The Elephant in the Room: Understanding the Pathogenesis of Charles Bonnet Syndrome

Running head: The Pathogenesis of Charles Bonnet Syndrome

Kilda Carpenter[1], Jasleen K. Jolly MSc[1-3], Holly Bridge DPhil[1*]

[1]Wellcome Centre for Integrative Neuroimaging, FMRIB Building, Nuffield Department of Clinical Neurosciences, University of Oxford, Oxford, UK

[2]Nuffield Laboratory of Ophthalmology, Nuffield Department of Clinical Neurosciences, University of Oxford, Oxford, United Kingdom; Oxford Biomedical Research Centre

[3]Oxford Eye Hospital, Oxford University Hospitals Foundation Trust, Oxford, United Kingdom

* Corresponding author. Centre for Functional Magnetic Resonance Imaging of the Brain, John Radcliffe Hospital, Headley Way, Headington, Oxford OX3 9DU. Phone: 01865 610482. Email address: holly.bridge@ndcn.ox.ac.uk

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Abstract

Purpose: Charles Bonnet syndrome (CBS) is a syndrome characterised by complex visual hallucinations in individuals who are cognitively normal, though often elderly and visually impaired. Although first described over 250 years ago, the condition remains poorly understood and difficult to treat.

Recent findings: Our understanding of CBS pathogenesis has advanced little since it was first described, and much of the recent literature consists of case studies strikingly similar to the first published account of CBS. However, imaging studies have provided some indication as to the cortical areas implicated in the genesis of complex visual hallucinations, and the existence of similar hallucinatory syndromes in other sensory modalities suggests a common underlying mechanism.

Summary: This review begins by describing what is currently known about CBS, focusing on epidemiology, clinical presentation and diagnosis. It then explores potential starting points for better understanding the pathogenesis of CBS, namely the existence of similar conditions in other sensory modalities and the reproduction of complex visual hallucinations in sensory deprivation scenarios. Finally, it discusses how CBS should be approached in clinical practice.

Introduction

The Swiss magistrate Charles Lullin was popular and well-respected in the 18th century. He was plagued by mysterious silent visions of birds, people and buildings, which began after he developed cataracts and lost his eyesight. In 1760, his polymath grandson Charles Bonnet wrote an account of Lullin's experiences, the first case report of 'Charles Bonnet syndrome' (CBS).(1) Bonnet himself suffered progressive visual loss beginning in his early twenties, and in old age he too began to experience hallucinations similar to those described by his grandfather.(2) The term Charles Bonnet syndrome was coined by neurologist Georges de Morsier, a fellow Swiss who later noted similar hallucinatory experiences in other elderly, visually impaired people.(3)**Error! Bookmark not defined.**

The visual hallucinations which characterise CBS are complex, consisting of formed images and/or abstract patterns which appear in focus and often move.(6) Patients commonly report seeing human figures, including those of 'acrobats balancing on bicycles',(7) 'Santa',(8) 'people who would pack their belongings and leave',(9), 'a girl, who would… enter through closed doors'(10) and 'naked men… they were accompanied by women and often indulged in sexual acts'(9). Animals also feature, from sheep (11) and birds (1) to 'snakes crawling out of people's heads',(12) 'spiders crossing [the patient's] meals'(13) and 'an elephant walking down the street with a child on its back'.(14) Despite the often bizarre nature of the hallucinations, patients retain insight that they are not really there (for this reason some authors prefer the term 'pseudohallucinations'), although insight may be delayed when the hallucination is context-appropriate.

The images are not usually frightening in themselves, but can produce fear when they first occur.(15) More often, patients report feeling positive or neutral emotions in response to their hallucinations, although they may become irritated when hallucinations are long-lasting.(2) Vukevic et al. provide an interesting rare example in which the nature of a patient's hallucinations changed to reflect a change in mental state. They describe an Australian CBS patient who was deeply traumatised by the Black Saturday bushfires of 2009, and reported that her low mood was accompanied by upsetting changes in her hallucinations. These had previously been short-lasting and pleasant, but now lasted many hours and involved the skin of her family members prickling and melting.(14)

