Hallucinations in Neurological Disorders

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Hallucinations are frequently observed in many neurological conditions. However, these false perceptions should not be considered as necessarily pathological conditions, since many healthy individuals and non-neuropsychiatric patients could experience them in some specific situations [1].

The first evidence of a defined neurobiological basis for hallucinations is due to the pioneering work of a Canadian neurosurgeon named Wilder Graves Penfield who, while conducting studies on surgical interventions to treat epilepsy, observed that electrical stimulation of specific regions of the temporal lobes induced olfactory, visual, and auditory hallucinations in conscious patients. These hallucinatory perceptions lasted as long as the electrode stimulations were present on the brain cortex [2].

7.1 Hypnic Hallucinations (HH)

HH are vivid visual experiences which can manifest in the phase just before falling asleep (hypnagogic hallucinations) or during awakening (hypnopompic hallucinations).

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The first known description of this phenomenon dates back to 1664 when the Dutch physician Isbrand Van Diemerbroeck (1609–1674) wrote a case history entitled "Of the Night-Mare." It described the experience of a 50-year-old woman who sometimes, when she was lying in her bed before falling asleep, saw the devil, a thief, or a big dog lie upon her and hold her down, and if she tried to throw them off, she was unable to move [3].

HH are often associated with hypnic paralysis in narcolepsy-cataplexy syndrome, but they can also occur in healthy individuals. Up to 70% of the general population may have this experience during life [4]. Curiously, they seem to occur more often in supine position of the body [3, 5]. It has been described that in narcoleptic patients 80% of hallucinations and 86% of sleep paralysis occur in supine position [6].

In most cases, HH are visual phenomena. They can manifest with kaleidoscopically changing geometric patterns, light flashes, and shapes, or with complex images like animals, human figures and faces, demons, or vampires in bright colors, often in detailed scenes and sometimes in a scary setting. In many descriptions of HH, a dreadful and evil presence, like a demon or hag, sits on the victim's chest and smothers or chokes the sleeper [3, 7]. Images can be static or moving. Insight is usually preserved. Subject is not directly involved in the scene, like in dreams, but he/she observes the scene from the outside. He/she can feel indifferent to that, but sometimes the experience is very disturbing or also fascinating to him/her. Images can last just a few seconds or some minutes and can be accompanied by auditory, such as voices or sounds, footsteps getting closer, phone or doorbell ringing, and/or tactile hallucinations or other anomalous sensations like out-of-body experience, floating, or flying sensations. Hypnopompic hallucinations are usually continuations of dreams during the first seconds or minutes of wakefulness [4, 8].

Sleep paralysis and hypnagogic and hypnopompic hallucinations form the basis for accounts of nocturnal attacks and rapes and paranormal experiences such as space alien abductions and ghostly visitations [3, 9, 10].

Narcolepsy-cataplexy syndrome is caused by a dysregulation of physiological rapid eye movement (REM) sleep cycle. Usually, in normal individuals, the first REM sleep period occurs in the first 90 min after sleep onset. Conversely, in patients affected by narcolepsy it presents within 20 min after sleep onset. Hallucinations seem to be related to this first REM period, especially when it is anticipated, because they can be a manifestation of REM sleep arising in a relatively high level of arousal [11]. This intriguing hypothesis may suggest that every hallucination could represent an intrusion of REM dreams into waking life [12]. However, some aspects seem to argue against this hypothesis; for example, sleep disorders and hallucinations, even if they often coexist, usually follow a separate clinical course, with sleep dysfunction preceding the onset of hallucinations [4]. The motor paralysis of REM sleep could lead to the experience of breathing difficulties when the person attempts to breathe deeply: this can explain the choking or suffocating sensations experienced by some subjects [9].

Most cases of narcolepsy are constitutional, but some cases of narcolepsy are secondary to lesions located in pons and midbrain, the same areas involved in

peduncular hallucinosis. These two conditions probably share a similar pathophysiological process [8].

Monoamine oxidase inhibitors, thanks to their serotonergic effect, and tricyclic antidepressants, like clomipramine or protriptyline, delaying onset of the first REM period and influencing 5-HT2 receptors, may be effective in reducing HH [8].

7.2 Peduncular Hallucinosis (PH)

Lhermitte, a French neurologist and neuropsychiatrist, described PH for the first time in 1922 [8]. PH is a very rare disorder [13]. Lesions localized in the rostral paramedian midbrain can manifest with visual hallucinosis characterized by complex changing scenes, described as movie-like. Other types of images have been described, like a sphere of light, humans, animals, and dwarves. The visions are typically stereotyped, vivid, and colorful; can last variable periods of time, from a few minutes to several hours; and can recur rarely or even many times in a day [8]. Tactile or auditory hallucinations can rarely be associated. Images usually disappear during daytime and turn up at night. The patient sees the images even with eyes shut, and while sleeping he/she often experiences particularly vivid dreams. Insight is usually preserved and the hallucinations are not considered threatening by the subject [8].

The etiology is more frequently ischemic or infective with bilateral involvement of the rostral brainstem. The most frequently affected structures are substantia nigra, red nucleus, medial longitudinal fasciculus, medial part of cerebral peduncle, and superior cerebellar peduncle [13]. In addition, lesions involving basal ganglia and thalamus (especially pulvinar and medial thalamus) have been described. In general, peduncular hallucinosis seems to be associated with lesions involving the brainstem reticular formation (reticular activation system, RAS) or its targets in the thalamus. Hallucinations start a few days after ischemic lesion and may persist for years [8].

Two possible pathogenetic hypotheses have been suggested: an altered neurotransmitter functioning in the reticular activating system, and a disruption of the loop between temporal lobe and basal ganglia. The frequent association of peduncular hallucinosis with sleep-wake cycle disturbance supports the first hypothesis. Some neurons placed in the RAS (pedunculopontine nucleus) have cholinergic connection with the lateral geniculate nucleus, originating the ponto-geniculo-occipital (PGO) pathway, which regulates REM sleep. This neural circuit is inhibited by serotonergic afferents from dorsal raphe nuclei. When the RAS is damaged, and inhibitory serotonergic afferents are interrupted, the PGO system activity increases. This leads to an increase in REM sleep, explaining the sleep-wake cycle disturbance. When patients quickly enter REM sleep, hallucinations may present.

The other possible mechanism involves a loop between the basal ganglia and inferotemporal lobe. The basal ganglia loop involves a direct pathway (through the substantia nigra pars reticulata and internal globus pallidus complex) and an indirect pathway (through the external globus pallidus and subthalamic nucleus) to the

temporal lobe via the thalamus. The inferotemporal lobe is responsible for recognition and discrimination of visual objects. It has been hypothesized that lesions in the midbrain involving the substantia nigra may block the excitatory connections from the subthalamic nucleus to the substantia nigra. This reduces the inhibitory control from the substantia nigra and internal globus pallidus to the thalamus and causes an increased temporal cortex activation by the thalamus [14, 15].

