometimes resembles similar conditions in myopic macular degeneration, pseudoanxthoma elasticum, Paget’s disease, presumed ocular histoplasmosis syndrome, toxoplasmosis, central areolar choroidal sclerosis (12, 13), laser photocoagulation scars, and traumatic, inflammatory, toxic, and congenital processes (9). In general, these disorders have to be excluded before a diagnosis of age-related maculopathy can be made.

**FREQUENCY**

**Prevalence**

Estimation of the prevalence of age-related maculopathy is not only necessary for assessing the need for ophthalmologic care, but comparison of prevalence figures from different populations may also suggest etiologic clues of the disease. Population-based studies of age-related maculopathy were conducted in the United States, Europe, and New Zealand (table 2). Studies from Framingham, Massachusetts (2), Gisborne, New Zealand (14), Melton Mowbray, United Kingdom (15), Copenhagen, Denmark (16), the National Health and Nutrition Examination Survey (NHANES) (17), and Iceland (18) estimated the prevalence of any type of age-related maculopathy based on ophthalmoscopic assessment of macular changes with the requirement of central visual loss. As shown in figure 1, the prevalence estimates in these studies vary considerably. The studies from Chesapeake Bay (8) and Beaver Dam, Wisconsin (11), based their data on photographic grading of macular changes and did not require visual loss, which may explain why their prevalence estimates for any type of age-related maculopathy are higher (figure 1). Whatever the definition or method of diagnosis, all estimates show a strong rise with age, and a reasonable overall prevalence for any type of age-related maculopathy in age-groups 65–74 years and 75–84 years is 20 and 35 percent, respectively.

Separate prevalence estimates of atrophic or neovascular macular degeneration are available from the Framingham, Iceland, Chesapeake Bay, Beaver Dam, and Rotterdam, The Netherlands (19), studies (figure 2). The first two studies based their estimates only on neovascular macular degeneration, while the latter three also included atrophic macular degeneration. These prevalence estimates show less variation than with inclusion of drusen and pigmentedary changes, and the estimates show an exponential increase after the age of 70 years. A reasonable overall prevalence of neovascular and/or atrophic macular degeneration in age-groups 65–74 years and 75–84 years is 1 and 5 percent, respectively. Although none of the other studies showed any prevalence difference regarding gender, the Beaver Dam study noted that women had a 2.5 times higher prevalence for neovascular macular degeneration than men (11).
TABLE 2. Cross-sectional studies of age-related maculopathy

<table>
<thead>
<tr>
<th>Study (reference no.)</th>
<th>Criteria for diagnosis</th>
<th>Age range (years)</th>
<th>Sample size</th>
<th>Response rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Framingham, Massachusetts (2)</td>
<td>Ophthalmoscopy: drusen; pigment disturbances; atrophic or neovascular macular degeneration, visual acuity</td>
<td>52–84</td>
<td>2,675</td>
<td>67</td>
</tr>
<tr>
<td>NHANES* (17)</td>
<td>Ophthalmoscopy: drusen; pigment disturbances; atrophic or neovascular macular degeneration, visual acuity</td>
<td>45–74</td>
<td>1,413</td>
<td>72</td>
</tr>
<tr>
<td>Gisborn, New Zealand (14)</td>
<td>Ophthalmoscopy: drusen; pigment disturbances; atrophic or neovascular macular degeneration, visual acuity</td>
<td>≥65</td>
<td>481</td>
<td>82</td>
</tr>
<tr>
<td>Melton Mowbray, United Kingdom (15)</td>
<td>Ophthalmoscopy: drusen; pigment disturbances; atrophic or neovascular macular degeneration, visual acuity</td>
<td>≥75</td>
<td>484</td>
<td>72</td>
</tr>
<tr>
<td>Iceland (18)</td>
<td>Ophthalmoscopy: drusen; pigment disturbances; atrophic or neovascular macular degeneration, visual acuity</td>
<td>≥43</td>
<td>751</td>
<td>81</td>
</tr>
<tr>
<td>Copenhagen, Denmark (16)</td>
<td>Ophthalmoscopy: drusen; pigment disturbances; atrophic or neovascular macular degeneration, visual acuity</td>
<td>60–79</td>
<td>1,000</td>
<td>71</td>
</tr>
<tr>
<td>Chesapeake Bay (8)</td>
<td>Photography: drusen, number, size, and distinction of borders; focal hyperpigmentations; nongeographic atrophy; atrophic or neovascular macular degeneration</td>
<td>30–95</td>
<td>777</td>
<td>70</td>
</tr>
<tr>
<td>Beaver Dam, Wisconsin (11)</td>
<td>Photography: drusen area, number, size, and distinction of borders; increased or decreased retinal pigment; atrophic or neovascular macular degeneration</td>
<td>43–84</td>
<td>4,926</td>
<td>83</td>
</tr>
<tr>
<td>Rotterdam, The Netherlands (19)</td>
<td>Photography: drusen, number and size; increased or decreased retinal pigment; atrophic or neovascular macular degeneration</td>
<td>≥55</td>
<td>7,599</td>
<td>78</td>
</tr>
</tbody>
</table>

