Article ▸ Charles Bonnet Syndrome: Comprehensive Review Providing an Optometric Approach to Diagnosis and Management

Theresa Zerilli-Zavgorodni, OD, VA Connecticut Healthcare System, West Haven Campus, West Haven, Connecticut

Sharon Bisighini, OD, VA Connecticut Healthcare System, Newington Campus, Newington, Connecticut

ABSTRACT

Given the aging population, the likelihood of eye care providers encountering Charles Bonnet syndrome (CBS) will be high. Awareness of CBS is essential so that misdiagnosis and subsequent treatment for a non-existent psychiatric disease is prevented. After vision loss, patients can experience simple hallucinations such as unformed shapes or patterns, or complex hallucinations in the form of recognizable figures or faces. The prevalence of CBS is likely underestimated since individuals are hesitant to discuss these visual disturbances for fear of being labeled as mentally unstable.

Since CBS is a diagnosis of exclusion, an extensive list of etiologies must be ruled out before the diagnosis is confirmed. Referrals to other medical disciplines are essential to ensure that the patient does not have another serious neurologic, psychiatric, or metabolic disorder that may be triggering the hallucinations.

This comprehensive review is designed to update the reader on recent advances into understanding the pathophysiology of CBS. It is important to classify and differentiate CBS from other types of visual hallucinations. Since there are no universal standardized criteria for diagnosis and treatment, we hope to elucidate and provide the clinician with current diagnostic criteria, recommended work-up, and management plans for CBS patients.

Keywords: Charles Bonnet syndrome, deafferentation, visual hallucinations, visual impairment

Introduction

Charles Bonnet syndrome (CBS) is defined as recurrent or persistent complex visual hallucinations that are perceived, in most cases, as pleasant to the individual experiencing them.[1] A typical CBS hallucination is described as a sudden, sharply focused, stationary image, most often of a person, which occurs when the patient is alert and has his or her eyes open.[2-4] The true prevalence of this syndrome is likely underestimated given patient hesitation to seek medical attention for fear of being labeled as mentally ill.[5] The exact pathogenesis of CBS is unclear; however, there have been several proposed theories. One popular theory is the deafferentation theory, possibly derived from and compared with the well-known "phantom limb" syndrome.[3,4,6,7] This theory is based on the belief that a lack of visual stimulation into the brain leads to a cortical release phenomenon that produces a visual hallucination.[8] This theory, as well as others, will be presented in greater detail in this paper.

Diagnosis of CBS is supported by the presence of recurrent visual hallucinations in a patient with known ocular disease who retains insight into the unreal nature of the hallucinations.[8] To be classified as authentic CBS, patients should not have concurrent cognitive, psychiatric, or neurological disease.[4] Furthermore, CBS hallucinations should not coexist with hallucinations in other sensory modalities such as auditory or olfactory.[4] Suspicion of CBS in a patient with a suggestive history, and after having a full comprehensive eye exam, warrants a full work-up with referrals to other specialists to exclude neurological, psychiatric, and metabolic causes. Only after all potential systemic and pathological causes of hallucinations have been ruled out can the clinician presume the diagnosis of CBS.

Once CBS has been diagnosed, treatment should begin with patient education and reassurance of the benign nature of the visual hallucination. In most cases, patient awareness and full comprehension of CBS will alleviate the patient's concerns of psychiatric disease. Maximizing the patient's remaining visual acuity and visual fields with the use of low vision aids, including telescopes, magnifiers, and prisms, has been shown to lessen hallucinations. The literature also suggests non-pharmacological and pharmacological recommendations to help resolve visual hallucinations in cases where the patient's daily functioning is being affected.[3,4,9]

Background

Visual hallucinations have been recognized since the 18th century, yet most scientific advances since then have been made in the areas of epidemiology, clinical characteristics, and risk factors. The exact pathogenesis of visual hallucinations continues to remain incomplete. Progress in the 21st century using modern imaging continues to provide insight into the possible neurological mechanisms involved. However, there

still remains ambiguity. Without a complete understanding of the pathophysiology, diagnostic and management criteria for CBS have not been universally standardized.

It is important to understand the differences between various types of imagery in hallucinations, since the pathogenesis and the clinical spectrum of associated disease will not be identical. Many terms are mentioned when discussing visual hallucinations and deserve clarification. In clinical practice the difference between such terms may not be obvious.

A hallucination is defined as a perception of an external object when no such object is present, and it is experienced by the individual as if it were real.[10-12] An illusion is a misinterpretation of a real object in space,[12,13] or simply put "[seeing] real things incorrectly."[10] For example, a bowl of spaghetti may be misinterpreted as a bowl of worms. Delusions are defined as false or erroneous beliefs that involve a misinterpretation of perceptions or experiences.[14] For example, a person with a delusion may believe that a newscaster on television is directly speaking to them. Pseudohallucinations are hallucinations where the individual has insight into knowing that they are not real.[10,15,16] Although CBS is referred to as including hallucinations, this is somewhat of a misnomer, given that these patients have insight into the unreal nature of the images. It is more suitable to refer to these hallucinations as pseudohallucinations.

Epidemiology

The prevalence of CBS varies widely, depending on the study cited. The reported rate of CBS in visually impaired patients ranges from 10-38%[8] but has been documented as high as 30-50%.[17] Menon[18] reported an average incidence of 63%; however, this study used leading questions which may have contributed to the reported higher incidence. The true prevalence is likely underestimated for several reasons: no universal standardized criteria for CBS exist, exclusion criteria are not uniform across studies, patients may hesitate to seek medical attention in fear of being labeled with a psychiatric condition, the techniques various doctors use to elicit information from the patient differ, and medical personnel who are unfamiliar with CBS tend to misdiagnose the condition as a mental illness.[3,4,19] Furthermore, most ophthalmological studies exclude simple hallucinations as part of their diagnostic inclusion criteria to classify CBS visual hallucinations.[20] The exclusion of simple hallucinations most likely underestimates the true prevalence of CBS in eye disease.[20] Studies that included simple hallucinations as part of their inclusion criteria indicated that simple hallucinations are much more common than complex visual hallucinations in eye disease.[20] All of these factors play a significant role in underestimating the frequency of this syndrome within the visually impaired population.

Pathogenesis

There are several proposed theories as to the pathogenesis of CBS. The most common explanation for CBS hallucinations is the Sensory Deprivation/Deafferentation Theory, traditionally called the Release Theory.[4,21] It is believed that any damage from ophthalmic/neurologic disease that affects the retina or any part of the visual pathway will result in decreased neuronal stimulation to the visual cortex[3,4,22,23] and may even alter receptive fields within the visual cortex.[24] This results in spontaneous, endogenous, cortical neuronal discharge, referred to as visual cortical excitability.[3,4,22,23,25]

Visual interpretation of our external world has a hierarchy. The visual cortex, referred to as the vision center of the brain, is broken down into the primary visual cortex, the secondary visual cortex, and associated visual cortices. Elementary perception from the retina is transmitted and further interpreted to complex-formed images by the primary visual cortex (Brodmann Area (BA) 17), the secondary visual cortex (BA 18), and the visual association cortices (BA 19 and BA 37).[24] Ocular pathology that results in sensory deprivation or deafferentation of the visual system results in cortical excitability. Furthermore, deafferentation does not have to be the result of pathology; even an induced reduction of visual input, as seen in blindfolding experiments, can cause a measurable increase in cortical firing resulting in a visual hallucination.[19,26,27] Previous neuro-imaging appears to support this cortical release phenomenon.[24,28]

Neuro-imaging studies provide useful insight into the possible pathogenesis of CBS. Functional magnetic resonance imaging (fMRI) measures blood flow to functioning areas of the brain during a specific cognitive activity. Ffytche[28] et al. investigated the pattern of cortical activation during episodes of visual hallucinations using fMRI in patients with CBS. They found increased fMRI activity during hallucinatory periods within the area of the brain that corresponded to the ventral extrastriate cortex (this region includes the ventral occipital lobe, within or around the fusiform gyrus, referred to as Brodmann Area 37).[24,28] Furthermore, hallucinatory content and detail, such as color, texture, faces, etc., correlated to the functional specialization of the particular region activated within the cortex.[28] For example, patients who hallucinated in color showed activity localized to the fusiform gyrus, a region involved in interpreting color perception known as V4.[24,28]

Ffytche[28] et al. also performed a second experiment which involved scanning the brains of two visually impaired groups while they viewed a non-specific visual stimulus. The groups were divided as such: Group 1: those who experienced CBS hallucinations, and Group 2: a matched control group who never had CBS hallucinations. In the non-hallucinators, the visual stimulus triggered activity in the primary visual cortex extending onto the ventral surface of the occipital lobe to include the fusiform gyrus. The same visual stimulus, in the CBS hallucinators, evoked activity in the primary cortex but failed to do so in the ventral striate or fusiform gyrus.