No specific treatment is required in some cases, as hallucinosis tends to disappear spontaneously over time and is not annoying for patients. When pharmacological treatment is required, atypical antipsychotics may be useful, like olanzapine or risperidone [16].

7.3 Charles Bonnet Syndrome (CBS)

Charles Bonnet, a Swiss philosopher and naturalist, described CBS for the first time in 1760. He described the phenomenon of complex visual hallucinations experienced by his 89-year-old grandfather, who was blind due to cataracts [17, 18]. Patients with a severe visual impairment due to a lesion in any part of the visual pathway, from the eye to the occipital areas of the cortex, can develop complex hallucinations. This is probably due to an inadequate stimulus to the visual system caused by sensory deprivation [17].

Visual hallucinations more often occur in patients with poor bilateral visual acuity, but they have also been described in cases with unilateral or fluctuating visual loss [19]. They localize in the part of the visual field affected by the lesion and they are more frequent during the evening or in early morning. Typically, insight is preserved. Patients are not affected by mental disorders; they are aware of the unreal nature of the images and usually are not distressed by them [18].

It is more frequent in elderly people; the mean age is between 70 and 85 years. Incidence ranges from 0.4 to 14% and it is increasing as the population age increases [17].

CBS is usually characterized by complex hallucinations. They are consistent with faces, people, animals, vehicles, buildings, and plants, but also simple images like light flashes, lines, or geometric shapes. Sometimes patients describe complex scenes of bizarre, funny, mundane, or beautiful content. Images can be colored or black and white, and can move across the visual field or can be motionless. Hallucinations generally occur with the eyes open, in the evening or at night, and can last only a few seconds or persist for hours. They may recur multiple times in a day or a week. It has not yet been clarified whether the images are reproductions of objects that the patient has previously seen in reality, or if they are newly created products of the mind [19]. Two cases of Charles Bonnet syndrome are described in Fig. 7.1.

Rarely, lesions along the auditory pathway, from the ear to the auditory association cortex, can also cause auditory hallucinations. They consist of unformed sounds (such as tinnitus) or complex perceptions. For example, patients with serious acquired hearing loss may experience musical hallucinations [18], often represented by persistent religious and patriotic music [20]. Predisposing factors are age, female sex, social isolation, and organic brain damage [21].

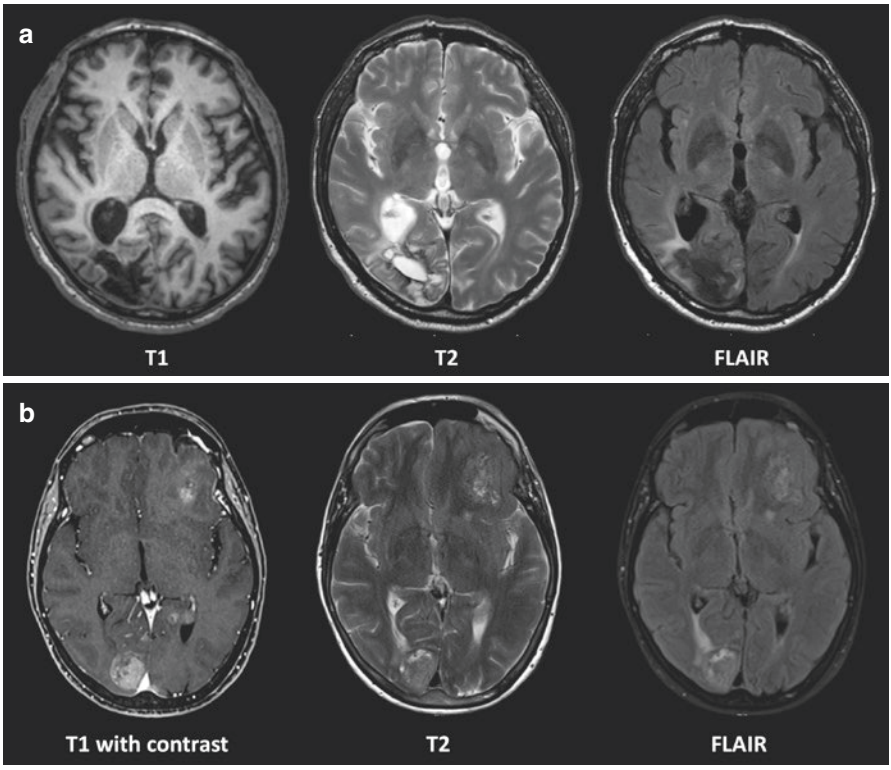

Fig. 7.1 Two cases of Charles Bonnet syndrome. Patient (**a**): male, 65 years old. He presented a hemorrhagic stroke in right occipital lobe with residual left hemianopsia. After 6 months, he went to the emergency room for acute visual hallucinations in left visual hemifield: colored pillow on the table, black worms on the wall, water puddles on the floor, and soccer players on the front of a building. Brain MRI showed a malacic area related to the old stroke (T1-weighted, T2-weighted, and FLAIR scans). EEG was negative. Hallucinations suddenly disappeared with valproate therapy. Patient (**b**): female, 62 years. She went to the outpatient department for headache lasting 2 weeks and visual hallucinations in left visual hemifield, with tigers and lions. Brain MRI showed multiple metastasis from mammalian cancer (gadolinium-enhanced T1-weighted, T2-weighted, and FLAIR scans). EEG was negative. Hallucinations appeared in the left visual hemifield, due to hemianopsia related to right occipital lobe lesion

In addition, focal brain lesions may be associated with musical hallucinations, especially when they involve the left hemisphere and temporal lobe. In this case, patients often report hearing modern music [20].

Age-related macular degeneration (ARMD) is the most common disorder associated with CBS. In a recent study up to 40% of patients with ARMD developed CBS [22]. Other eye diseases associated with CBS are cataracts, diabetic retinopathy, post-enucleation, macular photocoagulation, central retinal artery occlusion, Leber's hereditary optic neuropathy, glaucoma, and orbital pseudotumor. In addition, lesions interesting nervous visual pathways, like optic glioma, optic neuritis, optic chiasm meningioma, antero-mesial temporal lobectomy, occipital cortical resection, and occipital infarction, can cause CBS [17].

The most widely accepted theory of the CBS pathophysiology is the deafferentation theory. According to this theory, loss of visual input into the brain leads to increase in excitability of the visual association cortex with spontaneous neuronal discharge [23]. When a region becomes deafferented some of its neurons die, but the remaining neurons, receiving sufficient input from nearby cells, may survive and become more excitable. Therefore, defective visual input and processing, due to ocular pathology or damage to visual pathways, may result in an endogenous visual cortex activation with abnormal cortical release process. This especially happens in the Brodmann area 37, within or around the fusiform gyrus [24]. A variety of factors contribute to increasing visual cortex excitability: (1) the rise of neurotransmitter release in the presynaptic neuron, due to enlargement of the presynaptic bouton and increased number of neurotransmitter vesicles; (2) the increase in number and/or sensitivity of postsynaptic receptors caused by prolonged inactivity [17, 25]; and (3) the changes in the amount of gamma-aminobutyric acid and glutamatergic *N*-methyl-D-aspartic acid within the synapse. As a result, neurons are more sensitive and small amounts of remaining stimulus from the visual system can elicit visual hallucinations [23].

