

# Visual hallucinations in patients receiving intravitreal anti-VEGF agents in northern British Columbia: Prevalence and characteristics

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## Abstract

**Objectives** Visual hallucinations, also known as Charles Bonnet Syndrome, are sometimes experienced by patients with poor vision. The aim of this study was to determine the prevalence and characteristics of visual hallucinations in adult patients receiving intravitreal anti-vascular endothelial growth factor (VEGF) treatment for macular degeneration, diabetic retinopathy, and retinal vein occlusion (RVO).

**Study Design** Cross-sectional survey.

**Methods** Participants with poor vision were recruited from an anti-VEGF injection clinic for treatment of age-related macular degeneration (AMD), diabetic retinopathy, and RVO. Anti-VEGF agents included bevacizumab, ranibizumab, and aflibercept. Patients were screened for visual hallucinations, and vision was tested (best corrected visual acuity and contrast sensitivity).

**Results** 122 patients (mean age 75.3 years) were screened in a period of 6 weeks. 49 were male (40.2%). Diagnoses included AMD (n=92; 75.4%), diabetic retinopathy (n=21; 17.2%), and RVO (n=17; 13.9%). The prevalence of Charles Bonnet syndrome was 6.6% (n=8). Hallucinations usually involved images of people, were brief (<30 s-10 mins), and were associated with dim lighting (n=6). Poor visual acuity (p=0.002) and contrast sensitivity (p=0.001) were associated with visual hallucinations.

**Conclusions** Patients who see an ophthalmologist for treatment of eye diseases (macular degeneration, diabetic retinopathy, and RVO) can experience visual hallucinations that do not have a mental illness genesis. Patients will benefit from increasing health care professionals' awareness of Charles Bonnet syndrome, as hallucinations can be associated distinctly with poor visual acuity and contrast sensitivity, rather than secondary to mental illness.

**Abbreviations** CBS – Charles Bonnet Syndrome; VEGF – vascular endothelial growth factor; AMD – age-related macular degeneration; RVO – retinal vein occlusion

## Introduction

Charles Bonnet Syndrome (CBS) was first described by Swiss philosopher Charles Bonnet in the 18th century. He noted visual hallucinations in his grandfather, who was blind secondary to cataracts.<sup>1</sup> Bonnet described three key elements still used in modern clinical practice: patients with CBS experience visual hallucinations with preserved insight, have low vision secondary to eye disease, and have intact cognition.<sup>1-3</sup> CBS is commonly experienced by elderly patients, between 70-85 years old<sup>3,4</sup>, who have poor vision, yet clinicians and patients remain largely unaware of the diagnosis. The pathogenesis of CBS is uncertain, though two main theories exist. The “release theory” suggests that the visual cortex receives abnormal signals from a lesion in the visual pathway, leading to hallucinations.<sup>5</sup> Alternatively, the “deprivation theory” suggests that the visual association cortex produces images due to a reduction in sensory input.<sup>3,5</sup>

Reported visual hallucinations can be quite varied in their description, but commonly experienced hallucinations do not last more than a few minutes and include patterns, faces, objects, figures, and animals.<sup>3</sup> Hallucinations can be in colour or greyscale, and images can be moving or stationary. Other characteristics remain under study, as current studies report contradicting results regarding the effects of sex, living arrangements, light, time of day and other factors on the prevalence of CBS. Advanced age and low visual acuity have been shown to be risk factors for CBS, especially in patients who have advanced macular

degeneration (AMD).<sup>6,7</sup> Poor contrast sensitivity is another known risk factor for CBS.<sup>8</sup> Other eye diseases such as glaucoma, diabetic retinopathy, RVO, and cataracts are seen in patients with CBS.<sup>2,3,5,7-9</sup>

The prevalence of CBS in elderly patients is reported to be anywhere from 0.5-40%.<sup>1,5,10</sup> The high variance in rates of CBS can be attributed to the association of visual hallucinations and mental illness. Case reports have noted that patients can feel distress, and many do not seek medical advice for fear of diagnosis with mental illness or neurodegenerative diseases such as Alzheimer's dementia.<sup>11</sup> As much as 60% of patients experience confusion during visual hallucinations and 33% were fearful of impending insanity.<sup>5</sup> As such, it is important to clarify with patients that visual hallucinations are not always related to cognitive dysfunction.

