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What Associates Charles Bonnet Syndrome with Age-Related Macular Degeneration?

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A B S T R A C T

Charles Bonnet syndrome (CBS) is a condition related to patients with visual loss due to age related macular degeneration or glaucoma that are having complex visual hallucinations. The CBS was first described by Swiss physician Charles Bonnet in 1760. Affected patients, who are otherwise mentally healthy people with significant visual loss, have vivid, complex recurrent visual hallucinations (VHs). One characteristic of these hallucinations is that they usually are »Lilliputian hallucinations« as patients experience micropsia (hallucinations in which the characters or objects are distorted and much smaller than normal). The prevalence of Charles Bonnet Syndrome has been reported to be between 10% and 40%; a recent Australian study has found the prevalence to be 17.5%. The high incidence of non-reported CBS is thought to be as a result of patient's fear to report the symptoms as they could be labeled as mentally insane since those type of visual hallucinations could be found in variety of psychiatric and neurological disorders such as drug or alcohol abuse (delirium tremens), Alice in Wonderland syndrome (AIWS), psychosis, schizophrenia, dementia, narcolepsy, epilepsy, Parkinson disease, brain tumors, migraine, as well as, in long term sleep deprivation. VHs can also be presented as the initial sign of the Epstein-Barr virus infection in infectious mononucleosis. Patients who suffer from CBS usually possess insight into the unreality of their visual experiences, which are commonly pleasant but may sometimes cause distress. The hallucinations consist of well-defined, organized, and clear images over which the subject has little control. It is believed that they represent release phenomena due to deafferentiation of the visual association areas of the cerebral cortex, leading to a form of phantom vision. Cognitive defects, social isolation, and sensory deprivation have also been implicated in the etiology of this condition. This study was conducted on 350 patients diagnosed with Age-Related Macular Degeneration (AMD) and shows incidence of CBS in 13% of patients with AMD. Furthermore, we have found higher incidence of CBS in patients with massive loss of vision in peripheral visual field which is not age related.

Key words: *Charles Bonnet syndrome, age-related macular degeneration, visual hallucinations, micropsia, release phenomenon, deafferentiation*

Introduction

Charles Bonnet Syndrome (CBS) is condition that causes patients with visual loss to have complex visual hallucinations (VHs), characterized as »Lilliputian« hallucinations or micropsia. The condition was first described by Charles Bonnet in 1760, and is most common in the elderly but frequently goes unrecognized in clinical practice, due to both lack of awareness among doctors and patients unwillingness to admit the hallucinatory experiences, mainly for reason of being labeled as mentally unstable[1]. Despite the fact that CBS is more common in elderly, usually due to the condition such as age – related macular degeneration (AMD) or glaucoma, it seems that appearance of CBS in children with visual loss remains misdiagnosed mostly because of difficulties

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in verbal expression and description of VHs which are the main diagnostic criteria for CBS[2]. Considering difficulties in establishing the diagnosis of CBS in children with visual impairment it is comprehensible why there are just four cases of CBS described in the literature so far[2–4]. However, it should be emphasized that variety of pediatric conditions could be presented with symptoms of VHs such as temporal or occipital epilepsy, migraine and variety of inflammatory, vascular and expansive processes in the brain. The term »Lilliputian hallucination« was first introduced by John Todd, an English psychiatrist (1914–1987) who also called it the Alice in Wonderland syndrome (AIWS) and is found in patients suffering from severe migraine headache[5]. Furthermore, patients with CBS who comprehend the unreality of their hallucinations may be distressed by the real fear of imminent insanity. The hallucinations tend to be brief – lasting a few seconds or minutes and re-appearing after hours, days, months or even years. The VHs experiences in CBS may be upsetting, but with time most patients recognize them as hallucinations and usually learn to ignore them[6,7]. In the recent studies on CBS patients a certain pattern in the appearance of VHs was found. Patients usually report apparitions that usually fall into a group of categories including distorted faces and costumed figures[7–11]. The mechanism and neural basis responsible for the VHs, experienced in CBS remains controversial, with many hypotheses proposed[9,12]. The most commonly accepted hypothesis is the deafferentiation theory. Deafferentiation mechanism is defined as a loss of sensory input from a portion of the body (periphery) to the brain which is usually caused by interruption of the peripheral sensory fibers[12–14]. This decreased peripheral sensory input may stimulate increased intracerebral perception which consequently triggers spontaneous neuronal discharge (manifesting in the form of hallucinations) caused by lack of visual-sensory input into the cortex. The brain activity in the absence of visual input has been compared with »phantom limb« or »phantom pain« syndromes[13–15]. Another theory is the »release phenomenon« where missing peripheral input to primary visual areas causes a disinhibition of visual association areas, contributing to a release of visual hallucinations[16]. Over the years, several neurobiological models have been proposed in order to explain VHs in CBS. The most supported theory involves deafferentiation, the phenomenon where reduced afferent input creates, or releases, waves of discharges in the visual areas of the brain. In other words, as the brain is deprived of enough information from the eyes, it compensates with abnormally increased activity and invokes hallucinations from the random firing of nerve cells, a phenomenon also seen after bilateral enucleation. Recently, a neural network model approach has been used to understand VHs formation[8,17]. The recurrent nature of the VHs has been explained by adaptive character within neural networks and loosing their sustainability over the time. Studies conducted on CBS patents using brain imaging such as functional MRI (fMRI) while they were hallucinating showed that visual hallucinations were related to increases in activity within specialized areas within visual cortex and that the location of the increases defined the type of experience reported[18]. Generally speaking, color hallucinations are accompanied by increased activity in the part of visual cortex specialized for colors; face hallucinations by increased activity in cortical parts specialized for faces; object hallucinations by increased activity in cortical areas specialized for objects, etc. The brain imaging studies such as functional magnetic resonance (fMRI) implied that each specialized visual area had its own associated hallucination and the pathophysiology of the hallucinations involved a localized increase in cerebral activity[6,16,17]. Moreover, numerous neuroscientific studies on CBS showed exact location within the brain regions which are related to the three visual psycho-syndromes; ventral occipitotemporal cortex activated by objects[19,20] and extended scenes[21], superior temporal region sensitive to eye movements and gaze in face stimuli[22,23] and intra-parietal region containing eye-centered reference frames.

