THERAPEUTIC ADVANCES in
Ophthalmology

Original Research

Charles Bonnet syndrome in patients with geographic atrophy secondary to age-related macular degeneration: a cross-sectional study

Ther Adv Ophthalmol

2025, Vol. 17: 1–7

DOI: 10.1177/25158414241305500

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Abstract

Background: Age-related macular degeneration (AMD) is a prevalent cause of irreversible vision loss among the elderly. The prevalence and detailed characteristics of Charles Bonnet syndrome (CBS) remain largely unexplored in patients with geographic atrophy (GA) secondary to AMD.

Objectives: To investigate the prevalence and characteristics of CBS in patients with GA secondary to AMD.

Design: Prospective cross-sectional study.

Methods: A total of 149 patients with GA secondary to AMD were previously screened and examined for clinical studies. These patients were then prospective contacted by telephone for this study, and 120 patients responded and agreed to do an interview on symptoms of CBS. All with CBS were inquired about detailed characteristics of their hallucinations.

Results: Patients with GA secondary to AMD were aged 82.1 ± 6.2 years and 62% were of female biological sex. The prevalence of CBS was 25 in 120 (20.8%). Thirteen (52%) of those with CBS were not previously informed of the disease. We found no difference between those with and without CBS in terms of age, biological sex, hearing difficulties, whether living alone or with others, co-morbidity of psychiatric or neurological diseases, or psychotropic use. Characteristics of the visual hallucinations were reported to occur at various frequencies from daily to less than monthly, occur during various times of the day, and almost always last minutes at most. Ten in 25 (40%) had not told anyone of having CBS.

Conclusion: One in five with GA has CBS, which ranks GA as an eye disease with one of the highest reported prevalences of CBS. The condition presents with a significant variation across the patient group. A very large proportion of those with CBS were not informed of the disease and had never told anyone of their condition by their own initiative.

Plain language summary

Visual hallucinations in patients with atrophic late stage of age-related macular degeneration (AMD)

We investigated the prevalence and characteristics of visual hallucinations (Charles Bonnet syndrome) among patients with the atrophic late stage of age-related macular degeneration (AMD), termed geographic atrophy (GA). We found that one in five patients experiences visual hallucinations. Many patients were not informed about the benign nature of these hallucinations, and many had never shared their experience with anyone. These findings are important, as Charles Bonnet syndrome has been described to be stressful for the patient and contributes to a lower quality of life, which is an important finding in patients with GA.

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Keywords: age-related macular degeneration, Charles Bonnet syndrome, geographic atrophy, visual hallucinations

Received: 24 April 2024; revised manuscript accepted: 19 November 2024.

Introduction

Age-related macular degeneration (AMD) is a prevalent cause of irreversible vision loss among the elderly in the developed world.[1–3] Vision loss prevalently occurs in the late stages of the disease, which is defined by the development of macular neovascularization (MNV) or geographic atrophy (GA).[4] Visual symptoms include metamorphopsia, loss of central vision, and the Charles Bonnet syndrome (CBS) which is the presence of complex visual hallucinations in patients with vision loss.[4–6] Patients with CBS are aware of the unreal nature of the hallucinations, and there is an absence of delusions and hallucinations in other sensory modalities.[7] It is estimated that there are currently 47 million individuals with CBS worldwide, a number expected to increase with the demographic shift toward an increased geriatric population.[8]

Studies suggest that CBS is a relatively common symptom in AMD.[5] In patients with MNV secondary to AMD, studies reported a prevalence of CBS of 7.2%.[5] In these patients, a positive treatment response to intravitreal inhibitors of vascular endothelial growth factor was correlated with improvement of CBS symptoms.[9] One study reported that CBS was most prevalent in patients with AMD with MNV who also had GA.[6] However, knowledge of CBS in patients with GA and without MNV is scarce. As treatments are emerging for GA, there is increasing attention to visual symptoms and quality of vision in these patients, and clinical outcomes of treatment modalities are debated for whether they reflect what matters to the patients and their quality of life.[10]

In this cross-sectional study, we explored the prevalence of CBS in a group of Danish patients with GA secondary to AMD. Further, we examined the characteristics of CBS to understand the burden of this condition on those affected. Such details are paramount to understand the impact of CBS for those with GA and to understand if this symptom should be considered when planning clinical trials or when evaluating the impact of future interventions for CBS.

