The Charles Bonnet Syndrome in Patients With Neovascular Age-Related Macular Degeneration: Association With Proton Pump Inhibitors

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Submitted: December 9, 2016
Accepted: July 11, 2017

PURPOSE. We investigate the prevalence of the Charles Bonnet syndrome (CBS) in patients with neovascular age-related macular degeneration (AMD) and analyze the role of oral proton pump inhibitors (PPIs) and other potential risk factors.

METHODS. A total of 510 consecutive patients with neovascular-AMD followed at a single tertiary center in Portugal were screened for CBS. Using a structured questionnaire, psychatically healthy individuals were interviewed systematically and divided into a CBS group and a non-CBS group. Demographic data, current medication, and ocular risk factors were collected and compared between the two groups.

RESULTS. A total of 500 patients met the inclusion criteria and 471 with complete data were included in the final analysis. The prevalence of CBS was 9.0% (45/500). Using a binary logistic regression model, correlations were found between older age (P = 0.002), PPI intake (P = 0.022), poor visual acuity (P = 0.004), and development of CBS. PPIs doubled the risk of CBS from 7% (20/304) to 15% (25/167), with an odds ratio of 2.154. The increased risk for visual hallucinations caused by PPIs was independent of age (P = 0.598) and visual acuity (P = 0.739).

CONCLUSIONS. The prevalence of CBS in neovascular-AMD patients is high and mainly affects older individuals with poor visual acuity. PPIs seem to increase the risk of development of hallucinations independently of the degree of visual loss.

Keywords: Charles Bonnet syndrome, visual hallucinations, neovascular age-related macular degeneration, low vision, oral proton pump inhibitors

Charles Bonnet syndrome (CBS) affects visually impaired patients and is characterized by the occurrence of chronic visual hallucinations, not attributable to other causes.1 According to this definition, hallucinations are not associated with neurologic disease, such as Alzheimer, psychopathology, or the use of drugs, and patients are aware of the unreality of these images.2,3

Hallucinations in CBS can be classified as elementary, such as colored shapes, lights, or patterns, or complex, well-defined, recognizable forms, such as faces, animals, and objects.4–6 These images are localized in external space, contents are well organized, defined and clear,7 and several different types of presentations have been described.8–11 CBS traditionally was considered self-limited and well-tolerated but it can extend for years and cause negative and relevant clinical consequences in up to a third of patients.12

CBS has been associated with ocular pathology and visual loss, with the most commonly predisposing disorder being age-related macular degeneration (AMD).5,13 In fact, the prevalence of CBS has been reported to vary between 11% and 40% in patients with AMD5,10,13–15 and 0.4% to 3.5% in the general elderly population.5,16–18 Also, bilateral involvement and worse visual acuity have been associated with increased risk of visual hallucinations.5,10,13,14,16,19 These findings support the widely-accepted theory that CBS is caused by the deafferentation of neurons of the visual system, when deprived of normal afferent inputs these neurons develop spontaneous activity, which is the base of the hallucinations.20–22 It has been noted, however, that disorders of the central nervous system also may coexist and facilitate the hallucinatory activity.23

Proton pump inhibitors (PPI) have been used extensively for more than 20 years in the treatment of acid-related gastrointestinal disorders, by irreversibly inhibiting H+ secretion in gastric parietal cells.24 Recently, these drugs have been reported to induce or enhance visual hallucinations in patients with choroidal neovascular membranes secondary to AMD.25 Normally, these drugs do not cross the blood–brain barrier but in patients with a breakdown in the blood–retinal barrier they may be able to access the outer retina and disturb its function. The proposed mechanism is the blockage of the horizontal cell feedback to photoreceptors, with resulting visual hallucinations. However, these assumptions have not been evaluated in other clinical studies to date.

We aimed to calculate the prevalence of CBS in patients with neovascular AMD, and to characterize potential risk factors, such as PPI intake.
CBS in Wet AMD Patients: Association With PPIs

METHODS

A total of 510 consecutive patients with neovascular AMD followed at a single tertiary center were screened for CBS between December 2015 and April 2016. Patients with active and inactive disease were included and all underwent a full ophthalmic examination, including spectral-domain optical coherence tomography (SD-OCT) scanning. The study protocol was done in accordance with the tenets of the Declaration of Helsinki and received local institutional review board approval.

