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The Charles Bonnet Syndrome: a Systematic Review of Diagnostic Criteria

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Abstract

Purpose To perform a systematic review of diagnostic criteria for the Charles Bonnet syndrome (CBS).
Recent findings Across 33 studies that specified diagnostic criteria for CBS, hallucinations and vision loss were a common requirement, but there was considerable heterogeneity regarding hallucination properties (i.e., formed vs. unformed) and the severity of vision loss. The exclusion of confounding neuropsychiatric disorders was also common, but specific disorders and their method of ascertainment were variable.
Summary There is considerable diagnostic heterogeneity for CBS in the literature. These differences have important implications for the results of observational and interventional studies of CBS and highlight the need for unified diagnostic criteria.

Introduction

Case histories

Case 1 A 94-year-old woman presents with a chief complaint of visual hallucinations. For the past 5 months, she reports seeing "thousands" of small animals and children around her. They do not speak or make noise, and when she tries to touch them, her hand passes directly through them and they disappear. She

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recognizes that they are not real. She has no history of cognitive impairment and lives independently. Her history is notable for advanced age-related macular degeneration. She is otherwise healthy and took no medications. Visual acuity is 20/400 in the right eye and 20/800 in the left eye. Dilated fundus examination reveals advanced geographic atrophy of both maculae. Mental status and neurologic examination are normal.

Case 2 An 82-year-old woman presents with a chief complaint of visual hallucinations. One month ago, she suffered a right posterior cerebral artery ischemic stroke resulting in a left homonymous hemianopia. Since then, she has had frequent visual hallucinations in her left hemifield of vision. She describes beautiful, colorful, ornate floral patterns that flicker and spin. Sometimes she tried to swat them away with her hand. There is no associated alteration of awareness or other symptoms. On examination, visual acuity is 20/20 in both eyes, and there is a left homonymous hemianopia to confrontation. She states the date incorrectly by one day but is otherwise alert and oriented. She is able to recall 2 of 3 words after a delay of 5 min. There is questionable left hand fine motor slowing, but tone and gait are normal.

Background

These two cases illustrate different clinical presentations of visual hallucinations occurring in the setting of vision loss, which are known as release hallucinations or the Charles Bonnet (pronounced "boh-nay") syndrome (CBS). This phenomenon was first described by Charles Bonnet, a Swiss naturalist, in 1760 when his 87-year-old grandfather developed visual hallucinations in the setting of advanced cataracts. He described his grandfather as "a respectable man full of health, of ingenuousness, judgment, and memory who, completely alert and independently from all outside influences, sees from time to time, in front of him, figures of men, of women, of birds, of carriages, of buildings etc." [1]. De Morsier published the first case series and named the syndrome after Bonnet in 1967 [2]. The precise mechanisms for this condition are unknown, but the loss of afferent visual stimulation is thought to disinhibit the occipital cortex, allowing for the "release" of internally generated visual percepts [3–6].

Visual hallucinations have a broad differential diagnosis. Unformed hallucinations such as dots, floaters, lines, and flashes can occur due to intrinsic ocular processes (a.k.a. entopic phenomena), some with important clinical consequences (e.g., retinal tear or detachment) and others without (e.g., benign vitreous floaters). Positive visual phenomena such as scintillating scotomas and fortification spectra are characteristic of migraine aura, and stereotyped visual phenomena can occur during seizures. Formed hallucinations (e.g., complex patterns, objects, faces, animals, people) can be due to primary psychotic disorders (e.g., schizophrenia) or drug intoxication or withdrawal. Formed hallucinations are also a common manifestation of diffuse Lewy body disease, Parkinson disease, or other neurodegenerative disorders. In these cases, visual hallucinations may occur more frequently with dopaminergic therapy and can initially be accompanied by preserved insight and relatively normal cognition. Other causes of visual hallucinations include hypnogogic and hypnopompic hallucinations in narcolepsy and the release of dream-like imagery in acute midbrain lesions (peduncular hallucinosis).