Materials and methods

Study design

This was part of a prospective clinical study that took place at the Department of Ophthalmology, Zealand University Hospital, Denmark. All screened patients were explained the nature and purpose of the study. Informed oral and written consent was mandatory for inclusion in the study and was obtained at the time of initial visit. The study followed the tenets of the Declaration of Helsinki and was approved by The Scientific Ethics Committee for the Region of Zealand (approved June 25, 2021, reference number: SJ-736). A total of 149 patients were alive at the time of initiation of this study and were contacted for participation. No power analysis was performed for this study.

Participant eligibility

Two trained physicians independently reviewed all the retinal optical coherence tomography (OCT) scans to ensure the presence of GA secondary to AMD (M.K.N. and N.M.). Inclusion criteria were GA secondary to AMD. GA was defined as the presence of one or more localized demarcated atrophy of the outer retina and the retinal pigment epithelium. Exclusion criteria were other retinal diseases, that is, any other causes of the atrophic lesions, such as myopic degeneration or trauma. We attempted to contact all 149 patients by telephone, and 120 patients with GA secondary to AMD agreed to do an interview (Supplemental Figure).

Data collection

One physician (N.S.E.) conducted all the semi-structured interviews to ensure consistency in the approach to the interview. Patients were asked if they had experienced visual hallucinations using the question: "*Some people with similar eye problems as you, report seeing things which are not really there, or which other people do not see. Have you ever experienced this?*".[11] Variations of this question have been used to identify cases with CBS in previous studies, and we have previously used it in a

version translated to Danish to identify cases with CBS in a meaningful manner in several previous studies.[6,9,12–14]

All patients were inquired about hearing difficulties, whether they lived alone or with others, medical history, and specifically if they had had any neurologic or psychiatric diseases. Only patients with complex visual hallucinations who were aware of the unreal nature of the hallucinations were considered to have CBS. All patients with confirmed CBS were then inquired about the specific characteristics of their hallucinations. These characteristics included the time of day on which they experienced hallucinations, as well as the frequency, duration, and contents of the hallucinations. Further, patients were inquired on whether the hallucinations were causing them distress and whether they had told anyone about their experiences.

Statistical analysis

Prevalence data were reported with numbers and percentages. We then compared the characteristics of patients with and without CBS. Continuous data were compared using the Student's *t*-test. Categorical data were compared using the Chi-squared test unless numbers were low (<5), in which case the Fisher's exact test was used. A *p* value below 0.05 was considered a sign of statistical significance.

Results

A total of 120 patients with GA secondary to AMD participated in this study. Patients were aged 82.1 ± 6.2 years, 62 % were of female biological sex, 44% had hearing difficulties, 51% lived alone, 7% were diagnosed with any psychiatric or neurological comorbidities, and 3% used any psychotropics. Twenty-five (20.8%) of 120 patients with GA admitted to having experienced hallucinations and were diagnosed with CBS. We found no differences between those with and without CBS when comparing in age, biological sex, hearing difficulties, whether they lived alone or with others, psychiatric or neurological comorbidities, or use of psychotropics. However, those with CBS reported more frequently being previously informed about CBS (52%) than those who did not have any CBS (19%; $p = 0.001$). Detailed summary of participant characteristics and comparisons between those with and without CBS are presented in Table 1.

Most patients in the study had various comorbidities and regularly used systemic medication. Most of the medications were antihypertensives, cholesterol medications, and over-the-counter painkillers. A few GA patients ($N = 8.7\%$) were suffering from a psychiatric or neurological disease and only four (3 %) were taking psychotropics. One patient with CBS (4%) was depressed and was therefore being treated with antidepressants. Seven (7%) GA patients without CBS were

Table 1. Patient characteristics.

