

Positive Visual Phenomena: Classification, clinical profile and a scheme for diagnosis

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Introduction

Lesions in the eye or visual pathways affect vision most often by creating deficits or negative phenomena, such as blindness, visual field deficits or scotomas, decreased visual acuity and color blindness. Occasionally, they may also create false visual images, called PVP (PVP). These images can be a result of distortion of incoming sensory information leading to an incorrect perception of a real image called an illusion¹. When the visual system produces images which are not based on sensory input, they have been referred to as hallucinations².

PVP historically have been considered to be due to psychiatric disorders. The term “hallucination” was introduced in the English language by Lavater in 1572, to refer to “ghosts and spirits walking the night”³ whereas “illusion” was used by Freud in the context of a failure to adapt to reality⁴. However, the literature from the last thirty years makes clear that hallucinations and illusions are unlikely to be associated with psychiatric disorders.

As described above, **illusions** can occur in the form of misinterpretation of a real sensory input, such as a recurrence, persistence, duplication or change in the size of images. Illusions are not always pathologic. **Physiologic illusions** can be produced by the brightness, tilt, color, movement or pattern of the stimulus, whereas **cognitive illusions** are the result of the brain’s assumptions about ambiguous stimulus⁵. **Palinopsia** describes the illusion of a persistent visual image of an object in time after the actual object has disappeared. It is considered physiologic when the afterimage is preceded by a bright stimulus. On the other hand, when the image reappears after an interval of minutes to hours after initially disappearing, it may indicate that there is cerebral involvement, such as an ictal manifestation, a structural lesion or migraine; it has also been shown to be induced by drugs. **Polyopia** is a rare illusion of multiple images characterized by monocular diplopia, excluding refractive abnormalities. When objects are seen smaller or larger than in reality, the illusion is called **dysmetropsia** (micro/macropsia). Retinal dysmetropsia is the most common type; however, migraine related dysmetropsia may be more common than appreciated. An example of this kind of illusion is described by Lewis Carroll in his book, *Alice in Wonderland*, in which the character finds herself growing and shrinking. Unusual causes include cerebral cortex lesions and seizures. **Metamorphopsia** is the illusion

that objects are distorted. As in dysmetropsia, the retinal metamorphopsia is the more common type, although it has been described with seizures and temporal-occipital lesions.

Hallucinations are defined as visual perception without external stimulation. It must be distinguished whether the individual is able to recognize that the perception is not real, also called pseudo-hallucination, or that the individual endorses it as real, also called delusion⁶. It is only delusion that has serious psychiatric implications. The content of hallucinations is widely variable and can range from simple images including flashing or steady spots (**unformed hallucinations**), colored lines and shapes (**geometric hallucinations**) to vivid objects, flowers, animals and persons (**formed hallucinations**). Causes of formed hallucinations include hypnagogic visions, Charles Bonnet syndrome, psychiatric disorders and toxic-metabolic conditions. Unformed and geometrical hallucinations can be produced by entopic phenomena, migraine, epilepsy, hypoxia and toxic disorders among others.

This pilot retrospective review was intended to provide a basis for a new set of definitions of PVP that would be useful in categorizing these events in the light of underlying pathology and prognosis.

Materials and Methods:

We reviewed the medical records of 117 patients who came to the Doheny Eye Institute, Department of Neuro-ophthalmology; with a chief complain of PVP, in the period between 2005 and 2008.

All charts were classified according the symptoms into illusions and hallucinations (formed and unformed), and into the cause of the PVP. A description of the PVP was performed, including characteristics (duration, shape, color, bi or monocular), associated symptoms, visual acuity, slit lamp exam, ophthalmoscopy, visual field and neuro-imaging findings.

We classified PVP into three major groups:

- a- **Functional disorders:** Disturbance of the processing of visual input produced by hallucinogenic drugs or pharmacologic agents, or irritation of the visual pathway due to a neurotransmission alter.
- b- **Structural lesions:** Hallucinations with an anatomic damage.
- c- **Altered physiologic disorder:** Hallucinations in the context of psychiatric disease or malingering.

