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CASE REPORT

Visual Hallucinations and Pontine Demyelination in a Child: Possible REM Dissociation?

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An 11 year-old-boy acutely developed complex visual and acoustic hallucinations. Hallucinations, consisting of visions of a threatening, evil character of the Harry Potter saga, persisted for 3 days. Neurological and psychiatric examinations were normal. Ictal EEG was negative. MRI documented 3 small areas of hyperintense signal in the brainstem, along the paramedian and lateral portions of pontine tegmentum, one of which showed post-contrast enhancement. These lesions were likely of inflammatory origin, and treatment with immunoglobulins was started. Polysomnography was normal, multiple sleep latency test showed a mean sleep latency of 8 minutes, with one sleep-onset REM period.
The pontine tegmentum is responsible for REM sleep regulation, and contains definite "REM-on" and "REM-off" regions. The anatomical distribution of the lesions permits us to hypothesize that hallucinations in this boy were consequent to a transient impairment of REM sleep inhibitory mechanisms, with the appearance of dream-like hallucinations during wake.

Keywords: Peduncular hallucinosis, visual hallucinations, REM sleep, brainstem, dreams

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Complex visual hallucination can be consequence of lesions affecting the visual pathways, the arousal systems, the thalamus and the upper brainstem.[1] Hallucinations arising from upper brainstem lesions, located around the cerebral peduncle, configure the syndrome of "peduncular hallucinosis", which is characterized by complex visual hallucinations, sometimes polymodal, of prolonged duration, which occur mainly in the evening; usually consciousness is not altered and insight is preserved.[1]

Bischof and Bassetti[2] observed that complete bilateral occipital lobe damage in a patient caused total dream loss. Dreams are, in essence, complex visual hallucinations occurring during sleep. Dream experience is strongly associated with REM sleep; nevertheless, basic and clinical researchers have demonstrated that generators of REM sleep and dreaming, while overlapping, are essentially distinct.[2] As a consequence, the possibility exists of a dissociation between dreaming and REM sleep as a result of a brain damage.[2] This observation supports the hypothesis that in specific clinical situations, a link between dreaming and hallucinations may exist.

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We report the case of a boy who acutely developed visual hallucinations associated to small, punctuate inflammatory lesions located in the paramedian and lateral portion of the pontine tegmentum. We hypothesize that hallucinations in this boy were a result of transient impairment of pontine modulatory mechanisms, with consequent occurrence of dissociation between dream activity and REM sleep.

REPORT OF CASE

An 11-year-old boy with normal visual acuity, acutely presented with sore throat and fever (38°C). Antibiotic treatment was started, and fever remitted in 2 days. Previous medical history was unremarkable. The day after the resolution of fever, he began to present hallucinations. Hallucinations occurred in the afternoon, after watching TV. They were polymodal: he saw and heard Voldemort (an evil character of the Harry Potter saga). He did not realize his hallucinations were not real; he was extremely frightened, and he cried and searched his parents for protection. The episode lasted several hours, and was not associated with modification of vigilance or consciousness. The boy showed a behavioral change, characterized by inappropriate laughing and silliness. Two days later, a new hallucinatory episode occurred: again, he saw Voldemort, who appeared threatening, and he fought against him. A further episode, with the same features, occurred the following day. He interacted with the characters of the hallucination, and on one occasion, he wore a sword and helmet to fight against Voldemort. When

asked to recall the hallucinations, the boy said that they appeared real to him.

During all the episodes of hallucination, neurological examination was normal. EEG recordings performed during and after the hallucinatory episodes were normal. Protein and cells in the cerebrospinal fluid (CSF) were normal. Blood and CSF antibody titers and CSF cultures for bacteria, viruses, fungi, and mycobacterium were negative. The search for auto-antibodies was also negative. Oligoclonal bands were absent. A full-night, laboratory-based, video-EEG and polysomnographic study was performed. Montage included: 8 EEG leads (Fp_1, Fp_2, C_3, C_4, T_3, T_4, O_1, O_2), EOG, chin and intercostals EMG, EKG, airflow (nasal cannula), chest and abdominal effort, SpO_2, body movements. The main PSG parameters were normal: time in bed, 420 minutes; sleep latency, 11 minutes; sleep efficiency, 95%; slow wave sleep percentage, 33%; REM percentage, 23%; cyclic alternating pattern rate, 38%. No pathologic respiratory events were present.

