Depressive and Cognitive Disorders in Patients with AMD

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14.1 Introduction

Depression and cognitive impairment are two common psychiatric disorders in patients with age-related macular degeneration (AMD). Depression is fairly prevalent in AMD, and research that has studied its effects on quality of life and daily functioning are presented in this chapter. Methods for detecting depression are suggested. This is followed by a review of research that has tested the efficacy of various behavioral interventions to treat or prevent depression in AMD, as well as a discussion on the impact of rehabilitation on depression. This chapter also reviews research that has documented relationships between AMD and cognitive impairment. Theories that explain the mechanisms responsible for the co-occurrence of these two conditions are discussed.

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14.2 Depression in Age-Related Macular Degeneration

Depression in older adults is a serious yet often underdiagnosed and undertreated medical condition. Current research estimates the prevalence of depression among community-dwelling older people to be approximately 12 % (for both major and minor depression combined) (Steffens et al. 2009). Common risk factors for late life depression include female sex (Byers et al. 2010), recent bereavement, physical disability, medical comorbidity, sleep disturbance, and previous depression (Cole 2005). Vision impairment also confers a high risk for depression, with odds ratios averaging around 1.9 (Nyman et al. 2009). The prevalence of depression among older persons with impaired vision ranges from about 14–63 % (Brody 2001; Evans et al. 2007; Jones et al. 2009; Rovner and Ganguli 1998).

A diagnosis of major depressive disorder is based on a specific set of criteria whereby sad mood or an inability to experience pleasure (anhedonia), in addition to at least four other symptoms (e.g., sleep or appetite disturbance, trouble concentrating, feelings of guilt, hopelessness), are present for at least 2 weeks (American Psychiatric Association 2000). Subthreshold depression is a syndrome whereby a patient has at least 1 but fewer than 4 depressive symptoms. Both types of depression are common in older adults with impaired vision. In fact, subthreshold depression in visually impaired people is a strong risk factor for a future depressive episode (Rovner 2001, unpublished raw data).

H.P.N. Scholl et al. (eds.), *Ophthalmology and the Ageing Society*, Essentials in Ophthalmology,
DOI 10.1007/978-3-642-36324-5_14,

Most cases of late-onset vision loss in the US are attributable to age-related macular degeneration (AMD), with almost ten million people being affected (Congdon et al. 2004). The effect of AMD on a patient's life can be devastating. In a study of 86 AMD patients, overall ratings of quality of life were substantially lower than that of visually intact older people, older people with severe chronic obstructive pulmonary disease, and patients with AIDS (Williams et al. 1998). Compared to nonvisually impaired older people, patients with AMD were 8 times more likely to have trouble shopping, 13 times more likely to have difficulty managing finances, 4 times more likely to have problems with meal preparation, 9 times more likely to report difficulty with light housework, and 12 times more likely to have trouble using a telephone. AMD is also a risk factor for falls and subsequent hip fracture (Crews and Campbell 2004).

Given the disabling effects of AMD, it is not surprising that there is a high rate of depression in this population (most estimates hover around 30 %) (Brody et al. 2001; Hayman et al. 2007; Horowitz et al. 2005a; Rovner et al. 2002). These high rates are alarming due to the serious health consequences related to untreated depression in people with vision loss. A population-based study showed that comorbid vision impairment and depression in older people is associated with smoking, obesity, physical inactivity, and worse self-rated health (Jones et al. 2009). Vision impairment in older people is also a risk factor for suicide (Lam et al. 2008).

Depression can amplify the disabling effects of AMD. Depressed individuals with vision loss experience worse function and disability compared to their nondepressed counterparts (Jones et al. 2009). This effect is upheld even when controlling for severity of vision impairment (Rovner and Casten 2001), and it has been replicated in at least two other studies. Brody et al. (2001) found that depressed patients with impaired vision reported greater disability than nondepressed patients. In Rovner and Ganguli's (1998) study of 872 older adults, having combined vision impairment and depressive symptoms significantly increased the odds of functional impairment (Rovner and Ganguli 1998).

