SHORT REPORT

Isolated mediotegmental lesion causing narcolepsy and rapid eye movement sleep behaviour disorder: a case evidencing a common pathway in narcolepsy and rapid eye movement sleep behaviour disorder

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Narcolepsy is usually an idiopathic disorder, often with a genetic predisposition. Symptomatic cases have been described repeatedly, often as a consequence of hypothalamic lesions. Conversely, REM (rapid eye movement) sleep behaviour disorder (RBD) is usually a secondary disorder, often due to degenerative brain stem disorders or narcolepsy. The case of a hitherto healthy man is presented, who simultaneously developed narcolepsy and RBD as the result of an acute focal inflammatory lesion in the dorsomedial pontine tegmentum in the presence of normal cerebrospinal fluid hypocretin-1 levels and in the absence of human lymphocyte antigen haplotypes typically associated with narcolepsy and RBD (DQB1*0602, DQB1*05). This first observation of symptomatic narcolepsy with RBD underlines the importance of the mediotegmental pontine area in the pathophysiology of both disorders, even in the absence of a detectable hypocretin deficiency and a genetic predisposition.

Most cases of narcolepsy are idiopathic without evidence of causative brain lesions.[1] Cases of ''symptomatic narcolepsy'' were described in patients with lesions of the hypothalamus and, less often, of the midbrain, pons or other areas of the brain, in multiple sclerosis, head trauma, brain tumours, degenerative disorders and other causes.[2] In some patients, the causal or temporal relationship between the causative event and the emergence of narcoleptic symptoms was disputable.[2] Many patients considered to have symptomatic narcolepsy were human lymphocyte antigen-DR2 positive, indicating a genetic basis, and it was proposed that certain anatomical lesions might induce, facilitate or accelerate a narcoleptic syndrome only in genetically predisposed people.[3]

Rapid eye movement (REM) sleep behaviour disorder (RBD) represents an abnormal phenomenon of REM sleep, which is interpreted as the physical enacting of violent dreams. It is partly explained by the absence of the physiological REM-sleep muscle atonia, and was first described in cats after a lesion in the pontine tegmentum near the perilocus coeruleus α.[4] Today, RBD in humans is recognised as a frequent concomitant of Parkinson's syndrome, multiple system atrophy, Lewy body dementia, but also of idiopathic narcolepsy.[5] Most patients with RBD, and lesions proved on magnetic resonance imaging (MRI), did show clinical signs of a more widespread neurodegenerative disease,[6] hampering unequivocal conclusions on the clinicoanatomical relationship. Recently, a 70–year-old patient with RBD over 10 years was described, who showed a circumscript brain stem lesion in the paramedian upper pons.[7]

Although the association of idiopathic narcolepsy and RBD is well established and can even be considered to be typical of severe cases,[5] this is, to our knowledge, the first description of RBD in a patient with symptomatic narcolepsy, where the causative lesion might give a pathophysiological clue.

CASE REPORT

A 30-year-old previously healthy man not taking any drugs, without a history of alcohol or drug misuse, was admitted to our department with symptoms and signs of brain stem encephalitis. Three months before admission, he had a febrile illness with fever >39°C, severe headache and double vision. A bilateral weakness of eye abduction and convergence, a vertical nystagmus at upward gaze and a slightly unsteady gait was found. An MRI of the brain showed an isolated circumscript T2-hyperintense and contrast-enhancing lesion (fig 1) medially in the pontine tegmentum adjacent and rostral to both fourth nerve nuclei.[8] In particular, there was no additional lesion in the hypothalamus, and thyroid-stimulating hormone was normal. An inflammatory lesion was assumed, and steroids were given.

Six months later, double vision had partially subsided, but severe fatigue and hypersomnia evolved, with both prolonged night sleep as well as continually reduced alertness and episodes of superimposed sleep attacks. When seen in our department, the Epworth score[9] was 13 (normal <10). Apart from an isolated cataplexy-like episode, the patient reported new episodes of sleep paralysis with hallucinations while falling asleep or while awakening several times per month. He also recalled more unpleasant dreams and frequent nightmares. His wife reported violent motor activity and screaming during sleep. No psychiatric symptoms were reported.