Multiple sleep latency test (MSLT, 4 nap opportunities) showed a mean sleep latency of 8 minutes, with one sleep-onset REM period (SOREMP); this result was considered normal in light of the child's pubertal status (Tanner stage 3).[3]

Brain MRI scans, performed after the onset of hallucinations and during follow-up, showed areas of abnormal signal in the pons (Fig. 1 A, B, C). Treatment with immunoglobulins was started, and full remission of behavioral abnormalities and of the hallucinations occurred. At 3-month follow-up the boy presented no neurological or behavioral abnormality. In follow-up MRI, the lateral pontine lesion was no longer visible, whereas the pontine paramedian signal abnormalities were still evident. No post-contrast enhancement was present.

A definite diagnostic conclusion was not possible. The differential diagnosis included vasculitis, infectious disease, metabolic disease, and multifocal leukoencephalopathy. The presence of blood-brain barrier disruption suggested an inflammatory etiology. Vasculitis seemed unlikely due to the absence of signs of acute ischemia on diffusion-weighted images, the absence of hemorrhage, and the lack of leptomeningeal contrast enhancement. The absence of CSF abnormalities made infection an unlikely cause. The sparing of basal ganglia made metabolic disease unlikely. Among multifocal leukoencephalopathies, the most likely diagnosis was a transient demyelinating syndrome, definable as *clinically isolated syndrome* (CIS). A CIS is "a first acute-clinical episode of CNS symptoms with a presumed inflammatory demyelinating cause for which there is no prior history of a demyelinating event."[4]

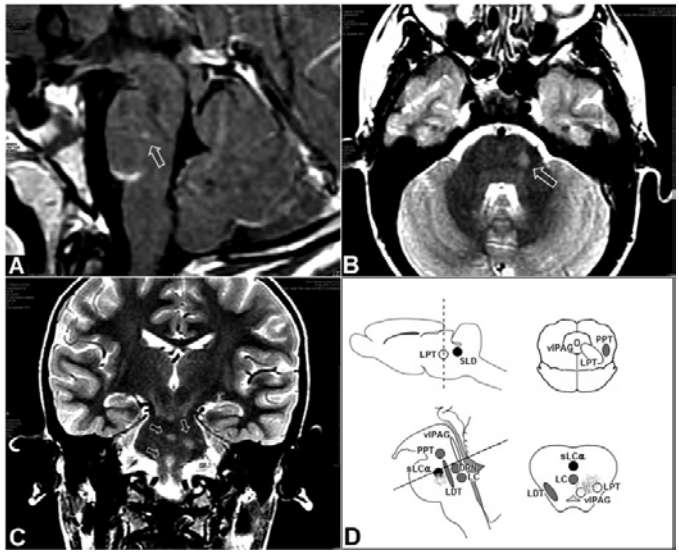

Figure 1—Brain MRI after the onset of hallucinations. **A**: Sagittal T1-W scan, after IV contrast injection. A small area of contrast enhancement is visible in the middle pons (white arrow), below the floor of the 4th ventricle. **B**: Axial T2-W sequence, at the level of the cerebral peduncles. A small area of signal hyperintensity is visible in the right lateral portion of the pons. **C**: Coronal T2-W sequence, passing through the brainstem. Three distinct areas of signal hyperintensity (arrows) are visible in the paramedian and lateral portion of the pons (arrows); the most cranial one corresponds to the area of post-contrast enhancement shown in panel A. **D**: scheme of the REM-on and REM-off areas in the pons, in rat and human. Left panel: sagittal view; right panel: axial view (the dotted lines indicate the level of the cut). In black: the REM-on region (sublaterodorsal tegmental nucleus (SDT) in rat, locus subceruleus-α [sLCα] in man). In white: the REM-off region: ventrolateral periaqueductal gray (vlPAG) and lateral pontine tegmentum (LPT). In gray the REM modulatory regions: in rostrocaudal order, pedunculopontine tegmentum (PPT), laterodorsal tegmentum (LDT), dorsal raphe nucleus (DRN), and locus ceruleus (LC). Gray dotted areas: sites of the inflammatory lesions.