Table 1: Neurologic disorders

Primary Organic Disease

- Hemispheric
  - infarction
  - intracranial tumor
  - arteriovenous malformation
  - aneurysm
  - head trauma
  - subdural hematoma
  - vertebro-basilar artery syndrome
- Brain stem disease/Peduncular Hallucinosis
- Parkinson's Disease
- Dementia
  - Alzheimer's
  - Vascular
  - Lewy body
- Narcolepsy-Cataplexy Syndrome
- Creutzfeldt-Jakob disease
- Inborn Errors of Metabolism
  - homocysteine remethylation defects
  - urea cycle defects
  - GM2 gangliosidosis
  - Neimann-Pick disease type C
  - α-mannosiderosis
- Anton's Syndrome
- Migraine
- Seizure

Metabolic Encephalopathies secondary to

- Cardiopulmonary Insufficiency
- Uremia
- Electrolyte Imbalance
- Endocrine Disturbances (thyroid/diabetes)
- Hepatic Disease
- Vitamin Deficiency
- Inflammatory or Infectious diseases
- Hallucinogenic Agents (LSD, mescaline, etc.)
- Delirium Tremens (Alcohol Withdrawal Syndromes)
- Medication or Toxin Side effects
- Severe Dehydration

Table 2: List of prescribed and illicit drugs associated with visual hallucinations

Analgesics/NSAIDS
Salicylates
Phenacetin
Pentazocine
Narcotics/Opiates
Opiod combo-drug (acetaminophen/pentazocine)
Nalorphine
Indomethacin

Anti-Anxiety/Sedatives
Benzodiazepine
Diazepam (Valium)
Alprazolam (Xanax)
Lorazapam (Ativan)
Clonazepam (Klonopin)

Antibiotics
Tetracycline
Cycloserine
Isoniazid
Podophyllum resin
Procaine penicillin
Sulfonamides
Antimalarial agents

Anticonvulsants
Ethosuximide
Phenobarbital
Phenytoin
Primidone

Anti-Depressants
Amitriptyline
Amoxapine
Bupropion
Doxepin
Imipramine
Lithium carbonate
Phenelzine sulfate
Desipramine
Maprotiline
Nortriptyline
Protriptyline
Trimipramine
Clomipramine

Antiparkinsonian
Amantadine
Anticholinergic drugs
Levodopa
Bromocriptine
Lisuride
Mesulergine
Pergolide

Cardiovascular
Digitalis
Methyldopa
Disopyramide
Propranolol
Quinidine
Reserpine
Timolol

Hallucinogens
Cannabis
Ecstasy
Lysergic acid diethylamide (LSD)
Dimethyltryptamine
Harmine
Ketamine hydrochloride
Mescaline
Phencyclidine hydrochloride (PCP)
Psilocybin
Tetrahydrocannabinol

Hormonal drugs
Levothyroxine sodium
Steroidal drugs

Stimulants
Amphetamines
Methamphetamines (eg. crystal methadone)
Cocaine
Methylphenidate
Diethylpropion hydrochloride
Ephedrine
Phenylephrine

Poison/Toxin
Solvents
- Ethers (gasoline,turpentine)
- Turpentine

Heavy metals (lead,arsenic,mercury)
Cathinone
Carbinoxamine
Baneberry
Jimsonweed
Hawaiian baby woodrose
Herb overdose of wormwood
Toxic mushrooms (Amanita species)

Others
Eszopiclone (Lunesta)
Baclofen
Tolterodine
Atropine
Bromide
Cimetidine
Disulfiram
Hexamethylamine
Metrizamide
Promethazine hydrochloride
Ranitidine
Vincristine
Anticholinergics other than for Parkinson's (e.g. Oxybutyrin, Benzotropine)

However, when correcting for the mean level of the fMRI signal and comparing the mean signal between the two groups, the CBS hallucinators had a significantly increased signal. This demonstrated that CBS hallucinators have elevated tonic ventral striate activity between hallucinations, and this increase in activity decreases the response to external visual stimuli. Both of the experiments by Ffytche[28] et al. have led to important deductions. Hallucinations experienced by CBS patients are the result of a fundamental increase in neuronal activity in the ventral striate cortex. Tonic increased activity persists between hallucinations and decreases the response to external visual stimuli, while phasic, transient activity results in the increase of hallucinations. Hallucinatory content such as faces, color, texture, etc., correlate to the functional specialization of the cortical region activated.[24,28]

Other methods of neuro-imaging have been investigated. Kazui[24] et al. used the methods of single photon emission computed tomography (SPECT) and magnetoencephalography to gain insight into the possible pathogenesis of hallucinations in two CBS patients. Their study found reduced regional cerebral blood flow (rCBF) in the primary and secondary visual cortices (BA 17 and BA 18) of CBS patients. In addition, they also found transient cortical activation in the region BA 37. Their conclusion was that deafferentation of the primary and secondary visual cortices leads to endogenous activation, particularly in the visual associated cortex, BA 37, which, in turn, results in visual hallucinations.[24]

Visual hallucinations in general occur across a gamut of ophthalmologic, neurologic, and psychiatric pathology. Table 1[3,26,29-35] provides a comprehensive list of the causes for visual hallucinations. Table 2[3,10,29-32,36-58] provides a comprehensive list of both illicit and prescription drugs that have been associated with visual hallucinations. These drugs may induce visual hallucinations through their mechanism of action on the neurological system. They may also indirectly induce hallucinations with overdosing or sudden cessation with chronic use. Included in this list are poisons or toxins that

Table 3: Ophthalmic disease associated with visual hallucinations

• ARMD
• Diabetic Retinopathy
• Glaucoma
• Cataracts
• Corneal Disease
• Enucleation
• Optic Neuritis/Optic Atrophy
• Central Retinal Artery Occlusion
• Retinitis Pigmentosa
• Macular Photocoagulation/Translocation
• Leber's Hereditary Optic Neuropathy
• Ocular Trauma
• AIDS and CMV Retinitis
• Choroideremia
• Cortex pathology

also have been associated with inducing visual hallucinations. Table 3[3,4,7,59-67] lists all the causes of ophthalmic disease that result in visual hallucinations classified as CBS. Visual hallucinations have also been cited to occur through blindfolding and photically-induced experiments.[26,27] They have been documented to occur in less than 2% of the patient population without ocular pathology, neurological, or psychiatric disease.[19]

Given the extensive list of possible etiologies of visual hallucinations, the question then arises as to whether the visual hallucinations are the pathophysiological endpoint of multiple diseases and risk factors.[26] If this was the case, it would be logical to assume that all different disorders should produce characteristically identical visual hallucinations.[26] As we know, this is not true. Certain neurological and psychiatric conditions will result in visual hallucinations not characteristic of CBS. Visual hallucinations that coexist with other sensory modality hallucinations, or patients who present without insight into the unreal nature of the visual images, are likely to have a pathology unrelated to CBS. [26] Therefore, the pathogenetic mechanisms for the different types of visual hallucinations must be different.

Ffytche[26] explains the different characteristic visual hallucinations by defining them as two main syndromes which have distinct pathophysiological mechanisms. He labels these two pathophysiological categories as syndrome 1 and syndrome 2. The syndrome by which a patient is defined is determined by the location of the primary pathology and what cortical regions are affected.[10] The primary pathology for syndrome 1 is found within the eye itself, retro-bulbar visual pathways, or the primary and associated visual cortices. In syndrome 2, the primary disorder lies within the brainstem/cholinergic system.[10,26]

Not all visually hallucinating patients will fit neatly into syndrome 1 or syndrome 2 since their pathology is unclear or unknown. Another reason proposed is because the mechanism involved may affect other brainstem neurotransmitters such as serotonin.[10] Conditions such as schizophrenia, bipolar disorder, and bereavement have pathophysiological mechanisms not fully understood; however, visual hallucinations for this group display characteristics that mimic syndrome 2.[10] A third group of patients are believed to have pathology within the serotonergic system. This group consists of visual hallucinations related to drugs affecting serotonin levels, such as lysergic acid (LSD), and also could possibly be seen in some forms of migraine.[21] The serotonergic pathway tends to produce visual hallucinations that blend characteristics from both syndrome 1 and 2.[21] Figure 1 is used to show the relationship between the different pathogenetic categories and the different characteristic visual hallucinations produced by each.[10,21,26]