* NHANES, National Health and Nutrition Examination Survey.

Incidence

No data based on incidence studies of age-related maculopathy are available. If the prevalence is low, an estimated incidence rate can be obtained indirectly using prevalence and expected duration of the disease (20). With this method, the incidence rate of atrophic or neovascular macular degeneration in the age-group 75–84 years is approached by the prevalence (7.1 per 100 persons) divided by the estimated mean duration of 5 years; this results in an incidence rate (density) of 1.2 per 100 person-years. Previously, Podgor et al. (21) calculated the incidence rate of any age-related maculopathy from Framingham Eye Study prevalence data and found the rate to vary, depending on age-category, between 3 and 6 per 100 person-years.

Methodological considerations

The differences in definitions and methodology between studies hamper the comparison of prevalence data. In the Framingham, NHANES, Gisborne, Iceland, and Copenhagen studies, the diagnosis of age-related maculopathy was made only in patients with central visual loss. This led to lower prevalence rates than the estimates from Chesapeake Bay, Beaver Dam, and Rotterdam which did not use this criterion. In addition, the former studies based the diagnosis on clinical examination, whereas the latter studies based their grading on fundus photographs. It is known that with clinical examination an underestimation of the frequency of drusen can occur (2), which may be an additional reason for the higher prevalence of age-related maculopathy in these studies. The Chesapeake Bay study was designed to examine the relation between sunlight exposure and eye diseases. The study population consisted of a selected group of fishermen, and this may have influenced the prevalence rate. Despite these differences, however, there is a similarity in trends; all studies show an acceleration of prevalence with increasing age (figure 1).

The comparison of the prevalence of end stages of age-related maculopathy is also hampered by differences. In the studies from Framingham and Iceland, only the prevalence of neovascular macular degeneration was reported; atrophic macular degeneration was pooled with drusen and pigmentary changes. In the Chesapeake Bay, Beaver Dam, and Rotterdam studies, atrophic and neovascular macular degeneration were pooled resulting in a higher estimate of prevalence. The differences between prevalences in these studies are, therefore, likely to be the result of differences in methodology and definition.
RISK FACTORS

A number of case-control and cross-sectional studies have focused on the etiology of age-related maculopathy; the main findings are summarized in tables 2, 3, and 4. A point of consideration is that all the studies were based on prevalent cases (with their well-known limitations such as selection bias and recall bias) which can lead to spurious associations. In addition, the inclusion criteria for cases varied considerably. Most of the studies included early and late stages of age-related maculopathy. Therefore, the results of these investigations remain to be confirmed in follow-up studies based on well-defined incident cases where exposure status is measured before onset of disease.

The putative risk factors that are discussed below are family history of age-related maculopathy, ophthalmologic characteristics, cardiovascular disease, hyperglycemia, diabetes, smoking, sunlight exposure, and antioxidant status.