The neurological examination showed a horizontal gaze-evoked nystagmus to both sides, with double vision. Smooth pursuit was saccadic, the vestibulo-ocular reflex was incompletely suppressed, and the Halmagy test was abnormal to both sides.

Multimodal evoked potentials and electroencephalogram were all normal. Cerebrospinal fluid (CSF) was normal (2 cells/mm^3, protein 36 mg%), without oligoclonal bands, and with normal hypocretin (266 pg/ml) and leptin (0.43 ng/ml) levels. These data have been included in a larger series of patients published earlier.[10] In the MRI, the persisting pontine lesion now showed less contrast enhancement than during the initial investigation. The diagnosis suggested an acute para-infectious brain stem encephalitis.

Abbreviations: CSF, cerebrospinal fluid; MRI, magnetic resonance imaging; MSLT, multiple sleep latency test; RBD, rapid eye movement sleep behaviour disorder; REM, rapid eye movement

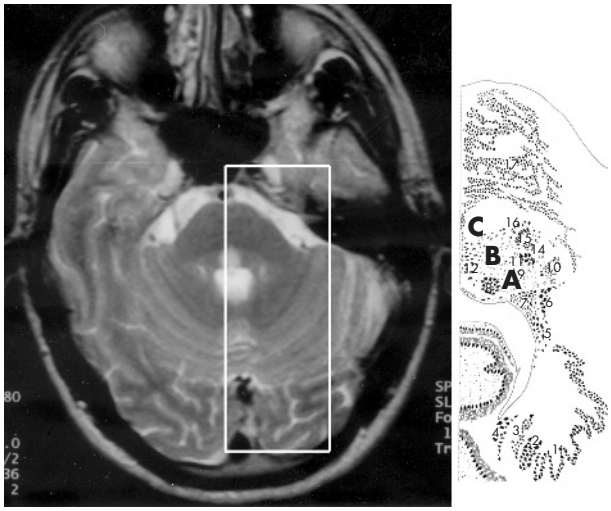

Figure 1 A magnetic resonance image of the brain showing a T2-hyperintense lesion medial and bilateral in the pontine tegmentum ventral to the fourth ventricle on the level of the fourth nerve nuclei. Right: for comparison, schematic illustration from Nieuwenhuys *et al*.[8] (A, six nerve nucleus; B, magnocellular nuclei; C, dorsal raphe nuclei).

An all-night video polysomnography (four electroencephalography leads) showed two episodes of violent motor activity, mainly in the legs, and screaming during REM sleep. REM sleep muscle atonia was partially preserved, but phasic activity was abnormally increased and also included proximal muscles, supporting the diagnosis of RBD. This exclusive occurrence during REM sleep and the non-stereotyped motor behaviour ruled out frontal lobe epileptic seizures. The sleep profile was fragmented, and the apnoea–hypopnoea index was normal (<1/h). The multiple sleep latency test showed a sleep latency of 5 min and two short REM episodes 17 and 13 min after the onset of sleep. HLA studies were negative for DRB1*1501 and DQB1*0602.

Treatment trials with clonazepam, diazepam and antidepressants had to be ceased because of intolerable side effects, such as increased diurnal sleepiness, dizziness, headache, dyspnoea and general weakness. Daytime sleepiness could be improved by methylphenidate, modafinil or amphetamines, but all were accompanied by severe headache even at low doses.

One year later, the Epworth score was 15. Besides ongoing episodes of sleep paralysis and hypnogenic hallucinations cataplexy-like episodes appeared rarely in situations with strong feelings of happiness. During the day, he occasionally experienced oneiric situations, with difficulty in differentiating between sleep and wakefulness. Video polysomnography again showed episodes of screaming during REM sleep, with increased phasic muscle activity in proximal muscles. The multiple sleep latency test (MSLT) again showed a shortened average sleep latency of <3 min and a short REM episode 5 min after the onset of sleep. CSF and MRI of the brain showed no relevant changes.