The purpose of this study will be to determine the prevalence of visual hallucinations in patients receiving intravitreal anti-vascular endothelial growth factor (VEGF) treatment in Prince George, British Columbia. It will also be possible to determine characteristics of any hallucinations experienced, such as description, onset, and triggering factors. This information can aid in our current understanding of CBS.

## Methods

This clinic-based study was undertaken in Prince George, a community in northern British Columbia. This population was chosen for sampling convenience (proximity to researchers, as well as common eye pathologies among participants). Participants over 18 years of age receiving treatment for AMD, diabetic retinopathy, and RVO were recruited through an injection clinic. All participants were receiving anti-VEGF agents (bevacizumab, ranibizumab, or aflibercept). Anti-VEGF agents help to preserve vision by preventing the formation of leaky blood vessels and

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edema. Over a period of 6 weeks, 122 patients gave informed consent to participate in the survey. Ethics approval was obtained from UBC Behavioural Research Ethics Board (ID=H15-02003).

Each patient was given a one-to-one short introduction to Charles Bonnet Syndrome. Patients were informed that people with poor vision like themselves can experience visual hallucinations, and that these hallucinations might not necessarily be caused by mental illness. Hallucinations were defined as concrete images without a stimulus. Thus, other visual disturbances such as scintillations, illusions, and distortions were excluded based on history. Patients who screened positive for visual hallucinations were asked further questions to describe their experiences. A standardized questionnaire explored the content of hallucinations, as well as onset, duration, frequency, triggers, and temporal relation to anti-VEGF treatment. All questionnaires were verbally administered by the same study researcher.

Patients were asked about their general medical health and were screened for a history of hypertension, stroke, migraines, diabetes mellitus, depression, schizophrenia, Parkinson's disease, and dementia. Diagnoses of ocular pathologies and best corrected visual acuity (binocular) were obtained directly from the patients' charts.

Finally, binocular contrast sensitivity testing was undertaken using a validated iPad contrast sensitivity test created by Ridgevue.<sup>12</sup> An iPad with retinal display was placed one metre away from the patient with the room lights off. The auto-brightness was turned off, and the brightness was adjusted to the middle of the scale. Each page of the test consists of two letters of equal contrast, and the contrast of subsequent pages decreases by 0.1 log units. Testing ended when the patient missed both letters on a given contrast page. Contrast sensitivity was scored as 0.05 x total number of correct letters.

A stepwise multiple linear regression analysis was used to develop a model for predicting Charles Bonnet Syndrome from vision code, contrast sensitivity, age of patients, RVO, diabetic retinopathy, cataracts, AMD and patient sex. Statistical significance was defined as  $p$ -value  $\leq 0.05$ . Best corrected visual acuities were stratified based on overall functionality (Canadian National Institute of the Blind vision code 0 = 20/20 to 20/69; vision code 1+ = 20/70 or worse).<sup>7</sup> Characteristics of visual hallucinations were tabulated.

**Table 1** | Prevalence of Charles Bonnet Syndrome, demographics.

	Number (%)	Number with Hallucinations (%)
Total Clients	122 (100)	8 (6.6)
Age		
>80	47 (38.5)	6(7.5)
65-80	54 (44.3)	2 (2.5)
<65	19 (15.6)	0
Sex		
Male	49 (40.2)	3(37.5)
Female	73 (59.8)	5(62.5)
Ocular Pathology*		
AMD	92(75.4)	7(87.5)
Cataracts	3(2.5)	0
Glaucoma	8(1.6)	1(12.5)
Diabetic Retinopathy	21(17.2)	0
Retinal Vein Occlusion	17 (13.9)	1(12.5)

\*Patients can have more than 1.