Material and Methods

We have tested 350 patients previously diagnosed with macular degeneration. The patients were divided into the groups according to age and the percentage of central and peripheral vision loss (macular area, peripheral visual field). In order to make a diagnosis of Charles Bonnet syndrome and presence of VHs, patients were discretely questioned about images they may experience, quality of the images (shape, color), and detailed description (if possible) of persons or objects that are seen in VHs (after CBS condition was carefully explained to them). Although an insight into the unreal nature of the images and exclusion of other mental disorders is required to make a diagnosis of CBS, patients may not have full insight at the onset of the symptoms. Patients may initially be confused about what they are experiencing and may act on their hallucinations. They may have to regularly reassure themselves that what they are seeing is not real, particularly if the image fits into the real setting as lack of insight should lead to consideration of other diagnoses.

Results

We have found positive symptoms of CBS with VHs presented in 13% of patients with AMD. In the age group of 40–55 years CBS was present in 5% of the cases while in the elderly age group (56–80 years) CBS was present in 17% of AMD cases. The difference in percentage of CBS was specifically related to the stage of visual loss in the central field (macular vision) and particularly to the extent of damage within the peripheral visual field[24–26]. The incidence of CBS was correlated with percentage of visual loss in the central field and it was more common in the group of patients with visual loss below 0.1. By detailed examination and specific analysis of the visual field defects we have found that incidence of CBS is strongly correlated with percentage of visual loss and increased deficits within peripheral visual field regardless of the age group.

Discussion

Charles Bonnet syndrome remains an under-recognized and common disorder in persons with serious visual impairment. Speculation still exists concerning the true pathophysiology of visual hallucinations in CBS, and medical treatments are not well established[6,10,12,17]. Other more serious etiologies of VHs must be ruled out before arriving at a diagnosis of CBS, including metabolic, toxic, neurological, and psychiatric disorders. Generally speaking, if the retina is damaged, the stream of impulses to the brain is reduced but at the same time other parts of the brain become hyperactive in order to compensate visual loss at the periphery. When brain do not receive as many pictures as it is used to, due to visual loss in AMD or glaucoma, it builds its own artificial images within the areas that are normally responsible for visual processing of faces, objects, landscapes and colors. The type of visual hallucinations depends on which part of the brain these increased impulses are located, but why only proportion of patients with macular degeneration experience visual hallucinations remains unknown, as well as, why younger patients with macular degeneration are less likely to have CBS than older ones. The most acceptable hypothesis is that neurons within the visual pathway from the retina to cortex become hyper-excitable, due to the loss of light receptors[6,17,18]. This phenomenon has been observed directly in the brain. Recently, neuroimaging technology has been used quite extensively in an attempt to understand the brain regions and circuitry involved in the generation of hallucinations[12,16]. Numerous structural and functional neuroimaging studies of patients with auditory and visual hallucinations as well as a small number of studies that have assessed cognitive processes associated with hallucinations in healthy volunteers suggests that in addition to secondary (and occasionally primary) sensory cortices, dysfunction in prefrontal premotor, cingulate, subcortical and cerebellar regions also contribute to hallucinatory experiences[12,16–18]. External visual stimuli are perceived in the retina and are transmitted to the primary visual cortex then to the secondary visual cortex and finally to the visual association cortical area. In general, our perception of external visual stimuli normally has an inhibitory effect on the endogenous activation of the visual cortex. Visual loss due to certain conditions, of which eye pathology (AMD, glaucoma, blindness) is the most commonly postulated in CBS patients, produces a state of sensory deprivation that releases the visual cortex from regulation by external stimuli, resulting in visual hallucinations (cortical release phenomenon). The results of previous neuroimaging studies suggest that the cortical release phenomenon hypothesis for the occurrence of visual hallucinations in patients with CBS is highly probable[12,17,18]. In addition, the results indicate that not only eye pathology, but also dysfunction in the primary and secondary visual cortex could result in deprivation of external visual stimuli thereby producing random images.