DISCUSSION

We describe the case of a previously healthy young man who concurrently developed a narcoleptic syndrome and a full-blown RBD after an acute brain stem encephalitis with an isolated inflammatory lesion in the dorsomedial pontine tegmentum. Presenting with hypersomnia, sleep paralysis, hypnagogic hallucinations and sleep onset REM periods (two in the first MSLT and one in the second MSLT), the patient fulfilled the criteria of narcolepsy,[11] although cataplexy was mild and rare. While the combined occurrence of idiopathic narcolepsy and RBD is probably underdiagnosed,[12] the combination of symptomatic narcolepsy and RBD has, to our knowledge, not been previously described.

An isolated brain stem lesion may easily explain RBD and cataplexy, but hypersomnia is more often observed in hypothalamic lesions. Focal lesions often lead to borderline narcoleptic syndromes, and it is rather unusual to find the full tetrad of narcolepsy symptoms. Subtle inflammatory involvement of other areas, not visible in the MRI, cannot be excluded with certainty in our patient, but the normal thyroid-stimulating hormone also speaks against a relevant hypothalamic involvement. The young age, negative family history for sleep disorders, absent HLA haplotypes typical of either narcolepsy or RBD, and the absence of clinical evidence or evidence from MRI for a widespread neurodegenerative disease, together with the close temporal link between the acute brain stem lesion and the onset of both sleep disorders, further corroborate the assumption of a symptomatic syndrome and speak against a pre-existing latent disease or a genetic predisposition. Nevertheless, long-time courses from the onset of RBD to the evolvement of dementia or Parkinson's disease were described,[13] outlasting the 8-year follow-up in our patient. Of interest is also the observation of normal CSF hypocretin-1 levels in this patient.

The precise pathophysiological mechanisms of both narcolepsy and RBD are still unknown. Our case underlines the significance of the dorsomedial pontine tegmentum for both cardinal clinical manifestations of narcolepsy and RBD. The known functional role of this area makes it an appropriate candidate for what could be called a ''common pathway for narcolepsy and RBD''. The area lies adjacent and rostral to the sixth nerve nucleus (fig 1A) and is known to be important for the generation of REM sleep, including muscle atonia,[14] postural tone, locomotion[15] and startle reaction.[16] At the same time, it is the origin of the cholinergic component of the ascending reticular activating system as described by Moruzzi and Magoun,[17] which is crucial for maintaining wakefulness. The region comprises the magnocellular and dorsal raphe nuclei (fig 1B, C), with the rostrally adjacent nuclei reticularis pontis caudalis, coeruleus, laterodorsal tegmental, and pendunculopontine nuclei. They form the anatomical basis of a complex interaction between cholinergic and catecholaminergic cell groups producing the aroused, yet atonic state of REM sleep, as proposed in the ''reciprocal interaction hypothesis''.[18] Recently, these nuclei, particularly the locus coeruleus, were shown to be the major synaptic target areas of the hypocretin-containing neurones in the hypothalamus,[19 20] the deficiency of which seems to play a key part in the development of human narcolepsy.[21]

The dorsomedial pontine tegmentum lesion in our patient is in line with both the only published case of RBD in an elderly woman due to an isolated focal lesion,[7] as well as with several cases of symptomatic narcolepsy caused by a single brain stem lesion.[22] Other patients with RBD with medially situated pontomedullary lesions had additional lesions visible on MRI in the periventricular region,[1 23] or clinical signs of a widespread neurodegenerative disease.[6] Symptomatic narcolepsy was also described in patients with isolated lesions in the diencephalon, hypothalamus, midbrain, medial pontine tegmentum and exceptionally in the ventral pons,[2] a region corresponding to the hypocretin projection pathway.

Finally, our patient bears striking resemblance to the recently described patients with Parkinson's disease and Lewy body dementia with a ''narcolepsy-like'' phenotype.[24 25] From this, we might speculate that the involvement of the locus coeruleus area not only impairs muscle atonia in narcolepsy and RBD but also explains the narcoleptic features in these synucleinopathies.

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