In a functional MRI study, it has been shown that lesions in different areas of the visual cortex may cause different types of visual hallucinations. For example, involvement of fusiform gyrus may cause face hallucinations, while anterior temporal lobe lesions produce objects and landscape images [17, 26].

According to another hypothesis, the release theory, the brain constantly receives a huge number of visual stimuli. Visual impairment can cause a reduced inhibition in the occipital cortex of irrelevant impulses from the conscious perception of images. This lack of inhibition leads to a release of previously subconscious perceptions into consciousness, resulting in visual hallucinations [8, 19, 23, 27, 28]. Rare cases of CBS with auditory hallucinations probably have a similar pathogenesis [17].

When visual deficit is reverted, the hallucinations usually disappear; therefore, the first step is to improve vision when possible. Interventions like improving eyesight with spectacles, laser photocoagulation for subretinal hemorrhage or cataract surgery may be useful. When this is not possible, a pharmacological approach may be considered. Some cases are successfully treated with atypical antipsychotics, like olanzapine, or antiepileptic drugs, like carbamazepine, valproate, clonazepam, and gabapentin. In addition, cholinesterase inhibitors, like donepezil, have been successfully used [29]. Non-pharmacological interventions may be helpful. Some patients can stop or reduce their hallucinations by using maneuvers like closing and opening their eyes, fixing vision on or away from the false image, or increasing visual stimuli by improving illumination [30, 31].

7.4 Migraine

Migraine is a primary headache disorder characterized by recurrent episodes of moderate-to-severe pulsating cephalalgia, affecting typically one half of the head and usually lasting several hours [13]. The prevalence of migraine in the general

population has been reported as between 15 and 29% [32]. Up to 31% of those with migraine had an aura [33], and nearly all of those with an aura had visual symptoms [34]. The classic visual aura starts as a flickering, uncolored, unilateral zigzag line, called scintillating scotoma, in the center of the visual field that gradually progresses toward the periphery, often leaving a scotoma, that lasts less than 30 min. Variations of this classic picture (such as colored patterns) also occur. These simple visual hallucinations are the most common, but more complex hallucinations can occur in migraine coma and familial hemiplegic migraine (FHM). FHM is an autosomal dominant disorder characterized by episodes of migraine with aura, which must include motor involvement (e.g., hemiparesis), and various degrees of cerebellar involvement. Spranger et al. reported a family with familial hemiplegic migraine presenting recurrent episodes of acute paranoid psychosis with complex auditory and visual hallucinations which followed migraine attacks [35].

Medical literature and popular culture describe a rich variety of strange and bizarre abnormal perceptions which have been repeatedly associated with migraine aura manifestations. For example, "Alice in Wonderland syndrome" (AIWS), mainly characterized by perceptual distortion of sizes, namely micropsia (the object appears smaller than it actually is), macropsia (larger), teleopsia (farther), and pelopsia (nearer), has been linked with migraine [36]. This syndrome is also known as Todd's syndrome, in reference to the psychiatrist Dr. John Todd (1914–1987), the author of the most significant description of this condition [36]. Todd observed that several of his patients suffering from migraine reported perception of disproportionate objects, altered sense of time, and distorted perception of their own body parts. None of these subjects had a brain lesion, impaired eyesight, or a known psychiatric disorder. The ability to distinguish these illusions from reality was conserved. Since Lewis Carroll, the celebrated author of *Alice's Adventures in Wonderland*, was a well-known migraineur, Todd speculated that he used his auras as a source of inspiration for his literary work [36]. Other reported causes of this condition are infectious diseases (e.g., Epstein-Barr virus infection), cerebral lesions (e.g., brain tumors or traumatic encephalopathy), temporal lobe epilepsy, medications (e.g., topiramate), and psychoactive drugs (e.g., LSD) [37].

Functional magnetic resonance imaging (fMRI) studies showed that migraine aura is likely caused by spreading cortical depression, starting from the occipital cortex moving forward [38]. Isolated observations have documented cases of migraine with auditory hallucinations, which are not currently a recognized aura symptom. Their high prevalence in patients with depression may suggest that auditory hallucinations are not necessarily a form of migraine aura, though could be a migraine trait symptom [39, 40]. Similar isolated observations of gustatory, olfactory, and somatic distortion hallucinations are described in the literature [41–44]. There is no specific abortive treatment for the symptoms of aura, but prophylactic therapy (e.g., valproate or topiramate) could prevent both migraine headache and aura; prophylaxis is particularly indicated in cases with prolonged or atypical aura [45].

7.5 Epilepsy

Epilepsy is a group of neurological disorders characterized by epileptic seizures [46]. During a seizure, an abnormal, excessive, hypersynchronous discharge of a group of cortical neurons can lead to hallucinations or illusions. These phenomena, when they forego an impairment of consciousness and/or a generalized seizure, are called epileptic auras. They can manifest in a fully awake state, but can also be associated with various degrees of disturbed consciousness and various other seizure manifestations, such as motor activity and automatisms.

The modalities of the symptoms can provide localizing information. For example, when epileptic focus is located in a brain region involved in sensory integration, the seizure discharge can give rise to auditory, gustatory, olfactory, somatic, and visual false sensations. More rarely, in addition to these elementary sensory perceptions, hallucinations can be more complex (e.g., perceptions of visuospatial scenes or hearing elaborated music). By involving emotional circuits of the brain, the seizures can lead to hallucinatory emotional states (e.g., fear or joy), illusions (e.g., *déjà vu* or *déjà vécu*), or delusional beliefs (e.g., identity change or bizarre religious experiences). Auditory hallucinations have a specific localization of epileptic focus near Heschl's gyrus and the auditory association areas [47]. Olfactory hallucinations are relatively infrequent in epilepsy and are a manifestation of temporal lobe epilepsy [48]. Gustatory hallucinations are also considered rare in epilepsy. Isolated brief gustatory hallucinations could be elicited from stimulation of the right Rolandic operculum, parietal operculum, amygdala, hippocampus, medial temporal gyrus, and anterior part of the right temporal gyrus [49]. Somatic hallucinations (e.g., abdominal and epigastric sensations) are associated with electric activity in the postcentral gyrus, parietal operculum, insula, and inferior parietal lobule [50]. Visual hallucinations, elementary and complex, and visual illusions are common in occipital seizures. Epileptic visual hallucinations are usually elementary, brief, stereotyped, and fragmentary. They can be divided into positive (flashes of color, bright-colored spots, phosphenes) and, more rarely, negative manifestations (amaurosis, scotoma). Elementary hallucinations usually last between 5 and 30 s. Their onset is usually monolateral, appearing in the temporal visual hemifield and then moving horizontally to the contralateral side [51]. If the hallucinatory images are restricted to one visual field, they have lateralizing value to the contralateral occipital cortex. Illusions, on the other hand, may appear as objects changing in size (macropsia and micropsia) and shape (metamorphopsia), or losing color (achromatopsia) [52]. Involvement of the posterior parietal and temporal association cortex renders the hallucinations more complex and colorful [53, 54]. Complex visual hallucinations tend to last from a few seconds to minutes, with the patient retaining insight into the unreality of the experience [52]. They may be more prolonged as a form of nonconvulsive status epilepticus and if occurring during sleep they can be interpreted as dreams. Palinopsia is a peculiar type of epileptic manifestation in which images persist or duplicate; in this case, the epileptic focus has been localized to the right posterior cerebral region. Another interesting phenomenon is autoscopy, in which subjects perceive mirror images of themselves of normal size, shape, and

density in situations from their past or performing complex tasks. This may arise from seizures affecting the occipital-temporal junction zone [55–57]. Complex visual hallucinations have a much more diffuse anatomical basis than simple hallucinations. It would seem that unless limbic structures are activated complex visual hallucinations do not occur [58].