The mechanisms of action involved in syndrome 1 are visual deafferentation (loss of visual input) or focal cortical disease. Both result in cortical excitability and consequently produce visual hallucinations.[26] These hallucinations are defined by certain characteristics. They can be either simple and unformed or complex. Typically, they are described as brief (lasting seconds to minutes), silent, confined to a particular part of the external space, occurring without other sensory hallucinations or delusional elaborations, self limiting, and typically diminish over time.[26] The prognosis of resolution for syndrome 1 is typically good. Holroyd and Rabins[68] reported that 60% of age related macular degeneration patients will no longer have hallucinations 18 months after onset. The loss of visual input in syndrome 1 does not need to be the result of pathology, it can simply be from inducing a decrease in visual stimulation, as with blindfolding.[4,26] In summary, cortical excitability in syndrome 1 is a result of either direct stimulation from local cortical disease, as with migraines or seizures, or secondary deafferentation from functional or lesional pathology.[26]

Type 2 syndrome, described by Ffytche, has a different mechanism for producing visual hallucinations. The pathophysiological mechanism of syndrome 2 is disease along the ascending brainstem cholinergic pathways.[26] The hallucinations of this syndrome typically consist of familiar objects such as isolated animals or figures. They can be brief, but they often last hours and even days, are associated with delusional components, and have poor prognoses.[26] Unlike in syndrome 1, these hallucinations are not simple and can occur with other multisensory hallucinations.[26] The widespread involvement of this mechanism includes the visual system, other sensory modalities, and delusional elaboration. Delusional elaboration is the result of the patient trying to

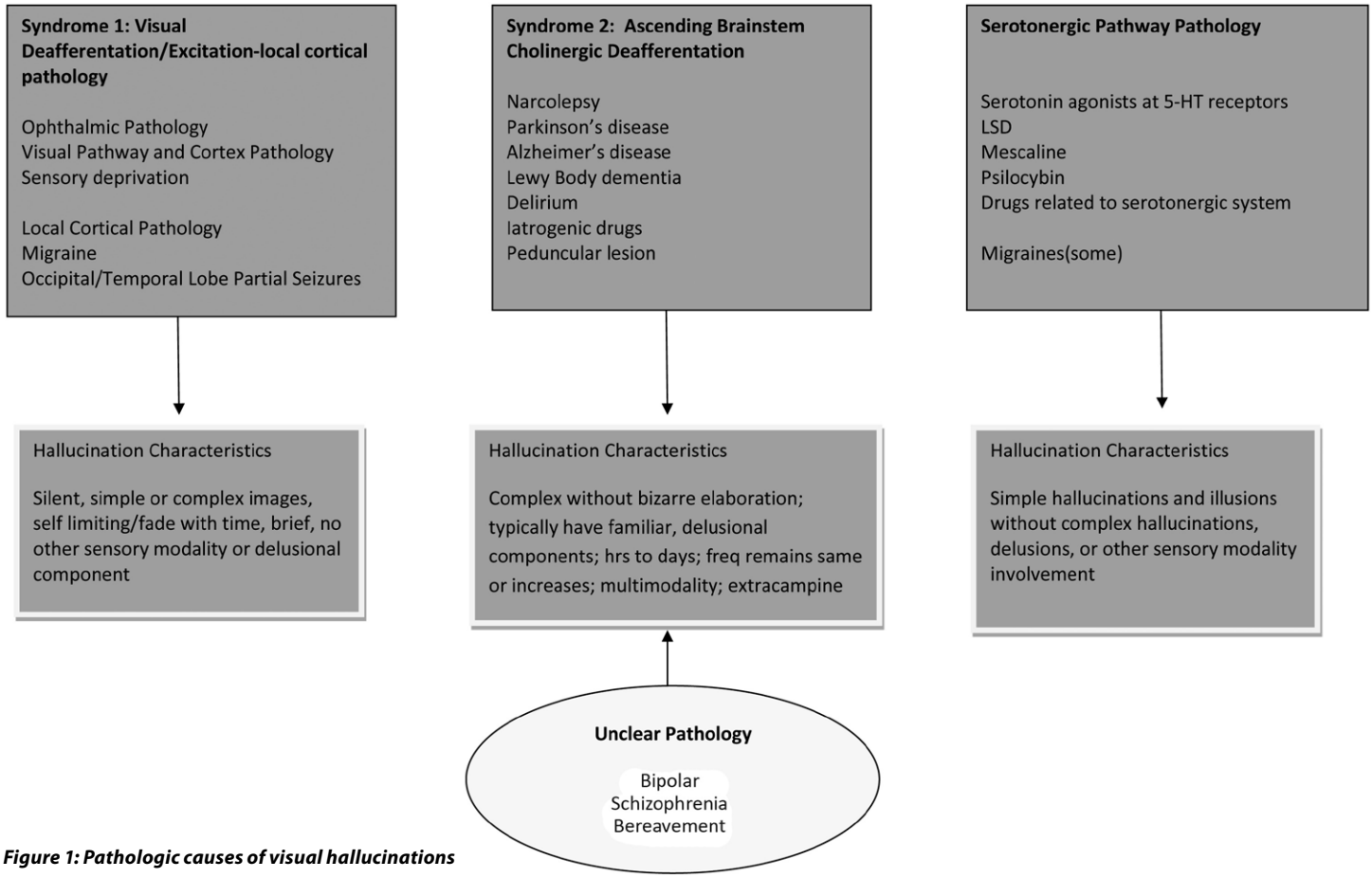

Figure 1: Pathologic causes of visual hallucinations

explain the hallucinatory experience, e.g. a person having auditory hallucinations may explain this as a transmitter having been put into their ear.[11] The multimodal involvement in syndrome 2 is likely the result of widespread cortical projections from the cholinergic system to multiple areas of the brain, including visual pathways.[26] Deafferentation of the cholinergic system leads to a reduced response and synchronization of visual neurons, hence visual cortical dysfunction with resultant visual hallucinations.[26]

Both syndrome 1 and 2 have pathogenetic mechanisms that result in deafferentation. In syndrome 1, the visual loss directly affects the visual driver inputs into the visual cortex, whereas in syndrome 2, the visual system is indirectly affected by deficits in the cholinergic system.[26] Cholinergic deafferentation will affect the modulation and synchronization of visual information into the visual system.[26] Both syndrome 1 and 2 create deficits in the visual system; however, the mechanism involved in doing so is different for each one.

Although these pathways are independent, they are not isolated from each other; instead, they can interact with each other under certain concurrent conditions. For instance, visual hallucinations, whether caused from syndrome 1 or syndrome 2, share a feature: they both tend to occur in states of "drowsy wakefulness,"[26] which is regulated by the ascending brainstem pathway.[26] The ascending brainstem cholinergic pathway is responsible for modulating hypo-transitional states of wakefulness.[26] A patient with syndrome 1, in conjunction with being drowsy, may have an increased risk of producing a hallucination.[26]

Conditions such as Parkinson's disease and Lewy body dementia (LBD) not only have primary pathology in the brainstem/cholinergeric pathways but may also have visual deficits in higher visual cortical centers secondary to these conditions.[10] Thus the primary pathology of the cholinergic system may also result in secondary disease within the visual system.[10] For instance, an LBD patient may have Lewy bodies form within higher visual areas, resulting in visual deficits.[10,69] This can then result in deafferentation in both the cholinergic system and the visual system. In such cases, primary pathology in one syndrome can indirectly cause a secondary pathology in another syndrome.

Patients may also have co-morbid disease affecting both syndrome types. For example, a patient with glaucoma or macular degeneration could have Parkinson's, a history of stroke, or even cognitive impairment.[10] The characteristic of the hallucination or imagery experienced by the patient will likely reflect the relative contribution from syndromes 1 and 2, if both syndromes are present.[26] If visual deafferentation is the major contributor, then the patient will have characteristics of syndrome 1, hallucinations, and vice versa if syndrome 2 disease is the major contributor.[26]