We reviewed patients with Charles Bonnet Syndrome. This diagnosis was based on the characteristic stereotypic and repetitive/persistent hallucinations and a previous history of decrease in visual acuity or blind portions of the visual field^{7,8}.

Results

Formed Hallucinations:

Eight patients with formed hallucinations were diagnosed with **Charles Bonnet syndrome**. They described the hallucinations as pleasant perceptions of men and women wearing colorful hats and shoes, human faces or animals, flowered wallpapers or gardens. These images persisted irrespective of opening or closing of eyes, and were stereotypic (repetitive). All patients had a decrease of visual acuity or a visual field defect and all of them were aware of the unreal nature of the images. The mean age was 78 years old (range 52 - 87 years). The prevalence in females was higher with male to female ratio being 2/6. In one subject, the hallucinations disappeared with recovery of vision after treatment of his maculopathy.

Unformed Hallucinations:

Charles Bonnet syndrome was diagnosed in six patients complaining of unformed and geometrical hallucinations, consisting of colored patterns or colorful spots or shapes. As in formed hallucinations, they were present with eyes closed and opened. The mean age for this type of hallucinations was 74 years (range 48 - 87) and the female/male ratio was 5/1.

Entopic phenomena were found to be the cause of hallucinations in 20 patients. Four patients were diagnosed with posterior vitreous detachment, and two with retinal detachment. All of them gave a history of a monocular flash of white light, mostly in the supero-temporal visual field, which lasted for seconds and was greater in the dark. Epiretinal membrane was observed in one patient that complained about brief flashes of light. Birdshot chorio-retinopathy, chorioretinopathy HLA-B27 positivity and chorioretinitis were found in three patients who presented with monocular flashes of light. Age related macular degeneration (ARMD) with choroidal neovascularization (CNV) was diagnosed in three patients; two of them described white spots of light whereas the other one claimed to see reddish-brown shapes. Three patients were diagnosed with retinal or choroidal disease and one with proliferative diabetic retinopathy based on ophthalmoscopic examination and fluorescein angiography. The four of them described colored shapes (with an increased prevalence of purple). The duration varied from seconds to hours. Other causes included dry eye and glaucoma.

Migraine was diagnosed in 21 patients, in which the chief complaint was hallucinations. Thirteen patients described the classic scintillating scotoma, five patients saw white spots with peripheral obscurations and one patient described colored jagged lines. In all cases, hallucinations were binocular and in eight patients their hallucinations were described to be in one hemifield. Hallucinations lasted from 5 to 30 minutes. Six patients presented persistent hallucinations, defined as white spots and interference in their peripheral vision. Only in three cases, headache did not follow the hallucinations. Associated neurological symptoms like numbness and tingling in arms and legs were present in four patients, an episode of hemisensory hemiplegia in one patient an associated aphasia in one patient. MRI was performed in eight

patients, three of them with the previous diagnosis of multiple sclerosis with the presence of plaques in the white matter, and the other five had a normal MRI. The mean age of this group was 39, with prevalence in female (15/6).

Transient ischemic attack (TIA) was found to be the cause of unformed hallucinations in 20 patients. Causes of TIA included cerebro-vascular disease, vertebro-basilar insufficiency and high blood pressure. Ischemic changes on MRI were found in five patients out of 11. Fifteen patients described their hallucinations as white flickering circles or jagged white lines followed by obscurations and three patients claimed to see bright colored lights, but in all cases the hallucinations were binocular. The time varied from 20 minutes to two hours. In one case, additional persistent hallucinations were described as white flurries fluttering above both eyes. In four cases, hallucinations preceded headache. In three cases, the hallucinations were accompanied by tingling of the legs and numbness of the hands, and three cases were accompanied by dysarthria and disorientation. The mean age was 74 (range 65- 89). The female/male ratio was 12/8.