It is worth noting that subthreshold depression also has a profound effect on functioning. Horowitz et al. (2005b) compared functional disability ratings among three groups of older patients presenting for low-vision rehabilitation services: (1) those with major depression, (2) those with subthreshold depression, and (3) those with no depression. Those with subthreshold depression had levels of disability comparable to those with major depression; both depressed groups had significantly greater disability compared to subjects with no depression. Similar findings were observed by Rovner et al. (2006) who examined the relationships between disability and subthreshold depressive symptoms in 206 nondepressed AMD patients. Those with subthreshold depression had significantly worse vision function than those with no depression despite similar visual acuities. This rather robust finding was evident for both self-reported vision function and function ratings based on observation of task performance (e.g., check writing, pouring liquid).

There are several potential explanations for the high rate of depression in AMD. Functional losses due to vision impairment can erode one's sense of personal control and lead to feelings of inadequacy and helplessness. Social isolation can arise from mobility restrictions (e.g., difficulty driving, limited walking due to fear of falling), embarrassment about vision loss, and impairments in processing visual stimuli (e.g., reading nonverbal facial cues). Moreover, vision impairment can lead to a diminution or cessation of activities and pastimes that give life meaning and richness. Other factors that may increase the risk for depression in patients with impaired vision include negative life events (Rees et al. 2010) and dual sensory impairment (i.e., concurrent vision and hearing loss) (Crews and Campbell 2004).

Research shows that concomitant disability and activity disengagement are common mechanisms linking AMD to depression. The inability to partake in both discretionary activities (e.g., leisure, socializing) and activities that serve to maintain independence (e.g., driving, meal preparation) are associated with the development of depression. This was confirmed in a longitudinal

sample of patients with recent onset bilateral AMD which showed that AMD is depressogenic to the extent that patients relinquish activities that are personally important (Rovner et al. 2002). The relationship between difficulty caring out activities and depression is mediated by the severity of emotional distress caused by vision impairment (Rees et al. 2010).

Given the foregoing, helping people to maintain their independence, facilitating the acceptance of assistance when needed, and fostering an active lifestyle may be key to maintaining optimal psychological well being. Patients with AMD may suddenly find that habitual ways of carrying out everyday activities are no longer effective (this may be particularly so in the case of neovascular disease). These patients need guidance and support so that they can adapt effective coping strategies (i.e., learning new strategies for carrying out familiar, routine activities, learning to accept assistance from others, acquiring new activities to replace ones that are no longer possible). We discuss ahead that activity disengagement is also a risk factor for (or perhaps a prodromal symptom of) cognitive decline, and this too should be considered when fostering healthy adaptation to vision loss.

14.2.1 Preventing Depression in Age-Related Macular Degeneration

In view of the fact that depression (both major and subthreshold) can have such serious consequences for people with impaired vision, there is a need for guidelines on how to best to deal with depression as it relates to AMD. Depression in this context needs to be considered on two levels: prevention of future cases and treatment of acute episodes.

The first step in dealing with acute depression is to identify it. There are several quick and easy to administer depression screening instruments that can be used by nonmental health professionals. Three commonly used ones are the Geriatric Depression Scale (GDS) (Yesavage et al. 1983), the Center for Epidemiological Studies Depression Scale (CES-D) (Radloff 1977), and the Patient Health Questionnaire (PHQ) (Kroenke et al. 2001). Each of these instruments asks patients to rate the severity and/or frequency of depressive symptoms, and each yields quantitative scores that capture severity of depression. Each also has established cut points that indicate the possibility of major depression.

The most recent preferred practice guidelines from the American Academy of Ophthalmology (2008) recognize that depression is a common comorbid condition of AMD and that screening and providing appropriate referrals for depression are necessary when depression is suspected. However, depression screening should be considered for all AMD patients because relying on clinical judgment may not be the best strategy. Ophthalmologists often underestimate the negative effect of AMD on patients' quality of life, particularly among patients with better acuities (Brown and Brown 2010). Consequently, depression in older adults with vision loss is undertreated. For example, a recent study of 143 older persons with vision loss found that only 20 % of the depressed patients (12 of 60) were being treated for their depression (Rees et al. 2010). Moreover, research examining relationships between depression and severity of vision loss is mixed. Some studies show no relationship (Rovner et al. 2002; Rovner and Casten 2005), while others indicate that depression severity is worse in those with more substantial vision loss (Augustin et al. 2007). Until this uncertainty is resolved, it may be best to screen all AMD patients for possible depression, regardless of their acuity, disease stage, suspected presence of depressive symptoms, or AMD treatment received [20 % of patients undergoing anti-VEGF treatment remain depressed 3 months post treatment (Casten et al. 2010)].