Characteristic	All patients (*N* = 120)	Those with CBS (*N* = 25)	Those without CBS (*N* = 95)	*p* Value
Age in years, mean (SD)	82.1 (6.2)	83.8 (4.9)	81.6 (6.4)	0.128[a]
Female biological sex, *N* (%)	74 (62)	19 (76)	55 (58)	0.111[b]
Hearing difficulties, *N* (%)	53 (44)	15 (60)	38 (40)	0.112[b]
Living alone, *N* (%)	61 (51)	15 (60)	46 (48)	0.371[b]
Psychiatric or neurological comorbidities, *N* (%)	8 (7)	1 (4)	7 (7)	0.473[c]
Psychotropic use, *N* (%)	4 (3)	1 (4)	3 (3)	0.612[c]
Previously informed about CBS, *N* (%)	31 (26)	13 (52)	18 (19)	0.001[b]

[a]Student's *t*-test.
[b]Chi-squared test.
[c]Fisher's exact test.
CBS, Charles Bonnet syndrome; *N*, number; SD, standard deviation.

Table 2. Characteristics of visual hallucinations.

Characteristic	*N* (%)
Time of day of the visual hallucinations	
Morning	1 (4)
Afternoon	6 (24)
Evening	6 (24)
At all times	12 (48)
Duration of the visual hallucinations	
Seconds	13 (52)
Minutes	11 (44)
Hours	1 (4)
Frequency of the visual hallucinations	
Daily	5 (20)
Weekly	6 (24)
Monthly	3 (12)
Less often than monthly	8 (32)
Unable to answer/do not know	3 (12)
Contents of the visual hallucinations	
Animals	5 (20)
Buildings	1 (4)
Cars	3 (12)
Flowers/plants	9 (36)
Persons	9 (36)
Other objects	6 (24)
Experience of distress from the visual hallucinations	
Yes	3 (12)
No	22 (88)
Ever told anyone of the visual hallucinations	
Yes	15 (60)
No	10 (40)

N, number.

suffering from a psychiatric or neurological disease (cerebral aneurysm, stroke, depression, and memory impairment) and three (3%) were taking psychotropics (all three were taking antidepressants). We found no statistically significant difference between patients with CBS and those without CBS ($p = 0.473$, Fisher's exact test; $p = 0.612$, Fisher's exact test; respectively, for psychiatric or neurological comorbidities, and psychotropics use).

The nature and frequency of the hallucinations are shown in Table 2. Patients with CBS reported that hallucinations could occur at various frequencies from daily to less than monthly, during various times of the day, and almost always last minutes at most. However, one patient (4%) reported hallucination episodes that could last hours. The content of the hallucinations was mainly persons, flowers/plants, or animals. Three individuals (12%) reported distress associated with the hallucinations. Ten individuals (40%) had never told anyone of these hallucinations before. Those who had told anyone about their hallucinations had done so almost always to their husband or wife.

Discussion

In this study, we report the prevalence and characteristics of CBS in patients with GA secondary to AMD. We report a prevalence of 20.8%, that is, approximately one in five with GA in AMD have CBS. This is a prevalence in the higher end compared to those reported in other studies of CBS in eye diseases.[5,15–19] In patients with glaucoma, Subhi et al. reported a prevalence of 2.8%, which rose to 13.5% in patient groups with bilateral impairment of central vision.[15] In patients with MNV secondary to AMD, reported a prevalence of AMD at 7.2%, which increased to 32% when both eyes were affected.[5] O'Hare et al. reported the prevalence of CBS in patients with advanced retinitis pigmentosa and found that 3 of 72 individuals (4.2%) experienced complex hallucinations.[16] In patients with Stargardt disease, Dhooge et al. reported a prevalence of CBS of 8.4%.[17] In line with these findings, Jones and Moosajee retrospectively summarized their pediatric cases of CBS and found that the majority of cases consisted of patients with Stargardt disease.[18] In a large study of CBS cases in a tertiary eye care center, Abdulhussein et al. reported that approximately half of all their cases were from patients with the medical retina subspecialty.[19] Taken together, these studies collectively demonstrate a pattern in which CBS is highly associated with impairment of central vision. In the case of GA, the visual impairment and the

development of scotomas rely on macular pathology, and we speculate that this may be the main explanation for the high prevalence seen in patients with GA secondary to AMD.