Complex visual hallucinations may occur as part of a broader psychosis that may feature delusions and paranoia, and may be indistinguishable from a primary psychotic disorder, especially if the seizures are of the complex partial type, presenting a difficult differential diagnosis for neurologists and psychiatrists [59]. Another source of diagnostic difficulty could arise from the fact that occipital seizures are frequently accompanied by a postictal headache, making them difficult to distinguish from migraines, delaying a proper diagnosis and an appropriate treatment.

The treatment of epilepsy with hallucinatory manifestations does not differ from other types of epilepsy, and indicates removing predisposing factors (e.g., fever), etiological therapies (e.g., tumor resection), and/or use of antiepileptic drugs [60].

7.6 Intellectual Disability

Intellectual disability (ID) is a generalized neurodevelopmental disorder characterized by significantly impaired intellectual and adaptive functioning. It is defined by an IQ score under 70 and deficits in two or more adaptive behaviors that affect daily life [61].

The prevalence of psychiatric disorders is higher in children and adults with ID [62]. Cognitive dysfunction seems to interact with environmental factors to increase susceptibility to mental illness. In this context, psychotic manifestations are commonly neglected and psychiatric disorders underdiagnosed because of the atypical presentations and the assumption that psychosis is an inherent part of the underlying ID [63].

Psychotic manifestations seem to be more frequent in patients with mild ID than in those with moderate-to-profound ID. However, this difference may be a reflection of the difficulty in diagnosing a psychotic illness in people with more severe ID. Indeed, the degree of reported hallucinations is dependent on the language ability of the patients; nevertheless, they can be seen talking to themselves or responding in some other way to these perceptions (e.g., looking for someone around the room). Hallucinations seem to be more commonly auditory in nature and the ID patient is more likely to interact with them. Moreover, in these fragile patients hallucinations can trigger agitation and self-injurious behaviors [64].

DiGeorge syndrome (also known as 22q11 deletion syndrome) is characterized by somatic abnormalities such as cleft palate and congenital heart defects and mild-to-moderate intellectual disability, and is strongly associated with an increased risk of psychosis, hallucinations included [65].

There is little evidence on the treatment of psychotic disorders in ID patients. However, actual trends in pharmacotherapy rely on the use of atypical instead of classic antipsychotics and serotonin-specific reuptake inhibitors (SSRIs) rather than tricyclic antidepressants [63].

7.7 Neurodegenerative Disorders

Complex visual, auditory, or tactile hallucinations are frequently described in patients affected with neurodegenerative disorders, such as Alzheimer's disease, frontotemporal dementia, Parkinson's disease, and dementia with Lewy bodies.

7.7.1 Alzheimer's Disease (AD)

AD is the most common neurodegenerative disorder, which typically manifests with a significant episodic memory impairment. Memory loss can be isolated or in association with other cognitive deficits and/or behavioral changes. It is due to a neuronal degeneration associated with deposition of extracellular amyloid plaques and intracellular accumulation of hyperphosphorylated tau (p-tau) protein, which typically begins in the hippocampal regions and then spreads to other parts of the brain. Recently, atypical forms of AD, represented by well-defined clinical phenotypes of non-amnestic focal cortical syndromes, such as logopenic aphasia, posterior cortical atrophy, and frontal variant AD, were included in the diagnostic algorithm [66].

Up to 50% of individuals with Alzheimer's disease may present psychotic symptoms (delusions and hallucinations), prevalence for hallucinations ranging from 6 to 41% with a pooled prevalence of 16% [67]. More frequently, hallucinations are visual; patients typically see people, animals, insects, and objects. Also auditory, somatic, olfactory, and tactile hallucinations have been described [68].

The occurrence of psychotic symptoms is associated with a more severe phenotype, with greater cognitive impairment and more rapid course of disease [69]. It is related to aggressive behavior, increased wandering, falls, purposeless activity, and worse general health [70], reducing quality of life and leading to a greater burden on caregivers [71].

Neuroimaging studies have shown that AD-associated psychosis is associated with a greater cortical damage with decreased grey matter volume on MRI and greater neocortex hypometabolism on [^{18}F]-fluorodeoxyglucose positron-emission tomography (FDG-PET) studies, especially in the frontal lobes [72]. Histopathological studies reported an increased density of neocortical aggregation of tau protein in comparison with AD patients without psychosis [73].

Interestingly, it has been observed that the risk of AD psychosis is transmitted in families [74]. Some genetic patterns may have a double effect: they increase vulnerability to damages caused by beta-amyloid or p-tau depositions, predisposing to AD onset, and they cause a synaptic vulnerability, predisposing to psychosis also in other neurodegenerative diseases (like Huntington's disease) or in schizophrenia. A recent genome-wide association study has shown that some of these genetic variants may correspond to single-nuclear polymorphism in *STK11* gene, or in *VSNL1* gene [75]. Also, carriers of *DRD1* (dopamine receptor D1) genetic polymorphisms, as well as those with the long allele of *5-HTTLPR*, a serotonin-transporter-linked promoter region, may have a higher risk of psychosis [76, 77].

Some pathological studies have found alpha-synuclein aggregation to be present in up to 50% of cases with neuropathologically confirmed AD [78]. The presence of comorbid Lewy body pathology in AD may contribute to psychosis, especially to visual hallucinations [72, 79].

Involvement of the temporal limbic area, a region which links perception to emotional states, may contribute to the onset of psychotic symptoms [80]. Recent studies identified the right anterior insula as a core region involved in AD patients with hallucinations [81].

In addition, the damage to the cholinergic system can explain the onset of this symptom, with a reduction of serotonergic activity and a higher muscarinic M2 receptor density in the middle temporal gyrus in AD patients with hallucinations [82].

