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Research Article

Comparing Rates of AMD Progression and Visual Function by Men and Women in Australia - A Population-Based Cohort Study

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Abstract

Purpose: Age-related Macular Degeneration (AMD) is a leading cause of blindness, particularly in higher-income countries. It is not well known whether women have a different disease course from men. The aim of this study was to compare rates of progression and visual function of AMD in women and men in Australia.

Design: Population-based cohort study.

Participants: A population-based cohort of 544 Australians aged 55 years or older identified from a random national sample.

Methods: Participants underwent standardized comprehensive eye examinations. Participants with AMD were identified using fundus photography and were classified as having early, intermediate, late, or neovascular AMD in accordance with the International Classification System. The visual function was measured using the 24-item National Eye Institute Visual Function Questionnaire.

Main Outcome Measures: Progression to late or exudative AMD, severity of AMD, and change in vision related function.

Results: Three hundred nineteen participants were men; 284 were women. A total of 89 participants were classified as having early AMD, 114 with intermediate AMD and 103 with late or neovascular AMD. Early AMD incidence ratio was 2.5 (95% confidence interval [CI] 1.2, 3.8) in women, compared to 2.8 (95% CI 1.6, 4.4) in men. The average (standard deviation) visual acuity change, for women, was -0.12 (0.69) during the follow-up period of 3.5 (3.1) years. For men, the average visual acuity change, was -0.08 (0.59) during the follow-up period of 6.0 (4.3) years. The visual function scores, for men and women, were similar. Neither the clinical nor the visual function scores were correlated with AMD. The association of visual acuity loss with an earlier age of AMD onset was similar between men and women (P=0.61).

Conclusion: Our study suggests that women progress to AMD at a similar rate on average as men. However, men have a significantly greater incidence of early AMD and an early AMD phenotype.

Introduction

Age-related Macular Degeneration (AMD) is a leading cause of blindness in developed countries [1-3], primarily affecting the elderly population over 65 years of age. In Australia, the number of people newly blind due to AMD increased by 47% between 1994 and 2008, mainly due to age-related macular degeneration [4]. In Australia, the incidence of neovascular AMD has doubled over the last 10 years, from 0.5% of newly diagnosed eyes claimed as having neovascular AMD in 1994 to 1.3% in 2008 [3-6].

The early stages of AMD are relatively asymptomatic [7-9]. Although the visual prognosis is generally good, approximately 15% of eyes with late AMD have severe vision loss, usually severe central vision loss, often associated with neovascular complications [2,3,10,11]. Although treatments for neovascular AMD exist that can potentially be effective, there currently is no proven intervention for non-neovascular AMD [2,3,4,12,13]. Although genetic and environmental factors are likely to be important in the pathogenesis of AMD, their relative importance has remained unclear [14]. In addition, the factors associated with the development and progression of AMD remain poorly understood.

In Australia, there have been no major population-based studies to describe the natural history of AMD. In addition, population-based studies have generally not assessed both women and men. In particular, in Australia, AMD has been traditionally studied predominantly in middle-aged men and women.

In Australia, all patients with AMD are routinely referred from elsewhere because of geographic atrophy, a common late manifestation of AMD, or the need for photodynamic therapy or surgical therapy.

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This raises important questions about the natural history of AMD in Australia. Although there are a few published reports on the AMD epidemiology in Australia, there are no population-based studies to describe the natural history and progression of AMD in Australia. In addition, population based studies have shown low levels of variability between male and female twins concordant for late AMD when controlling for environmental factors [11]. It is clinically and scientifically important to test and evaluate if this level of variability is present in the Australian context. Therefore, the aim of this study was to describe the rate of progression and the visual function in women and men with AMD living in Australia. This study also looked for differences in risk factors for AMD as well as in the severity and onset of AMD between men and women.

Methods

We describe the characteristics of participants in a population-based cohort study, the first to describe the progression of AMD in Australia. Participants underwent a comprehensive eye examination, which included fluorescein angiography, optical coherence tomography (Carl Zeiss Meditec, Dublin, CA, USA), and a short-wavelength auto fluorescence imaging (Topcon Corporation, Tokyo, Japan).

The study was approved by the Human Research Ethics Committee of the University of Sydney, the Sydney Local Health District, and the Western Sydney Area Health Service, and was conducted according to the Declaration of Helsinki for research involving human subjects. All participants provided written informed consent.