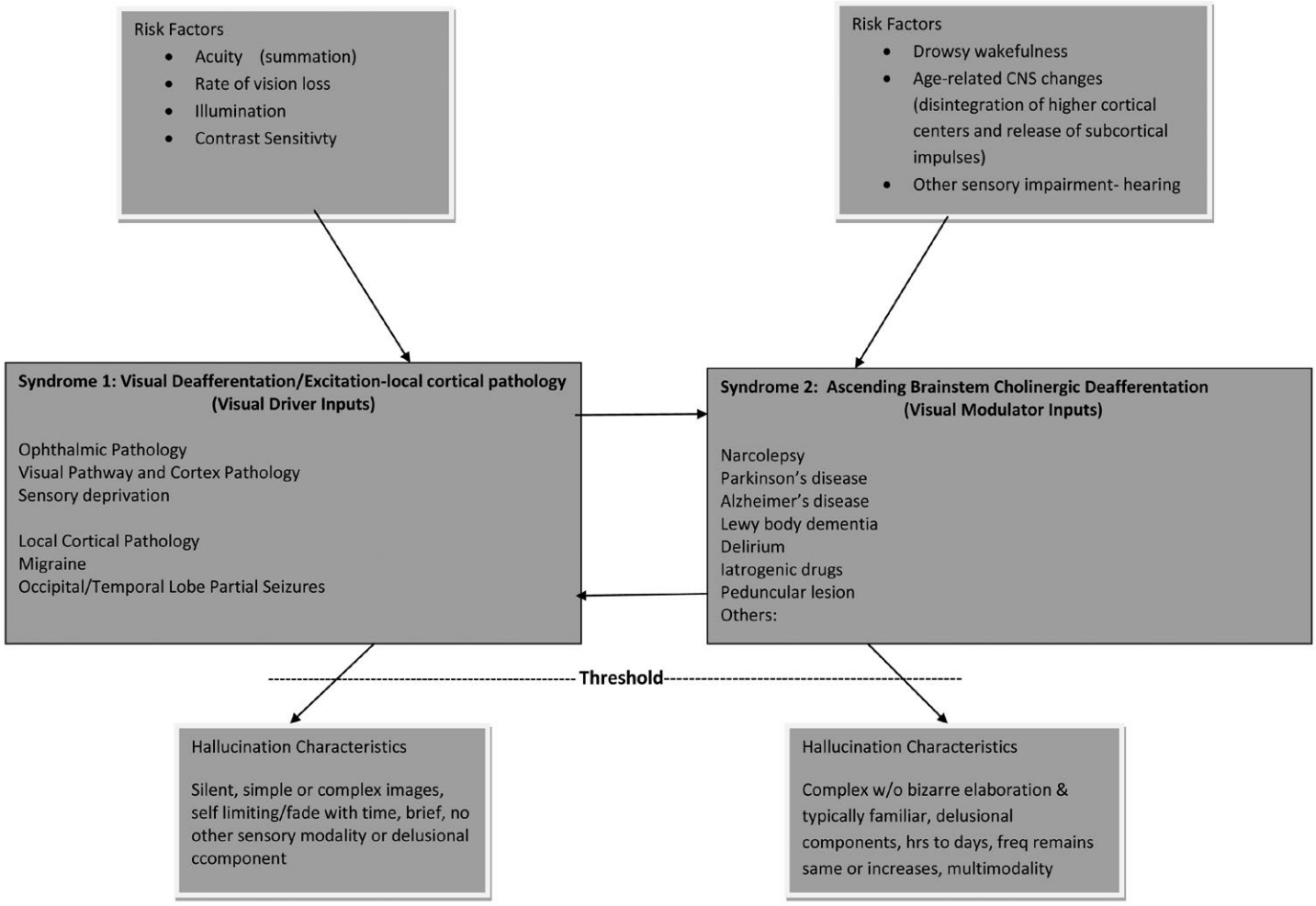

Figure 2: Risk factors and interaction of syndromes 1 & 2

Many confounding variables exist in patients with visual hallucinations. Patients who experience CBS hallucinations are typically elderly, are on multiple medications, and have co-morbid disease. Multiple risk factors may predispose visually impaired patients to experiencing CBS. This may help explain why not all visually impaired patients with similar profiles get CBS. It seems plausible that multiple visual risk factors may place a patient with syndrome 1 over a certain threshold which results in a visual hallucination characteristic of CBS. For instance, a patient with age related macular degeneration, moderate bilateral vision loss, and a recent decline in acuity, who is in low ambient illumination, may experience CBS. However, a patient with the same acuity but who does not have these other risk factors does not have hallucinations. Similarly, a glaucoma patient with more age related central nervous system (CNS) changes and moderate contrast sensitivity loss may have characteristic CBS, while the equivalent patient without CNS changes and better contrast may not hallucinate. These are examples to illustrate that whether or not a patient experiences CBS will likely depend on multiple factors. Figure 2 illustrates the risk factors for syndrome 1 and 2, the interaction of the syndromes, and the end result of the hallucination produced.

Clinical Characteristics

CBS is typically found in elderly patients with deteriorating vision.[70] The vision loss is bilateral in most cases.[3] CBS is not restricted to the elderly and has been reported in children who have incurred acute vision loss.[71] It is likely that the preponderance of diagnoses in the elderly is due to the high prevalence of vision loss in this population.[4] Crumbliss et al.[7] compared the mean age of their low vision population experiencing CBS to those without CBS. Although both groups were elderly, there was no statistical significance in age difference between the two groups, possibly highlighting that age is not associated with CBS.[7] Khan et al.[59] also did not find an association of CBS with increasing age. Similarly, Menon[18] did not find an age correlation in his studied CBS group, whose ages ranged from 43-96.

There is no uniform consensus as to whether CBS occurs more frequently in men versus women.[4] In his original report of CBS, DeMorsier[72] reported a higher incidence in males. More recent studies[4,59,73] have demonstrated a higher occurrence of CBS in females; however, this may be attributed to the fact that females survive longer than males and are therefore more likely to have a higher percentage of vision loss. Large scale CBS studies have not confirmed a gender bias.[18]

The current literature reports a strong association between CBS and reduced visual function. The high incidence of CBS coexisting with ARMD may be explained by the fact that ARMD is one of the most common ocular pathologies in developed countries.[3] Although ARMD is the most reported associated eye disease linked to CBS, any ocular pathology, occurring anywhere along the visual pathway from the eye,[26] including all neuronal connections coursing to the primary visual cortex as well as the visual cortex itself, has the potential to result in CBS.[3,4] Visual field defects, with normal central acuity in patients with glaucoma, have likewise been associated with CBS.[60] Similarly, cerebral disease, as in the case of occipital infarction resulting in homonymous hemi-field visual field loss, has been documented in CBS cases.[3] The visual hallucinations in these patients typically appear within the new visual field defect or on the border of the unaffected/affected field.[6] A comprehensive list of the many eye diseases previously documented in association with CBS can be found in Table 3.[3,4,7,59-67]

Although the patient may at first be deceived by the hallucination, he or she will quickly come to retain insight into the unreal nature of the hallucination.[3,9] CBS hallucinations should not occur or be associated with hallucinations in any other sensory modalities, such as auditory or olfactory.[4] CBS hallucinations are perceived in most cases as pleasant to the individual experiencing them,[1] although a few patients have reported that the hallucinations are disturbing and frightening[18] and can even cause distress.[4] Menon[18] investigated 30 patients with CBS and reported that even though all patients were aware that the images were not real, 60% of the patients experienced confusion at first encounter.

CBS hallucinations are, in most cases, recognized as complex formed hallucinations.[74] They have been described as simple[3] or elementary.[4] Elementary or simple hallucinations are characterized as unformed, colored or colorless, lights, flashes, stars, shapes, patterns, etc.[3,4] Complex hallucinations are classified as formed hallucinations with a recognizable shape, such as a face or an animal.[3,4] Most of the current literature excludes simple hallucinations as part of the CBS clinical spectrum.[74] Some of this bias toward limiting CBS hallucinations to complex ones is likely a consequence of the originator himself, Charles Bonnet. He focused on describing his grandfather's complex hallucinations while de-emphasizing and even omitting reports of simple visual hallucinations.[26] His grandfather's most frequent hallucinations were simple in nature. One example of these simple hallucinations experienced by his grandfather has been reported as "a multitude of atoms whirling about in his field of view," however other unformed hallucinations were also described by him as well.[26]

Gilmour et al.[19] did include simple hallucinations as part of the CBS inclusion criteria in their study. They reported that these unformed spot-like or bright light images should not be disregarded because, often with further questioning and investigation, these hallucinations can be classified as CBS. There is documented evidence to suggest that the type of visual hallucination experienced is correlated to the region of the brain activated.[26] The type of image viewed, whether simple or complex, will depend on which part of the cortex is pathologically stimulated. Therefore, separating the two types of hallucinations and excluding simple hallucinations may contribute to the underestimated prevalence of this syndrome.[26]

CBS visual hallucinations are commonly depicted in the literature as complex and formed images that appear suddenly, are sharply focused, stationary, most often represented as a person, and typically occur when the patient is alert and has his or her eyes open.[4] People, followed by geometric patterns, are the more frequent images reported by CBS patients with age-related macular degeneration.[59] The visual hallucinations are always localized in external space and well defined. They are also sharp and clear, in contrast to the blurred real objects.[4] The hallucination may be stationary, moving, or may have internal movement.[1,4,70] Images are generally non-threatening to the individual, as there are no emotional ties or familiarity to the hallucinations.[3,4] Faces are not known by the patient, and objects do not have significance to the patient.[3] Typically, the same CBS image is repeated, but this may not always be the case as some can perceive different hallucinations per episode.[4] Some of the more common characteristics of CBS hallucinations are: a person, distorted faces, animals, figures, geometric forms, overlapping patterns, and branching structures.[3,4,9,19,74] Hallucinations can be perceived in color or in black and white.[4] Khan et al.[59] reported the common occurrence of colored images in 72% of a studied CBS population secondary to ARMD. Furthermore, the images may be normal in size, larger, or smaller.[3,4]

CBS hallucinations are associated with ophthalmic disease, and the onset of these hallucinations can occur anytime after vision loss.[4] The hallucinations can come on gradually or very suddenly, occurring several times a day.[4] The moment in time and the frequency with which these images occur vary among CBS patients.[75] The pattern of occurrence may be episodic, periodic, or continuous[4]/chronic.[75] Episodic hallucinations happen for a period of days to months and then resolve permanently.[4] The periodic variety is characterized by phases of active hallucinations and phases of inactivity.[4] Chronic or continuous CBS describes constant hallucinations without dormant phases.[4] The duration of the hallucination varies from seconds to minutes and even hours. According to Vukicevic and Fitzmaurice,[75] visual hallucinations lasted on the order of minutes in 70% of the patients studied. CBS can last after its onset for days, months, and even years, but it tends to diminish over time as sight is lost.[4] Jackson and Bassett reported that 28% of CBS patients no longer had visual hallucinations one year after initially reporting them.[76] Holroyd and Rabins[68] reported that 60% of patients had resolution of their hallucinations at 18 months.