We did not find differences between those with CBS and those without CBS in terms of age, biological sex, hearing difficulties, whether they lived alone or with others, medical history, and specifically if they had had any neurologic or psychiatric diseases. To a certain extent, these findings confirm those demonstrated in previous studies. Although it can be argued that CBS may occur more frequently in the elderly, this may be a bias due to age being an important risk factor for prevalent eye diseases such as AMD and glaucoma.[1–4,20,21] One meta-analysis explored the association of age, biological sex, and living alone as risk factors for experiencing CBS in patients with AMD.[5] Age and living alone were not found to be significant risk factors, similar to our results, but found a small positive association between biological female sex and a higher prevalence of CBS.[5] Whether this is indeed a reflection of biological differences or rather a cultural difference in the interview response or health-seeking behavior remains to be determined.[5,19]

Characteristics of visual hallucinations in our study provide insight into the experience of the patients. We were unable to find any clear pattern of when CBS occurs or how the hallucinations are present. In the vast majority, the hallucinations lasted for minutes at most. It may not be surprising that these unpredictable frequent visual hallucinations are associated with significant impairment in the vision-related quality of life.[21–24] Randeblad et al. reported that patients with primary open-angle glaucoma with CBS had significantly lower scores on the National Eye Institute Visual Function Questionnaire-25 when compared to matched patients with primary open-angle glaucoma without CBS.[24] The authors were also able to calculate that the presence of CBS accounted for nearly 40% of the vision-related quality of life scores on the visual functioning scale and for 34% on the socioemotional scale.[24] In our study, 12% of those with CBS reported to experience distress due to visual hallucinations, and 40% had not told anyone about their symptoms. Abdulhussein et al. reported that the majority of patients with CBS reported that CBS had a negative impact on their life,[19] which is in line with the poor vision-related quality of life found among patients with GA.[25] It is clear that CBS in patients with GA is more than just a symptom—it may cause distress and negatively impact the patient's life.

Important limitations must be kept in mind when interpreting these results. Our data is based on patient recollection and therefore some recall bias is unavoidable, and we cannot exclude the possibility of other causes of the hallucinations in our patients. Also, we did not determine whether the visual hallucinations were present before disease onset. This is important as hallucinations are not uncommon in the background population.[26] However, we did not find any differences between the groups with or without CBS regarding neurological or psychiatric diseases or the use of psychotropics. Patients were not clinically examined at the time of the telephone interview and thus the diagnosis of CBS, and therefore lesion size and visual acuity measured at another time could not be included as meaningful parameters in this study. Also, we cannot rule out the possibility of other diseases that might affect visual function since the time of the last examination. No power analysis was performed prior to inclusion. Finally, it can be speculated that patients willing to participate in a study about their visual experiences may be less likely to experience distressful visual hallucinations, less likely to have told anyone about their experiences, and less likely to be informed about CBS, which altogether risk underestimating the impact of CBS in this study group.

In conclusion, we here report the prevalence and the characteristics of CBS in a large sample of patients with GA secondary to AMD. We find that CBS is more prevalent in GA than in many other eye diseases. We suggest that inquiries on CBS should be considered when planning comprehensive care for GA patients and that CBS should be considered when planning future trials on the efficacy of treatments for GA.

Declarations

Ethics approval and consent to participate

Informed oral and written consent was mandatory for inclusion in the study, and was obtained at the time of initial visit. The study followed the tenets of the Declaration of Helsinki and was approved by The Scientific Ethics Committee for the Region of Zealand (approved June 25, 2021, reference number: SJ-736).

Consent for publication
Not applicable.

Author contributions
Nathalie Skovgaard Eriksen: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Project administration; Writing – original draft.

Nabi Mousavi: Data curation; Methodology; Validation; Writing – review & editing.

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Acknowledgements
None.

Funding
The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This research was funded by grants from the Interreg ØKS and the Solar Foundation.

Competing interests
Author Y.S. declares to have received speakers fee from Bayer and Roche, not related to this study. Remaining authors declare that they have no potential conflicts of interest. None of the funding bodies had any role in study design, execution, interpretation, or the decision to publish.

Availability of data and materials
The data that support the findings of this study are available from the corresponding author, M.K.N., upon reasonable request.

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Supplemental material
Supplemental material for this article is available online.

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