Eleven patients were diagnosed with **retinal migraine**. All of them had monocular symptoms, which lasted from 30 seconds to one hour. Six of them described kaleidoscope effects with colored flashes of light, and four described bright lights, all associated with obscurations. One patient described metamorphopsias for 20 min. Carotid Ultrasound was performed in four patients, which were normal, and MRI was performed in four patients which were also normal. Fundus examination was normal in 10 cases whereas in one case, attenuation of arterioles and tortuous veins was found. Visual symptoms were followed by headache in four patients.

Autoimmune retinitis was diagnosed in three patients. Two of them complained of persistent colored lights and shadows in both eyes, with eyes open and closed and the other one saw persistent white lights. One patient described afterimages. Positive anti-retinal antibody was found in two patients whereas positive anti-retinal antibody and anti-enolase antibody, associated with breast cancer, as part of a paraneoplastic syndrome, was found in one patient. The visual acuity and ophthalmoscopy was normal in all patients.

One patient presented with a **toxic** effect to voriconazole, which produced hallucinations for 13 years. She described these hallucinations as jagged lines and flickering flashes of lights that lasted for several hours.

Epilepsy was diagnosed in a 75 year old patient who complained of bright flashes of lights in both eyes, triggered by light, after history of trauma.

Altered physiologic disorder was observed in two patients of 15 and 21 years old.

In nine patients, the cause remained unknown. It is interesting that a 40 year old woman, with a past medical history of ocular aplasia in the right eye, with no light perception since she was

born, developed hallucinations in that eye, described as permanent colorful jagged lights. This opens the question whether release phenomena can occur after a lifetime of vision loss.

Illusions:

Six patients complained about **metamorphopsias**, and three of them had age related macular degeneration diagnosed. One patient was diagnosed with migraine and in two patients, the cause remained unknown. **Polyopia** was the chief complaint of two patients; in one of them, this was due to cataract and in the other one, by dry eye. Migraine was found to be the cause of **Palinopsya** in six patients. In five of them, the visual symptoms were followed by headaches. Three of them presented with associated symptoms such as tinnitus, tingling over the head and hemisensory hemiplegia. After images was found to be due to a toxic effect of 3,4-metilendioximetanfetamina (MDMA) in one patient.

Binocular **persistent hallucinations** were observed in six patients as a symptom of migraine. These were described as interference, static TV or visual snow. Three of these patients gave similar descriptions that their hallucinations were mostly in the peripheral visual field. In two of these patients, attenuated arterioles and microvascular occlusions were observed in ophththalmoscopy. MRI was normal in three of these patients whereas one of them showed plaques in white matter. Binocular persistent hallucinations were also observed in a patient with cerebrovascular disease, described as peripheral white spots. Five patients complained of binocular colored lights; two of them where diagnosed with retinal ischemia and three with autoimmune retinitis. In one patient with monocular persistent colored hallucinations, the cause remained unknown.

Table 1: Classification of PVP by pathophysiology

Functional Disorders	Structural Lesions	Altered Physiology
<ul style="list-style-type: none"> - Migraine - Epilepsy - TIA - Mechanical traction of the retina - Inflammation of the retina - Autoimmune retinitis (without ischemia) - Retinal Migraine 	<ul style="list-style-type: none"> - Charles Bonnet Syndrome - TIA (with ischemic damage) - Mechanical distortion of the retina - Ischemia of the retina - Autoimmune retinitis (with ischemia) 	<ul style="list-style-type: none"> - Psychiatric conditions
<i>Mean Age (sd): 49 (18.4)</i>	<i>Mean Age (sd): 74 (12.6)</i>	<i>Mean Age 19</i>