Patients were systematically asked a screening question based upon that used by Lannon et al.\textsuperscript{15} and translated to Portuguese: “We are asking this question to every patient being examined here. Sometimes people with poor eyesight see things that they know are not actually there. Has this ever happened to you?”

Patients who answered positively were interviewed further in detail using a structured questionnaire to ascertain that they truly experienced visual hallucinations, characterize their nature, and assess their current medication and medical history. Patients were not tested formally for cognitive status but had to be capable of giving informed consent, cooperating in full ocular and SD-OCT examinations, and completing all questions of the study questionnaire.

Patients were included in the CBS group if the following inclusion criteria proposed by Abbott et al.\textsuperscript{4} and Gold et al.\textsuperscript{26} were met:

- Patients fully understood the question and were not reluctant to answer.
- The hallucinations were not entoptic phenomena, such as photopsias or floaters.
- The contents of hallucinations were well organized, defined and clear.
- The hallucinations should be exclusively visual and recurrent (not just an isolated event).
- Insight was fully retained.
- Patients had no history of dementia or major psychiatric disorders, such as schizophrenia, psychotic depression, or mania.
- Patients had no history of drug or alcohol abuse.

Other diagnosed neurologic conditions, such as parkinsonism, history of stroke, epilepsy, or migraine, that had no clear signs of dementia did not exclude patients from the study. Patients taking medications that could cause hallucinations also were not excluded.

Reported visual hallucinations were classified as either simple (shapes or patterns, without a recognizable form) or complex (well-defined, recognizable forms, such as objects or faces).

The non-CBS group comprised patients who answered negatively to the question or reported visual symptoms that were not associated with CBS. Of these, 50 control patients were given a short questionnaire regarding possible risk factors for CBS, including present pharmacologic treatment and medical history.

Detailed data of all screened patients from the two groups were collected from hospital and primary health care physician charts. It comprised:

- Demographic data including sex and age.
- Current medication, including use of PPIs and drugs with possible hallucinatory effects.\textsuperscript{27}
- Medical history.
- Best corrected visual acuity (BCVA) measurement for each eye, using Early Treatment of Diabetic Retinopathy Study (ETDRS) charts (then converted to logMAR scale).
- Bilaterality of AMD.
- Presence of active disease, defined as evidence of fluid on SD-OCT or time to last intravitreal anti-VEGF treatment $< 3$ months.
- Follow-up time, that is, time interval between the first and the study visits.
- History of treatment with intravitreal anti-VEGF drugs.
- Total number of intravitreal anti-VEGF sessions, either unilateral or bilateral.

Assuming a definition of visual impairment as BCVA logMAR $\geq 0.5$, subjects were categorized according to visual acuity into three groups as follows: best visual acuity of both eyes poorer or equal to 0.5 logMAR; one eye poorer or equal to 0.5 logMAR and other eye better than 0.5 logMAR; both eyes better than 0.5 logMAR.

Chronic medication, including PPIs, was collected by reviewing patients’ hospital charts, questionnaires, and primary health care physician data. All patients with a history of psychiatric disorders or psychotic episodes were excluded from the analysis. There was no significant difference between the CBS patients and the non-CBS patients in relevant drug use outside of PPIs.

Ten patients who initially reported visual symptoms that could be attributed to CBS did not meet the inclusion criteria and were excluded. The characteristics of the remaining 500 patients were analyzed.

In addition, 29 patients from the non-CBS group did not respond to the questionnaire and their medication data were either unavailable or outdated. Thus, a total of 471 patients were included in the final logistic regression analysis.

Data and Statistical Analysis

Statistical analysis was performed using the SPSS statistical software (version 21.0 for Mac OS; SPSS, Inc., Chicago, IL, USA). Quantitative variables are expressed as the median and range, and qualitative variables are provided with their frequency distributions.

To select the statistical test for comparisons, the normality of the quantitative data was assessed using the Kolmogorov-Smirnov; Mann-Whitney $U$ test was used for qualitative data (age, BCVA, duration of follow-up, number of intravitreal anti-VEGF treatments) due to nonnormal distribution of data. The $\chi^2$ or Fisher’s exact test was performed for categorical variables comparison (sex, AMD, bilaterality, disease activity, history of intravitreal anti-VEGF treatment, PPI, psychotropic, and other possible hallucinogenic drug intake).