The majority of case series and reviews describe CBS hallucinations as silent.(2) (16) (17) (18) Indeed, Gold and Rabins suggest that hallucinations in other modalities preclude a diagnosis of CBS.(4) However, other diagnostic criteria make no such stipulation (Table 1). Hori et al. reported on two patients in which CBS-like visual experiences were accompanied by auditory hallucinations. They argue that a CBS diagnosis would be appropriate in such patients, as they retained insight that their hallucinations were not real.(19)

CBS hallucinations typically develop soon after the onset of visual impairment.(20) (21) A large survey-based study by Cox et al. suggests that hallucinatory episodes most often occur on a weekly basis, and are short-lasting, typically disappearing within seconds or minutes.(15)

Hallucinations commonly occur in times of stress and drowsiness(16) (22); many patients, including Lullin himself, reported worsening symptoms at the end of the day.

In terms of prognosis, Gold and Rabins suggest that CBS tends to resolve spontaneously within a year, as was the case for Lullin.(4) However, more recent studies indicate that Charles Bonnet syndrome may take years to subside. Santhouse et al. found that hallucinations were still present in 45% of a CBS cohort four years after diagnosis,(6) while Khan et al. report ongoing symptoms in 41% after eight years.(23) Results from the survey conducted by Cox et al. suggest an even longer course(15); CBS symptoms had only resolved in 25% of the patients included in their survey after nine years (symptom resolution was defined as having had no hallucinations in the preceding three month period). Over time, hallucinations tend to become less frequent until they cease altogether.(24) (25)

CBS patients are a homogeneous group in two respects. Firstly, they are invariably visually impaired(26); CBS has been reported in association with a huge variety of conditions causing visual loss.(27) (16) (28) Studies of patients referred to low vision units and ophthalmology clinics estimate a prevalence in the range of 10-15% of visually impaired older adults. (22) (29) (17) Surveys of groups of patients with specific ocular pathologies, notably age-related macular degeneration, (30) choroidal neovascularisation (31) and homonymous hemianopia, (20) have produced similar results, with some exceptions. Of note, Khan et al. report that CBS was present in 27% of 360 patients with age-related macular degeneration (AMD). (23) Similarly, Gilmour et al. report a prevalence of 34% in patients attending a low vision clinic, most of whom had a diagnosis of AMD. (32)

Table 1: proposed diagnostic criteria for CBS; descriptions are reproduced from the papers cited
'†': factor recognised as common, but not necessary for diagnosis

Author(s)	Description	Advanced Age	Visual Impairment	Insight	Lack of cognitive impairment
Damas-Mora *et al.* (1982)(2)	Persistent or recurrent visual pseudohallucinatory phenomena of a pleasant or neutral nature occur in a clear state of consciousness. Despite its vividness, clarity and impelling character, it is recognised as unreal. The condition tends to occur in the elderly with clinically preserved intellectual functions and is often associated with ocular pathology	Yes†	Yes†	Yes	Yes†

Gold & Rabins (1989)(4)	Visual hallucinations which are a. formed b. complex c. persistent or repetitive d. stereotyped Insight is fully or partially retained Absence of primary or secondary delusions Absence of hallucinations in other modalities	No	No	Yes	No
Podoll *et al.* (1989)(5)	1. The predominant symptom is the occurrence of visual hallucinations in elderly individuals in normal mental health. 2. There is no evidence of delirium, dementia, negative impact on intellectual capacity, deterioration as in the affective syndromes, paranoid developments, psychosis, intoxication, or neurological disease. 3. Loss of vision as a consequence of ocular disease is found in most cases as a specifying factor but is not obligatory for diagnosis.	Yes	Yes†	No	Yes

Secondly, the vast majority of patients are also advanced in age, although cases have been reported in children.(8) It remains unclear whether old age is an independent risk factor for CBS given the prevalence of visual impairment in the elderly.(33) There is also disagreement about whether old age is a necessary condition for a diagnosis of CBS. Several sets of diagnostic criteria are in use, whose similarities and differences are outlined in Table 1 (more historical criteria are excluded as they offer insufficiently detailed descriptions). The majority of authors do not apply a specific set of diagnostic criteria, but rather work under the assumption that CBS refers to complex visual hallucinations in individuals who are visually impaired, and commonly elderly. It is this definition which will be used in this article.