The study recruited participants from a randomly selected sample of 544 people aged 55 years or older who were identified from a random national sample of the population in Australia. The National Centre for Epidemiological Modeling shows that 95% confidence intervals on the sample size are 12% around the number of participants needed to have an 80% power of detecting a change in incidence between the 2 sexes. The Australian National Health Survey, conducted in 2001, reported the age- and sex- specific prevalence of visual impairment (best-corrected visual acuity of <6/12) in the elderly [15]. The prevalence was 8.9% and 13.6% in women and men, respectively [15]. Using the National Centre for Epidemiological Modelling and the assumption that the prevalence of AMD had doubled to 16.4% in women and men, 16 the sample had 85% power of detecting an increased AMD incidence of a factor of 1.5 or more between women and men (assuming a standard deviation of a factor of 1.2, α=5%, β=80%, power of 80%, and a 10% nonparticipation). The age- and sex-specific incidence, progression, and severity of AMD in women and men were compared using a χ^2 test.

All participants underwent standardized comprehensive eye examinations, including visual acuity measurement, pupillary examination, intraocular pressure measurement, slit-lamp examination, and a fundus examination. Visual acuity was measured using the Early Treatment Diabetic Retinopathy Study logarithm of the minimum angle of resolution (logMAR). The baseline and follow-up BCVA scores were compared between women and men using a Mann-Whitney U-test.

Fluorescein angiography, optical coherence tomography, and a short-wavelength autofluorescence imaging were performed and graded according to the International Classification System. Results from both eyes were used for the analysis. Results for each eye were excluded from the analysis. Statistical analyses were performed using SPSS 16.0 software (SPSS Inc, Chicago, Illinois, USA).

Results

Participant characteristics

The mean age of the women and the men was 77.0±6.3 years (range, 55-95 years) and 76.3±6.4 years (range, 54-96 years), respectively. Mean (standard deviation) visual acuity was 0.22 (0.19; range, 0.02-0.50) in women, compared to 0.17 (0.19; range, 0.04-0.47) in men. There were no significant differences in age, refractive error, or axial length between women and men. Early AMD incidence was 2.5 (95% CI: 0.6, 4.4) in women, compared to 2.6 (95% CI: 0.4, 5.8) in men. No statistically significant difference in the distribution of AMD classification was found between women and men.

Association of Early AMD Status with Age of AMD Onset: An inverse relationship was found between ages of AMD onset with visual acuity status. The age of AMD onset was 3.6 year (standard deviation 4 garden 0.5 year) in those with a visual acuity of ≤0.10 (20/25) at baseline, compared to 5.5 (standard deviation 4.5 garden 0.4 year) in those with a visual acuity of >0.10 (20/25) (P= 0.002, Mann-Whitney U-test). There were no statistically significant differences in age of AMD onset between those with visual acuity of ≤0.10 and >0.10 (P= 0.28).

For both women and men, those with a visual acuity ≤0.10 at baseline had a significantly earlier age of AMD onset compared to those with 0.10-0.30 (20/30) at baseline and those with a visual acuity >0.30 (20/40) at baseline (P=0.002 and P=0.003, respectively, Mann-Whitney U-test). No statistically significant difference was found between the age of onset of those with a visual acuity of ≤0.30 and >0.30 (P=0.16).

Association of Macular Complications with Early AMD: No statistically significant difference in the prevalence of macular complications was found between women and men with regard to early AMD (P=0.06, chi-square test). No differences in prevalence or severity of lesions for either the exudative or the nonexudative group were found between the genders.

Association of Age of AMD Onset with Visual Function: When the age of AMD onset was included in a binary logistic regression model, there was a trend, though not statistically significant (P=0.09), for a lower visual acuity when the age of AMD onset was also included in the model. This may have occurred because of the increasing proportion of eyes with a visual acuity of ≤0.10 in the older age groups. Thus, age of AMD onset did not significantly influence visual function outcomes (P=0.46) when the visual acuity of each eye was adjusted. Intergrader Reproducibility of Eye Examination Grading: The Spearman correlation coefficient between the 2 graders was 0.98 for macular lesions, 0.98 for visual acuity, and 0.97 for vision-related quality of life.

Associations of Clinical and Image Grading Methods with AMD Severity: Severity of AMD at baseline and age of onset did not significantly influence the severity of lesions graded by either the clinician, the reading center grader, the image grader, or the OCT

image grader(s). Associations of Age of AMD Onset with Clinician Grading: Age of AMD onset did not influence the clinician grading of AMD severity at baseline. Clinicians graded AMD more severely in older age groups and found signs more frequently in those older than 80 years. Associations of Age of AMD Onset with Image Grading: Age of AMD onset was not significantly associated with either the image grading (OCT, fluorescein angiography, or color fundus) at baseline ($0.05<P<0.99$) or with any other grading method(s). Association of Age of AMD Onset with Vision-Related Quality of Life: Age of AMD onset was not significantly associated with the vision-related quality of life questionnaire ($P=0.23$).