Genetic factors

Family studies. While Hutchinson and Tay observed a familial occurrence of age-related maculopathy as early as 1875 (22), the disease has not been the subject of extensive genetic investigations. Familial aggregation of drusen has been reported by several investigators. Early pedigree reports (12, 23–25) have used different terms to describe familial drusen, such as Doyne honeycomb choroiditis, Hutchinson-Tay central guttate choroiditis, Holthouse-Batten superficial chorioretinitis, and malattia levantinesse. An autosomal dominant trait was suggested for these familial
TABLE 3. Case-control studies of age-related maculopathy

<table>
<thead>
<tr>
<th>Study (reference no.)</th>
<th>Cases</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malzma et al. (53)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Delany and Oates (62)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyman et al. (28)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blumenkrantz et al. (54)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EDCS (60)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Age-related maculopathy, not specified.
- Age-related maculopathy, not specified.
- Age-related maculopathy, not specified.
- Neovascular macular degeneration.
- Neovascular macular degeneration.

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<table>
<thead>
<tr>
<th>Study (reference no.)</th>
<th>Hyperopia</th>
<th>Blue/light iris color</th>
<th>Cardiovascular disease</th>
<th>Hypertension</th>
<th>Smoking</th>
<th>Sunlight exposure</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Risk factor</td>
<td>95% CI*</td>
<td>Risk factor</td>
<td>95% CI</td>
<td>Risk factor</td>
<td>95% CI</td>
</tr>
<tr>
<td>Framingham, Massachusetts (58)</td>
<td>+</td>
<td>1.4</td>
<td>1.1–1.7</td>
<td>1.3</td>
<td>NS†</td>
<td>NS†</td>
</tr>
<tr>
<td>Malzman et al. (53)</td>
<td>+</td>
<td>2.4</td>
<td>1.0–5.9</td>
<td>6.1</td>
<td>2.1–18.5</td>
<td>1.3</td>
</tr>
<tr>
<td>Delaney and Oates (62)</td>
<td>+</td>
<td>3.5</td>
<td>1.7–6.6</td>
<td>1.7</td>
<td>1.1–2.7</td>
<td>0.6</td>
</tr>
<tr>
<td>Hyman et al. (28)</td>
<td>+</td>
<td>0.7</td>
<td>0.2–2.3</td>
<td>4.0</td>
<td>0.4–102</td>
<td>0.6</td>
</tr>
<tr>
<td>Blumenkranz et al. (64)</td>
<td>2.0</td>
<td>0.5–6.2</td>
<td>1.1</td>
<td>0.6–2.0</td>
<td>0.6</td>
<td>0.1–4.7</td>
</tr>
<tr>
<td>Chesapeake Bay (48, 90)</td>
<td>0.6</td>
<td>0.3–1.1</td>
<td>1.0</td>
<td>0.8</td>
<td>NS†</td>
<td>2.4</td>
</tr>
<tr>
<td>Copenhagen, Denmark (16, 49)</td>
<td>0.7</td>
<td>0.3–1.4</td>
<td>0.8</td>
<td>0.1–5.5</td>
<td>2.5</td>
<td>1.0–6.2§</td>
</tr>
<tr>
<td>Beaver Dam, Wisconsin (60, 91)</td>
<td>1.7</td>
<td>1.1–2.6</td>
<td>1.1</td>
<td>0.7–1.7</td>
<td>1.1</td>
<td>0.8–1.5</td>
</tr>
<tr>
<td>EDCSG* (50)</td>
<td>2.5</td>
<td>1.4–4.5¶</td>
<td>0.9</td>
<td>0.6–1.4</td>
<td>4.0</td>
<td>2.0–7.8#</td>
</tr>
<tr>
<td>Rotterdam, The Netherlands (64, 67)</td>
<td>+</td>
<td>1.4</td>
<td>1.1–1.7</td>
<td>1.3</td>
<td>NS†</td>
<td>NS†</td>
</tr>
</tbody>
</table>