Aside from visual impairment and old age, other risk factors have been reported to be associated with CBS. Social isolation, which like visual impairment is more common in elderly individuals,(34) has been linked with CBS,(21) and patients report higher levels of loneliness and lower extraversion than individuals without CBS.(35) Other personality-related factors have also been implicated; one case series suggests that the highly educated are more likely to develop CBS.(36) In Parkinson's disease, visual hallucinations have been linked to a high capacity to form mental images,(37) though it is not known if a similar association exists

in CBS patients, or whether the incidence of visual hallucinations is lower among 'aphantasiacs', who cannot generate mental images.(38)

Double-Blind Leading the Blind: Published Accounts of CBS

In the centuries following Bonnet's original work, relatively little has been published on the subject of CBS, and the literature has remained dominated by case studies and small-scale case series. The lack of literature on CBS can be largely explained by under-reporting: public awareness of Charles Bonnet syndrome is low, even among the visually impaired.(36) Unaware that visual hallucinations can occur in those with normal cognition, a fear of being labelled insane prevents many patients from reporting their symptoms at first onset. A study of two Indian patients by Nair *et al.* found that one sought treatment seven months after the onset of hallucinations; another waited over a year.(9) Amongst their visions were religious figures and people performing sexual acts; Nair posits that the taboo surrounding sex in India, particularly among older generations, could have contributed to the reluctance of these patients to report their symptoms. He further states that religious visions may not be considered hallucinations by some believers; cultural beliefs relating to the content of hallucinations can also play a role in under-reporting.

Although findings from case studies are clearly valid when they can be shown to apply to most patients, excessive reliance on case studies has led to some over-generalisation in the CBS literature. The fact that hallucinations remit on progression to total blindness is repeated in several reviews, but seems to be based on a description of a single patient in a case series by Olbrich and colleagues(17); others describe hallucinations continuing in blind patients.(39) The role of co-morbidities in hallucinosis is often overlooked; many authors suggest a potential role for nocturnal oxygen therapy in reducing CBS hallucinations based on findings from Frohnhofen and colleagues.(13) However, the single patient in whom oxygen therapy proved successful also suffered from obstructive sleep apnoea and fractured sleep. There is a possibility that the success of oxygen therapy in this woman was due to a reduction in apnoea and subsequent improvement in sleep quality and reduction in fatigue, rather than a direct effect of increased oxygen saturation on hallucinosis.

The use of excessively restrictive diagnostic criteria also poses a problem in the field as it exacerbates the problem of underdiagnosis, and means that links between CBS and other

neurological disorders are potentially being missed. Whether CBS can exist in patients with cognitive impairment is a particular point of contention. While the criteria of Podoll and de Morsier preclude a diagnosis of CBS in patients with cognitive impairment, Menon et al. suggest that there may in fact be an association between the two, arguing that the prevalence of CBS has been shown to be higher in those with lower cognitive scores.(16) In 1996 Pliskin published a promising link between CBS and early signs of dementia, having found mild cognitive impairment at a higher frequency in CBS patients than in age-matched controls.(40) Similarly, a 2013 retrospective study of CBS patients by Lapid *et al.* found an increased prevalence of dementia, most often with Lewy bodies.(41) Clinicians should be aware that CBS and cognitive impairment may co-exist in some individuals, and that in such patients diminished insight may make the diagnosis difficult; Menon et al. suggest using the term 'CBS plus' in such cases.(16) It may also be of use to screen for cognitive decline in patients presenting with CBS-like symptoms.

Clearly, in identifying patients with CBS, a balance must be struck between inclusion and exclusion. On the one hand, diagnostic criteria must be applied with sufficient rigour to exclude patients whose hallucinations can be explained by another disorder. On the other hand, such criteria must not be so prescriptive as to exclude any patient not mirroring exactly the archetypal presentation of Lullin, recognising that CBS and other disorders may co-exist.

Theories of CBS Pathogenesis: A Shot in the Dark?

