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Journal of the Neurological Sciences 253 (2007) 73–76

Journal of the Neurological Sciences

www.elsevier.com/locate/jns

Short communication

A unique episode of REM sleep behavior disorder triggered during surgery for Parkinson's disease

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Received 29 March 2006; received in revised form 2 November 2006; accepted 6 November 2006
Available online 29 December 2006

Abstract

REM sleep behavior disorder (RBD) is characterized by vigorous movements during REM sleep. Here, the authors report the case of a patient who presented such a disorder immediately after the implantation of the definitive electrode for left subthalamic stimulation. Interestingly, this was and has remained a unique episode in his medical history. It was found that a microlesion in or near the upper part of the pars compacta of the substantia nigra was very likely responsible for this phenomenon.

Keywords: Parkinson disease; REM sleep behavior disorder; Subthalamic nucleus stimulation

1. Introduction

REM sleep behavior disorder (RBD) is characterized by a loss of atonia during REM sleep, leading to dream enactment. This can involve vigorous and even violent movements with often vivid dream recall [1,2]. RBD is most common in elderly males. Although it can be idiopathic, this disorder is frequently associated with Parkinson's disease (PD) [1,2], multiple system atrophy [3] and dementia with Lewy bodies [4]. The polysomnogram shows the presence of musculature tone during REM sleep, without any nocturnal epileptic activities [5]. The physiopathology of RBD still remains unclear, although several observations (frequent association of RBD with PD, decrease in striatal presynaptic dopamine transporter and striatal dopaminergic terminals in idiopathic RBD, improvement of idiopathic RBD by pramipexole, a D2–D3 receptor agonist) have suggested that the nigrostriatal dopaminergic pathway could play a role [6]. Here, we report the case of a Parkinsonian patient who presented a unique episode of such a disorder beginning immediately after the implantation of the definitive electrode for subthalamic stimulation. As far as we know, this is the first description of this kind of side-effect during an operation for PD.

2. Case report

A 56-year-old man was diagnosed with an akineto-rigid type of Parkinson's disease (reaching UKPDSBB criteria) when he was 44 (in 1991). His treatment with Levodopa began one year after diagnosis with an excellent response to treatment. Late side-effects of Levodopa (dose-related motor fluctuations, middle-dose dyskinesias and off-dystonias) began in 1994. Dose-unrelated motor fluctuations appeared more recently, in 2001. For the 3 months before operation, treatment consisted of Prolopa 3 × 125 mg/day, Pergolide 3 × 2 mg/day and Amantadine 2 × 100 mg/day. The response to Levodopa was excellent, estimated at 80% according to the

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doi:10.1016/j.jns.2006.11.005