The posterior variant of Alzheimer's disease, posterior cortical atrophy (PCA), is characterized by the main involvement of complex visual skills. Patients typically develop progressive decline in visuospatial, visuoperceptual, literacy, and praxic skills with a progressive neurodegeneration of the parietal, occipital, and occipitotemporal cortical areas. Phenomena of altered visual perception have been described, such as abnormally prolonged color afterimages, reverse-size phenomena, and perception of movement of static stimuli [83]. Visual hallucinations have been reported in up to 25% of patients with PCA. Many cases reported of PCA with visual hallucinations were associated with symptoms like parkinsonism, rapid eye movement sleep behavior disorder, and myoclonic jerks, also meeting the clinical criteria for probable dementia with Lewy bodies; the latter should be considered as a possible differential diagnosis [84, 85].

Use of antipsychotics may be useful in AD associated with psychosis. Between conventional antipsychotics, haloperidol is the most studied. It has a good efficacy, but causes serious side effects, like parkinsonism, tardive dyskinesia, and akathisia [86]. For this reason, atypical antipsychotics, such as olanzapine, aripiprazole, and risperidone, are increasingly used. They have similar efficacy with lower rates of motor side effects. However, they increase the risk of cerebrovascular events [87]. Finally, nonpharmacological interventions may be attempted such as brightly colored rooms, turning on the light during the night or creating surroundings with appropriate sound modulations [71].

7.7.2 Parkinson's Disease (PD)

PD is the second most common neurodegenerative disorder after AD, involving 1% of the population worldwide after the age of 65 [88]. Clinical diagnosis of PD requires the presence of bradykinesia and at least one between muscular rigidity, slow resting tremor, and postural instability; in addition, a good response to levodopa treatment is one of the more relevant supportive criteria for PD diagnosis (UK PDS Brain Bank criteria) [89].

Hallucinations are relatively common in PD, more frequently in the late stages of the illness. Epidemiological studies estimate that approximately a quarter of PD patients had hallucinations (Cummings 30% [90], Graham et al. 24.8% [91],

Sanchez-Ramos et al. 25.7% [92]). Fénelon et al. reported a higher rate of PD patients suffering from hallucinations (39.8%); this is probably due to the inclusion of illusions in the count [93]. These illusions are very often characterized by a false sensation of the presence of persons or animals in the room and are a very typical feature of PD.

Phenomenologically, hallucinations in PD are generally visual, but auditory, olfactory, and tactile modalities are not uncommon [93–95]. However, these nonvisual modalities are almost always associated with visual manifestations [96]. Visual hallucinations are usually rich and complex, commonly nonthreatening, and sometimes even amusing [97]. PD patients very often maintain an adequate level of insight.

The hallucinations of PD are commonly considered a side effect of dopaminergic therapy. However, historical reports of PD from the pre-levodopa era suggest that hallucinations could be part of late PD itself [98]. Moreover, hallucinations were not associated with dosage of dopaminergic medication in various studies [91–93, 99, 100]. Dopaminergic therapies may be considered as trigger factors for hallucinations, but also non-dopaminergic pharmacological agents (e.g., anticholinergics) can elicit hallucinations in PD patients [101]. The principal risk factors for hallucinations developing in PD are considered cognitive decline, older age, longer duration of disease, and depression [93].

The limiting factor for PD psychosis treatment is that antipsychotic agents can worsen extrapyramidal symptoms. Clozapine was the first medication shown to be safe and effective in treating psychotic manifestations of PD [102]. Low doses of clozapine are considered safe and significantly improve psychosis without worsening parkinsonism [103]. However, due to the risk of agranulocytosis and the need for frequent blood testing, alternatives have been pursued [104]. Olanzapine and risperidone gave conflicting results and worsened motor features [105–113]. Quetiapine did not appear to exacerbate PD motor symptoms and it is currently widely considered the best choice; however, it did not equal clozapine's ability to treat psychosis in PD [114–117]. Since clozapine at the low doses at which it is effective in PD does not sufficiently block limbic dopaminergic D2 receptors, it has been hypothesized that its antipsychotic activity in PD is attributable to serotonin 5-HT2A receptor blockade [118]. The observation that PD patients with visual hallucinations showed increased 5-HT2A receptor binding in the ventral visual pathway supported this hypothesis [119]. Pimavanserin, a 5-HT2A receptor inverse agonist, displayed significant improvement of psychotic symptoms in PD, without worsening motor function [120]. Since PD patients with dementia have extensive cholinergic deficits, cholinesterase inhibitors may provide benefits for patients with this condition [121, 122]. Rivastigmine and donepezil were overall well tolerated, improved cognitive functions, and resolved visual hallucinations [123–126].

7.7.3 Dementia with Lewy Bodies (DLB)

DLB is the second most common cause of dementia in elderly patients after AD [127]. According to the last report of the DLB Consortium, the diagnostic criteria

for probable DLB require the presence of dementia and at least two of the following features: fluctuating attention and concentration, recurrent well-formed visual hallucinations, and spontaneous parkinsonian motor signs. When parkinsonism is the earliest feature, consensus opinion recommends that dementia within the first year is necessary for a diagnosis of DLB. If dementia occurs later, a diagnosis of PD with dementia is more plausible. The definite diagnosis of DLB requires a specific neuropathology, characterized by diffuse neocortical neuronal cytoplasmic inclusions, called Lewy bodies (LB) [128].

Epidemiological studies agree on the fact that hallucinations involve approximately half of DLB patients (McKeith et al. 48% [129], Klatka et al. 60.7% [130]; Ballard et al. 65% [131], Rockwell et al. 56% [132]).

Differently from PD and AD, hallucinations appear in the early stage of the disease and are relatively stable. Visual hallucinations are the most commonly experienced psychiatric symptom and are often accompanied by delusions, anxiety, and behavioral disturbance [133]. These false visual perceptions are often fully formed, detailed three-dimensional objects, people, or animals, evoking a great range of emotional responses, from joy to fear, even to indifference [134]. Auditory hallucinations are also frequently observed, but they rarely occur in patients without visual hallucinations [134, 135]. In addition, musical hallucinations have been reported, often represented by religious and patriotic songs [20].

A strong association between distribution of LB in the temporal lobes and visual hallucinations has been observed. In fact, cases with well-formed visual hallucinations had higher densities of LB in the amygdala, parahippocampus, and inferior temporal cortex [136]. Brain perfusion imaging demonstrated reduced primary and secondary visual occipital cortex uptake in hallucinated DLB patients [137].

Visual hallucinations can be exacerbated by low levels of arousal and attention; strategies to increase these by social interaction and environmental novelty may reduce their impact [133].

When pharmacologic intervention is required, cholinesterase inhibitors are the current best choice. Visual hallucinations are associated with greater deficits in cortical acetylcholine and are thought to be a predictor of a good response to cholinesterase inhibitors [138, 139]. Randomized, placebo-controlled trials demonstrated the effectiveness of rivastigmine and donepezil [140, 141]. The reduction of hallucinations appears to be mediated by improved attentional function [139]. If cholinesterase inhibitors are ineffective or insufficient, a cautious trial of an atypical antipsychotic could be necessary, without neglecting the possibility of a severe sensitivity reaction [142]. Typical antipsychotics should be avoided [143]. Quetiapine, olanzapine, and aripiprazole may give some benefits, but randomized, placebo-controlled clinical trials are warranted [144–147]. In a randomized, double-blind, placebo-controlled trial, memantine, a NMDA glutamate receptor antagonist, seemed to improve global clinical status and neuropsychiatric features, including hallucinations [148, 149] (Table 7.1).