In the absence of large-scale studies in the field of CBS, theories about how it may arise must be developed from other sources. For instance, it may be of great benefit to consider the existence of similar syndromes in other sensory modalities. Phantom limb syndrome, in which amputees attribute painful sensations to the missing limb, was first observed in 1551 and has since been extensively described, particularly in military veterans.(42) (43) A 'phantom eye syndrome' has also been described in individuals who have lost an eye.(44) Musical hallucinations are particularly evocative of Charles Bonnet hallucinations. They consist of complex, 'formed' sounds and have been linked to activity in auditory association areas rather than primary auditory cortex. Furthermore, when not associated with primary neurological disease or psychiatric illness, they occur most commonly in the hearing impaired and elderly.(45) (46) The hallucinations of Charles Bonnet syndrome could similarly represent 'phantom vision' in those with visual loss. How a reduction in sensory input to the relevant parts of the cortex results in hallucinatory experiences is unclear. One option is that some

individuals are prone to cortical hyperexcitability,(47) leading to visual perceptions. Alternatively, it has been proposed that abnormal neuronal activity in the visual brain is usually suppressed by sensory input, but brought to the fore when this input is reduced in the visually impaired, resulting in complex hallucinations.(27) The brain contains both feedforward and feedback connections which allow the higher brain areas to modify signal processing earlier in the pathway.(48) With sensory input reduction in the feedforward direction, CBS may represent the prominence in the feedback signals from other areas of the brain.

If Charles Bonnet hallucinations are caused by the 'release' of abnormal neuronal activity usually suppressed by visual input, one would also expect hallucinations to occur when visual input was reduced not through pathology, but through some external action. Indeed, work with healthy volunteers has shown that the onset of hallucinations can be rapid when visual input is reduced. Heron and colleagues spent six days with limited auditory, tactile and visual stimulation. Within a day, all experienced visual hallucinations.(49) More recently, a group of healthy individuals reported visual hallucinations, including complex images, within the first two days of five consecutive days spent wearing a blindfold.(50) One group of individuals who also experience sensory deprivation scenarios which may be analogous to visual impairment are hostages, thus far overlooked in CBS review articles. Indeed, individuals kept blindfolded or in darkness as hostages have reported complex visual hallucinations, including seeing family members, 'devils… cops and monsters', 'scenes of [a] recent vacation in the mountains', 'Christmas tree lights', and 'tall modern skyscrapers'.(51)

The exact site at which the functional changes described above may occur is unclear, but several areas in the visual brain have been implicated in the production of CBS-like phenomena. Complex hallucinations have been observed in patients with abnormalities of the basilar and posterior cerebral arteries, the latter of which form the main supply to the visual cortex.(52) The visual association areas in particular have been linked to the genesis of complex visual hallucinations by stimulation(53) and lesion cases,(54) as well as imaging; Parkinson's patients with visual hallucinations have more active visual association areas than those without.(55) The ventral 'object recognition' stream appears to be key. Allen *et al.* reviewed imaging trials in patients experiencing visual hallucinations,(56) both with schizophrenia and without, and reported a temporal correlation between visual hallucinatory episodes and activity in the visual brain, particularly in the ventral 'object recognition' stream. Imaging in CBS patients specifically found similar ventral hyperactivity both during

and between hallucinatory episodes, with a link between the perceptual function of the overactive area and the content of hallucinations.(57) Adachi and colleagues also studied changes in cortical blood flow during hallucinations, reporting that a group of CBS patients all exhibited hyperperfusion of the thalamus, striatum, and lateral temporal cortex, the latter of which is a target of the ventral visual stream.(58) The neurotransmitters in the brain play a role in modulating vision. It is possible acetylecholine may also have a role in the presence of hallucinations when sensory input is reduced.(59)(60)

The existing evidence paints a picture of a complex interplay of risk factors in the pathogenesis of CBS. Perhaps age-related structural or vascular changes in the areas described above render them more vulnerable to produce abnormal activity when deprived of input, either by visual impairment or sensory deprivation. Social isolation may too increase the brain's vulnerability, or indeed represent a form of deprivation in itself. Figure 1 illustrates a possible mechanism by which these factors interact to produce 'phantom vision' in CBS.

