Unusual presentation of hypothalamic hamartoma with hypersomnia in an adult patient

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ABSTRACT – We report a patient with polysomnography findings related to hypersomnia, as a primary presenting symptom, who was shown to have stereotypical gelastic seizures. Her cranial magnetic resonance imaging revealed a hypothalamic hamartoma in the posterior region of the hypothalamus. The patient had no previous history of gelastic seizures. We suggest that patients who present with hypersomnia should be investigated for gelastic seizures in order to avoid misdiagnosis and receive appropriate treatment.

Key words: hypothalamic hamartoma, hypersomnia, seizure, gelastic seizure, polysomnography (PSG), sleep

Hypothalamic hamartomas (HHs) are uncommon tumours arising from the tuber cinereum and inferior hypothalamus. They are often associated with gelastic seizures, precocious puberty, epilepsy, behavioural problems, and learning difficulties (Maixner, 2006). Evidence for a role of HHs in the generation of gelastic seizures has been reported using stereotactic depth electrode recordings and stimulation of HHs (Munari et al., 1995; Kahane et al., 2003), as well as functional imaging studies showing HH hypermetabolism or hyperperfusion (Kuzniecky et al., 1997; Palmini et al., 2005).

Most of the literature on the subject describes the clinical manifestations in children, but there are also a few reports of adult patients with HH (Mullatti, 2003; Mullatti et al., 2003; Oehl et al., 2010). There is variation in seizure semiology amongst adult patients with HHs (Oehl et al., 2010); they tend to have non-gelastic seizures including focal seizures with or without secondary generalisation and tonic-clonic seizures, and are mostly resistant to antiepileptic drugs (Oehl et al., 2010; Troester et al., 2011). Secondary epileptogenesis and alternative propagation networks via limbic circuitry, connecting to the mammillary bodies and mammillothalamic tract, including the anterior thalamic nuclei, have been suggested in the generation of pseudotemporal lobe seizures in...
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HHs (Cascino et al., 1993; Oehl et al., 2010). Due to the refractory nature of seizures and the heterogeneity of HH, different neurosurgical and radiosurgical procedures, including surgical resection or disconnection, gamma knife radiosurgery, and stereotactic radiofrequency thermocoagulation, are considered (Cascino et al., 1993; Rosenfeld et al., 2001; Fohlen et al., 2003, Regis et al., 2007).

The manifestations of HH in adults are poorly understood and rarely reported (Mullatti, 2003; Mullatti et al., 2003; Oehl et al., 2010). However, with improvements in neuroimaging, it is expected that a greater number of adults with HH, some without the typical manifestations, will be detected. Here, we report a rare form of HH in adulthood in a young female, whose presenting symptom was hypersomnia.

Case study

A 25-year-old female biologist was admitted to our neurology department with hypersomnia. She had irresistible urges to sleep during daytime and she complained about sleep paralysis which had occurred for two to three years. The daytime sleep periods lasted less than one hour and she felt better after these naps, indicating narcolepsy rather than idiopathic hypersomnia. Sometimes, she also had hypnagogic hallucinations and sleep paralysis. Her Epworth Sleep Scale score was 18, showing excessive daytime sleepiness. She had no history of any other sleep disorders leading to insufficient night-time sleep or excessive daytime sleepiness.

Furthermore, she did not describe cataplexy but reported a history of laughing attacks during the evaluation of cataplexy in her medical history. Her laughing attacks had occurred daily for 1-2 minutes since the age of 4. These attacks did not cause her distress and she therefore did not report them in a health centre. Her family history was unremarkable. Moreover, she had no history of pubertas praecox.

She was referred to our video-EEG-polysomnography (PSG) monitoring unit to investigate the aetiology of her excessive daytime sleepiness. Her sleep efficiency was 87% and sleep maintenance was 90%. Her sleep latency was 17 minutes and rapid eye movement (REM) sleep latency was 79 minutes. Of her sleep, 26% was REM stage, while 15% was deep non-REM stage. There was no finding related to other primary sleep disorders, such as sleep-related breathing disorders or movement disorders. The multiple sleep latency test (MSLT) revealed early sleep onset within seven minutes and she had a sleep-onset REM (SOREM) in five sessions. Due to lack of resources, we could not check the orexin level in cerebrospinal fluid or perform HLA-DQB1* 0602 testing in serum for narcolepsy. According to the International Classification of Sleep Disorders, Second Edition: Diagnostic and Coding Manual (ICSD-2), she had findings of hypersomnia with decreasing sleep latency in the MSLT, of less than eight minutes. However, we were unable to conclude that she had narcolepsy, because she had less than two SOREMs in five of the MSLT periods.

Her video-EEG-PSG monitoring was continued for three days to record her laughing attacks. Her first attack, with a feeling of laughing, occurred for 40 seconds on the second day of monitoring. There was no emotional component and she did not lose consciousness. It was not possible to interpret her EEG due to muscle artefacts, but she had three more stereotypical attacks. In two of these attacks, there was mild slowing on the left side. Her interictal EEG revealed infrequent slow wave activities in the left temporal lobe. Her cranial magnetic resonance imaging (MRI) revealed a HH in the posterior region of the hypothalamus (figure 1).

She did not want to take any drug for her seizures; she stated that “I can tolerate these gelastic seizures. I do not want to experience the side effects of drugs”. She had acneiform eruptions on her face and also had a history of allergy, urticaria, of unknown origin. Oxcarbazepine was started and gradually increased to 600 mg/day to prevent her focal gelastic seizures. Although she showed mild improvement in daily seizure frequency (several times a week), she did not want to increase or change the drug, or undergo surgery (gamma knife surgery) for HH.