Table 7.1 Features of hallucinations in neurological disorders (adapted from Manford M and Andermann F, Complex visual hallucinations Clinical and neurobiological insights, Brain, 1998, 121, 1819–1840)

Disease	Modality	Special features	Duration	Consciousness	Insight	Lesion
Hypnic hallucinations	Visual	On falling asleep (hypnagogic) or during awakening (hypnopompic) Typically scaring	Seconds to minutes	Drowsy	Preserved	No lesion
Peduncular hallucinosis	Visual	More often in evening Typically movie-like	Prolonged	Normal	Preserved	Lesion in brainstem or thalamus
Charles Bonnet syndrome	Visual Auditory	Localized to disturbed visual field Typically bizarre and funny	Prolonged	Normal	Preserved	Lesion of visual pathway (from retina to striatal cortex)
Migraine	Visual	Typically flickering, uncolored, unilateral zigzag line from the center of the visual field to the periphery	Minutes	Normal	Preserved	No lesion
Epileptic hallucinations	Visual Auditory Gustatory Olfactory Tactile	Modality depending on epileptic focus Stereotyped	Seconds	Normal	Preserved	Cortical epileptic focus
Intellectual disability	Auditory	Typically associated to other psychiatric symptoms and cognitive dysfunction	Variable	Normal	Reduced	Variable
Alzheimer's disease	Visual Auditory	More often associated to delusions and modification of behavior	Minutes to hours	Normal	Reduced	Frontal lobe degeneration
Parkinson's disease	Visual Auditory	Commonly nonthreatening Often characterized by a false sensation of the presence of persons or animals in the room	Minutes to hours	Normal	Usually preserved	Basal ganglia degeneration

Dementia with Lewy bodies	Visual Auditory	Typically in the early stage of disease Often fully formed, detailed three-dimensional objects, people, or animals, evoking a great range of emotional responses	Minutes to hours	Fluctuating levels of arousal	Reduced	Temporal lobe degeneration
Frontotemporal dementia	Visual Auditory	More often associated to psychosis	Minutes to hours	Normal	Reduced	Temporal lobe degeneration
Prion disease	Visual Auditory Tactile	More frequently during the course of the disease In the Heidenhain variant typically at disease onset	Prolonged	Normal	Reduced	Basal ganglia and occipital lobe degeneration
Delirium	Visual Auditory	Polymodal	Often prolonged	Fluctuating levels of arousal	Reduced	No lesion Underlying medical illness
Autoimmune diseases	Visual Auditory	Typically associated to other psychiatric symptoms and cognitive dysfunction	Often prolonged	Normal or altered	Reduced	Localized inflammation of grey matter
Neurosyphilis	Visual Auditory	Typically associated to progressive cognitive and personality changes	Often prolonged	Normal	Reduced	Cerebral *Treponema pallidum* infection
Inborn errors of metabolism	Visual Auditory	Typically associated to other psychiatric and neurological symptoms	Variable	Normal or altered	Reduced	Variable

7.7.4 Frontotemporal Dementia (FTD)

FTD is a neurodegenerative disorder mainly characterized by behavioral changes and/or language disorder. The behavioral variant of FTD (bvFTD) is a clinical syndrome characterized by a progressive deterioration of personality, social conduct, and cognition. It is caused by frontotemporal lobar degeneration associated with a range of different pathologies, such as p-tau inclusions, TDP-43 inclusions, FUS inclusions, or others [150].

In FTD hallucinations prevalence is approximately 10% [151]. However, recent genetic research has revealed a higher prevalence of psychosis in certain genetic groups. In particular, FTD patients with genetic mutations of *C9ORF72* and *GRN* genes display a higher frequency of psychosis. Prevalence of hallucinations in FTD cases with *C9ORF72* mutations ranges from 0 to 50% [152], while in patients with *GRN* mutations it is about 30% [153]. Clinicopathological reports have shown higher frequency of psychosis in TDP-43 type B [151] and FUS pathologies [154]. In some cases, it is reported that hallucinations may precede the onset of dementia [152].

Hallucinations in different modalities have been described [155]. Selective degeneration of supragranular layers of the temporal lobes can lead to a release of the infragranular layers from a regulatory control. This may cause an excessive activation of association in cortical areas causing hallucinations. Furthermore, a serotonergic deficit has been demonstrated in the brain of patients affected by FTD [70]. This can contribute to development of hallucinations. For this reason, studies have been performed to assess the efficacy of serotonergic therapy in treating psychotic symptoms in FTD patients, giving controversial results [156–158]. Treatment with atypical neuroleptic drugs, like quetiapine, olanzapine, risperidone, and aripiprazole, may be useful [71].

7.8 Prion Diseases

Prion diseases are severe neurological disorders caused by spread of prion protein, an infectious protein agent, in different cerebral areas. Five human prion diseases are currently recognized: kuru, Creutzfeldt-Jakob disease (CJD), variant Creutzfeldt-Jakob disease (vCJD also known as new variant CJD), Gerstmann-Sträussler-Scheinker syndrome (GSS), and fatal familial insomnia (FFI).

CJD is the most frequent of the human prion diseases. It is characterized by rapidly progressive mental deterioration and motor symptoms, especially myoclonus, ataxia, and extrapyramidal signs [159]. Mental deterioration may be manifest as dementia, with concentration, memory, and judgment difficulties [160], and/or as behavioral changes, including psychiatric symptoms such as fatigue, anxiety, and change in personality. Hallucinations in different modalities have been described. Optical and tactile hallucinosis has been reported at clinical onset [161], but the incidence of hallucinations at presentation is low (about 1%) and they occur more frequently during the course of the disease [162, 163].

One of the different sporadic CJD phenotypes known as the Heidenhain variant is characterized by mainly visual involvement at disease onset, reflecting the early targeting of prions to the occipital cortex [164]. Heidenhain variant is associated with the pathological prion protein (PrPSc) type 1 or 2C and the methionine/methionine prion protein gene (*PRNP*) genotype at codon 129 [164, 165]. Typical visual perceptual abnormalities are illusions, characterized by distorted perception in the objects' shape (metamorphopsia), size (micropsia/macropsia), and axis (tilt); color distortion (dyschromatopsia); and complex optical hallucinations, such as bugs crawling or substances oozing from the ceiling [166]. Other manifestations include blurred vision, visual field defects, visual agnosia, dyslexia, optic ataxia, or cortical blindness [162, 163, 166, 167]. Patients affected by Heidenhain variant seem to have a worse prognosis with a shorter disease course as compared to patients with classical CJD phenotype. Neuropathological studies revealed main alterations in the occipital lobe. Magnetic resonance images may show hyperintensities in T2- and proton-weighted sequences localized in the basal ganglia or grey matter of the occipital cortex [167].