CBS occurs more commonly in those patients with higher degrees of vision loss that is typically bilateral.[3,4] Visual acuity

was found to be the most common statistically significant risk factor for CBS in six out of nine previous studies.[4,73,77-80] Gilmour[19] reported CBS in those having a visual acuity that ranged from 20/40 to 20/1600. He found that those patients whose acuity ranged from 20/300 to 20/800 were twice as likely to have CBS.[19] Khan et al.[59] reported that best binocular acuity of less than 20/120 was associated with the occurrence of CBS. This makes sense given the high prevalence of CBS in ARMD patients who have reduced central acuity. The macula has the highest density of photoreceptors and corresponds to "50% of the retinal ganglion cell output," even though it constitutes 7.3% of the retina.[81] Therefore, poorer central acuity will equate to a greater degree of deafferentation or loss of visual input. However, we cannot ignore the fact that other eye diseases not affecting central acuity result in CBS hallucinations, as in the case of glaucoma. This may be explained by looking at the combined vision loss of both eyes versus looking at each eye's acuity independently.[21] As suggested by Khan et al.,[59] combined acuity measures may serve as a better predictor for visual hallucinations than just looking at best and worst acuity independently.

The degree and severity of vision loss, along with progression of visual function, have not been correlated with the complexity of the hallucinations.[59,82] The rate of vision loss has been suggested by some to be more of a predisposing factor for CBS than the actual nature of the ocular pathology or the severity of the visual impairment.[3] Patients who experience acute/sudden vision loss appear more likely to have CBS compared to those whose vision is gradually lost over a period of time.[3]

The literature has focused on visual acuity[83] and its relationship to CBS. A recent study conducted by Jackson et al.[83] looked at the association between visual hallucinations as a function of visual acuity and contrast sensitivity. Reduced contrast sensitivity appears to have more of an impact on one's daily activities of living than reduced visual acuity alone.[22,83,84] Jackson et al. concluded that reduced/low contrast sensitivity levels were strongly associated with CBS hallucinations.[83] The same authors did not find a correlation between visual acuity and visual hallucinations after controlling for several variables including: age, contrast sensitivity, gender, report of depression, and independence. Similarly, Crane et al.[77] did not find an association between visual acuity and CBS. They additionally concluded that the presence and extent of the central scotoma was not correlated to the presence of visual hallucinations.[77] Patients with Parkinson's disease are known to have reduced contrast sensitivity, and the occurrence of visual hallucinations is well documented in this patient population.[85-87] "Approximately 25% of patients with untreated Parkinson's disease, who are not demented or psychotic, have been documented to report visual hallucinations."[83] The relationship to contrast sensitivity is promising; the literature is currently limited on this topic. Further investigation following the onset and termination of hallucinations in relation to changes in contrast sensitivity may shed more light into its role in CBS.

In approximately 56% of low vision patients with CBS studied by Gilmour et al.,[19] a trigger was not involved in stimulating a visual hallucination. CBS occurs without triggering factors; however, certain stimuli have been implicated in causing or stimulating CBS. These include general sensory reduction, social or physical isolation, level of illumination (dim/bright), states of drowsiness or relaxation, the rate of vision loss, fatigue, and stress[3,4,19] As per Gilmour et al.,[19] the most common triggering factors were illumination level (20%), fatigue (8%), stress (4%), and loneliness (2%).[19] From a theoretical point of view, it seems plausible that reduced sensory stimulation, as in the case of living in isolation or of having a lack of social contact, would trigger CBS hallucinations. However, outside of two studies,[73,78] this finding has not been duplicated. On the contrary, Khan et al.[59] found the opposite effect, for which he did not find an explanation; those married or living with someone were more likely to have CBS. Part of the inconsistency relating to sensory deprivation and its relationship to CBS hallucinations may be a result of the difficulty and accuracy of measuring sensory deprivation variables in the context of a clinical setting.[21]

Diagnosis

Currently there is no universal consensus regarding the requirement of visual impairment and cognition in diagnosing CBS. There are some authors[88-91] who mandate impaired vision as part of the diagnostic criteria for CBS. Ormond[92] contends that visual hallucinations of CBS occur only in acquired eye disease and are not found in those born blind. Charles Bonnet actually correlated these hallucinations in the context of visual impairment.[4] Others maintain that there are numerous causes for visual hallucinations, but that CBS should refer to a specific type of visual hallucination, those associated only with visual deafferentation.[26,88-91]

Though vision loss commonly occurs with CBS, it may not be required for diagnosis.[72,93] DeMorsier,[72] the first to coin the term "Charles Bonnet syndrome," did not mandate visual dysfunction but acknowledged its frequent coexistence with CBS.[4] Unfortunately, most of the published research studying the prevalence of CBS is done in the low vision population. Thus, the percentages of CBS prevalence pertains mostly to the visually impaired.[18,19,55,59,70] Gilmour et al.[19] compared the prevalence of CBS in the low vision population versus an age-matched control group with little or no vision loss. They found that less than 2% of the general population experienced CBS,[19] indicating that ocular pathology does not have to coexist with CBS.[19] Additionally, Kazui et al.,[25] through neuroimaging studies, implied that eye disease is not always present in CBS. They found that any dysfunction in the primary or secondary visual cortices may result in "deprivation of external visual stimuli." They further proposed that even without clinically evident organic

cortical abnormalities, those with CBS may still have a "dysfunction in the occipital lobe, especially in the primary and secondary visual cortices," that may be responsible for the hallucination.[25]

The role of impaired cognition and neurologic disease and their association with CBS is also controversial. The implication of cognitive impairment predisposing patients to CBS is a valid consideration and warrants being addressed. Some studies claim that CBS patients show neuropsychological changes that are characteristic of early dementia.[68,94-97] Longitudinal studies on changes in cognition and cerebral disease in CBS patients would help to verify or refute the link between cognitive impairment and susceptibility to CBS. Currently there is not any data available in the literature.

On the other side of this argument, there are those who assert that reduced cognition excludes patients from a diagnosis of CBS.[68,95,98] Evidence to support this stance comes from studies that have shown stable cognitive scores on follow-up visits of those diagnosed with CBS and ARMD.[68] Chapman et al.[94] looked at 50 probable Alzheimer's patients and found that CBS was confined only to those visually impaired.[94] Some authors have a middle-ground stance.[96,99,100] They hold that vision and cognition alone are not enough to cause CBS, but together they contribute to a state of sensory deprivation that leads to hallucinations.[96,99,100] There is a disintegration of higher brain centers with normal aging. This finding, in addition to the release of subcortical impulses in the visually impaired, act synergistically to produce CBS hallucinations.[4] This middle-stance point of view may shed some light as to why not all visually impaired patients have CBS. Visual impairment with other unknown predisposing factors may be the cause of CBS.

Discussion

Recommended Clinical Application

Without a general consensus about the role of cognition, neurological disease, and vision loss in standardizing the diagnostic criteria of CBS, it is difficult for a clinician to affirm that the patient is truly having CBS hallucinations. After an extensive review of the literature, we have summarized a proposed criterion based on a collaboration of past works.[3,4,6,8,21,26,74] The inclusion of simple, unformed images is typically not seen in past studies, therefore, the literature is biased in excluding them. However, as mentioned earlier, there is evidence to suggest that the type of visual hallucination experienced is correlated to the region of the brain activated.[26] Simple hallucinations have been documented to occur in diseases such as optic neuritis, occipital lobe tumors, occipital seizures, or other structural abnormalities, all of which may result in deafferentation and hence CBS hallucinations.[6] Therefore we have decided to include them in our criteria.