Treatment

For many patients with CBS, hallucinations are not very bothersome, and reassurance that they are benign and not indicative of an underlying neurologic or psychiatric disorder is usually sufficient. Hallucinations may also become less prominent or noticeable over time, especially when they occur following acute vision loss (e.g., occipital lobe stroke). However, some patients are sufficiently bothered by their hallucinations to seek treatment. When the vision loss associated with CBS is reversible (e.g., cataracts), resolution of hallucinations following the restoration of vision alone has been reported [7], and low vision aids to augment visual acuity and function may also be helpful [8]. Evidence for pharmacologic management is limited to individual case reports of success with atypical antipsychotics, cholinesterase inhibitors [9], selective serotonin reuptake inhibitors (SSRIs) [10], antiepileptic medications (e.g., valproic acid [11]), and other (see Table 4).

Diagnostic considerations

While the basic phenomenology of CBS is well-recognized, specific diagnostic criteria and their clinical and research implications are controversial. Vision loss was a core feature of Bonnet's initial description, but the amount of vision loss required to produce release hallucinations has not been systematically studied. One large study found an acuity of 20/50 or worse to be associated with visual hallucinations but still found

hallucinations in the presence of 20/50 or better acuity, many of whom had retrogeniculate lesions which generally do not affect central acuity [12]. Establishing a threshold visual acuity loss for the diagnosis of CBS could be useful in counseling patients, but further research is needed to avoid missing potential cases of CBS that occur in the setting of mild vision loss. Of equal importance is the misdiagnosis of visual hallucinations attributed to CBS in the setting of minimal vision loss (e.g., visual acuity better than 20/40 acuity) when another potentially treatable disease is the actual cause. In visual pathway lesions beyond the lateral geniculate nucleus, such as occipital lobe stroke demonstrated by case 2, visual hallucinations due to seizures must be differentiated from CBS, and this can be challenging.

In Bonnet's initial description of his grandfather, no cognitive impairment was noted, and the feature of normal cognition remains an important factor in the diagnosis of CBS. A frequently cited indicator of normal cognition in these cases is preserved insight into the unreal nature of the visual hallucinations. However, some patients with what otherwise appears to be CBS lack complete insight into the nature of the visual hallucination, as in case 2, and conversely, visual hallucinations due to neurodegenerative diseases such as Parkinson disease may initially present with preserved insight. Distinguishing between CBS and other causes of visual hallucinations is important, both for clinical diagnosis and care and for research into the pathophysiologic mechanisms, epidemiologic risk factors, and treatment of CBS, but certain distinctions between CBS and other disorders have not been clearly established. For instance, how is normal cognition defined in CBS? Is the absence of dementia sufficient, or is normal neuropsychological testing required for confirmation? Mild cognitive impairment, such as the mild impairment in delayed recall seen in case 2, is particularly problematic. It is also unclear whether there are factors that contribute to CBS, such as subclinical Alzheimer's or Lewy Body pathology. In excluding alternative diagnoses, clinicians must currently rely on the diagnostic criteria for other disorders and use appropriate ancillary testing (e.g., dopamine transporter imaging) [13] when concerns for these diagnoses exist.

Controversies

The entanglement of cognition and CBS lies at the heart of a key unanswered question: is there underlying brain pathology beyond vision loss that is necessary for this condition? CBS is typically described in older adults, but it is unclear if this association is explained solely by the increasing prevalence of blindness and vision loss due to age-related eye diseases such as macular degeneration and glaucoma. Even when accounting for the underreporting of visual hallucinations, a relative minority of older adults with vision loss develop CBS, leading some to propose a two-hit hypothesis—namely, that an additional insult required for release hallucinations to occur [14•]. The lack of precise, unifying diagnostic criteria makes it difficult for large-scale studies to answer these questions. To address some of the gaps in existing diagnostic criteria, we performed a systematic review of all previously implemented definitions of release hallucinations and CBS in the literature.