In 1996, a new variant Creutzfeldt-Jakob disease was described in the United Kingdom [168]. It has been hypothesized that this variant represents the bovine-to-human transmission of bovine spongiform encephalopathy [169]. Compared to typical sporadic CJD it is characterized by younger age of symptom onset (median 26 years), less rapid progression of illness, and different clinical features [170]. The majority of cases present with psychiatric manifestations, including depression, apathy, anxiety, irritability, social withdrawal, agitation, and insomnia [171]. Florid psychiatric symptoms, such as delusions or auditory and visual hallucinations, have also been described [172].

Hallucinations also occur occasionally as a late feature in familial CJD and GSS. Complex hallucinations and vivid dreams are reported in the more advanced stages of FFI. Reported hallucinations frequently involve scary people or animals that often appear to be disfigured, diseased, or deformed [162, 163].

A successful therapeutic approach to delay the progression or mitigate symptoms of these disorders is currently unavailable [173].

7.9 Hallucinations Associated with Other Medical Conditions

7.9.1 Delirium

Delirium is a condition of confusional state, more frequent in elderly people, associated with an underlying medical illness. It is characterized by a fluctuating disturbance in attention and awareness, developed over a short period of time (usually hours to days), associated with other cognitive deficits caused by a medical condition, substance intoxication or withdrawal, or medication side effect [61].

A wide spectrum of medical conditions can lead to delirium. Prescribed drugs, especially opioids, sedative-hypnotics, antipsychotics, anticholinergic drugs, and

infections, especially sepsis, are probably the commonest causes. Other frequent causes include drugs of abuse and withdrawal states, metabolic imbalance such as electrolyte and endocrine disturbances, hypoxemia, surgery, systemic organ failure (cardiac failure, liver failure, pulmonary disease, hematologic alterations, renal failure), and neurologic disorders (e.g., stroke, seizures). An underlying dementia is a risk factor [174].

Disturbed perception is common and includes illusions (misperceptions) and hallucinations. Visual hallucinations are more typical; however, hallucinations in auditory and other sensory modalities have also been described [174].

The best way to treat delirium is to identify and treat the underlying cause. In some cases, it can be necessary to begin a pharmacological therapy; in this case, antipsychotics (e.g., haloperidol) can be useful [175].

Delirium tremens is a particular form of delirium, which represents a severe manifestation of alcohol-withdrawal syndrome. It is defined by the presence of hallucinations, disorientation, tachycardia, hypertension, hyperthermia, agitation, and diaphoresis in the setting of acute reduction or abstinence from alcohol. Prolonged visual complex hallucinations (especially animal images, zooscopies) are typical and insight is often reduced, especially in later stages. Patients may also experience auditory or tactile false perceptions [176].

Treatment includes supportive care, including intravenous fluids and nutritional and multivitamin supplementation, and intravenous high-dose therapy with benzodiazepines. In cases of refractory delirium tremens, administration of barbiturates can be helpful [177].

7.9.2 Paraneoplastic Neurological Syndromes

Cerebral involvement is quite common in paraneoplastic syndromes. Paraneoplastic encephalitis is an inflammatory autoimmune process typically involving structures of the limbic system (limbic encephalitis), but clinical and radiological findings often extend also to other regions of the nervous system, such as brainstem, cerebellum, and spinal cord.

Limbic encephalitis usually manifests with behavioral changes, cognitive dysfunction especially memory impairment, and complex-partial seizures. Other disease manifestations include hypothalamic dysfunctions (hyperthermia, somnolence, endocrine abnormalities), or symptoms of spinal cord involvement [178].

Many different tumors have been described as being associated with paraneoplastic limbic encephalitis; the most typical are small-cell lung carcinoma, seminoma, thymoma, breast cancer, and Hodgkin's lymphoma, and the type of associated autoantibody varies with tumor type [179].

Psychiatric symptoms, including hallucinations, represent a typical manifestation of anti-*N*-methyl-D-aspartate (NMDA) receptor encephalomyelitis, a well-defined form of paraneoplastic encephalomyelitis associated with anti-NMDA receptor antibodies and ovarian teratoma. At the onset patients typically complain of flu-like symptoms, followed in a few days by severe neurological manifestations

including memory deficits, seizures, insomnia, altered level of consciousness, dyskinesias, autonomic dysfunctions, and language dysfunctions. Psychiatric symptoms are prominent and generally precede neurologic signs and symptoms. They include anxiety, agitation, bizarre behavior, hallucinations, delusions, and disorganized thinking [180]. Hallucinations have been described in about 40% of patients. Auditory, visual, and olfactory phenomena have also been reported [179].

Brain MRI is often normal or shows FLAIR alterations or contrast enhancing in cortical (brain, cerebellum) or subcortical regions (hippocampus, basal ganglia, white matter) [181].

Treatment of limbic encephalitis involves resection of the tumor, administration of glucocorticoids (e.g., methylprednisolone 1 g daily for 5 days), intravenous immune globulin (i.e., 0.4 g/kg daily for 5 days), and plasma exchange [179, 180].

Morvan's syndrome is another paraneoplastic neurological syndrome characterized by coexistence of peripheral nerve hyperexcitability (neuromyotonia), autonomic hyperactivity, and neuropsychiatric symptoms (insomnia, cognitive impairment, memory loss, and seizures). It has been associated with anti-contactin-associated protein-like 2 (Caspr2) antibodies. Sometimes patients have a thymoma, but it may be diagnosed with or without an associated tumor. Hallucinations have been described in about 52% of patients, especially visual hallucinations. A good clinical response to immunotherapy has been reported [181].

7.9.3 Systemic Lupus Erythematosus (SLE)

SLE is a chronic autoimmune disease characterized by a wide range of clinical and serological manifestations and can affect virtually every organ. It typically manifests with systemic symptoms, such as fever, fatigue, and weight loss, associated with inflammatory damage in several organs. Most frequently affected organs are skin and mucous membrane (facial erythema, discoid lesions, oral and nasal ulcers), joints (arthritis and arthralgias), vascular system (Raynaud phenomenon, vasculitis, thromboembolism), kidneys, gastrointestinal tract, lungs, heart, and eyes [182].

Neuropsychiatric involvement has been reported to occur in 10–80% of patients either at clinical onset or during disease course [183, 184]. A wide range of different neurologic and psychiatric manifestations have been reported, involving both the central and peripheral nervous systems. Most typical are aseptic meningitis, cerebrovascular disease, demyelinating syndrome, headache, movement disorder, myelopathy, seizures, Guillain-Barré syndrome, autonomic neuropathy, mononeuropathy, myasthenia gravis, cranial neuropathy, plexopathy, and polyneuropathy. Reported psychiatric symptoms are anxiety, acute confusional state, cognitive dysfunction, mood disorder, and psychosis. The latter is reported in up to 8% of SLE patients and is characterized by delusions or hallucinations. Auditory hallucinations are more frequent [185], for example third-person auditory hallucinations [186], but visual and tactile perceptions have also been reported [187]. SPECT areas of hypoperfusion in the parietal lobes and frontal lobes have been described in up to 80% and 65%, respectively, of patients with neuropsychiatric SLE [188]. In cases of

psychotic manifestations due to lupus activity in the central nervous system, an association has been noted with the presence of serum autoantibodies to ribosomal P protein or CSF antibodies to neuronal cells [189, 190].