T-test comparison

Structural lesions mean age greater than Functional disorders $p < 0.0001$

Table2: Causes of PVP

	Etiology	No	Gender F-M	Mean Age
Formed Hallucinations	Charles Bonnet	8	6-2	78
Unformed Hallucinations	Charles Bonnet	6	5-1	74
	Entopic Phenomena	20	14-6	63
	TIA	20	12-8	74
	Migraine	21	15-6	39
	Retinal Migraine	11	4-7	62
	Autoimmune retinitis	3	2-1	54
	Toxic/metabolic	1	1-0	37
	Epilepsy	1	1-0	75
	Altered Physiology	2	1-1	19
	Unknown	9	5-4	57
Illusions	Migraine	7	3-4	34
	Entopic Phenomena	5	3-2	62
	Toxic	1	0-1	23
	Unknown	2	0-2	38
Total		117	72-45 <i>p</i> = 0.01	

Figure 1: Etiology by age

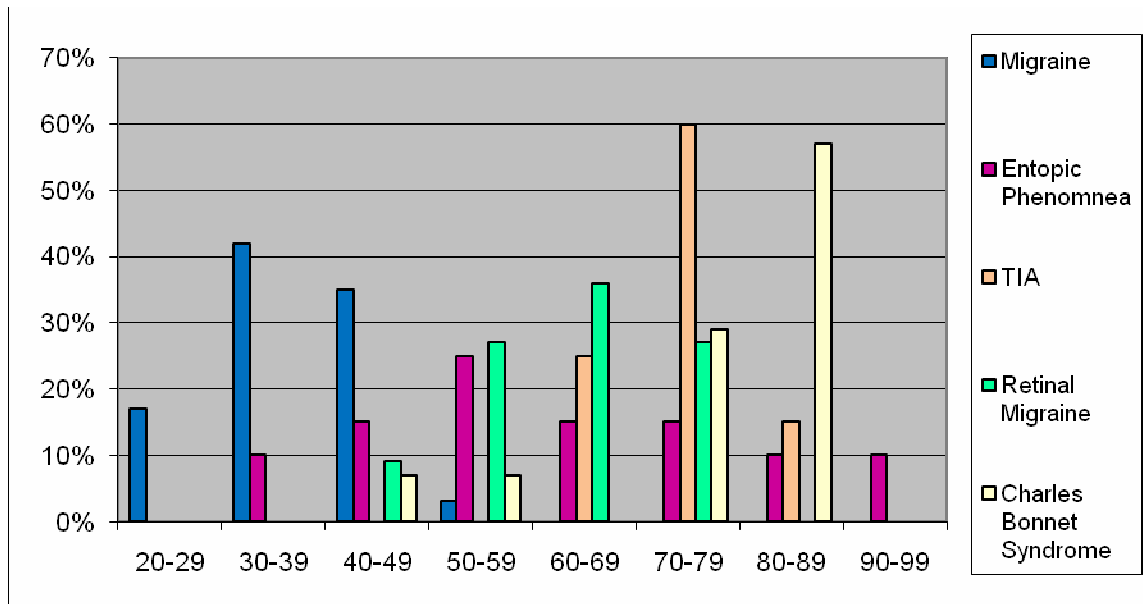


Table 3: Average age by pathology type

Pathology type	N	Mean age (sd)	Analysis of variance p-value
			<0.0001
Entopic Phenomena	20	63 (18.0)	
Migraine	20	39 (8.8)	
TIA	20	74 (6.1)	
Retinal Migraine	11	62 (9.5)	

Pairwise comparisons with Bonferroni adjustment.

	Migraine	Ischemia	Retinal Migraine
Entopic Phenomena	p<0.0001	p=0.04	p=1.00
Migraine		p<0.0001	p<0.0001
Ischemia			p=0.10

Table 4: Characteristics of Hallucinations

	Eye		Color		Duration			
	Monocular	Binocular	White	Colored	< 1 min	5 – 60 min	>1h	Persistent
CBS	-	14	-	14	-	-	-	-
EP								
-MEP	7	-	7	-	7	-	-	-
-IEP	3	-	3	-	3	-	-	-
-CNV	2	1	2	1	1	2	-	-
-RI	2	2	-	4	-	-	1	3
TIA	-	14	14	6	3	6	5	1
M	-	20	19	1	-	16	-	5
RM	11	-	4	6	2	9	-	-
AR	-	3	1	2	-	-	-	3