DISCUSSION

Peduncular hallucinosis syndrome consists of visual hallucinations due to lesions in the upper brainstem and thalamus (the peripeduncular area).[1] Hallucinations arising from lesions in these areas can be a consequence of (1) impairment of structures involved in visual control; (2) dysfunction of arousal systems; (3) epilepsy (either as ictal or as postictal phenomena); (4) psychiatric disturbances.[1]

The pontine tegmentum plays a pivotal role in the regulation of sleep and arousal. According to the classical model by Hobson and McCarley, NREM/REM alternation is entrained by the reciprocal interaction of two cellular populations in the pons ("REM-on" and "REM-off" cells). A new model of REM sleep regulation has recently been proposed; this model is based on a sort of flip-flop switch arrangement, in which GABAergic REM-on neurons (located in the sublaterodorsal tegmental nucleus) inhibit GABAergic REM-off neurons (located in the ventrolateral periaqueductal gray matter and lateral pontine tegmentum) and vice versa[5] (Fig. 1D). According to this model, the traditional REM On/Off cells (peripeduncular tegmentum, laterodorsal tegmentum, dorsal raphe nuclei, locus coeruleus) actually serve to modulate the REM-on and REM-off regions, rather than drive REM directly. The demonstration of independent pathways mediating atonia and the EEG components of REM provide a basis for their occasional dissociation in pathological states.[5]

Intrusion of REM sleep and dreams into the wake state is considered the pathogenetic mechanism of hallucination in delirium tremens.[6] Several observations support the hypothesis that a dysregulation of REM sleep can produce visual hallucination. Arnulf et al.[7] suggested that visual hallucinations in Parkinson disease may be dream imagery. Analogously, Cohen et al.[8] proposed that hallucinations and delirium in patients with

Guillain-Barré syndrome are consequent to dissociation between sleep state and dreamy activity. According to this model, visual hallucinations may reflect a disorder of REM sleep.

As regards the pathogenesis of hallucinations, the epileptic origin was unlikely because of the absence of EEG abnormalities, the deep subtentorial localization of the MRI lesion and the absence of cortical lesions. Psychiatric etiology is unlikely. According to the DSM-IVR, a "short lasting psychotic disorder (298.8)" was ruled out by the presence of a medical condition, that is the inflammatory brain disease. "Delirium secondary to medical conditions (293.0)" was excluded by the lack of impairment of consciousness.

No supratentorial, and particularly, no structure related to the visual system, was involved. Therefore, the hallucinatory symptoms were presumably related to a transient dysfunction of a neuronal system involved in arousal regulation. In our patient lesion were small, punctuate, and distributed along the paramedian and lateral portions of the pontine tegmentum (Figure 1B, C). The presence of lesions in the mesopontine tegmentum allows us to hypothesize the dysfunction of REM-related structures; and in particular, of the REM-off cells, located in the vlPAG and in the LPT. This could result in a weakened inhibition of the REM-on generators during other sleep stages, and possibly during full wakefulness. In conclusion, it can be speculated that transient lesions of pontine tegmentum can induce visual hallucinations resembling those commonly described as peduncular hallucinosis, due to a transient imbalance between REM-on and REM-off pontine circuitry. This could result in the intrusion of a dream-like state into wakefulness.

ABBREVIATIONS

CSF:	Cerebrospinal fluid
DRN:	Dorsal raphe nucleus
LDT:	Laterodorsal tegmentum
LPT:	Lateral pontine tegmentum
MRI:	Magnetic resonance imaging
MSLT:	Multiple sleep latency test
PSG:	Polysomnography
SDT:	Sublaterodorsal tegmental nucleus
sLCα:	Sub-locus ceruleus-α
SOREMP:	Sleep-onset REM period
vlPAG:	ventrolateral periaqueductal gray
PPT:	Pedunculopontine tegmentum
LC:	Locus ceruleus

DISCLOSURE STATEMENT

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