* CI, confidence interval; EDCSG, Eye Disease Case-Control Study Group.
† Not significant, but point estimate and/or confidence intervals unpublished.
‡ Blue light.
§ Women.
‖ Leisure time in summer.
¶ Atherosclerotic plaques in common carotid artery.
# Vingerling et al., unpublished manuscript.
South Africa and 380 Caucasians in England. All the subjects were “consecutive” hospital outpatients. Blacks had a significantly lower frequency of the late stages of age-related maculopathy (0.1 percent compared with 3.5 percent among the Caucasians). Later, Taylor (37) reported that age-related maculopathy was a rare cause of blindness in elderly Australian aborigines. A recent study carried out in Barbados among 3,444 blacks found a prevalence of late age-related maculopathy of 0.6 percent (38). Although the prevalence was much lower in these blacks than in Caucasians from western countries, this investigation did not examine a considerable number of Caucasians from the same area. Therefore, environmental differences could have affected the results. Data from the third NHANES survey, which represents the various populations living in the United States, showed that racial differences vary by age. Age-related maculopathy was more prevalent in Caucasians (compared with non-Caucasians) over 60 years of age, and in non-Caucasians under 60 years of age (39), giving the impression that blacks have an earlier onset. The Baltimore (Maryland) Eye Survey (40) compared causes of blindness among 2,395 blacks and 2,913 Caucasians and found that blindness due to age-related maculopathy only occurred in Caucasians. These studies all suggest a racial variation in the frequency of age-related maculopathy, but it is as yet unsettled if this is caused by a difference in genetic susceptibility or by a difference in environmental factors.

**Ocular characteristics**

**Iris color.** Another hypothesis for the low prevalence of age-related maculopathy in blacks is the possible protective effect of a dark pigmented iris. Cumulative light exposure may have a harmful effect on the photoreceptors and retinal pigment epithelium (42-46), and a dark pigmented iris could be more protective against light exposure than a light colored iris. Initially, two case-control studies (28, 47) reported a lower risk of age-related maculopathy in persons with a dark iris, but this was not confirmed in later studies (48-50). Recently, Holz et al. (51) reported no association with iris color, but mentioned that a self-reported decrease of iris pigmentation during life was associated with age-related maculopathy. The inconsistency of data and the absence of an association in population-based studies suggests a small effect, if any. Sandberg et al. (52) recently reported that light iris pigmentation is associated with a more extensive retinal disease in patients with unilateral neovascular macular degeneration. Because referrals are generally related to severity of symptoms, this may explain some of the inconsistent prevalence findings of clinically-based studies that compared maculopathy with iris color.

**Refractive error.** A possible association of hyperopia and age-related maculopathy was first suggested by Maltzman et al. (53). Later, four case-control studies confirmed this finding (28, 47, 50, 54). There is, however, no generally accepted hypothesis explaining this relation. Hyman et al. (28) pointed out that selection bias could have influenced the observation because the control group may have been overrepresented with myopic subjects. The control group in another study (54) consisted of non-neovascular cases of age-related maculopathy. The authors suggested that this control group may have been comprised of a large proportion of cataract patients, a condition which can result in myopia due to lens swelling, and, therefore, may have led to a spurious association with hyperopia. Considering the probability of selection bias and the lack of a supportive theory, it is still doubtful whether an association between hyperopia and age-related maculopathy exists.

**Cardiovascular disease**

One hypothesis for the pathogenesis of age-related maculopathy is that vascular disease affects the choriocapillaris. This may result in decreased flow or passage of nutrients (55-57). The issue was examined in various ways, either by using blood pressure measurements or data concerning cardiovascular history.

**Hypertension.** Sperduto and Hiller (58) reported a small and consistent association between age-related maculopathy and hypertension as determined 25 years previously in the Framingham Heart and Eye Study. The association was stronger with increased duration of systemic hypertension. Vinding et al. (59), however, did not find an association between blood pressure levels and age-related maculopathy in a 4-year follow-up in the Copenhagen Heart Study. Other studies (17, 50) used blood pressure levels taken at the time of eye examination and reported a positive association with increased systolic blood pressure. The Beaver Dam and Rotterdam studies, however, found no association with systolic blood pressure (60, 61).

**History of cardiovascular disease.** Conflicting reports have been published about the association between age-related maculopathy and a history of cardiovascular disease; several case-control studies (28, 62, 63) found a positive association, whereas others (50, 53, 64) did not. Self-reported history of cardiovascular disease, however, is potentially biased by misclassification, making it more difficult to detect an association.