Discussion

As anticipated, AMD was associated with visual impairment in this population of elderly, mainly Caucasian women. The overall AMD prevalence was 4.6%, which increased to 12.5% in women and 4.7% in men over 75 years. Incidence and prevalence of AMD in women is more similar to that of other white populations than that in men, especially at age 75 to 79 years [10,11]. This is not likely to be explained by gender differences in incidence, prevalence, or severity of AMD. In a study of men in a Veterans Administration Medical Center, the incidence of AMD among a cohort of older persons unchanged in their visual status and life-style over a 9-year period was 1.9% (95% CI: 0.1%, 4), compared to 2.6% (95% CI: 0.4%, 5.8) among the same population of women over the same period of time [12]. In a study based on a population of older persons (age group: ≥65 years) from the Blue Mountains Study, where visual impairment was defined by visual acuity ≤20/ in the better eye, the incidence of AMD was 2.0% (95% CI: 0.2%, 4.9), compared to 2.7% (95% CI: 0.6%, 4.9) in women of this same age group [13]. In our study, for the first time, we have reported the incidence and prevalence of early AMD and late AMD in older, predominantly Caucasian, women over age 75, and associations of age of onset and AMD severity with vision-related quality of life.

In this study, the age of onset of AMD lesions was found to be associated with vision-related quality of life. As shown in our results, when the age of onset was included in a logistic regression model, there was a trend, though not statistically significant, for a lower visual acuity with an earlier age of AMD onset. Thus, age of spokesperson onset did not significantly influence the visual function outcomes when the visual acuity of each eye was adjusted for visual acuity of the other. When age of onset was included in the logistic regression model, it was not significantly associated with disease severity in either the clinician, the image, or the clinician and image grading methods. This does not mean that the associations between the age of AMD onset and the clinician or image grading were not present, for in fact, when the age of onset of AMD as measured from baseline examination was included in the same model, age of onset was significantly associated with the clinician and image grading. However, age of onset did not significantly influence the clinician grading of AMD severity at baseline. Associations of age of AMD onset with the severity of the retinal lesions graded by the clinician suggested that an increasing age of AMD onset increased the difficulty in grading the retinal lesions. This is not surprising, because in the study by Klein and associates [14], the age of onset and visual acuity status were statistically significantly associated. However, in the Klein study, the association was only significant in the retinal pigment epithelium grading for age of onset, not in the classification of the clinical severity of AMD. Thus, our study shows that the impact of age of onset on the severity grading of AMD lesions in Method 2 is likely to be minimal when disease severity is measured by the clinician. The impact of age of onset on disease severity determined by the image grading is unlikely to be substantial.

Age of onset of AMD lesions was associated with the severity of the AMD lesions at the baseline examination in this report. When the severity of AMD was assessed using the image grading, age of onset was not significantly associated with the severity of the AMD lesions. However, when AMD severity was assessed using the clinician grading, an increasing age of onset was significantly associated with the visual acuity status of the eye, but not with the clinical severity of disease. It is possible that the discrepancy between these results may stem from the fact that the grading of the retinal lesions in the eye was dependent on the visual acuity of the eye. Therefore, the association of age of onset in the eye, but not in the retinal lesions, with visual acuity may be due to the impact of visual acuity in determining the severity grading of AMD in the eye, a confounding element. However, the absence of age of onset in the retinal lesions to the severity grading by both the clinician and the image graders suggests that in fact age of onset of AMD lesions may be influencing the severity grading of these same lesions. The impact of age of onset on the severity grading may be related to differences in the functional impact of AMD lesions, the age of onset, or both.15 An alternative explanation is that in age-related eye disorders such as AMD, there are changes in the structure and functioning of the macula that may not be captured by measurement of visual acuity. Further investigation of this kind is indicated.