To determine the capacity of the set of demographic and clinical variables selected to discriminate between CBS and non-CBS groups and to establish the presence of interactions or confounding factors among the variables, a binary logistic regression model was constructed in which the dependent variable was the presence or absence of hallucinations, and the demographic (age, sex) or clinical (AMD, bilaterality, BCVA of the better eye, follow-up time, PPI intake) factors examined were the independent variables. The area under the receiver operator characteristic (ROC) curve (AUC) was used as a measure of the best regression equation.

Statistical significance was set at a $P$ value less than 0.05. STROBE guidelines were followed for manuscript elaboration.\textsuperscript{28}

RESULTS

A total of 500 patients with exudative AMD and no major psychiatric disorder were analyzed initially. Of these, 45 (9%) reported symptoms that were compatible with the definition...
of CBS. Six patients experienced simple, 6 simple and complex, and 35 complex hallucinations. The median age of participants was 80 years (range, 55–102). There were 296 females (59%) and 204 males (41%), with a median follow-up of 51 (range, 0–109) months. A total of 294 patients (59%) had bilateral disease and the median logMAR visual acuity of the better eye was –0.5 logMAR (C20) and other eye poorer or equal to 0.5 logMAR. Of the patients, 66% percent had active disease and 88% were treated previously with anti-VEGF drugs (median of 16 intravitreal injections). Table 1 compares the two groups.

Of patients with CBS, 67% had a visual acuity poorer or equal to 0.5 logMAR in both eyes as opposed to 37% in the non-CBS group. In the CBS group, 27% had a visual acuity of the better eye better than 0.5 logMAR and other eye poorer or equal to 0.5 logMAR; while in 7% visual acuity in both eyes was better than 0.5 logMAR. There was a significant difference among the 3 categories of visual acuity ($P < 0.001$, Table 1).

Of the 471 patients for whom information about chronic medication was available, 56% with CBS (25/45) were being treated with PPIs, compared to 35% (142/426) of non-CBS patients ($P = 0.003$). However, the intake of specific subtypes of PPIs was not statistically different between groups ($P = 0.405$). Among the 167 patients taking PPIs, 52% (13/25) with CBS and 68% (97/142) of controls had active disease, but this was not a significant predictor of CBS ($P = 0.113$, $\chi^2$ test). In addition, the proportion of patients on PPIs was similar among those experiencing simple, simple and complex, and complex hallucinations ($P = 0.122$, Fisher’s exact test). No significant difference was shown between the groups with respect to relevant drug use outside of PPIs.

Variables from the 471 patients with complete data that were significant in univariate analysis were evaluated in a binary logistic regression model (Table 2). Factors associated with CBS were older age ($P = 0.002$), PPI use ($P = 0.022$), and poor visual acuity ($P = 0.004$). CBS developed in 15% (25/167) of patients on PPIs compared to 7% (20/304) of patients not taking these drugs, with an odds ratio of 2.154. The increased risk for visual hallucinations caused by PPIs was independent of age ($P = 0.598$) or visual acuity ($P = 0.739$). In addition, visual acuity was independent of age ($P = 0.319$). Overall, no interaction was found between variables. For this model, the area under the curve was 0.770 (Fig.).

**DISCUSSION**

Our study aimed to examine CBS characteristics in patients with a diagnosis of AMD, which has been reported to be the most common cause of low vision associated with the syndrome. 14,29 We exclusively studied patients with neovascular AMD in at least one eye, with early and late disease, and obtained a prevalence of 9% in our sample. This is slightly lower than previous studies in which the prevalence of visual hallucinations varied between 11 and 40%. 4,5,10,13–15 Different definitions of CBS and different methodologies can justify the discrepancy; particularly, we included patients who, despite the diagnosis of neovascular AMD, still maintained good vision (34% had better eye BCVA $\leq 0.3$ logMAR).

Interestingly, the current criteria for the definition of CBS is imprecise and diverges between medical subspecialties: 11 visual impairment is used by ophthalmologists as a necessary criterion for CBS, 7 while it often is not required for neurologists or psychiatrists. 26,30 The incidence of CBS in our study was statistically higher in patients with worse visual acuity of the better eye compared to patients without CBS ($P < 0.001$). Our study may have been limited by the small number of patients in the non-CBS group, leading to a lack of statistical significance in some of the comparisons. However, our results support the hypothesis that PPIs may be a risk factor for CBS in patients with neovascular AMD, warranting further investigation in larger cohorts.
changes of the deafferented neurons. This is consistent with the deafferentation model of CBS, where reduced afferent input leads to spontaneous discharges in visual areas of the brain due to structural and biochemical changes of the deafferented neurons.