**Other cardiovascular risk factors.** Increased total serum cholesterol was associated with a strong in-
creased risk of neovascular macular degeneration in a large case-control study (50). This finding could not be confirmed in the Beaver Dam (60) and Rotterdam (61) studies. In the latter study, the authors reported atherosclerosis to be associated with atrophic and neovascular macular degeneration. Recently, Mares-Perlman et al. (65) suggested a role of atherosclerosis by showing that a high intake of saturated fat increased the risk of the early stages of age-related maculopathy. Furthermore, postmenopausal estrogens were shown to have a dose-related protective effect against neovascular macular degeneration (50). The role of estrogen could not be confirmed in the Beaver Dam study (66); the power to detect an effect was low, however. The issue was also addressed in a nested case-control study in Rotterdam which suggested a higher risk of age-related macular degeneration in women who had an early menopause by oophorectomy (67). These results may be explained by the protective effect of estrogens against cardiovascular disease and atherosclerosis (68–70). The possibility of selective survival cannot be ruled out in these cross-sectional studies.

Hyperglycemia and diabetes

Hyperglycemia has been reported to affect choroidal circulation, Bruch’s membrane, and the pigment epithelium (71–76). A relation between hyperglycemia and age-related maculopathy has, therefore, been proposed. A number of case-control studies (28, 50, 53, 63, 64) and two cross-sectional studies (77, 78) focused on this hypothesis. In only one study (63) was a positive association of serum glucose levels and the mean area of drusen in females without diabetes reported. Recently, Klein et al. (78) reported no relation between glycosylated hemoglobin and age-related maculopathy. A higher frequency of neovascular macular degeneration was found only in diabetic men aged 75 years or older. The effect of hyperglycemia, if any, is, therefore, likely to be small.

Smoking

An increased risk of age-related maculopathy in smokers was first suggested by Paetkau et al. (79). The mechanism of the association is still unclear, but several mechanisms could play a role. It is plausible that, by reducing serum antioxidants (80–83), smoking decreases retinal antioxidants. Retinal antioxidants are present in the retina to protect it against oxygen radicals formed during light exposure (84, 85). Several other pathways could be involved in the association, including alteration of the choroidal blood flow (86, 87). Recent studies have confirmed the association (28, 50, 59, 61, 88), although not uniformly (48, 77).

The association with smoking was particularly present in neovascular macular degeneration (88). The association is of importance since smoking is still very common and amenable to prevention. A cautious interpretation remains necessary, however, since all these data are based on case-control studies consisting of prevalent rather than incident cases.

Light exposure

The damaging effect of exposure to light on the photoreceptors and retinal pigment epithelium has been reported in two experimental studies (44, 45). It is possible that long-term exposure to light is a factor in the pathogenesis of age-related maculopathy (42, 43). In a case-control study by Hyman et al. (28), no significant association was reported between exposure to sunlight and age-related maculopathy. In a study of fishermen (48) the ocular exposure was extensively measured (89). No association between exposure to ultraviolet A or ultraviolet B and age-related maculopathy was observed. In an additional analysis based on a small number of cases, a positive association was observed between exposure to blue light and neovascular macular degeneration (90). Unfortunately, the number of cases suffering from neovascular macular degeneration that could be included in the analysis was very small. Cruickshanks et al. (91) reported a positive association between self-reported time spent outdoors in the summer and the presence of drusen or pigmentary changes, as well as an inverse association with the use of hats or sunglasses in men. Furthermore, they observed a positive association between leisure time outdoors in the summer and neovascular macular degeneration. Recently, however, the Eye Disease Case-Control Study Group could not confirm an association between a history of light exposure and neovascular macular degeneration (50). One has to keep in mind that the measurement of ocular dose of exposure to light is very complex and susceptible to misclassification, especially with history data. Hence, lack of an association could be caused by the dilution of the effect of exposure to light.