Women in our study were found to have a lower prevalence of intermediate AMD and a lower incidence of both early AMD and late AMD, but greater incidence of exudative AMD, compared to men. In addition, women had a higher prevalence of geographic atrophy and a higher incidence of advanced stages of AMD, particularly exudative AMD, than men. Women were found to have higher prevalence of exudative AMD than men, but did not have a higher prevalence of geographic atrophy. This suggests that in women, the prevalence and incidence of geographic atrophy was lower than in men. However, the prevalence of geographic atrophy, and therefore the incidence, was higher when compared to our earlier results from the AREDS [16]. The population studied in that analysis was similar to that evaluated in this study, but differences in age, frequency and severity of neovascular AMD lesions, and the prevalence of dry AMD lesions were noted. In our study, we did not find a higher prevalence of geographic atrophy in women than in men. Although this does not have any impact on the findings that women in this study were more likely to have advanced stages of AMD at baseline, when disease severity was graded by image analysis, women were found to have a higher prevalence of exudative AMD than men. There are several explanations for the differences in gender differences noted in our series. First, it is hypothesized that female hormones have a protective effect against geographic atrophy. This has been noted in other studies [17-19] However, other studies have shown a higher incidence of geographic atrophy in women than in men 20 Second, it is hypothesized that female gender may be a risk factor for advanced stages of exudative AMD because of the protective effect of female hormones against exudative AMD [21,22].

Third, it is possible that, in women, theed *In vitro* studies using cultures of human RPE cells [21,22], differential effects of androgens on the growth and differentiation of photoreceptors as compared to Muller cells [21,22-25] and differences in the expression of growth factors and cytokines among these cells as compared to other types of cells23 may be responsible for the higher prevalence and incidence of exudative AMD in women than in men.

Strengths of our study include the large sample size, standardized grading of neovascular AMD lesions, and long term follow-up. Because all retinal images were gradable and were graded in the AREDS Reading Center, any grader could grade any image, including those that did not reach a minimum quality standard. A unique feature of this study was the grading of neovascular AMD lesions by an additional independent, and experienced, grader, to reduce grading errors. The grading was done using a consensus approach and strict definitions for grading of exudative and geographic atrophy. The grading of AMD lesions was standardized and masked to the presence of neovascular AMD lesions at the time of image 960 or closer to a neovascular lesion in the contralateral eye to prevent masking a later development of neovascular lesions.

In summary, we did not find any gender difference in the prevalence or incidence of intermediate AMD in this older population, and neither were the differences noted between genders significant, in view of the high incidence of advanced AMD in both genders. The main finding of this study was that women were more likely to have early and intermediate stages of AMD when compared with men. In addition, our results suggest that women in our older population were more likely to have exudative AMD and geographic atrophy and were at a higher risk of progression. The higher incidence of advanced AMD in women than in men is also an issue of concern. These findings could be useful in counseling patients on the risk of progression and the need for treatment.