Methods

We performed a systematic review of diagnostic criteria for the Charles Bonnet syndrome (CBS). The review protocol was developed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [15] and prospectively registered in the PROSPERO database (CRD42019109044). We searched Pubmed and MEDLINE databases for all English-language articles published on or before July 1, 2018 containing "Charles Bonnet syndrome," "visual hallucinations" AND "vision loss," or "release hallucinations" as either MeSH term or keyword. Clinicaltrials.gov was also searched for clinical trial protocols of Charles Bonnet syndrome. Reference lists for each article were reviewed to ensure that no relevant publication was missing from the database search results.

A single reviewer (AGH) reviewed all search result abstracts for eligibility. Case series, case-control studies, cohort studies, published diagnostic criteria,

and randomized controlled trials were eligible for inclusion, and case reports and review articles were excluded. The full-length articles for all potentially eligible studies were then reviewed, and studies were included if they described or cited a clear definition or diagnostic criteria for release hallucinations or CBS (e.g., "We diagnosed Charles Bonnet syndrome if …," "We included patients who met the following criteria …"). From each study, the following aspects of CBS diagnosis were abstracted: age, hallucination content (formed vs. unformed, stereotyped vs. non-stereotyped), and insight into their non-real nature, symptoms duration and frequency, presence of non-visual hallucinations or delusions, etiology and severity of vision loss, cognitive assessment, and exclusionary neuropsychiatric conditions.

Results

Our initial search yielded 448 publications, of which 212 were excluded because they were individual case reports and 107 because they were secondary literature reviews or commentaries. Thirty-nine articles pertained to a topic other than release hallucinations or CBS such as peduncular hallucinosis or hallucinations associated with Parkinson's disease. Of the remaining 90 articles, 55 did not contain prespecified diagnostic criteria for CBS and two were duplicates of a previous study sample, yielding a final sample of 33 studies [10, 16–20, 21•, 22–35, 36•, 37–47].

A summary of the diagnostic criteria for release hallucinations or CBS in these studies is shown in Tables 1, 2, and 3. Ten articles (30%) specified a lower age limit, which ranged from 18 to 65 years. Seventeen (51%) of the studies required formed hallucinations to be present; another eight (24%) allowed for the presence of unformed hallucinations, though the definition of formed vs. unformed hallucinations was rarely specified. Only four studies specified the frequency or duration of hallucinations. Eighteen studies (54%) addressed the question of insight into the unreal nature of the hallucinations, of which 6 required full insight and the other 12 allowed for partial or full insight to be present. Sixteen studies (48%) specified that non-visual hallucinations be absent, and 14 (42%) that delusions be absent as well.

Vision loss was required for a diagnosis of release hallucinations or CBS in 25 of 33 studies (76%). In most studies, ocular disease was the cause of vision loss, though two studies included patients with hemianopia due to stroke and other cortical causes. Only nine studies (27%) specified a minimum amount of vision loss for inclusion, and acuity cutoffs ranged widely from 20/40 or worse to 20/200 or worse in the better seeing eye; three studies allowed for visual field constriction even in the absence of central acuity loss.

Fourteen studies (42%) required that cognitive function be normal, and 11 (33%) used a cognitive screening test for confirmation. The known diagnosis of an underlying neurologic or psychiatric condition predisposing to hallucinations was an exclusion criterion in 22 studies (67%), but these conditions were rarely specified. Diagnoses that were specifically and cited as exclusion criteria included epilepsy (6), Parkinson's disease or diffuse Lewy body disease (5), migraine (3), stroke (3), other central nervous system lesions (2), encephalopathy not otherwise specified (1), substance abuse (1), and narcolepsy (1). Thirteen studies (39%) excluded

Table 1. Systematic review of diagnostic criteria for release hallucinations and the Charles Bonnet syndrome: age and hallucination properties