Focusing efforts on the prevention of depression in AMD may be a cost-effective strategy because treating an active depressive episode is expensive, untreated depression may have significant health consensuses (heart disease, increased disability), and depression treatment is moderately efficacious at best (Gartlehner et al. 2007). Preventative interventions are catego-

rized at three levels: primary (goal is to decrease incidence), secondary (goal is to decrease prevalence), and tertiary (goal is relapse/recurrence prevention) (Mrazek and Haggerty 1994). Prevention efforts in AMD tend to focus on primary prevention, that is, strategies for averting the onset of a depressive episode. Primary prevention is conceptualized at three levels, depending on the target population. Universal interventions are aimed at the general population, for example, all patients who have AMD. Selected interventions target subgroups that have risk factors for depression (e.g., dual sensory loss), and indicated interventions are directed towards patients who are showing signs of the disease (i.e., subsyndromal depressive symptoms). A selected intervention approach is probably the most cost-effective strategy in AMD. Although the prevalence of depression is high (about 30 %), most patients with AMD will not become depressed.

An ideal target for prevention is patients with a recent decline in vision and subsequent new functional losses. The "Preventing Depression in AMD" trial (Rovner et al. 2007) tested the efficacy of a psychosocial intervention, problem-solving treatment (PST), to prevent depression in patients with new onset vision loss due to AMD. This standardized intervention was based on the premise that inaccurate appraisals of problems and dysfunctional problem-solving skills contribute to the onset of depression. Teaching patients effective problem-solving skills, therefore, may foster independence, preserve function, and prevent depressive symptoms. This study enrolled 206 nondepressed patients with bilateral neovascular AMD and recent vision loss. Subjects were randomized to either PST or a usual care control condition. The primary outcome was incidence of depressive disorders at 2 months (short-term effect); the trial also evaluated effects at 6 months (maintenance effect). A secondary goal was to determine whether PST could prevent the loss of participation in valued activities. PST-treated subjects had 6 in-home sessions in which a specially trained interventionist taught subjects in a systematic, step-by-step process for dealing with vision-related problems (e.g., trouble cooking, difficulty reading). Results indicated that PST successfully prevented depression at 2 months. About 12 % of the PST group became depressed compared to 23 % of the usual care group ($p < .05$). There was a parallel effect for function; 23 % of PST-treated subjects relinquished an important activity versus 37 % of usual care subjects. A meditational analysis determined that PST prevented depression to the extent that activity relinquishment was avoided. These effects, however, were not sustainable, as rates of depression were similar in both groups at 6 months (21 % of PST subjects developed depression vs. 27 % of control subjects).

This trial demonstrated that depression can be prevented in the short term; however, beneficial effects decay over time. Because neovascular AMD is characterized by episodes of sudden vision loss and corresponding functional declines, ongoing efforts to prevent depression may be needed throughout the course of the disease. This may involve monitoring and screening for events that may trigger depression and then administering maintenance or booster treatments as needed.

Brody et al. (2002) evaluated the benefits of self-management intervention in patients with AMD. Their 6-week intervention was led by a health professional and consisted of didactic instruction regarding basic information about AMD and rehabilitative strategies. It also contained a behavioral component that emphasized dealing with some of the challenges presented by AMD. Their data showed that the intervention group evidenced a significant improvement in mood 6 weeks post baseline and that this effect was most pronounced for those who were depressed at baseline. Intervention subjects also displayed improved function, and again this effect was most apparent for depressed subjects. A follow-up study at 6 months supports the intervention's sustained effects; benefits were greatest for subjects who were depressed at baseline. Importantly, the incidence of depression from baseline to 6 months was significantly lower in the intervention group. Discrepancies in long term effects between the Rovner and the Brody studies could be due to sampling differences. The

Rovner study did not include depressed subjects, while the Brody study did, and the intervention was most advantageous for this subgroup.

Evidence for the benefit of low-vision rehabilitation on depression is mixed. In a group of older people newly referred for low-vision rehabilitation, active participation in rehabilitation was related to a decrease in depressive symptoms over a 2-year period (Horowitz et al. 2005a). Girdler et al. (2010) compared the benefits of a usual care model of low-vision rehabilitation with an enhanced one. The enhanced intervention included an intensive group-level component whereby subjects were taught self-management strategies. Subjects in the enhanced intervention reported higher levels of activity engagement. At 12 weeks follow-up, 17 % of subjects in the enhanced intervention reported depressive symptoms, compared to 51 % of control subjects. This study shows that rehabilitation may not be enough to prevent and treat depression. Nevertheless, rehabilitation presents an optimal opportunity to improve function and possibly prevent or reduce depression.