Conclusion

Popular neuroscientific theory suggests that the brain is attempting to compensate for a shortage of visual stimuli, especially when considering the fact that each human eye normally receives data at a rate of about 8.75 megabits per second, a bandwidth which is significantly greater than most high-speed Internet connections. The visual associative cortex is the most complex system in the human brain, filled with neuronal pathways which control processing of visual data before transferring it to the conscious part of the brain[12]. When disease such as AMD begins to twist that information, large network of neurons are left standing »idle« (at rest) and then starting to compensate the lack of visual information from the periphery by random discharging and creating non-existent images[10]. In gradual-onset blindness such as in the cases of AMD or glaucoma, it is possible that these complex brain pathways attempt to fill in the new obscured areas within the visual field. Since the damaged eyes are sending reduced amounts of data from the periphery with a greater frequency of errors, the visual cortex may produce more and more bizarre guesses[17]. Our clinical results are clearly showing that CBS appears in close relation with degree of visual defects, particularly with damage to the peripheral visual field frequently accompanied with optic nerve atrophy. We should also emphasize that CBS is less correlated with loss in central vision. Finally, we have concluded that CBS appears to be more associated to the degree of deficit in peripheral vision then to the patient's age. The apparent neurobiologically based clustering of VHs in CBS has implications which extend beyond visual science. It suggests that syndrome's links between specific pathological mental experiences are not accidental or subjective details, but rather a clue to the complex brain process and functional pathology. Visual hallucinations in CBS provide a model for generating and testing different neuroscientific hypotheses of hallucinations in general[12,17,18]. Given the recent prosperity in modern, neurobiologically based research into the visual system over the last two decades, CBS provides opportunity to study the detailed relationship between psychopathology and the brain using modern technology such as neuroimaging[16]. The challenge within the field of modern psychiatry is to understand the complex neurobiology of the visual system and thereby formation of bizarre visual hallucinations in order to properly explain the associations between psychiatric symptoms and visual pathology in CBS.

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ŠTO POVEZUJE SINDROM »CHARLES BONNET« I MAKULARNU DEGENERACIJU?

S A Ž E T A K

Sindrom »Charles Bonnet« (CBS) se nalazi kod pacijenata s oštećenjem vida nastalim zbog makularne degeneracije ili glaukoma, a karakterizira ga pojava kompleksnih vidnih halucinacija. Sindrom »Charles Bonnet« je prvi puta opisan u literaturi 1760. godine od strane švicarskog liječnika Charles Bonnet-a. Pacijenti s CBS-om su mentalno zdrave osobe sa značajnim gubitkom vida i živopisnim vidnim halucinacijama (VHs) koje se stalno ponavljaju. Jedna od karakteristika ovog tipa halucinacija su tzv. »Liliputanske halucinacije« tj. pojava mikropsije (vidne halucinacije u kojima su slike likova i objekata iskrivljene i puno manjih dimenzija). Prevalencija sindroma »Charles Bonnet« u populaciji se kreće između 10% i 40%, a nedavna australska studija je pokazala da je uobičajena prevalencija CBS-a oko 17,5%. Smatra se da postoji visoka incidencija nedijagnosticiranog CBS-a zbog straha pacijenata od stigme mentalnih bolesnika s obzirom na činjenicu da se vidne halucinacije mogu naći u nizu psihijatrijskih, ali i neuroloških poremećaja kao što su zloporaba droga i alkohola (delirium tremens), sindroma »Alice iz zemlje čudesa« (AIWS), psihoza, shizofrenije, demencije, narkolepsije, epilepsije, Parkinsonove bolesti, moždanih tumora, migrenske glavobolje te kod dugotrajnog poremećaja spavanja. Vidne halucinacije se mogu pojaviti i kao jedan od početnih simptoma kod infekcija kao što je infekcija virusom Epstein Barr (infekcijska mononukleoza). Pacijenti s CBS-om imaju uvid u svoje stanje tj. svjesni su iskrivljenog realiteta tijekom doživljavanja vidnih halucinacija koje mogu biti sadržajno ugodna iskustva, ali i neugodna što kod pacijenata uzrokuje stanja jakog stresa. Smatra se da vidne halucinacije nastaju kao posljedica tzv. fenomena otpuštanja zbog deaferencijacije u vidnom asocijativnom korteksu velikog mozga, što sve dovodi do tzv. fantomskog vida. U etiologiji CBS-a inlau ulogu razni čimbenici kao što su kognitivni deficiti, socijalna izolacija i osjetilna deprivacija. Naše istraživanje, koje je provedeno na 350 pacijenata s dijagnozom makularne degeneracije, pokazuje da je incidencija CBS-a kod ove populacije 13%. Također smo pronašli veću učestalost pojave CBS-a kod pacijenata koji imaju znatnija oštećenja perifernog vida koje nije povezano s dobnom skupinom.