Our recommended criteria to diagnose CBS should follow as below adopted and modified:[3,4,6,8,21,26,74]

- Hallucinations can be simple and/or complex
- No evidence of neurologic or psychiatric disease
- Cognitively intact
- No involvement of other sensory modalities (auditory, olfactory)
- Insight into unreal nature of the hallucination
- Visual impairment

When suspecting that your patient fulfills the criteria for CBS with a careful history, a thorough eye exam must be completed. A comprehensive history is critical and should be focused on obtaining a good description of the hallucination features, including:[10]

- Is the hallucination simple or complex?
- Is the image familiar or unfamiliar?
- Is the image in bizarre dressings or realistic?
- Duration?
- Are other sensory hallucinations involved?
- Does the patient have insight or are they delusional?

Visual hallucinations are associated with many other neurologic, psychiatric, toxic, and metabolic diseases. A list of differential diagnoses that need to be ruled out before concluding CBS is responsible for the hallucinations can be found in Table 1.[3,26,29-35]

When presuming a diagnosis of CBS, a full work-up with referrals to other specialties will be warranted. Referrals should be made for:[6,3,10,24,101]

- Cognitive evaluation
- Comprehensive psychiatric work-up
- Neurology screening, which may include: magnetic resonance imaging (MRI) or computed tomography (CT), electroencephalography (EEG), and/or Alzheimer's disease assessment scale (ADAS)[25]
- Primary care physician (medication review/blood labs). Please see Table 2.

It is very important that a primary care provider review the patient's current medications and determine whether there is any correlation between the onset of hallucinations and start dates, changes in dosing, or discontinuation of a medication. A review of medications, paying attention to anticholinergic load, is important, as minimizing this group of medications in itself may resolve hallucinations.[10] The list of medications that are associated with visual hallucinations should be reviewed in relation to the patient's current medications. Blood labs are recommended to rule out vitamin deficiencies or concurrent infections that also may contribute to hallucinations.[10] Once the appropriate referrals and full work-up have eliminated other potential causes for visual hallucinations, CBS can be diagnosed and treatment initiated.

Management and Treatment

Once CBS has been diagnosed, rehabilitation should begin with patient education and assurance of the benign nature of the hallucinations. In many cases, patients are not bothered by the visual hallucinations and, therefore, will not need intervention.[8] Patient awareness, assurance, and full comprehension of CBS will alleviate concerns of psychiatric disease. There are suggested non-pharmacological and pharmacological recommendations to help improve visual hallucinations, especially if the hallucinations interfere with a patient's activities of daily living.[3,4,9]

There are different treatments suggested for CBS. They can be broken down into three categories: 1. Can the patient's vision be improved? 2. Preventative techniques, and 3. Pharmacological intervention. Improving the level of a patient's current vision may increase visual stimulation and, in turn, diminish or alleviate the hallucinations.[9] Improvement in vision, whether by spectacles, magnifiers, telescopes, or other low vision aides, has been shown to reduce CBS hallucinations. A low vision referral is warranted in all CBS patients as often visual acuity will not improve; however, maximizing remaining vision with low vision devices can be an effective treatment. Surgical procedures such as cataract surgery, photocoagulation, anti-VEGF injections, etc. may improve visual function and halt symptoms.[9]

If these treatment options are not indicated given the state of disease, other non-pharmacological interventions can be considered. Typically, these interventions involve modifications to the patient's environment in an attempt to increase sensory stimulation and reduce the frequency of visual hallucinations. Some recommended techniques include: blinking eyes rapidly, increasing the patient's social network, and increasing lighting.[3,4] In addition, Merabet et al.[102] suggested treatment with transcranial magnetic stimulation as a possible procedure for suppressing complex visual hallucinations.

Currently, there is no established, standardized medical treatment for CBS as no clinical trials have been conducted to date. Only limited evidence is available through small-scale reports and case studies.[103-107] Pharmacological intervention has had a low success rate.[4] It remains uncertain whether permanent remission of hallucinations can be achieved with medication. Partial resolution has been reported with some medications such as anti-convulsants, anti-psychotics, and cholinesterase inhibitors.[3,4,9] If medications are used, they must be tailored to the individual patient because of the possible worsening of hallucinations, the potential adverse reactions, and the effect on co-existing disease states.

Ffytche[26] suggests that treatment should be based on whether the visual hallucinations are the result of syndrome 1 or syndrome 2. If syndrome 1 is the cause for the visual hallucinations, he contends that the patient will respond to "reassurance and optimization of visual function." However, if the hallucinations are caused by syndrome 2, the patient may respond to medications such as cholinesterase inhibitors, anti-convulsants, and anti-psychotics.[26]

It is important for the clinician to realize that even with meeting the CBS diagnostic criteria, and with a non-revealing work-up, the diagnosis is still presumed. On follow-up visits, ask the patient about changes in the characteristics of their current hallucinations. A red flag should be raised if other sensory modality hallucinations or delusional components become involved, if the frequency and/or duration have changed suddenly, or if the hallucinations re-occur after a period of dormancy. If atypical features become obvious, then another referral is warranted. Bourgeois et al.[101] reported on a case of a visually impaired patient who was given a presumed diagnosis of CBS when the initial work-up was negative for neurological, psychiatric, and cognitive disease. Her initial blood labs did, however, reveal a vitamin B_{12} deficiency. The association between the hallucinations and vitamin B_{12} deficiency was based on analyzing the blood labs and vitamin supplementation pattern within the context of the visual hallucinations. The initial hallucinations occurred when the blood labs revealed low vitamin B_{12} levels, followed by disappearance with vitamin B_{12} supplementation. Discontinuation of vitamin B_{12} supplements lead to a re-appearance of the hallucinations and, with re-initiation of vitamin B_{12} supplements, there was cessation of the hallucinations. This case exemplifies why even after a presumed diagnosis of CBS, the clinician must continue to be vigilant. The elderly population is susceptible to many disorders that predispose them to visual hallucinations. The clinician then must watch for dual diagnosis of CBS and other conditions such as dementia,[74] vitamin B_{12} deficiency,[101] and cerebral infarction, all of which may make the aging population more vulnerable to visual hallucinations.

Limitations of the Literature

The literature regarding CBS is extensive and dates as far back as 1760 when Charles Bonnet himself described visual hallucinations experienced by his grandfather. However, our knowledge of the pathophysiology, diagnosis, and treatment of CBS has advanced modestly over the years. The majority of the literature focuses on clinical characteristics, risk factors, and epidemiology of CBS, all of which assist clinicians in identifying the syndrome. Unfortunately, universal diagnostic criteria are not currently recognized, making the diagnosis presumptuous. A standardized medical work-up of visually impaired patients who present with hallucinations also does not exist. It is clear that all patients should be subjected to a cognitive and psychiatric screening, yet it remains unclear whether every patient should undergo a through neurologic evaluation including neuro-imaging with CT scan and MRI. Treatments of visual hallucinations vary depending on the literature reviewed. Without evidence-based medical treatments it is uncertain which patients may or may not benefit from the use of pharmacological intervention.

Ophthalmology, neurology, and psychiatry have all published extensive data on CBS. Each discipline appears to have its own approach to work up, diagnosis, and treatment. Additional advances in understanding the pathogenesis of hallucinations should assist all three disciplines in establishing a collaborative, universal diagnostic and treatment guideline for CBS.

Conclusion

Awareness of CBS among optometrists is critical in avoiding the wrong diagnosis and therefore exposing a patient to treatment for a non-existent psychiatric disease. Given the prevalence of CBS, the likelihood of encountering a patient is common. When taking a patient history, it is imperative to ask specific questions to uncover the existence of hallucinations, but to do so in a very sensitive and sympathetic manner. Once visual hallucinations have been confirmed and documented, a thorough eye and neurological exam is warranted to rule out other causes. Referral for low vision examination is warranted since many times maximizing visual function can lessen the hallucinations. Sympathy, compassion, and reassurance are essential for patient management.