**Table 2** | Correlations between Charles Bonnet Syndrome and predictive factors.

	Charles Bonnet Syndrome	P value
Vision Code 1+ (20/70 or worse)	0.25	0.002
Contrast sensitivity	-0.31	0.001
Sex of Patient	0.02	0.411
AMD	0.15	0.047
Cataracts	-0.04	0.322
Diabetic Retinopathy	-0.12	0.105
Retinal Vein Occlusion	-0.012	0.449

## Results

Out of 122 clients, 49 were male (40.2%). Average age of participants was 75.3 years. Diagnoses included AMD (n=92; 75.4%), diabetic retinopathy (n=21; 17.2%), and RVO (n=17; 13.9%). Out of 122 clients, 8 met the diagnostic criteria for Charles Bonnet Syndrome (prevalence rate of 6.6%). Demographics of the patient cohort is shown in Table 1. Higher vision code (poor visual acuity;  $p=0.002$ ) and poor contrast sensitivity ( $p=0.001$ ) were significant predictors of Charles Bonnet Syndrome. The one-predictor model was able to account for 6% of the total variance in Charles Bonnet Syndrome,  $F(1, 117) = 8.01, p < .01, R^2 = 0.06, 95\% \text{ CI } [0.02, 0.14]$ . Further correlations between Charles Bonnet Syndrome and predictive factors can be found in Table 2.

In the cohort which screened positive for visual hallucinations (n=8), the quality of the hallucinations were explored (see Table 3). The most common hallucination experienced was that of people and faces (n=7). There was a mixture of chromatic and greyscale, although most participants had stationary hallucinations (n=7). Hallucinations tended to be brief (<30 seconds to 10 minutes), and often occurred in situations with dim lighting (n=6). The onset of hallucinations ranged from 1+ months to several years. Very few participants (n=2) had previously discussed their experiences with a physician.

## Discussion

The findings in this study are congruent with past studies, and confirmed that visual hallucinations are not uncommon in patients with low visual acuity. The overall prevalence rate was 6.6%, which is lower than the rate of 18.8% seen in a recent large CBS cohort study.<sup>7</sup> The high variance in rates of CBS can be attributed to the association of visual hallucinations and mental illness, and it is possible that some patients were hesitant to disclose. Past studies reported a prevalence of CBS to be anywhere from 0.5 to 40%.<sup>1,5,10</sup>

The findings in this study also suggest that visual hallucinations are associated with both poor visual acuity and poor contrast sensitivity, which is consistent with past studies.<sup>6-8</sup> These findings also support one of the proposed etiologies of CBS, known as deprivation or deafferentation theory. Poor visual acuity and poor contrast sensitivity can contribute to sub-threshold visual input, which causes the visual association cortex in the brain to produce images—visual hallucinations.<sup>3,5</sup> Although the underlying etiology of CBS remains unclear, the finding that there was no difference in the prevalence of CBS in each eye pathology suggests that the vision loss itself plays a bigger role in the etiology of visual hallucinations.

By exploring the quality of visual hallucinations in our small cohort of 8 people, a wide variety of visual hallucinations were seen. All 8 patients confirmed that they experienced hallucinations prior to starting anti-VEGF treatment. The most common hallucination experienced was that of people and faces, and usually these hallucinations were stationary.

