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LETTER TO THE EDITORS

Charles Bonnet syndrome in Leber's hereditary optic neuropathy

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Dear Sirs,

Charles Bonnet Syndrome (CBS) is a condition characterized by visual hallucinations in patients with visual loss and normal neuropsychiatric status. Although there is no consensus on diagnostic criteria for CBS, most experts describe stereotyped hallucinations, complex or simple, static or moving, with better clarity than expected given the residual vision [1]. The condition was first described by Swiss naturalist Charles Bonnet in his 87-year-old grandfather who had severe visual loss due to bilateral cataracts [2]. So far, only one patient with Leber's Hereditary Optic Neuropathy (LHON) has been reported with CBS [3].

Here, we present ten patients (6 male, 4 female; age range 22–67 years) with genetically confirmed LHON who experienced CBS during the course of their disease. All patients suffered from acute-subacute onset of bilateral visual loss at age 15–65 years. The Table 1 summarizes their clinical characteristics, genotype and phenomenology of the hallucinations. Symptoms of CBS developed in a variable time after LHON onset, ranging from a few weeks to 10 years. In most of our cases, hallucinations occurred on a daily basis and lasted between few seconds to 1 h. Five of the patients had persistent hallucinations in the central visual field that only disappeared when falling asleep. While three patients developed complex hallucinations with vivid images of figures and animals, the others reported to perceive photopsias, various shapes or grid-like patterns. Hallucinations in Patient 4, 6 and 7 represented well-defined colourful geometric forms as is documented by one of the patient's drawing (Fig. 1). None of the patients was aware of any triggering factor. Patient 1 presented at age 64 years with subacute bilateral visual loss. After genetic confirmation, treatment with idebenone 900 mg/day was started from 7 months after onset. 15 months after onset, she noticed simple visual hallucinations in the form of intermittent rosa-lila strips and some months afterwards, complex visual hallucinations, especially images of animals. The patient sometimes beats at the hallucinations, to get rid of the unpleasant perception, but she confirmed that she is always aware of their illusional nature. She had been reluctant to report her visual hallucinations, but showed significant relief when informed of their nature and how to deal with them. Patient 3 perceived images of monsters and stuffed toys as frightening and reported an improvement after receiving the correct diagnosis and an explanation of its benign nature. Hence, especially for patients suffering from complex visual hallucinations, a correct diagnosis of CBS and reassurance of the patient may lead to better outcomes.

The visual hallucinations in CBS are thought to be caused by spontaneous discharges of the visual association cortex, occurring after deafferentation of visual inputs or damage to the visual pathway [1]. This may result in visual perceptions replacing the deprived stimuli, similar to auditory hallucinations in deafness or phantom pain syndrome. CBS with colour hallucinations has been primarily described in patients with age-related macular degeneration [4]. Functional MRI studies showed a hyperactive colour area of the visual association cortex resulting from damage to parvocellular pathways [4]. Selective involvement of papillomacular fibres belonging to the parvocellular pathway has also been observed in LHON, and is responsible for decreased contrast

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Table 1 Characterization of ten patients with Leber's hereditary optic neuropathy and Charles Bonnet syndrome