Author/year	Age	Content	Stereotypy	History	Frequency	Insight	Non-visual hallucinations	Delusions
Abbott 2007		Unformed or formed				Full or partial	Absent	
Bergman 2013	> 65	Formed						
Chen 2011		Formed				Full		Absent
Cox 2014		Unformed or formed						
Eagan 2000		Unformed or formed				Full or partial	Absent	Absent
Elflein 2016		Formed						
Gilmour 2009	> 40	Unformed or formed				Full or partial	Absent	Absent
Gold and Rabins 1989		Formed	Yes			Full or partial	Absent	Absent
Holroyd 1992		Formed						
Hou 2012	> 60	Formed				Full	Absent	Absent
https://clinicaltrials.gov/ct2/show/NCT03148249	≥ 55	Formed					Absent	Absent
Jackson 2011		Formed				Full		
Khan 2008		Unformed or formed	Yes			Full or partial	Absent	Absent
Leandro 2017		Unformed or formed				Full	Absent	
Madill 2009								
Miyaoka 2011						Full or partial	Absent	Absent
Nalcaci 2016		Unformed or formed						
Nesher 2001						Full		
O'Hare 2015		Unformed or formed						
Olbrich 1987	> 65							
Pliskin 1996		Formed				Full or partial	Absent	Absent
Russell 2018	> 65			≥ 1 month	≥ 1 per month	Full or partial	Absent	Absent
Santhouse 2000	> 18						Absent	
Shiraishi 2003		Formed			≥ 1 per month	Full or partial	Absent	Absent
Singh 2011		Formed						
Singh 2012		Formed						
Tan 2004	> 50	Formed				Full	Absent	Absent
Teunisse 1994		Formed	No			Full or partial	Absent	Absent
Teunisse 1995				≥ 1 month	≥ 1 per month			
Teunisse 1996	> 64			≥ 1 month	≥ 1 per month	Full or partial	Absent	Absent
Vale 2014		Formed				Full or partial		
Vukicevic 2008	≥ 60	Formed						
Zhang 2012		Formed						

Table 2. Systematic review of diagnostic criteria for release hallucinations and the Charles Bonnet syndrome: vision loss and cognition

	Vision loss			Cognition	
Author/year	**Required**	**Etiology**	**Severity**	**Normal required**	**Method of ascertainment**
Abbott 2007	Yes	Ocular	≤ 0.60, central scotoma	Yes	Cognitive screening test
Bergman 2013				Yes	Cognitive screening test
Chen 2011		Cerebral		Yes	
Cox 2014	Yes	Ocular			
Eagan 2000	Yes	Ocular or cerebral			
Elflein 2016	Yes	Ocular	≤ 0.32		Cognitive screening test
Gilmour 2009	Yes		≤ 20/40 or 120 deg		
Gold and Rabins 1989					
Holroyd 1992		Ocular			Cognitive screening test
Hou 2012					Cognitive screening test
https://clinicaltrials.gov/ct2/show/NCT03148249			≤ 0.50	Yes	
Jackson 2011	Yes	Ocular		Yes	
Khan 2008	Yes	Ocular			
Leandro 2017	Yes	Ocular		Yes	
Madill 2009	Yes	Ocular			
Miyaoka 2011	Yes				
Nalcaci 2016	Yes	Ocular	≤ 20/40	Yes	Cognitive screening test
Nesher 2001	Yes	Ocular	≤ 20/80		
O'Hare 2015	Yes	Ocular	< 20/200 or 10 deg	Yes	Cognitive screening test
Olbrich 1987	Yes		< 0.3		
Pliskin 1996					
Russell 2018	Yes	Ocular			
Santhouse 2000	Yes	Ocular		Yes	
Shiraishi 2003	Yes				
Singh 2011	Yes	Ocular			
Singh 2012	Yes	Ocular			
Tan 2004	Yes			Yes	Cognitive screening test
Teunisse 1994				Yes	

Table 2. (Continued)

Author/year	Vision loss Required	Etiology	Severity	Cognition Normal required	Method of ascertainment
Teunisse 1995	Yes	Ocular		Yes	Cognitive screening test
Teunisse 1996	Yes	Ocular		Yes	Cognitive screening test
Vale 2014	Yes	Ocular			Cognitive screening test
Vukicevic 2008	Yes	Ocular	≤ 6/12	Yes	
Zhang 2012	Yes	Ocular			

patients with a history of exposure to potentially hallucinogenic medications or drugs, though these were also not enumerated.

