AES ANNALS OF EYE SCIENCE
AN OPEN ACCESS, PEER-REVIEWED JOURNAL COVERING BASIC AND CLINICAL RESEARCH IN OPHTHALMOLOGY

Peer Review File

Article information: https://dx.doi.org/10.21037/aes-21-37

Reviewer Comments

Comment 1: This manuscript describes the prevalence of the Charles Bonnet syndrome (CBS) in patients with low vision. As the visual hallucinations in CBS may be very upsetting to the patient, reassurance begins with awareness of the prevalence of this syndrome. With the prevalence estimate between 17.4 to 21.3%, this manuscript will convince ophthalmologists to more often screen low vision patients for hallucinations.
This is an important message, however, some aspects need to be clarified / addressed.

Reply 1: Thank you for your time and comments.

Comment 2: General comments
Over the years, various diagnostic criteria for CBS have been proposed and different investigators disagree about, for instance, the significance of ocular pathology in relation to CBS. The wide range of prevalences that is currently reported in literature arises from the use of the different diagnostic criteria. It is therefore very important to clearly describe the criteria that have been used to define CBS. Within table 1, the diagnostic method is often described, but the CBS criteria are missing. We cannot tell if ocular pathology was necessary for diagnosis. Please split the definition and diagnosis column of CBS in two separate columns and clearly define the CBS criteria that were used within the different studies.

Reply 2: We have now split the definition and diagnosis into two separate columns as suggested.

Changes in the text: Table 1, definition and diagnosis are now split into separate columns.

Comment 3: Abstract and methods state that low vision population was not further specified and did not contain specific restrictions. Later, low vision was defined as ≤6/18 in best seeing eye according to the WHO criteria. Please rephrase this within abstract and methods. WHO definition of moderate visual impairment or worse is <6/12 (PMID: 28779882) and not 6/18 as was stated in methods line 124. CBS is almost never prevalent in the WHO category blindness (PDVA-BE <3/60). The vision categories for this manuscript could therefore be specified even more: a recent study suggested that CBS must be identified in patients in the WHO category of vision impairment (PDVA-BE <6/12, but ≥3/60) (PMID: 34348923).

Reply 3: We have now rephrased this in the abstract and in the methods section. The statement regarding CBS being almost never prevalent in the WHO category blindness remains to be further confirmed in convincing studies. The study referred to by the reviewer is to a small study of in Stargardt patients with 7 patients, which should be interpret with caution.

Changes in the text: Page 2, line 30, rephrased abstract as suggested. Page 6, line 100, and page 7, line 127, rephrased methods as suggested.

Comment 4: Methods: there seems to be an age criterion, although somewhat hidden: Lines 42/43 The pooled prevalence of CBS in low vision (≤6/18 in the best-seeing eye) patients (aged ≥40 years) was 19.6 % (95 % confidence interval: 14.7 to 24.9 %). Is that the case and if so, why? We understand the choice to enforce age restriction to focus on acquired causes of visual impairment. However, CBS prevalence have been described for pediatric and young persons and the CBS prevalence within these groups is currently underestimated. (PMID: 32933935, PMID: 27342586, PMID: 34348923). Highlighting this group separately would be of added value to this manuscript and the current knowledge about CBS. In addition, the age limit ≥40 years is of course arbitrary. Please define why the age limit of ≥40 years was chosen. If they authors are seriously concerned with the underestimation of CBS, and I am sure they are, why exclude an important group of patients, namely those under 40.

Reply 4: Thank you for this comment. Pediatric CBS is an interesting area of research. We have another review submitted regarding this topic, which in our understanding is more complex in pathophysiology, diagnosis, and prevalence estimation than that seen in acquired causes of visual impairment. To focus on acquired causes of visual impairment, and because data relies on that reported in other studies, we need to enforce restrictions to be able to focus on acquired causes of visual impairment. Within that context, the age limit of ≥40 years makes good sense.

Changes in the text: Page 14, lines 257-259, added discussion regarding lack of CBS cases from pediatric cases and cases from inherited causes of visual impairment as a limitation of this study. References, added #34 (PMID 32933935) and #35 (PMID 34348923).

Comment 5: A serious issue is that only 9/280 studies were included in this review. This is very modest in view of the broadly defined primary outcome measure: "… the prevalence of ABS in low vision patients …. There were no further definitions or specific restrictions for both low vision and CBS diagnosis. This raises the question on the quality of the literature search or at least at the precise exclusion criteria.