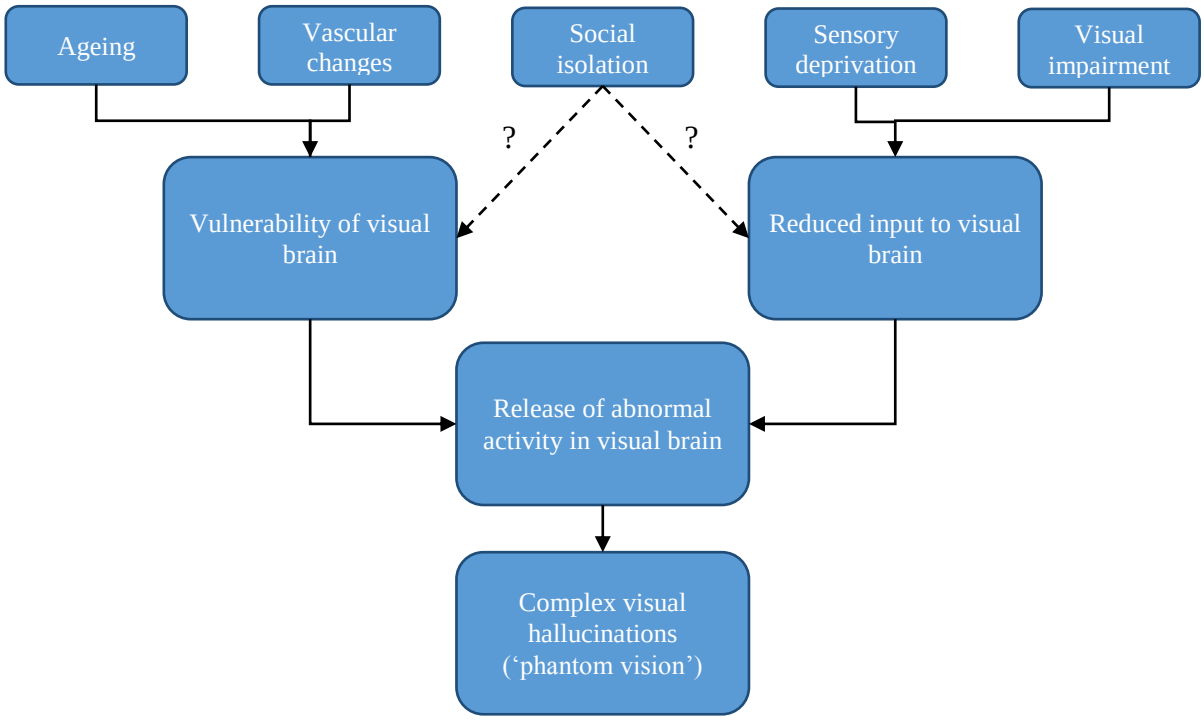

Figure 1: Interplay of factors contributing to Charles Bonnet syndrome pathogenesis

CBS in Clinical Practice

In clinical practice, identifying patients with CBS may be difficult. Even among patients with visual impairment, awareness about CBS is low, and many patients experiencing

hallucinations may worry that they are developing dementia or 'going crazy'.(10) Cox et al. report that in a group of 492 CBS patients, 67% had not heard of the syndrome at symptom onset, and less than half had discussed their symptoms with a healthcare professional. (15) Sensitive questioning by those in contact with visually impaired patients may be of value in encouraging patients to disclose their symptoms. Practitioners may wish to highlight that visual hallucinations are common in those with visual impairment, emphasise that they are benign and not psychiatric in origin, offer some examples of typical hallucinations, and then enquire whether the patient has ever had a similar experience. The survey by Cox et al. confirms the importance of patient education and reassurance in improving the quality of life of those with CBS; patients who were not aware of CBS at symptom onset, or who received an unclear explanation from a medical professional, were more likely to state that CBS had a negative effect on their life. In those who received clear information about CBS, 63% felt 'relieved or reassured'.(15) After an explanation has been given, the clinician may wish to offer a leaflet, or direct the patient and their family to appropriate websites where further information is available, such as www.charlesbonnetsyndrome.org and www.charlesbonnetsyndrome.uk.