Her major problem of excessive daytime sleepiness was partly resolved by changing her daily sleep schedule for a few months. These changes included taking naps in the early and mid-afternoon. Despite the naps, she was readmitted due to excessive day-
time sleepiness after 3 months. A 100-mg daily dosage of modafinil was prescribed. For a period of almost 2 months, the drug did not affect seizure frequency, but led to a large improvement in her daytime sleepiness.

Discussion

Our patient had a HH and presented with hypersomnia and gelastic seizures, however, her major symptom leading to admission was hypersomnia, not gelastic seizures. There are many reported HH case series involving gelastic seizures or endocrinological problems (Maixner, 2006). The reported sleep problems related to HH are very rare (Dunn et al., 2001).

The symptom of hypersomnia is commonly encountered in clinical practice and can occur as a result of a primary sleep disorder, or may also occur secondary to other causes of disturbed nocturnal sleep. Our patient had symptoms of heavy hypersomnia according to the Epworth Sleep Scale, with sleep attacks lasting for minutes, and she also had sleep paralysis and hypnagogic hallucinations. The classic symptoms of primary central hypersomnia narcolepsy include excessive daytime sleepiness, cataplexy, hypnagogic hallucinations, and sleep paralysis (American Academy of Sleep Medicine, 2005). Our patient's history and nocturnal sleep PSG did not reveal any other primary sleep disorder. The quality and quantity of her nocturnal sleep was poor, except for a slightly shorter period of deep NREM sleep, but her MSLT findings revealed hypersomnia with shorter sleep latency, of less than eight minutes. Moreover, one SOREM was recorded in five sessions during the MSLT. We were unable to check a lower orexin level in CSF or positivity of HLA-DQB1* 0602 in serum to diagnose narcolepsy. However, SOREM episodes, as observed in classic forms, may be absent in patients with secondary narcolepsy (Bassetti et al., 2003; Maia et al., 2006).

While most cases of narcolepsy are idiopathic and are not associated with clinical or radiographic evidence of brain pathology, secondary narcolepsy may occur occasionally in association with lesions of the diencephalon, midbrain, andpons. Head trauma, tumours involving the posterior hypothalamus, stroke, multiple sclerosis, encephalitis, cerebral sarcoidosis, pituitary lesions, craniohypophyseal, and arteriovenous malformations can lead to secondary narcolepsy (Nishino and Kanbayashi, 2005).

The posterior hypothalamus facilitates the awake state and contains orexin neurons. Von Economo was the first to study the brains of people affected by encephalitis lethargica, a presumed viral illness that causes profound sleepiness. He noted the relationship between lesions of the posterior hypothalamus and profound sleepiness (Pearce, 1996). Neurons that synthesize the excitatory peptides, orexins, located in the perifornical region of the posterior hypothalamus, promote wakefulness and suppress sleep. Lack of orexins, or their receptors, is associated with narcolepsy/cataplexy, a disorder characterised by an increased pressure for REM sleep. Although our patient had no heavy REM pressure during daytime sleepiness and cataplexy, it is possible that the HH in the posterior region impaired the function of neurons and their pathways involved in awakening. Furthermore, our patient had no other primary sleep disorder leading to low sleep efficiency and daytime sleepiness. There were also no frequent arousals from seizures or interictal activity resulting in reduction of sleep efficiency.

Sleepiness and hypersomnia are common in patients with hypothalamic tumours, even when orexin levels are normal. However, to the best of our knowledge, hypersomnia presenting and/or associated with HH has not been reported before. Dunn et al. evaluated six patients with HH and gelastic seizures, and noted their sleep. In contrast to the present case, their patients had sleep difficulties or, in particular, a reduction in REM sleep (Dunn et al., 2001). In another reported case of HH (case 2), although the major problem was not related to sleep, an absence of REM sleep and a decrease of deep non-REM sleep was also reported (Mullatti, 2003). Alteration of the circadian clock and disturbance in the function of sleep centres in these patients with HH were suggested.

Our patient's interictal and ictal EEG recordings with mild changes were not surprising. In patients with HH, interictal and ictal EEG findings are variable, with generalised, multifocal, and focal findings (Troester et al., 2011). However, the possible lack of interictal and ictal EEG changes, as in our case with gelastic seizures, can result in a delay in diagnosis. Furthermore, these epileptiform discharges can be mislocalised to the temporal or the frontal lobe in adulthood (Troester et al., 2011).

A large spectrum of therapeutic approaches have been proposed, including gamma knife surgery (Regis et al., 2007) and surgery/microsurgery using different routes (Cascino et al., 1993; Rosenfeld et al., 2001; Fohlen et al., 2003) in patients with HH. In severe cases, early surgical intervention is probably to be recommended in an attempt to minimise or prevent the cognitive and behavioural problems commonly observed with this epileptic syndrome. These surgical therapies may also decrease the disturbance in the function of sleep centres. However, the effect of resection on sleep disorders is not known. We did not insist on these types of invasive procedure in our patient due to the relatively high risk of complications, such as temporary seizure exacerbation after irradiation, transient hormonal problems (diabetes insipitus,
increasing appetite, or vascular complications (Rosenfeld et al., 2001). Her symptoms related to hypersomnia decreased almost 50% and so she did not want to undergo any invasive procedures.

In conclusion, adult patients with sleep disorders, such as hypersomnia, are mostly evaluated for central nervous lesions, particularly within the region of the third ventricle, thalamus, and hypothalamus. At the same time, patients should be investigated with regards to gelastic seizures in order to avoid misdiagnosis and receive appropriate treatment.

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