AMD is a serious public health problem, robbing patients of independence and destroying their quality of life. As the population ages, greater numbers of Americans will be affected by this disease and subsequent depression. Thus, targeting depression, a major contributor to vision-related disability, is one strategy for maintaining independence and improving quality of life. Moreover, because depression and function are so closely intertwined in AMD, developing interventions that incorporate depression management into rehabilitation might be the best course of action.

14.3 Cognitive Decline in Age-Related Macular Degeneration

Many studies have linked vision loss with cognitive decline and physical disability. Crews and Campbell (2004) examined the 1994 Second Supplement on Aging involving 9,447 older persons and found that those with self-reported vision loss were 2.2 times more likely to be cognitively impaired than those without vision loss (Bäckman et al. 2003). Reyes-Ortiz et al. (2005), using the population-based Hispanic Established Populations for Epidemiologic Studies of the Elderly, found that objective measures of vision impairment were associated with cognitive decline (Bäckman et al. 2003; Breitner 2006). Data from the Health and Retirement Study revealed that untreated poor vision is associated with Alzheimer's disease (Rogers and Langa 2010). Persons with poor vision who did not visit an ophthalmologist had a 9.5-fold increased risk of Alzheimer's disease and a 5-fold increased risk of cognitive impairment but no dementia. By contrast, individuals with very good or excellent vision had a 63 % reduced risk of dementia. The North Carolina Established Populations for the Epidemiologic Studies of the Elderly Participants found that individuals with coexisting visual and cognitive impairment were at high risk for disability in instrumental activities of daily living [odds ratio (OR) 6.50], mobility (OR 4.04), basic activities of daily living (OR 2.84), and incident ADL disability (OR 3.66). These odds ratios were greater than the odds ratio associated with visual or cognitive impairment alone, indicating that visual and cognitive impairment contribute additively to disability risk (Whitson et al. 2007).

One mechanism that links cognitive decline and age-related changes in the visual system involves retinal vascular pathology. Because retinal and cerebral arterioles share similar pathologic processes, microvascular disease in the retina (e.g., microaneurysms, hemorrhages, and soft exudates) may reflect microvascular disease in the brain. To better understand this relationship, Lesage et al. (2009) examined retinal microvascular abnormalities and longitudinal changes in cognition in a community population (Wang et al. 2006). Participants underwent four cognitive assessments between 1990–1992 and 2004–2006, using the Word Fluency Test (which assesses language and executive function), the Digit Symbol Substitution Test (which assesses visual processing and psychomotor speed), and Delayed Word Recall (episodic memory) as well as retinal photography in 1993–1995. Over time,

individuals with retinopathy showed declines in executive function and psychomotor speed compared to those without retinopathy. This finding indicates that retinal vascular changes can serve as markers of the cerebral microvasculature and highlight the importance of cerebral microvascular disease as a cause of cognitive decline in older persons.

Other researchers have noted intriguing relationships between age-related macular degeneration (AMD) and cognitive decline (Klaver et al. 1999). Clemons et al. (2006) found that increased macular abnormalities and reduced vision were associated with lower cognitive function and that persons with vision acuity worse than 20/40 in both eyes were more likely to be cognitively impaired than persons with better visual acuity (Crews and Campbell 2004). Baker et al. (2009) studied the association of early AMD and cognitive function and dementia in the 2,088 persons aged 69–97 years who participated in the Cardiovascular Health Study. Cognitive function was assessed using the Digit Symbol Substitution Test and the Modified Mini-Mental Status Examination. After controlling for age, sex, race, and study center, persons with low Digit Symbol Substitution Test scores were more likely to have early AMD (OR, 1.38) than were persons with higher scores. In analyses controlling for education, systolic blood pressure, cholesterol level, diabetes mellitus, smoking status, and apolipoprotein E genotype, the association was even stronger (OR 2.00).