References:

1. Damas-Mora J, Skeleton-Robinson M, Jenner FA. The Charles Bonnet syndrome in perspective. Psychol Med 1982;12:251-61.
2. Schultz G, Needham W, Taylor R, Shindell S, et al. Properties of complex hallucinations associated with deficits in vision. Perception 1996;25:715-26.
3. Kester EM. Charles Bonnet syndrome: case presentation and literature review. Optometry 2009;80:360-6.
4. Menon GJ, Rahman I, Menon SJ, Dutton GN. Complex visual hallucinations in the visually impaired: The Charles Bonnet syndrome. Surv Ophthalmol 2003;48:58-72.
5. Fernandez A, Lichtshein G, Viewg WVR. The Charles Bonnet syndrome: A review. J Nerv Ment Dis 1997;185:195-200.
6. Jacob A, Prasad S, Boggild M, Chandratre S. Charles Bonnet syndrome—elderly people and visual hallucinations. BMJ 2004;328(7455):1552-4.
7. Crumbliss KE, Taussig MJ, Jay WM. Vision rehabilitation and Charles Bonnet syndrome. Semin Ophthalmol 2008;23:121-6.
8. Jackson ML, Ferencz J. Charles Bonnet syndrome: Visual loss and hallucinations. CMAJ 2009;181:175-6.
9. Rovner BW. The Charles Bonnet syndrome: a review of recent research. Curr Opin Ophthalmol 2006;17(3):275-7.
10. Ffytche DH. Visual hallucination and illusion disorders: A clinical guide. Adv Clin Neurosci Rehab 2004;4:16-8.
11. Glossary of Psychiatric terms. http://bit.ly/GlossPsych. Last Accessed September 12, 2012.
12. Borruat FX. Visual hallucinations and illusions, symptoms frequently misdiagnosed by the practitioner. Klin Monatsbl Augenheilkd 1999;214:324-7.
13. Duke-Elder S, Scott GI. Disorders of perception: visual hallucinations. In: Duke-Elder S, ed. System of Ophthalmology, Vol. XII. London: Henry Kimpton,1971,562-9.
14. American Psychiatry Association. What's the Difference Between a Delusion and a Hallucination? http://bit.ly/DelusHalluc. Last Accessed September 7, 2012.
15. Sedman G. A comparative study of pseudohallucinations, imagery, and true hallucinations. Br J Psychiatry 1966;112(482):9-17.
16. Taylor FK. On pseudo-hallucinations. Psychol Med 1981;11:265-71.
17. Jackson ML. Vision rehabilitation for Canadians with less than 20/40 acuity: The SmartSight model. Can J Ophthalmol 2006;41:355-61.
18. Menon GJ. Complex visual hallucinations in the visually impaired: A structured history-taking approach. Arch Ophthalmol 2005;123:349-55.
19. Gilmour G, Schreiber C, Ewing C. An examination of the relationship between low vision and Charles Bonnet syndrome. Can J Ophthalmol 2009; 44:49-52.
20. Santhouse AM, Howard RJ, Ffytche DH. Visual hallucinatory syndromes and the anatomy of the visual brain. Brain 2000;123:2055-64.
21. Ffytche DH. Visual hallucinations in eye disease. Cur Opin Neurol 2009; 22:28-35.
22. West SK, Rubin GS, Broman AT, Munoz B, et al. How does visual impairment affect performance on tasks of everyday life? The SEE Project. Salisbury Eye Evaluation. Arch Ophthalmol 2002;120:774-80.
23. Tan CS, Sabel BA. Dynamic changes in visual acuity as the pathophysiologic mechanism in Charles Bonnet syndrome (visual hallucinations). Eur Arch Psychiatry Clin Neurosci 2006;256:62-3.
24. Kazui H, Ishii R, Yoshida T, Ikezawa K, et al. Neuroimaging studies in patients with Charles Bonnet syndrome. Psychogeriatric 2009;9:77-84.
25. Rover BW. The Charles Bonnet syndrome. Visual hallucinations caused by visual impairment. Geriatrics 2002;57(6):45-6.
26. Ffytche DM. Visual hallucinations and the Charles Bonnet syndrome. Curr Psychiatry Rep 2005;7:168-79.
27. Boroojerdi B, Bushara KO, Corwell B, Immisch I, et al. Enhanced excitability of the human visual cortex induced by short-term light deprivation. Cereb Cortex 2000;10(5):529-34.
28. Ffytche DH, Howard RJ, Brammer MJ, David A, et al. The anatomy of conscious vision: an fMRI study of visual hallucinations. Nat Neurosci 1998;8:738-42.
29. Manford M, Andermann F. Complex visual hallucinations. Clinical and neurobiological insights. Brain 1998;121:1819-40.
30. Teeple RC, Caplan JP, Stern TA. Visual hallucinations: differential diagnosis and treatment. Prim Care Companion J Clin Psychiatry 2009;11:26-32.
31. Cummings JL, Miller BL. Visual hallucinations. Clinical occurrence and use in differential diagnosis. West J Med 1987;146:46-51.
32. Causes of Visual hallucinations. http://bit.ly/CauseVisual. Last Accessed September 7, 2012.
33. van Lommel P, van Wees R, Meyers V, Elfferich I. Near death experience in survivors of cardiac arrest: A prospective study in the Netherlands. Lancet 2001;358:2039-45.
34. Ffytche DH, Pins D, Guy CN. The neural correlates of Purkinje patterns. In: Washington DC: Society for Neuroscience. Abstract viewer/Itinerary planner CD-ROM; 2002: Program no.260.15.
35. Roever CP, Vyas BB, Barnett MC, Sheyner I, et al. Visual hallucinations in long-term care. Annals of Long-Term Care: Clinical Care and Aging. 2012;20(2):25-30.
36. Drug side effects hallucinations. http://bit.ly/DrugsHalluc. Last Accessed September 7, 2012.
37. Goetz CG, Tanner GM, Klawans HL: Pharmacology of hallucinations induced by long-term drug therapy. Am J Psychiatry 1982;139:494-7.
38. Cummings JL, Barritt CF, Horran M. Delusions induced by procaine penicillin: Case report and review of the syndrome. Int J Psychiatry Med 1986-1987;16:163-8.
39. Filley CM, Graff-Richard NR, Lacy JR, Heitner MA, et al. Neurologic manifestations of podophyllin toxicity. Neurology 1982;32:308-11.
40. Miller RR. Clinical effects of pentazocine in hospitalized medical patients. J Clin Pharmacol 1975;15:198-205.
41. Drugs that cause psychiatric symptoms. Med Lett Drugs Ther 1984;26:75-8.
42. Herridge CF, a'Brook MF. Ephedrine psychosis. Br Med J 1968;2:160.
43. Petursson H. Diethylpropion and paranoid psychosis. Aust N Z J Psychiatry 1979;13:67-8.

44. Lucas AR, Weiss M. Methylphenidate hallucinosis. JAMA 1971;217:1079-81.

45. Greer HD III, Ward HP, Corbin KB. Chronic salicylate intoxication in adults. JAMA 1965;193:85-8.

46. Golden RN, James SP, Sherer MA, Rudorfer MV, et al. Psychoses associated with bupropion treatment. Am J Psychiatry 1985;142:1459-62.

47. Sheehy LM, Maxmen JS. Phenelzine-induced psychosis. Am J Psychiatry 1978;135:1422-3.

48. Hall RCW, Stickney SK, Gardner ER. Behavioral toxicity of non-psychiatric drugs. In: Hall RCW, ed. Psychiatric Presentations of Medical Illness. New York: Springer Medical & Scientific Books,1980:337-49.

49. Estroff TW, Gold MS. Medication-induced and toxin-induced psychiatric disorders. In: Extein I, Gold MS, eds. Medical Mimics of Psychiatric Disorders. Washington, DC: American Psychiatric Press,1986:185-98.

50. Price W, Coli L, Branstetter RD, Gotz VP. Ranitidine-associated hallucinations. Eur J Clin Pharmacol 1985;29:375-6.

51. Sandyk R, Gillman MA. Lithium-induced visual hallucinations: Evidence for possible opioid mediation. Ann Neurol 1985;17:619-20.

52. Shawn DH, McGuigan MA. Poisoning from dermal absorption of promethazine. Can Med Assoc J 1984;130:1460-1.

53. Barnes FF. Precipitation of mania and visual hallucinations by Amoxapine Hydrochloride. Compr Psychiatry 1982;23:590-2.

54. Olanow CW, Alberts MJ. Double-blind controlled study of pergolide mesylate in the treatment of Parkinson's disease. In: Fahn S, Marsden CD, Jenner P, eds. Recent Developments in Parkinson's Disease. New York: Raven Press,1986:315-21.

55. LeWitt PA. Clinical and pharmacological aspects of antiparkinsonian ergolide lisuride. In: Fahn S, Marsden CD, Jenner P, eds. Recent Developments in Parkinson's Disease. New York: Raven Press,1986:347-54.

56. Moses H III, Uhl G, Preziosi T. Mesulergine (cu 32-085) in idiopathic parkinsonism. In: Fahn S, Marsden CD, Jenner P, eds. Recent Developments in Parkinson's Disease. New York: Raven Press,1986:363-8.

57. Yates D. Syncope and visual hallucinations, apparently from timolol. JAMA 1980;244:768-9.

58. Delirium in the Elderly: Medications, Causes, and Treatment. http://bit.ly/USP_CE Last Accessed September 12, 2012.

59. Khan JC, Shahid H, Thurlby DA, Yates, JR, et al. Charles Bonnet syndrome in age-related macular degeneration: The nature and frequency of images in subjects with end-stage disease. Ophthalmic Epidemiol 2008;15:202-8.

60. Tan CS, Lim VS, Hoy DY, Yeo E, et al. Charles Bonnet syndrome in Asian patients in a tertiary ophthalmic centre. Br J Ophthalmol 2004;88:1325-9.