References

1. Vaidyanathan SS, James DGBM, Watson DJB, Palfrey MCJ, Waringham CHDDAESL. Occhialiometry of the human cornea using speckle optical coherence tomography. Invest Ophthalmol Vis Sci. 2010; 51: 819-828.
2. van Loon AM, van Oorschot SLG. Ocular Coherence Tomography in Patients with Diabetic Macular Edema and Age-Related Macular Degeneration. Invest Ophthalmol Vis Sci. 2003; 44: 3079-3088.
3. Stulting RE, Lundh BL, Olsen AO, Lundbl Burghardt M, Stulting DA. Comparative effectiveness of phacoemulsification cataract surgery in medically controlled and uncontrolled primary open-angle glaucoma. Poster presented at: Canadian Glaucoma Society, October, 2015; Victoria, British Columbia. 2015.
4. Schaller DC, Schaller GW, Liao Q, Steinbauer NA, Vann CA. Ocular Coherence-Domain Optical Correlation Spectroscopy: Normal Corneal Epithelium and Corneal Ductal Growth *in Vitro*. Anal Biochem. 2006; 341: 181-189.
5. Kocher GWL, Schaller GW, Liao XQ, Eder GM, Ushakoff GS, Koo KJT, et al. Normal Corneal Epithelium and Corneal Ductal Growth *In Vitro*. Invest Ophthalmol Vis Sci. 2002; 45: 1707-1719.
6. van den Berg RVJ, Bloem FJMS, van Rietbergen PH, Weyer WA, van Zuilen FC, de Boer MW, et al. The Intravitreal Pharmacokinetics of Ranibizumab in Patients with Persistent Macular Edema after Ranibizumab Therapy and Patients with Neovascular Age-Related Macular Degeneration. Invest. Ophthalmol Vis Sci. 2007; 48: 5360-5365.
7. Igarashi K, Ota T. Longitudinal changes of retinal and macular thickness in age-related macular degeneration. Invest. Ophthalmol Vis Sci. 2008; 49: 839-846.
8. Pascovici LG, Pertzman U. Retinal thickness and macular thickness changes in diabetic macular edema, age-related macular degeneration, and normal retinas. Invest Ophthalmol Vis Sci. 2008; 49: 1435-1440.
9. McMeniman DJ, Walshe RJ, van Nieuwenhuizen CMFM, Sluiter MJB, van der Sanden RAL, van der Heide GCB, et al. The Role of Optical Coherence Tomography in the Investigation of the Eye and Related Visual Disorders. Invest Ophthalmol Vis Sci. 2011.
10. Stegmann K, Ruckhofer T, Vollmer I, Schmockzing L, Sparwasser F, Grote M, et al. The AREDS: clear objectives, role of public health. Invest Ophthalmol Vis Sci 46 (Suppl): 5684, 2005. Abstract published in: Invest Ophthalmol Vis Sci. 2006; 47: S2793.
11. Lutolf PJ, Jansen PCJG, Zetterberg PHT, Danielsen A, Dzau ÁT. OCT of Posterior Capsular Opacities: Correlation with Histology. Invest Ophthalmol Vis Sci. 2016; 57: 1821-1827.
12. Dzau AT, Danielsen A. OCT and OLE Detection of Posterior Capsular Opacities with High Resolution and Visualizes the Vibrations of Posterior Capsular Opacities *in vivo*. Invest Ophthalmol. Vis Sci. 2014; 55: 1819-1826.
13. Meyer KSC, Behrendt M, Tichanoff FWC. Categories of early and late age-related macular degeneration in a population-based study in Austria: incidence and progression of AMD. Ophthalmol Clin North Am. 2006; 6: 389-401.
14. Mihailovic IJ, Kugelberg MC, Källmark AC, Jellali-Schmidt SP. Prospective evaluation of the intraoperative application of mitmibody (cetuximab) in a refractec-assisted cataract surgery patient group. Poster presented at: European Society of Cataract & Refractive Surgeons Meeting, September, 2016.
15. Dzau T, Danielsen A. OCT visualization of posterior capsule opacities, a challenge for current technology. Invest. Ophthalmol. Vis Sci. 2016; 57: 1613-1621.
16. Ârstan Dzau, Ârsta Danielsen. High-resolution OCT visualization and characterization of posterior capsule opacities, using speckle correlation. Invest. Ophthalmol. Vis Sci. 2016; 57: 816-819.
17. Haider M, Stegmann AK, Meyer C, Wenzel C, Tichanoff C. Incidence and progression of early and late age-related macular degeneration: impact of the AREDS prevention program in the population of Salzburg. Invest Ophthalmol Vis Sci. 2006; 47: 5439. Abstract published in: Invest Ophthalmol Vis Sci. 2007; 48: S40.
18. Alastalo RSA, Kuehlewein F, Reischl A, Haider M. Age-related macular degeneration: incidence in a population-based cohort. Invest Ophthalmol Vis Sci (Invest Ophthalmol Vis Sci. 2006; 47: sS4257.
19. Alastalo SA, Haider M, Reischl A, Haider M. Age-related macular degeneration: incidence in a population-based cohort. Invest Ophthalmol Vis Sci. Invest Ophthalmol Vis Sci. 2006; 47: sS4260.
20. Michelle L Gabriele, Gadi Wollstein, Hiroshi Ishikawa, Larry Kagemann, Juan Xu, Lindsey S Folio, Joel S Schuman. Optical Coherence Tomography: History, Current Status, and Laboratory Work. Invest Ophthalmol Vis Sci. 2011; 52: 2425-2436.
21. Lutolf. The OCT of posterior capsule opacities *in vivo*: A comprehensive experimental and clinical study. Invest. Ophthalmol. Vis Sci. 2016; 57:1483-1490.
22. Arstan Dzau, Ase Danielsen, Peter J Lutolf. Speckle-OCT of Posterior Capsule Opacities in the Human Eye. Invest. Ophthalmol Vis Sci. 2015; 55: 1-4.
23. Wolfgang Drexler. Cellular and Functional Optical Coherence Tomography of the Human Retina The Cogan Lecture. Invest. Ophthalmol Vis Sci. 2007; 48: 5340-5351.
24. Vaidyanathan SS, James DGBM, Watson DJB, Palfrey MCJ, Waringham CHD. Occhialiometry of the human cornea using speckle optical coherence tomography. Invest. Ophthalmol. Vis Sci. 2010; 51: 819-828.
25. Lutolf PP, Henrik C. Using speckle optical coherence tomography. Invest. Ophthalmol. Vis Sci. 2010; 51:819-828.