Regarding the treatment of CBS, several authors are in agreement that improving vision where possible can be an effective way to reduce the frequency of hallucinations in CBS patients.(16) (28) (61) Eperjesi and Akbarali report that hallucinations became less frequent in patients in whom visual acuity was improved by interventions such as cataract removal and laser treatments, and also by simpler measures including provision of better optical devices and home lighting. When these interventions were halted, hallucinations became frequent again.(62) They, among other authors, also highlight the role of social isolation as a possible contributory factor in CBS, hypothesising that increased social interaction could attenuate hallucinations, perhaps in the form of local support groups for patients.(16) (62) (63) As well as treating ocular pathology and adapting the patient's home environment, clinicians and eye care practitioners may wish to suggest strategies which some CBS patients have found effective in ceasing a hallucinatory episode. These include blinking or closing the eyes, moving to a different room, looking in another direction, or even attempting to interact with the hallucination.(61) (62)

At a national level, clinicians may soon have access to new guidelines to aid them in their management of patients with CBS. The SHAPED trial (Study of HAllucinations in Parkinson's disease, Eye disease and Dementia) is a multi-centre UK-based trial which began

in August 2014. The large group of participants comprises controls and patients with Parkinson's disease (PD), dementia, eye disease, and comorbid dementia and eye disease. These individuals are monitored over 91 weeks via semi-structured interviews and questionnaires, with an aim to provide the NHS with an evidence base to create guidelines for practitioners, patients and their families, as well as model the economic impact of visual hallucinations on the NHS. Preliminary results characterising patients with visual hallucinations versus those without from the SHAPED trial were published in 2017.(64) They noted that the prevalence of complex hallucinations was similar in patients with PD, dementia and eye disease, but that the prevalence of other types of visual hallucinations varied greatly between these groups. For instance, 75% of patients with eye disease experienced simple hallucinations, while this figure was only 25% and 30% for dementia and PD respectively. Among PD patients, 50% experienced presence hallucinations ('feeling someone nearby'), while only 19% of dementia patients and 7% of eye disease patients did so. The similarities in the rates of complex hallucinations between these patient groups suggest that treatment strategies which work for CBS patients may also be effective in those with dementia or PD, and vice versa, and could inform future studies. However the significant differences in terms of other types of visual hallucinations could indicate that the pathophysiological mechanism underlying the hallucinations differs between the groups.

A better understanding of the functional changes underlying CBS may pave the way for the development of effective pharmacological treatment. Thus far, there has been no large-scale clinical trial for CBS medication, but a number of drugs have shown promise in reducing hallucinations in individual patients, and are good candidates for further investigation. These include several antipsychotics,(65) (66) the 5-HT3 antagonist cisapride,(67) and anti-epileptics,(68) (69) including in combination.(70) The traditional Japanese herbal preparation yi-gan san also proved effective in an open-label trial of 20 patients.(71) The mechanism by which these medications may improve hallucinations in CBS remains unclear. Improving vision where possible reduces symptoms in some patients,(72) and remains the first port of call in the treatment of CBS, along with reassurance and education.(10)

Two major reviews in the CBS literature (16) (28) have made brief mention of the similarities between CBS and other 'phantom' sensations, as detailed above. However, the treatment implications of these similarities merit further discussion. Given the possible mechanistic link between CBS and other conditions involving 'phantom' sensations, strategies shown to be effective at reducing symptoms in these conditions may also attenuate CBS hallucinations. In

phantom limb pain, psychological treatments have proven most effective thus far, including relaxation,(73) cognitive behavioural therapy and hypnotherapy.(74) These are therefore promising candidates for further investigation in CBS.

Increasing awareness among clinicians, at-risk groups and the general public about CBS will likely have a positive impact at several levels. Increased self-reporting of symptoms will increase the size of the CBS cohort, facilitating large-scale trials to better understand the syndrome.

Concluding Remarks

In 1967, de Morsier wrote 'after two centuries we do not know much more' than Bonnet himself did when first describing his eponymous syndrome. Fifty years later, under-reporting, inconsistent diagnostic criteria and a lack of systematic large-scale investigations mean that this remains true for Charles Bonnet syndrome. As the population of developed countries continues to age, increasing numbers of elderly, visually impaired and isolated people will be vulnerable to Charles Bonnet syndrome. The priority now must be to integrate education and counselling on visual hallucinations into elderly care, while working to reduce isolation and vision loss wherever possible.

To advance our understanding of the syndrome, we must first acknowledge that there may be no 'true CBS' resembling exactly the experience of Lullin. Rather, complex visual hallucinations are a common result when visual cortical areas are deprived of input; and low vision, advancing age, structural changes and social isolation may interact to produce a unique subjective experience in each individual. As we learn more about Charles Bonnet syndrome and similar conditions, we may also gain a better understanding of the behaviour of the input-deprived cortex, and a better ability to treat sensory hallucinations of different modalities.

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