61. Kolmel HW. Complex visual hallucinations in the hemianopic field. J Neurol Neurosurg Psychiatry 1985;48:29-38.

62. Kurata A, Miyasaka Y, Yoshida T, Kunii M, et al. Venous ischemia caused by dural arteriovenous malformation: Case report. J Neurosurg 1994;80:552-5.

63. Price J, Whitlock FA, Hall RT. The psychiatry of vertebro-basilar insufficiency with the report of a case. Psychiatr Clin (Basel) 1983;16:26-44.

64. Plummer C, Kleinitz A, Vroomen P, Watts R. Of Roman chariots and goats in overcoats: the syndrome of Charles Bonnet. J Clin Neurosci 2007;14:709-14.

65. Burke W. The neural basis of Charles Bonnet hallucinations: A hypothesis. J Neurol Neurosurg Psychiatry 2002;73:535-41.

66. Tan CS, Sabel BA, Goh KY. Visual hallucinations during visual recovery after central retinal artery occlusion. Arch Neurol 2006;63:598-600.

67. Ross J, Rahman I. Charles Bonnet Syndrome following enucleation. Eye 2005;19:811-2.

68. Holroyd S, Rabins PV, Finkelstein D, Nicholson MC, et al. Visual hallucinations in patients with macular degeneration. Am J Psychiatry 1992;149:1701-6.

69. Harding AJ, Broe GA, Halliday GM. Visual hallucinations in Lewy Body disease relate to Lewy bodies in the temporal lobe. Brain 2002;125:391-403.

70. Teunisse RJ, Cruysberg JR, Hoefnagels WH, Kuin Y, et al. Social and psychological characteristics of elderly visually handicapped patients with the Charles Bonnet syndrome. Compr Psychiatry 1999;40:315-9.

71. Schwartz TL, Vahgei L. Charles Bonnet syndrome in children. J AAPOS 1998;2:310-3.

72. De Morsier G. The Charles Bonnet syndrome: Visual hallucinations in the aged without mental deficiency. Ann Med Psychol 1967;2:678-702.

73. Holroyd S, Rabins PV, Finkelstein D, Lavrisha M. Visual hallucinations in patients from an ophthalmology clinic and medical population. J Nerv Ment Dis 1994;182:273-6.

74. Shadlu AP, Shadlu R, Shepherd JB. Charles Bonnet syndrome: a review. Curr Opin Ophthalmol 2009;20:219-22.

75. Vukicevic M, Fitzmaurice K. Butterflies and black lacy patterns: The prevalence and characteristics of Charles Bonnet hallucinations in an Australian population. Clin Experiment Ophthalmol 2008;36:659-65.

76. Jackson ML, Bassett KL. The natural history of the Charles Bonnet syndrome. Do the hallucinations go away? Eye 2010;24:1303-4.

77. Holroyd S, Rabins PV. A three year follow-up study of visual hallucinations in patients with macular degeneration. J Nerv Ment Dis 1996;184:188-9.

78. Crane W, Fletcher D, Schuchard R. Prevalence of photopsias and Charles Bonnet syndrome in a low vision population. Ophthalmol Clin North Amer 1994;7:143-9.

79. Scott IU, Schein OD, Feuer WJ, Folstein MF. Visual hallucinations in patients with retinal disease. Am J Ophthalmol 2001;131:590-8.

80. Teunisse RJ, Cruysberg JR, Verbeek AL, Zitman FG. The Charles Bonnet syndrome: A large prospective study in the Netherlands. A study of the prevalence of the Charles Bonnet syndrome and associated factors in 500 patients attending the University Department of Ophthalmology at Nijmegen. Br J Psychiatry 1995;166:254-7.

81. Curcio CA, Allen KA. Topography of ganglion cells in human retina. J Comp Neurol 1990;300:5-25.

82. Abbott EJ, Connor GB, Artes PH, Abadi RV. Visual loss and visual hallucinations in patients with age related macular degeneration (Charles Bonnet syndrome). Invest Opthalmol Vis Sci 2007;48:1416-23.

83. Jackson ML, Bassett K, Nirmalan PV, Sayre EC. Contrast sensitivity and visual hallucinations in patients referred to a low vision rehabilitation clinic. Br J Ophthalmol 2007; 91:296-8.

84. Owsley C, Sloane M. Contrast sensitivity, acuity, and the perception of "real world" targets. Br J Ophthalmol 1987;71:791-6.

85. Pierre V, Diederich NJ, Raman R, Goetz CG. Decreased color discrimination and contrast sensitivity in Parkinson's disease. J Neuro Sci 2000;172:7-11.

86. Biousse V, Skibell BC, Watts RL, Loupe DN, et al. Ophthalmologic features of Parkinson's disease. Neurology 2004; 62:177-80.

87. Diederich NJ, Goetz CG, Raman R, Pappert EJ, et al. Poor visual discrimination and visual hallucinations in Parkinson's disease. Clin Neuropharmacol 1998;21:289-95.

88. Rosenbaum F, Harati Y, Rolak L, Freedman M. Visual hallucinations in sane people: Charles Bonnet syndrome. J Am Geriatr Soc 1987;35:66-8.

89. Kolmel HW. Visual illusions and hallucinations. In: Kenard C, ed. Visual perceptual defects, Bailliere's Clinical Neurology, Vol 2, No. 2. London: Baillieres Tindall,1993:243-64.

90. Hecaen H, Albert ML. Disorder of Visual Perception. In: Hecaen H, Albert ML, eds. Human Neuropsychology. New York: John Wiley & Sons,1975:71-9.

91. Schultz G, Melzack R. The Charles Bonnet syndrome: 'phantom visual images.' Perception 1991;20:809-25.

92. Ormond AW. Visual hallucinations in sane people. BMJ 1925;2:367-7.

93. Teunisse RJ, Zitman FG, Raes DC. Clinical evaluation of 14 patients with Charles Bonnet syndrome (isolated visual hallucinations). Compr Psychiatry 1994;35:70-5.

94. Chapman FM, Dickenson J, McKeith I, Ballard C. Association among visual hallucinations, visual acuity, and specific eye pathologies in Alzheimer's disease: Treatment implications. Am J Psychiatry 1999;156:1983-5.

95. Gold K, Rabins PV. Isolated visual hallucinations and the Charles Bonnet syndrome: A review of the literature and presentation of six cases. Compr Psychiatry 1989;30:90-8.

96. Pfeiffer RF, Bodis-Wollner I. Charles Bonnet syndrome. J Am Geriatr Soc 1996;44:1128-9.

97. Berrios GE, Brook P. The Charles Bonnet syndrome and the problem of visual perceptual disorders in the elderly. Age Ageing 1982;11:17-23.

98. Teunisse RJ. Charles Bonnet syndrome, insight and cognitive impairment. J Am Geriatr Soc 1997;45:892-3.

99. Ball C. Charles Bonnet syndrome. Br J Psychiatry 1995;166:677-8.

100. Cole MG. Charles Bonnet hallucinations: A case series. Can J Psychiatry 1992;37:267-70.

101. Bourgeois V, Desbordes M, Follet M, Haouzir S, et al. Charles Bonnet syndrome and vitamin B12 deficiency: A case report. General Hospital Psychiatry 2010;32:446.e7-8.

102. Merabet LB, Kobayashi M, Barton J, Pascual-Leone A. Suppression of complex visual hallucinatory experiences by occipital transcranial magnetic stimulation: a case report. Neurocase 2003;9:436-40.

103. Hori H, Terao T, Shiraishi Y, Nakamura J. Treatment of Charles Bonnet syndrome with valproate. Int Clin Psychopharmacol 2000;15:117-9.

104. Ranen NG, Pasternak RE, Rovner BW. Cisapride in the treatment of visual hallucinations caused by vision loss: The Charles Bonnet syndrome. Am J Geriatr Psychiatry 1999;7:264-6.

105. Paulig M, Mentrup H. Charles Bonnet syndrome: complete remission of complex visual hallucinations treated by gabapentin. J Neurol Neurosurg Psychiatry 2001;70:813-4.

106. Miyaoka T, Furuya M, Kristian L, Wake R, et al. Yi-gan san for treatment of Charles Bonnet syndrome (visual hallucination due to vision loss): an open label study. Clin Neuropharm 2011;34:24-7.

107. Coletti Moja M, Milano E, Gasverde S, Gianelli M, et al. Olanzapine therapy in hallucinatory visions related to Bonnet syndrome. Neurol Sci 2005;26:168-70.

Correspondence regarding this article should be emailed to Sharon Bisighini, OD, at Sharon.Bisighini@va.gov.

Zerilli-Zavgorodni T, Bisighini S. Charles Bonnet Syndrome: comprehensive review providing an optometric approach to diagnosis and management. Optom Vis Perf 2014;2(1):26-38.

The online version of this article contains digital enhancements.