Reply 5: Thank you for this comment. We fully agree that a further clarification is needed. We focused on studies considering a consecutive group of low vision patients,

i.e. not studies of specific eye diseases but rather prevalence studies in low vision clinics or population-based studies of low vision individuals.

Changes in the text: Page 6, lines 101-104, added further clarification regarding the definition of the population of interest.

Comment 6: Several reports seem to match the inclusion criteria, but were not included: PMID: 18661281, PMID: 3609761, PMID: 14757336, PMID: 15767477. These are only reports related to the prevalence of CBS within a low vision population.

Reply 6: Thank you for these studies. Olbrich et al. (1987) evaluated inpatients, some preoperative, some postoperatively. This study population is slightly different than our focus population. Kinoshita et al. (2009) evaluated correlates in the US National Comorbidity Survey Replication study, where 85 had self-reported visual impairment. Theoretically, this can be anywhere from suboptimal refractive correction to complete blindness and thus provides too unreliable data for our review. The two other studies highlighted are indeed eligible and now included in the manuscript.

Changes in the text: Changes due to inclusion of additional studies to: Figures 1 & 2, Tables 1 & 2, Supplementary files 3 & 4. Changes throughout the Results section (pages 9-12) as well as Discussion (page 13) due to inclusion of these additional studies.

Comment 7: There are many other studies that report the prevalence of CBS in specific diseases resulting in vision loss (like AMD or glaucoma). The reviewer realizes that the database search was performed in April 2021, but to ensure an up-to-date manuscript at the publication date, at least two relevant studies of a more recent date (i.e., after April 2021) should also be considered: CBS prevalence in Stargardt disease (British J Ophth, August 2021) and CBS prevalence in the AREDS2 population (Ophthalmology; August 2021).
These reports could also be included to give a more comprehensive overview of the exact CBS prevalence. Especially since most of all included studies contained mostly AMD patients (48-76% had AMD).
It is therefore highly questionable whether you have studied the prevalence of CBS in low vision, more likely you studied the prevalence of CBS in AMD.

Reply 7: Thank you for highlighting this issue, which is related to the lack of clarity of our population of interest. This issue is addressed in relation to a previous comment by the reviewer. The two studies highlighted in this comment is one on Stargardt disease and the other on the AREDS2 population, which both are focused on specific conditions, and not on a consecutive sample of low vision patients. We agree that any consecutive sample of low vision patients is automatically, at least in developed countries, a question of a large sample of AMD patients, but that is because of the

high prevalence of AMD and therefore only representative of the low vision population in general.

Changes in the text: Page 6, lines 101-104, added further clarification regarding the definition of the population of interest.

Comment 8: Minor
Introduction line 61: 'Vision loss with visual hallucinations is the hallmark feature' follows the description of CBS by Charles Bonnet himself and by the Morsier. However, both considered visual impairment not obligatory for diagnosis. (PMID: 5585700) A different reference is needed to describe how the current definition of CBS was reached.

Reply 8: This problematic line is now removed from the manuscript.

Changes in the text: Page 4, line 64-65, removed according to suggestion.

Comment 9: As stated, study selection with regard to employment of the 'eligibility criteria' is not entirely clear. Why were the five records (line 156) excluded? A brief explanation might help us understand how these broadly defined criteria (line 98) were enforced.

Reply 9: Thank you for this comment. We fully agree that a further clarification is needed. We focused on studies considering a consecutive group of low vision patients, i.e. not studies of specific eye diseases but rather prevalence studies in low vision clinics or population-based studies of low vision individuals.

Changes in the text: Page 6, lines 101-104, added further clarification regarding the definition of the population of interest.

Comment 10: The aim of this study is to determine the prevalence of CBS in low vision population. In the introduction, the prevalence of CBS in AMD and glaucoma is reported (and not the previously reported prevalence's in the low vision population). Its arbitrary to only report the prevalence in AMD and glaucoma as estimated in two single studies, especially in a literature search study. Either describe a more comprehensive paragraph concerning the prevalences that have been described before or leave these two prevalences out of the introduction.

Reply 10: These two prevalence estimates are now leaved out from the paragraph as suggested.

Changes in the text: Page 4, lines 67-71, removed according to suggestion.

AES Annals of Eye Science
An open access, peer-reviewed journal covering basic and clinical research in ophthalmology

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