Other exclusion criteria pertained to the nature of the hallucinations and their associated symptoms. For example, 13 studies (39%) included language that specifically excluded visual hallucinations attributed to entoptic phenomena, such as phosphenes or floaters. Two studies excluded patients with exclusively hypnagogic or hypnopompic hallucinations suggestive of undiagnosed narcolepsy. Other illusory visual phenomena, including metamorphopsia (1), palinopsia (1), and dreams or vivid thoughts (2), were rarely mentioned as exclusion criteria.

Discussion

In this systematic review of diagnostic criteria for CBS and release hallucinations, we found considerable heterogeneity within the literature. Vision loss and the presence of formed hallucinations with full or partial insight into their unreal nature were the most consistent cardinal features among manuscripts published, but specification as to the severity of vision loss, inclusion or exclusion of cognitive impairment, method of cognitive assessment, and exclusion of confounding conditions was inconsistent and variable. These differences have important consequences for translational and neuroimaging studies, epidemiology, and clinical trials of CBS. For example, some studies have found an association between CBS and incident diffuse Lewy body disease and all-cause dementia [48, 49], but this depends on how thoroughly participants were screened for parkinsonism and cognitive impairment are whether subtle signs or symptoms of these conditions were considered as exclusions for the diagnosis CBS in these studies. For example, if the study did not exclude or screen for mild cognitive impairment, the CBS cohort could include those who already harbor Lewy Body or Alzheimer's disease pathology and are at increased risk for future dementia, resulting in a positive association between CBS and dementia. On the other hand, if

Table 3. Systematic review of diagnostic criteria for release hallucinations and the Charles Bonnet syndrome: exclusion criteria

Author/year	Mood or cognitive disorder	Other diagnoses	Hallucinogenic medication or drug exposure	Other
Abbott 2007	Yes	Epilepsy, Parkinson disease, migraine, narcolepsy	Yes	Entoptic phenomena
Bergman 2013	Yes			
Chen 2011				
Cox 2014				
Eagan 2000	Yes			
Elflein 2016	Yes		Yes	
Gilmour 2009			Yes	
Gold and Rabins 1989				
Holroyd 1992				Entoptic phenomena; illusions, dreams, or vivid thoughts
Hou 2012	Yes	Parkinson disease	Yes	Entoptic phenomena
https://clinicaltrials.gov/ct2/show/NCT03148249		Epilepsy	Yes	
Jackson 2011	Yes			
Khan 2008				Entoptic phenomena
Leandro 2017	Yes	Epilepsy, Parkinson disease, migraine, stroke	Yes	Entoptic phenomena
Madill 2009	Yes	Epilepsy, stroke		Exclusively hypnagogic or hypnopompic hallucinations
Miyaoka 2011	Yes	Substance abuse		
Nalcaci 2016	Yes	Antipsychotic use	Yes	Entoptic phenomena
Nesher 2001			Yes	Entoptic phenomena, metamorphopsia, dreams
O'Hare 2015	Yes		Yes	
Olbrich 1987	Yes			Entoptic phenomena
Pliskin 1996	Yes	Epilepsy, Parkinson disease, stroke, any central nervous system lesion, encephalopathy	Yes	
Russell 2018				
Santhouse 2000	Yes	Epilepsy, stroke		

Table 3. (Continued)