Nevertheless, it has been reported that in many cases psychotic symptoms, particularly auditory hallucinations, are a consequence of steroid therapy and not a primary disease manifestation [191].

Neuropsychiatric symptoms due to corticosteroid therapy generally resolve with discontinuation or lowered dose of glucocorticoids. Psychosis due to direct cerebral involvement by SLE usually responds to steroids. If no improvement is seen within 2–3 weeks, administration of cytotoxic therapy (e.g., cyclophosphamide) is required [192].

7.9.4 Hashimoto's Encephalopathy

Hashimoto's encephalopathy is a rare neurological syndrome, also known as steroid-responsive encephalopathy associated with Hashimoto's thyroiditis, a chronic autoimmune disease causing hypothyroidism. It is typically characterized by subacute onset of behavioral changes and confusion with altered consciousness level, and is often associated with other neurological symptoms such as seizures, myoclonus, cognitive decline, stroke-like episodes, and/or ataxia. Psychiatric features, such as hallucinations, delusions, and paranoia, have been reported. About 26% of patients experience hallucinations in different modalities [193].

Hashimoto's encephalopathy is considered an autoimmune disease and elevated thyroid antibodies are frequently present. Cerebrospinal fluid analysis may reveal elevated protein, and antithyroid peroxidase antibodies (anti-TPO) have also been detected in adult patients' CSF. Brain MRI is usually normal. Administration of corticosteroid therapy or intravenous immunoglobulin is recommended [194].

7.9.5 Behçet's Syndrome

Behçet's syndrome is a systemic autoimmune disease characterized by recurrent oral aphthae associated with several clinical manifestations including ocular disease, genital ulcers, joint arthritis, skin lesions, gastrointestinal disease, neurologic involvement, and vascular disease [195].

Neurologic manifestations have been described in about 10% of patients (neuro-Behçet). They may consist of an immune-mediated meningoencephalitis, which typically involves the brainstem, but can also involve the basal ganglia, thalamus, cortex, white matter, spinal cord, or cranial nerves, or as a consequence of thrombosis within the dural venous sinuses [196]. In the case of parenchymal disease, psychiatric symptoms, including hallucinations, have been reported. Psychiatric manifestations tend to develop some years after neurological symptoms first occurred. Nevertheless, a case has been reported of neuro-Behçet's syndrome with a psychiatric presentation characterized by visual and auditory hallucinations, behavioral disturbances, anxiety, loss of appetite, and worsening of communication

abilities [197]. Treatment requires corticosteroid administration and long-term immunosuppressive therapy, such as azathioprine. Antipsychotic drugs may be useful in controlling acute psychotic symptoms [198].

7.9.6 Neurosyphilis

Neurosyphilis, a manifestation of late syphilis, is a progressive dementing illness that usually develops 10–25 years after *Treponema pallidum* infection. Its incidence has highly declined in the last decades, thanks to the widespread use of antibiotics [198]. It is characterized by progressive cognitive decline, especially memory and judgment impairments, and personality change. Psychiatric symptoms have been described, including depression, mania, and psychosis. Auditory (e.g., people talking), tactile, and complex visual (e.g., insects, animals) hallucinations have all been reported during the disease course [199, 200]. As shown by several studies, in recent years neurosyphilis clinical features are changing and psychiatric and neurocognitive symptoms at clinical onset are becoming more frequent [201]. In particular, auditory hallucinations are common at presentation [202, 203], and a few cases have been published with visual hallucinations at onset [204]. Treatment requires administration of penicillin G (18–24 million units per day for 10–14 days). To better control psychiatric symptoms, administration of atypical antipsychotics, such as quetiapine or olanzapine, can be useful [200, 205].

7.9.7 Inborn Errors of Metabolism

Inborn errors of metabolism (IEM) are a large class of genetic disorders due to defects of genes encoding for enzymatic proteins. The accumulation of substances not appropriately metabolized or the defective synthesis of essential compounds leads to the disease. IEM are a rare cause of psychiatric manifestations. Psychiatric signs can remain isolated for years before more specific organic signs become observable [206].

Urea cycle disorders may present with psychosis, in particular delusions and visual hallucinations. Recurrent psychotic episodes may be misdiagnosed as schizophrenia. Metabolic attacks can be spontaneous or triggered by high-protein intake, hypercatabolism, or pharmacological treatments. During metabolic attacks, psychiatric symptoms are often accompanied by headache, nausea, and vomiting [207, 208].

Methylene tetrahydrofolate reductase (MTHFR) deficiency and cobalamin metabolism defects (CblC) may present with chronic or subacute psychiatric symptoms. Symptoms include disorganized behavior, delusions, and hallucinations (auditory and visual). These can be followed by alteration of consciousness, subacute paraplegia, and coma. Treatments with methylfolate and methylcobalamin for MTHFR deficiency and hydroxocobalamin for CblC can be very efficient if started in good time [209–211].

Adult forms of metachromatic leukodystrophy often begin with psychiatric manifestations. These symptoms, including delusions, hallucinations, and disorganized behavior, can imitate schizophrenia. Neurological signs, such as dementia, spastic paraparesis, cerebellar ataxia, and polyneuropathy, may become evident some years later [212, 213].

Late-onset GM2 gangliosidosis usually presents with lower motor neuron disease, cerebellar ataxia, and dystonia. Acute episodes of psychosis are relatively common and may remain isolated for years before the appearance of motor signs. Patients often exhibit delusions, disorganization of thought, agitation, and hallucinations which may persist between attacks. Phenothiazines are poorly effective and can worsen motor and psychiatric signs [214–216].

Niemann–Pick type C patients may also suffer from isolated psychiatric problems for years. Onset can be progressive or acute, with spontaneous remissions and relapses. Most patients presenting with hallucinations and delusions as initial manifestations have normal neurological examination. Vertical oculomotor apraxia is a characteristic sign of the disease but may appear later. Splenomegaly, however, is an almost constant feature, even in the earliest stages [217].

Alpha-mannosidosis is characterized by mild intellectual disability, progressive neurosensory hearing loss, visual loss, skeletal dysmorphism, and progressive spastic ataxia. In addition, patients may exhibit recurrent episodes of confusion and psychosis including delusions and hallucinations, auditory and visual in nature. These may last several weeks and are followed by somnolence and asthenia [218, 219].

In summary, hallucinations are frequently observed in many neurological disorders and other medical conditions affecting brain function. Differently from hallucinations in psychiatric diseases, neurological ones are rarely isolated and are more often accompanied by a set of signs and symptoms suggesting an organic disease. Moreover, medical history, brain imaging, and neurophysiological studies allow us to distinguish almost with certainty functional and organic hallucinations.

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