**Table 3** | Characteristics of hallucinations experienced in Charles Bonnet Syndrome.

Hallucination Characteristics	Patient 1 82 yo F	Patient 2 78 yo M	Patient 3 84 yo F	Patient 4 84 yo F	Patient 5 72 yo M	Patient 6 89 yo F	Patient 7 84 yo M	Patient 8 83 yo F
Ocular pathology	AMD, glaucoma	AMD	AMD	AMD	AMD	AMD, detachment 25 years ago	AMD	Central RVO
Visual Acuity in best eye (score)	20/50	20/400	Hand motions	20/25	20/40	20/200	20/50	20/100
Contrast sensitivity	0.65	N/A	0.9	1.5	1.5	1.1	1.4	1.05
Description of hallucinations	People	People and faces (cartoonish)	Shapes	People (elf-like)	People (sometimes familiar)	Faces only	People (sometimes half body)	People (half body)
Onset	2-3 years ago	1 year ago	6 months ago, have stopped	1+ months ago	3-4 months ago	5 years ago. Stopped 1 year ago	6 months ago	6 months ago
Duration	1-2 mins	1 min +	2-3 mins	<30 seconds	3-10 mins	2-3 minutes	4-5 seconds	Few seconds to few minutes
Frequency	1-2x per week	Up to 10 per day	2-3 per day	Twice	Unable to quantify	1 per month	1 every 2 weeks	1 every 3-4 weeks
Chromatic or Greyscale	Both	Colour	Colour	Colour	Greyscale	Greyscale	Greyscale	Both
Moving or Stationary	Stationary	Stationary	Stationary	Stationary	Moving	Stationary	Stationary	Stationary
Triggers	Dim lighting	When trying to focus	Dim lighting	None	Dim lighting	Dim lighting	Dim lighting	Dim lighting
Recreational Drug Use	Oral marijuana (hallucinations 1 year before use)	No	No	No	No	No	No	No
Discussed with others previously	No	With physician	No	With daughter	With physician, wife	No	No	Family members
Degree of distress	Initially, none now	None	Initially, none now	A little distress at time	Some distress	None	None	None

Hallucinations tended to be brief (minutes in duration). Dim lighting was a notable trigger in our CBS cohort, which supports deprivation theory. Because these patients had been experiencing hallucinations for an extended period of time (months to years), they did not report significant distress when hallucinations recurred. However, all patients reported feeling relieved when they were reassured that visual hallucinations can be a consequence of their vision loss. Interestingly, very few participants had previously discussed their experiences with a physician. This suggests that there is still a stigma with mental illness.

### Research limitations

Although efforts were made to screen for other causes of visual hallucinations, including mental illness, it is possible that some patients who met the criteria for Charles Bonnet Syndrome might in fact have another underlying cause of hallucinations other than poor visual acuity and contrast sensitivity. As discussed previously, it can be difficult to determine the true prevalence rate of CBS due to the inherent stigma of mental illness. As a result, it is possible that some patients were reluctant to disclose that they were actually having visual hallucinations. It was hoped that this reluctance would be minimal due to the time spent in explaining CBS to each patient.

In hindsight, it would have been beneficial to explore whether or not visual hallucinations preceded low or reduced vision. In addition, this study had a relatively small sample size, a very specific patient population, and is only limited to northern British Columbia.

### Conclusion

The findings in this study are congruent with past studies, and confirmed that visual hallucinations are common in patients with low visual acuity. Many elderly patients with poor visual acuity can experience hallucinations, and thus it is important to increase the awareness of Charles Bonnet syndrome in the medical community in order to improve patient care. Healthcare providers have a great capacity to inform patients that visual hallucinations are not always associated with mental illness. In addition, appropriate referrals can be made to other healthcare professionals to

rule out other conditions that can cause visual hallucinations.

There appears to be an association between poor contrast sensitivity and visual hallucinations. Although the etiology of CBS remains unclear, it is possible that contrast sensitivity can play an important role in the etiology of visual hallucinations (deprivation theory). Currently, there is limited research in this field, and future research endeavours might be beneficial in furthering our understanding of visual hallucinations. It would also be beneficial to further explore patient perspectives on visual hallucinations in the future.

### Footnotes and disclosure

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