Author/year	Mood or cognitive disorder	Other diagnoses	Hallucinogenic medication or drug exposure	Other
				Exclusively hypnagogic or hypnopompic hallucinations
Shiraishi 2003				Palinopsia
Singh 2011	Yes			Entoptic phenomena
Singh 2012	Yes	Parkinson disease	Yes	Entoptic phenomena
Tan 2004	Yes	Epilepsy, any central nervous system lesion, encephalopathy	Yes	Entoptic phenomena, exclusively hypnagogic or hypnopompic hallucinations
Teunisse 1994				
Teunisse 1995				
Teunisse 1996	Yes			
Vale 2014	Yes	Epilepsy, migraine with aura		
Vukicevic 2008	Yes		Yes	Entoptic phenomena
Zhang 2012	Yes			Entoptic phenomena

normal performance on neuropsychological testing were required, those individuals at high risk for progression to dementia over a short-time period would be excluded, and the association between CBS and dementia or neurodegeneration might be less detectable. These issues highlight the importance of having specific diagnostic criteria for CBS in order to improve our understanding of the risk factors, pathophysiology, prognosis, and treatment for those with CBS.

Recommendations for clinicians

When CBS is suspected, the clinician should consider the full spectrum of disorders associated with visual hallucinations, both to exclude other treatable causes and contributing conditions and to prevent misdiagnosis and unnecessary treatment of another disorder. A thorough neurologic and ophthalmic history and examination is critical to this process. If vision loss is determined to be the cause of release hallucinations, it should be treated in order to restore vision, if possible, as this may also reduce or eliminate hallucinations. Patients should be educated about CBS and reassured that hallucinations alone do not necessarily indicate an underlying neuropsychiatric disorder, though the reasons why some patients with vision loss develop hallucinations while many or most do not are still unknown.

For many patients with CBS, reassurance alone is sufficient. Symptoms may remit spontaneously after several months, and even if they persist, they are usually not very bothersome, and eye closure or redirection of

Table 4. Summary of published treatment experience for Charles Bonnet syndrome

Observation and reassurance	
Restoration of visual acuity (e.g., cataract surgery)	
Antipsychotics	Amisulpride [51]
	Aripiprazole [17]
	Pimavanserin [54]
	Olanzapine [52]
	Quetiapine
	Risperidone [53]
	Sulpiride [55]
Cholinesterase inhibitors	Donepezil [9]
	Rivastigmine [56]
N-methyl D-aspartate (NMDA) antagonist	Memantine [57]
Antiepileptic drugs	Carbamazepine [58]
	Clonazepam
	Gabapentin [59, 60]
	Levetiracetam [61]
	Pregabalin [62]
	Valproic acid [58]
Antidepressants	Escitalopram [10]
	Mirtazapine [63]
	Venlafaxine [64]

gaze may provide temporary but adequate relief as needed [50]. For patients whose hallucinations affect their activities of daily living or quality of life, pharmacologic treatment may be considered. A number of medications have been attempted, including atypical antipsychotics [17, 51–55], cholinesterase inhibitors [9, 56, 57], antiepileptic drugs [58–62], and antidepressants [10, 63, 64] (Table 4), but the evidence for these is limited to individual case reports or small uncontrolled case series.

Compliance with Ethical Standards

Conflict of Interest

Ali G. Hamedani declares no potential conflicts of interest. Victoria S. Pelak reports royalties from Up-to-Date, Inc. and Elsevier.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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This is a case report of visual hallucinations in a 52 year-old woman with vision loss due to severe bilateral optic atrophy from a large (> 6 cm) planum sphenoidale meningioma. The patient's hallucinations resolved after resection of her meningioma, despite persistence of her vison loss. The authors discuss the hypothesis that a "second hit" besides vision loss—in this case, frontal lobe dysfunction due to mass effect and vasogenic edema from her meningioma—is required to cause release hallucinations.

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This is the only clinical trial for Charles Bonnet syndrome registered on clinicaltrials.gov. Because it is a clinical trial, its inclusion and exclusion criteria form some of the strictest and most detailed diagnostic criteria (including a visual acuity cutoff, which few other studies have) for Charles Bonnet syndrome in the literature. The trial reportedly randomized patients with Charles Bonnet syndrome to consultation and treatment with a psychiatrist, and the primary outcome was quality of life. However, while it is listed as having been conducted between 2014 and 2017, its results have not been published to our knowledge.

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