Patient ID	Gender (M/F)	Current age (years)	Primary LHON Mutation	Visual acuity OD/OS (logMAR) at nadir; and at last follow-up	Age at onset of visual loss OD/OE (years)	Time between visual loss of 2nd eye and CBS (months)	Type of visual hallucination	Visual hallucination static/moving; intermittent (duration)/permanent	Description of hallucination
1	F	67	m.3460G>A	1.68/HM; HM/HM	65.5/65.5	Simple: 16; complex: 20	Both simple and complex	Intermittent (5–10 min once weekly)	Rose or violet strips, mosaic-like black and white grids; and vivid images of animals (e.g. cats)
2	M	30	m.11778G>A	1.40/CF; 0.13/1.30	20.4/20.3	N/A	Both simple and complex	Moving; Intermittent (once daily)	Black and white spots, red and yellow flashes; and people, teddy bears
3[a]	F	56	m.11778G>A	0.70/0.60; N/A	40.6/40.3	Simple: < 1; complex: 129	Both simple and complex	Simple: permanent; complex: intermittent	Red, green and yellow dots, black dots; and stuffed toys, monsters
4[b]	F	23	m.11778G>A	LP/HM; LP/HM	16.8/16.6	< 1	Simple	Moving; permanent	Yellow stains, red ellipses
5	M	32	m.11778G>A	CF/CF	15/15	N/A	Simple	Moving; permanent	Golden, red and greyish dots
6	M	22	m.3733G>C[c]	N/A; 1.20/1.20	21.5/21.7	< 1	Simple	Permanent	Neon green dots surrounded by light red in the centre of the visual field
7	M	25	m.11778G>A	1.40/1.30; 1.30/1.20	24.5/24.7	N/A	Simple	Intermittent (seconds' duration), later permanent	Blue and green dots; and colourful strip like a rainbow
8	M	24	m.11778G>A	CF/0.20	24.5/24.5	< 1	Simple	Intermittent	Luminescent dots in the centre of vision
9	M	23	m.11778G>A	1.30/1.30; 1.20/1.10	20.6/20.9	N/A	Simple	Intermittent	Neon-like strips
10	F	58	m.11778G>A	1.68/CF; 1.62/1.62	55.5/55.5	4	Simple	Intermittent (1 h/day)	Blue and yellow dots in the central visual field

CF counting fingers, *CBS* Charles Bonnet syndrome, *F* female, *HM* hand motion, *logMAR* log of the minimum angle of resolution, *LP* light perception, *M* male, *min* minutes, *N/A* not available, *OD* right eye, *OS* left eye

[a]Patient has the diagnosis of Harding's disease, rare association of LHON and multiple sclerosis

[b]Graphical representation of the visual hallucination as depicted by Patient 4, reproduced in Fig. 1

[c]Rare mtDNA mutation, causal for LHON

Fig. 1 Drawing by Patient 4 of her visual hallucinations in the central visual field bilaterally. The patient describes a dynamic character of the hallucinations, which are permanent but moving, with the red circles constantly rotating in different directions

sensitivity [5] and likely also for the coloured hallucinations described by our patients.

In our cohort of 190 symptomatic LHON patients, ten (5.3%) reported visual hallucinations compatible with CBS. Three patients (1.6%) reported complex in addition to simple visual hallucinations. Still, CBS may be markedly underestimated, given inadequate awareness among physicians and low disclosure by patients for fear of being labelled as mentally ill. The prevalence of visual hallucinations has been estimated between 11 and 15% for complex, and between 41 and 59% for simple hallucinations, in patients with visual loss due to diverse etiologies [6]. Since LHON is one of the most common causes of hereditary blindness, physicians should be aware of CBS as a possible complication of this challenging mitochondrial disorder. Anecdotal reports on treatment of CBS with antiepileptic drugs or antipsychotics showed varied efficacy. Most patients are bewildered by the visual hallucinations but daily activities are only rarely disturbed in a significant manner. Establishing the diagnosis and discussing with the patient the benign character of the hallucinations and strategies of dealing with complex hallucinations may significantly alleviate stress and anxiety in these patients, improve quality of life and avoid risks of inappropriate therapy.

Compliance with ethical standards

Conflicts of interest Drs. Priglinger and Klopstock have received research grants from Santhera Pharmaceuticals and from GenSight Biologics. Drs. Catarino and Klopstock received travel costs from Santhera Pharmaceuticals and from GenSight Biologics. Dr. Kolarova received speaker and consulting honoraria from Santhera Pharmaceuticals. Dr. Klopstock received speaker and consulting honoraria from Santhera Pharmaceuticals and from GenSight Biologics.

Ethics statement The data presented here were collected in the context of standard medical care. Beyond, phenotyping of patients with mitochondrial disorders and analysis of the respective data has been approved by the ethics committee of the University of Munich in the context of the German network for mitochondrial disorders (mitoNET) and has, therefore, been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

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