(CBS: Charles Bonnet Syndrome, EP: Entopic Phenomena, MEP: Mechanical Entopic Phenomena, IEP: Inflammatory Entopic Phenomena, CNV: Choroidal Neovascularization, RI: retinal ischemia, M: Migraine, RM: Retinal Migraine, AR: Autoimmune Retinitis)

Discussion

There is no consensus on the classification of PVP. The present study suggests that the classification scheme into functional and structural disorders may be useful in understanding the pathophysiology and management of these phenomena. Functional disorders such as migraine

trended to occur in young people, whereas structural disorders were found in older people. TIA, whether due to functional or structural causes was also prevalent in the elderly. Duration of PVP was also found to be helpful in differentiating these disorders. Hallucinations due to migraine were self-limiting and lasted less than 40 minutes whereas hallucinations due to TIA persisted over time, and eventually lead to structural damage. The color of the hallucinations was specifically relevant when hallucinations were due to entopic phenomena. Retinal ischemia led to purple colored PVP whereas mechanical traction or inflammation of the retina produced achromatic hallucinations. Entopic phenomena or retinal migraine mostly produced PVP in one eye, whereas involvement of both eyes was mostly found in cerebral cortex disorders. In general, PVP were more prevalent in females.

Each etiology produced PVP with singular characteristics. Formed hallucinations occurring as a result of decreases in visual acuity or blind portions of the visual field correlated well with **Charles Bonnet Syndrome**. This is due to a release phenomenon, which were also found to be the cause of unformed and geometric colored hallucinations. Release phenomena were characterized for being stereotypic. Formed hallucinations can also arise in the context of psychiatric condition, so it is essential to differentiate whether the patient is able to recognize the unreal nature of the hallucinations.

Entopic Phenomena are visual perceptions in which the source is within the eye^{9,10}. The mechanism of this phenomenon can be divided into mechanical, inflammatory or vascular. Unformed hallucinations such as flashes of lights, colored and achromatic spots or shapes can be produced by abnormal stimulation of the retina. Mechanical distortion of the macula leads to bleaching of the photoreceptors that produces afterimages. White shaped flashes of lights occur in posterior vitreous detachment or retinal tears, due to the stimulation of photoreceptors by vitreous traction, called Moore's lightning streaks. Choroidal neovascularization is characterized by neo-formed vessels in which its contracting fibrovascular membrane exerts traction and may lead to a stimulation of the retinal pigment epithelium¹¹. Infection or inflammation of the outer retina (birdshot chorioretinopathy) may produce irritation of the photoreceptors, with the subsequent perception of white flashes of light. Vascular causes include transient ischemic attacks of the retina, due to vasospasm. Chronic ischemia can be observed in patients with retinal insufficiency. Across all entopic phenomena, we found that geometric purple shapes correlated very well with retinal ischemia, whereas brief flashes of light and metamorphopsias were present in patients with mechanical or inflammatory phenomena.

According to the International Classification of Headache Disorders, **Retinal Migraine** consists of repeated attacks of monocular scotoma or blindness, or PVP that last for less than one hour. Its criteria have been re-defined by the ICHD in 2004 which requires at least two attacks of fully reversible monocular positive and/or negative phenomena associated with migraine^{12,13}. The pathophysiology may consist of a retinal hypoperfusion due to central retinal artery vasospasm¹⁴.

In our study, 3 out of 4 patients presented colored unformed and geometric hallucinations. As in entopic phenomena, colored hallucinations may represent a transient retinal ischemic process.

Migraine was the most frequent cause of PVP in young people. The typical symptom consists at a scotoma with a scintillating border that begins near the center of the vision and gradually spreads across the visual field. Its electrophysiology was explained by Leao in 1944, who developed the theory of spreading depression (SD)^{15,16}. The SD is characterized by a brief excitation of a group of neurons followed by a prolonged depolarization that spreads from the site of initiation in the occipital lobe within 10 minutes. It clinically correlates in time with the scintillating scotoma, in which the symptom is a flash of light that moves around one hemifield (brief neuronal spreading hyperexcitability) followed by scotoma (neuronal depression)^{17,18}. In our study, all the patients described white or colored visual hallucinations.