We found three patients reporting visual hallucinations with a BCVA of < 0.5 log MAR in each eye. Two of these three patients were being treated with PPIs, which may have contributed to the hallucinatory activity in the presence of wet AMD.

Although rarely, a variety of frequently prescribed medications have been directly or indirectly associated with visual hallucinations, including psychotropic drugs, such as benzodiazepines and antihypertensive drugs (beta-blockers and thiazides). In addition, psychotropic drugs are used to treat neurologic and psychiatric conditions that may themselves trigger hallucinatory activity. Notably, patients with anxiety disorders seem to have a higher likelihood of reporting visual or auditory hallucinations than those with no mental disorder. However, the percentage of CBS patients medicated with psychotropic and other possible hallucinating drugs was similar to that of non-CBS patients, so these probably did not substantially affect the comparisons between groups.

Similarly, intravitreal anti-VEGF therapy was reported to trigger self-limited hallucinatory episodes that occur between 1 and 3 days from the intravitreal treatment, apparently due to the reduction of retinal edema and realignment of photoreceptors that may promote the release phenomenon. In this study, a history of anti-VEGF treatment and the total number of anti-VEGF injections did not increase the risk of patients experiencing CBS. However, we did not specifically assess if the hallucinations had a temporal link with the treatment sessions.

PPIs are one of the most commonly prescribed classes of medications and quite often in an inappropriate way. Intrigued by the findings of Hanneken et al., we wanted to assess if PPIs could be associated with visual hallucinations in neovascular-AMD patients. In fact, hallucinations are not cited as a frequent adverse effect of these drugs and Food and Drug Administration (FDA) prescribing information on omeprazole categorizes hallucinations as a rare event, occurring in < 1% of patients.

However, the percentage of patients with neovascular-AMD reporting visual hallucinations while using PPIs was as high as 56% (24/45) and these drugs may confer a 2 times greater risk of CBS development (Table 2). Presumably, access of PPIs to the outer retina due to the blood-retinal barrier breakdown and blockage of the horizontal cell feedback to photoreceptors may be responsible for the hallucinatory activity. To further confirm this hypothesis, it would be interesting to assess their effect in other ocular pathologies that do not involve disruption of the blood-retinal barrier, such as glaucoma.

One possible limitation of the study is the fact that the current medication of patients was reviewed retrospectively. However, we gathered information from multiple sources to assure that medication collection was precise. Particularly, we reviewed the records from the primary health care physician who was responsible for medical prescriptions to the patients. This allowed us to access their chronic medication accurately at the time the screening question was made. When information was not available or outdated, these cases were excluded from the final analysis (29 patients).

Despite the putative role of PPIs on CBS, it was noted that one-third of patients were taking these drugs and did not suffer hallucinations. Possible reasons for this finding include differences in drug penetration, which might be affected by the extent of blood-retinal barrier breakdown, the degree of outer retinal disorganization, and the presence of fibrosis. In our analysis, among patients taking PPIs, the activity of disease at the time of the screening question was not a factor associated with CBS. However, all patients with inactive disease had evidence of past neovascular activity so we cannot definitely exclude its contribution to the hallucinatory episodes.

In addition, PPIs show considerable differences in their physicochemical properties, which could affect their propensity to cause hallucinations. For example, the plasma concentration of omeprazole is more dependent on the polymorphisms of hepatic cytochrome P450 than other PPIs. However, no significant differences were seen in the use of different types of PPIs between the two groups. As stated, regardless of the factors that may influence the occurrence of visual phenomena associated with PPIs, they seem to be independent of visual acuity score.

Conclusions
We reported on one of the largest groups with neovascular-AMD screened for the Charles Bonnet syndrome and confirmed its high frequency in individuals with advanced age and severe visual impairment. We also showed an association between PPIs and visual hallucinatory experiences in neovascular-AMD patients. Their occurrence may be associated with the disruption of retinal inhibitory feedback that allows spontaneous activity of neurons in higher regions of the visual system. However, substantial unanswered questions remain about the ocular and individual factors that may increase the risk for this adverse effect.

Acknowledgments
Disclosure: J.E. Leandro, None; J. Beato, None; A.C. Pedrosa, None; J. Pinheiro-Costa, None; M. Falcão, None; F. Falcão-Reis, None; A.M. Carneiro, None

References