Similarities in the pathologies of AMD and Alzheimer's disease (AD) also suggest a linkage. Previous studies have observed degeneration of the optic nerve and retina in Alzheimer's disease (Clemons et al. 2006). In both AMD and AD, misfolded amyloid beta peptides accumulate and may play a central role in their onset (Yoshida et al. 2005). In AMD, an accumulation of drusen, which contain amyloid and the products of neurodegeneration, may promote further degenerative changes in the macula. In AD, increased production or reduced clearance of toxic amyloid oligomers leads to nerve cell dysfunction and cell loss. Some studies show that amyloid beta increases vascular endothelial growth factor (VEGF) and may lead to retinal pigment epithelium atrophy (Yoshida et al. 2005). There are also similarities in vascular risk factors for both AMD and AD, such as advanced age, hypertension, unhealthy diet, physical inactivity, obesity, and cigarette smoking. Both AMD and AD have also been linked to an increased risk of stroke (Mares et al. 2011; Middleton and Yaffe 2009; Tan et al. 2008). The Atherosclerosis Risk in Communities study found that persons with signs of late AMD were significantly more likely than those without AMD to have incident coronary heart disease over 10 years (30.9 % vs. 10.0 %) and higher incidence of stroke (4.1 % vs. 2.1 %) (Wong et al. 2006; 2007). The pathogenesis of both AMD and AD also appears to involve atherosclerosis, inflammation, and oxidative stress, which provide further evidence of shared pathogenetic mechanisms in the two diseases. Alternatively, vision loss may lead to cognitive decline via deafferentation of the visual system from the sensory cortex (Lindenberger and Baltes 1994). Interestingly, the two diseases apparently have different genetic risks (i.e., the APO 4 allele increases the risk for AD but decreases the risk for AMD) (Gandy 2005; Hinton et al. 1986).

Vision loss may also result in behavioral changes, such as relinquishing valued activities like reading and socializing, that indirectly and adversely affect neural function and can lead to or unmask incipient cognitive decline (Hendrie et al. 2006). To determine whether relinquishing cognitive, physical, and social activities is associated with an increased risk of cognitive decline in patients with AMD, we conducted a 3-year longitudinal study of older, nondemented patients with AMD who had participated in the Preventing Depression in AMD Trial (Rovner et al. 2007). This was a 12-month randomized controlled clinical trial comparing the efficacy of problem-solving treatment (PST) versus usual care to prevent depression in older patients with AMD. At the baseline visit of the clinical trial, we assessed the extent to which the 206 enrolled subjects had relinquished specific activities that

other research suggests prevent cognitive decline. Then 3 years later, we interviewed the 160 available knowledgeable informants of subjects who were originally enrolled in the clinical trial to ascertain whether subjects had declined cognitively. We tested the hypothesis that relinquishing more valued activities was associated with an increased risk for cognitive decline.

Over 3 years, 23 subjects (14.4 %) declined cognitively. Age, sex, education, decline in visual acuity, and number of dropped activities were associated with cognitive decline; each additional dropped activity increased the risk by 58 %. Subjects who relinquished 3 activities were 3.87 times [95 % CI 1.95, 7.76] more likely to become demented than subjects who relinquished no activities; those who relinquished 5 activities were 9.54 times [95 % CI 3.05, 30.43] more likely. A multivariate model demonstrated that the number of dropped activities was a powerful predictor of cognitive decline after controlling for relevant risk factors, particularly for subjects less than 80 years of age.

In AD, we know that cognitive activities such as reading or playing board games or musical instruments reduce the risk of dementia as do physical and social activities (Bennett et al. 2006; Sturman et al. 2005; Verghese et al. 2003; Wang et al. 2006; Wilson et al. 2002). The mechanism by which these activities maintain cognition is uncertain but may involve enhancing the brain's capacity to tolerate neuropathology (i.e., increased neural reserve) via beneficial effects upon neuroplasticity, neurogenesis, or cortisol regulation (Bird 2005; Schmidt et al. 2002). In our sample, activity loss may have triggered or hastened the onset of cognitive decline. Although other mechanisms are possible, our finding that activity loss is associated with cognitive decline in AMD underscores the importance of maintaining activities in the face of vision loss. This finding may also apply to patients with other chronic diseases that lead to the loss of or restrict participation in valued activities. If so, promoting optimal cognitive and physical health has wide relevance to the care of the growing population of older adults with chronic disabilities.

Conclusion

There are a number of possible mechanisms that link vision loss, due to AMD in particular, with cognitive decline. They include a common pathogenesis that involves shared histopathological features, inflammatory processes, and vascular risk factors.

Acknowledgments Conflict of interest: none; Ethical standards: Informed consent – not applicable; Animal rights – not applicable

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