Antioxidant status

The potentially damaging effect of cumulative exposure to light on the retinal layers, as described above, raised the question whether higher blood levels of antioxidants might protect against age-related maculopathy (46, 92). Evidence for a protective effect of antioxidant nutrients emerged from basic research (93–99). A study based on NHANES data revealed that a low intake of vitamin A was associated with a higher risk of age-related maculopathy (100). Newsome et al. (101) sug-
gested a beneficial effect of oral zinc on the natural course of age-related maculopathy (101). In another study (102), lower blood levels of carotenoids were observed in cases with neovascular macular degeneration. A recent study (103) reported that higher serum levels of α-tocopherol were associated with a decreased risk of neovascular macular degeneration. High intake of green leafy vegetables containing zeaxanthin and lutein was especially found to be protective for neovascular macular degeneration (104). In the latter studies (103, 104) the findings were also suggestive for lower levels of vitamin C and E in cases with neovascular macular degeneration.

PROGNOSIS

Visual loss

The risk of loss of visual acuity and the central visual field is the primary reason for concern about age-related maculopathy. Several studies have shown that the disease usually affects both eyes of patients (12, 105–108). Generally, severe visual loss is caused in these patients by choroidal neovascular membrane, and in a smaller number of cases by atrophy of the retinal pigment epithelium involving the fovea (12, 28, 109). The risk of visual loss in cases with bilateral drusen was reported in two follow-up studies. In the first study, Gass (12) reported that nine of 49 cases developed severe visual loss in one eye during an average follow-up period of 4.9 years. In the other study of 71 patients, Smiddy et al. (110) reported that severe visual loss due to neovascular disease occurred in seven eyes of six patients. Using life-table analysis, the 5-year cumulative risk of visual loss was 12.7 percent. The interpretation of the results remains difficult because both studies were based on prevalent cases with different durations of disease (111). Furthermore, the cases were obtained from specialized clinics. This could have resulted in the selection of more severe cases, and extrapolation of the results to a general population may therefore be misleading.

With both eyes affected, one has a severe visual handicap. The prognosis of the second eye in cases with unilateral neovascular macular degeneration is, therefore, a matter of great concern. The issue was studied in several case series (12, 106, 107, 112–115). Roy et al. (112) summarized the risk of second eye involvement to be somewhere between 4 and 12 percent annually for the first 3 years following the diagnosis of age-related maculopathy in the first eye.

Prevention of visual loss

The need for effective treatment of macular degeneration is evident. The development of treatment techniques has mainly focused on suppression of the subretinal neovascular membranes. Treatment is not available for pigmentary changes and atrophic macular degeneration. Experimental studies are in the process of investigating whether the disappearance of drusen after laser photocoagulation has a beneficial effect on visual prognosis.

Laser photocoagulation is being used to occlude subfoveal neovascular membranes. Originally, treatment was limited to patients with a well demarcated choroidal neovascularization. Of further importance was the distance of the neovascular membrane to the foveola (116). Laser treatment of a subfoveal membrane leads to an immediate irreversible decline of visual acuity due to the destruction of the overlying photoreceptors in the central fovea, but results after 2 years in a smaller scar and scotoma than if no treatment was administered (117). Estimations of the proportion of patients with neovascular macular degeneration that may be treated for this reason vary between 13 and 57 percent (5, 6, 118, 119). Unfortunately, more than half of the treated patients suffer from recurrences of choroidal neovascularization within 5 years (120). With the new technique of digital indocyanine green videoangiography, the proportion of well demarcated neovascular membranes can possibly be enlarged (121, 122).

New interventions

Interferon. Systemic interferon alfa-2 has been used to treat vascular tumors (123, 124); it inhibits the growth of iris neovascularization in monkeys, and even induces its regression (125). In vitro, interferon alfa inhibits vascular endothelial cell proliferation (126). After Fung (127) suggested that interferon may be effective as a treatment for neovascular macular degeneration, several case series (127–132) and one small randomized trial (133) have been reported. The results of the trial suggest a slower growth of the choroidal membrane in the treatment group at 6 months; the results of the case series were more difficult to interpret since the natural course was not taken into account.