Similar hallucinations were found in patients with ischemic processes, such as scintillating scotomas, or flashes of white light followed by obscurations, but colored hallucinations was more prevalent in this group. It has been postulated that the same process of spreading depression may be triggered by hypoxia or hypoglycemia, being called spreading depression like or hypoxic spreading depression (HSD)^{19,20}. However, there are several differences between SD and HSD. SD is thought to be a self limiting process whereas HSD may persist over time and may lead to ischemic changes, which are not present in SD. Patients with migraine reported that their hallucinations lasted for 5 to 30 minutes, whereas there were patients with TIA in which their hallucinations last for several hours²¹. There is a relative tolerance of ischemia in which the process can be reversible. Unlike SD, in HSD, if oxygen is not restored soon after depolarization, then permanent damage will occur.

A **seizure** that localizes in the occipital lobe manifests with hallucinations or visual deficit. It is produced by a change in the synchronized firing of neuronal brain ensembles that leads to a synchronous discharge. The result is a brief unformed hallucination, predominantly multicolored but sometimes white^{22,23,24}. Ninety percent of partial occipital seizures are followed by generalized seizures; so that, hallucinations are unlikely to be the chief complaint. In our review, only one patient complaining about unformed colored and white hallucinations was diagnosed with seizures, and this was secondary to trauma.

Retinopathies associated with antiretinal antibodies are observed as part of visual paraneoplastic disorders, most frequently in small-cell carcinoma of the lung, but also in patients with breast cancer. It has also been reported in association with retinal degenerative disorders and retinal infections. The identified antigens are recoverin and enolase. Antibodies against these antigens result in cellular depolarization and eventually, photoreceptor cell death. Clinically, it presents with acute or subacute vision loss, symptoms of night blindness, photopsias, loss of peripheral visual field and color blindness^{25,26}. In our study, all patients with such retinopathy reported colored, bilateral and persistent hallucinations.

Persistent hallucinations were observed in a variety of etiologies in patients with normal visual acuity and visual field. In our study, there was a great significance whether the hallucinations were colored or white. In the first group, hallucinations were found to be due to retinal abnormalities, such as autoimmune retinitis and retinal ischemia, whereas achromatic hallucinations were found in the context of migraine and TIA. The International Headache Society defines persistent aura without infarction, when the aura symptoms persist for more than one week without radiographic evidence of infarction. Jäger et al reported that no changes in relative cerebral blood volume were detected in patients with persistent visual phenomena²⁷, contrary to migraine aura, in which abnormal flow in the occipital lobe has been documented by neuroimaging during the attack^{28,29}. The pathophysiology of persistent visual aura in migraine has not been established. Liu et al. proposed that discharges from the lateral geniculate nucleus or visual cortex, as a result of the fail of inhibition or modulation of extrastriate cortex might be a mechanism for persistent visual phenomena, as in release phenomena, described by Cogan; but this has not been proved³⁰. The absence of neuro-imaging findings, along with the characteristics of this kind of hallucinations (symmetry, entire or peripheral visual involvement and achromatic hallucinations) suggests that a metabolic process may be involved in the pathogenesis of this type of hallucinations.

Each cause of presents PVP has specific features. Characteristics such as duration, color and nature are useful in diagnosing the PVP. The prognosis for functional disorders was found to be more benign than structural lesions. Hence recognizing the structural lesions is essential in patient management.

Future studies could be directed to measuring the oxygenation of the blood flow of the retina with laser Doppler OCT in patients with monocular colored hallucinations, to confirm whether there is an ischemic process.

We found that a detailed description of the symptoms was helpful in classifying PVP as functional and structural. This aided in accurate diagnosis and proper management. Hence, we suggest prospective studies with more patients using this category scheme to improve patient management and further enhance our understanding of the underlying pathophysiology of PVP.

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