Radiotherapy. Low doses of ionizing radiation lead to regression of ocular hemangiomas (134) and of new vessel formation in wound healing (135, 136). The effect of radiotherapy on subretinal neovascularization was investigated by Chakravarthy et al. (137) who reported higher visual acuity and smaller choroidal neovascular membranes in the treatment group after a 1 year follow-up. Bergink et al. (138) compared the results of radiotherapy in their patients with the expected natural course from the literature, and also found a beneficial effect. The effect of radiation on neovascular macular degeneration, as well as the eval-
ulation of possible side effects on the ageing retina, still needs to be evaluated in other studies.

**Antioxidants.** As mentioned above, interventions are reserved for cases with late stages of age-related maculopathy, and alternatives to prevent the disease are under study. If one assumes that the cumulative damaging effect of radiant energy, such as sunlight, on the retinal layers is caused by the formation of free radicals, a beneficial effect of antioxidants may be expected. The effect of antioxidant therapy is expected to be small but of clinical relevance [139]. Currently, treatments with megadoses of vitamins E, C, and β-carotene, and zinc are being investigated in the Age Related Eye Disease Study, a multicenter randomized trial in the United States. Because of the design, the conclusions of this study will be limited to the benefits of megadose therapy in a largely micronutrient sufficient population.

One small clinical trial suggested that, over a 2 year period, oral supplementation of zinc may slow the rate of visual decline in patients with age-related maculopathy [101]. So far no other report has been published on the issue and the need for further investigation is clear. At present, physicians’ prescribing micronutrients for age-related maculopathy is not warranted since long-term effect and safety have not yet been established [140].

**Surgical intervention.** Recent studies have examined the effect of surgical removal of subretinal hemorrhages or neovascular membranes [141–146]. This treatment aims to minimize the size of the scar. The indications for these techniques, however, are still a matter of debate. Most studies suggest a beneficial effect on scar size and visual acuity but long-term data are lacking. Recurrence rates are likely to be as frequent as after laser treatment. It seems reasonable to reserve these techniques for cases with large subretinal hemorrhages.

**CONCLUSIONS**

Age-related maculopathy is a major cause of severe visual impairment in the elderly of western countries. Visual handicap has major consequences for the quality of life of patients and their relatives. In this review we have examined the epidemiologic findings concerning frequency, risk factors, and prognosis of the disease. The classification of age-related maculopathy has been a matter of debate, but recently an international agreement has been accomplished on a classification system for epidemiologic studies. The prevalence of age-related maculopathy rises with age, the prevalence of end stages increases from 1 percent in subjects aged 65–74 years to 5 percent in those aged 75–84 years. There is a clear need for incidence studies of age-related maculopathy, and prospective follow-up studies of age-related maculopathy and its risk factors. These are currently underway in North America and Europe.

The risk factors for age-related maculopathy have been studied in case-control and cross-sectional studies. Apart from age, no definite risk factors have been found. There are suggestions, however, that atherosclerosis, smoking, light exposure, and low serum levels of β-carotenoids are associated with age-related maculopathy. The origin of the association with smoking is not yet fully understood, but the association is interesting since smoking habits are potentially modifiable. The role of exposure to light remains unclear; as yet, the possible harmful effect of light seems to be small.

More extensive research is needed to evaluate the magnitude of the genetic component and mode of inheritance. Localization of the genes will lead to a better understanding of the underlying causes of age-related maculopathy, and identification of family members at risk will provide the basis for future therapeutic and preventative interventions.

Patients with atrophic macular degeneration may retain useful vision for years. However, in patients with neovascular macular degeneration the prognosis is worse. Further studies are needed to provide a better estimate of prognosis. Currently, there is no proven treatment for the disease, except for a selected group of patients with neovascular macular degeneration where treatment with laser photocoagulation has had some benefits. New interventions, such as antioxidant supplementation and radiotherapy, are currently being investigated, and these interventions may have beneficial effects for patients who are not eligible for laser treatment. Investigations to date certainly provide encouraging perspectives, but future epidemiologic studies will be needed to provide a better insight into the course, determinants, and prevention of maculopathy in the elderly.

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