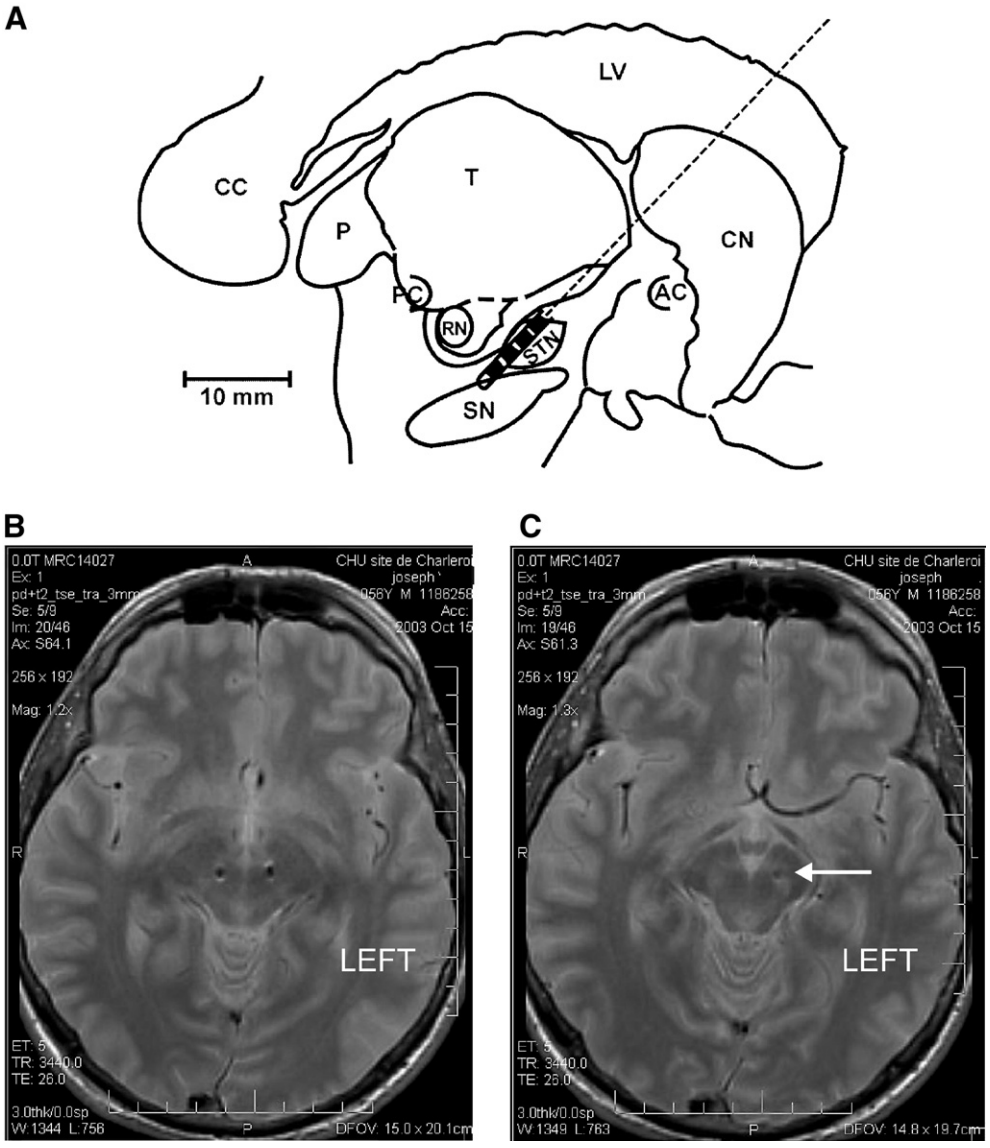

Fig. 1. Location of the tips of the electrodes. A. Sketch showing the position of the end of the left electrode on a parasagittal section at 9 mm from the sagittal plane (redrawn from the *Atlas for Stereotaxy of the Human Brain* by Schaltenbrand and Wahren). The electrode has four active contacts (in black), each 1.5 mm long, separated from each other by 0.5 mm and an inactive tip (1.5 mm long). The left electrode which crosses the intercommissural plane with an angle of 46 deg, enters the substantia nigra. STN: subthalamic nucleus; T: thalamus; P: pulvinar; LV: lateral ventricle; CN: caudate nucleus; PC: posterior commissure; AC: anterior commissure; CC: corpus callosum; RN: red nucleus. B.C. Post-operative MRI. On the upper slice (B), the sites of passage of both left and right electrodes can be seen. On the lower slice (C), only the tip of the left electrode (arrow), ending in the substantia nigra, is visible.

UDPRS-III motor score (60 off, 9 on). The Hoen and Yahr score was 4.0 during off-phases and 2.2 during on-phases. The cerebral MRI was normal, as well as the neuropsychological testing. The score for the Beck questionnaire was 14.

The decision to operate on the patient was made because of severe motor fluctuations and dyskinesias. The UPDRS-IV score was 9, with off-time during waking estimated at 30%. During the 2 weeks prior to the operation, medication was progressively reduced to Prolopa 3×125 mg/day and Pergolide 1.5 mg/day. On 30 September 2003, a Medtronics 3389 stimulation multi-electrode was implanted in the left subthalamic area under local anesthesia. On the eve, a ventriculography with the stereotaxic frame already in place had been performed without any per- or post-operative complications. On the operation day, the precise position of the target was searched for, using 5 long microelectrodes (FHC) aimed at the target area defined by the landmarks obtained by the ventriculography. Along the five parallel tracks followed by the 5 microelectrodes, multi-unit recordings and stimulations were carried out in a systematic way [7]. At each tested site, the effect of stimulation on rigidity and bradykinesia was assessed. During this long procedure, the only observed side-effect was dyskinesia. However, immediately after the implantation of the definitive electrode (diameter: 1.27 mm) the patient fell asleep. More remarkably, from time to time during his sleep he

presented episodes of behavioral agitation or aggression. The EEG recording performed 1 h after the onset of this sleep state showed paradoxal sleep activity without concomitant muscular atonia on the EMG recording of mentalis muscles. The EEG was devoid of epileptic activity. The patient kept sleeping for 12 h. At awakening, he told nightmares like, for example, that of him beating his grandson to death. The cerebral CT scan and two MRIs (performed on days 2 and 14) excluded any hemorrhagic or ischaemic lesions. A polysomnogram recorded overnight for 12 h on day 7 showed no RBD episodes. No other significant clinical event was observed in the post-operative period.

The implantation of a stimulation electrode on the right side was performed on 14 October 2003, without any per- or post-operative complications. The motor evaluation 3 months after the second electrode implantation showed a UDPRS-III score of 11, a UPDRS-IV of 0, without any motor fluctuation or dyskinesia. At that time, the medical treatment was Levodopa 250 mg/day and Pergolide 2.50 mg/day (given in 3 doses).

The reported RBD episode was triggered after the implantation of the left electrode but not after a similar operation on the right side. Therefore, it was important to know whether there were any differences in the locations of the implanted electrodes. This was performed using superimposition of X-ray films taken at the end of each implantation over X-ray films taken during ventriculography. The definitive electrodes were found to follow nearly symmetrical trajectories. However, the tip of the left electrode was definitely lower than that of the right one. The precise positions of the tips of the two electrodes were determined using their *X–Y–Z* coordinates and the "Atlas for Stereotaxy of the Human Brain" by Schaltenbrand and Wahren. The tip of the left electrode was found to enter the pars compacta of the substantia nigra in the upper midbrain (Fig. 1A). The MRI performed after the second operation confirmed this calculated position (Fig. 1B and C).

During the lapse of time between the operation in 2003 and now (July 2006), the patient and his spouse reported no night event suggestive of an RBD episode. On 17 July 2006, 7 and 8 October 2006 the patient was brought in for overnight control polysomnographies. These revealed no RBD episode.

3. Discussion

In the case described here, the precise temporal relationship between the implantation of the electrode aimed at the left subthalamic nucleus and the onset of the RBD episode strongly suggests that a microlesion made by the electrode was responsible for triggering the observed parasomnia. However, other causes or precipitating factors must be ruled out. Our patient did not present any neurological signs other than Parkinsonism. He never presented any episodes of RBD before the operation day, nor during the nearly 3-year post-operative period. He was not treated by mirtazapine known to induce RBD in Parkinsonism [8]. As a disorder of the dopaminergic pathway has been suggested to play a role in RBD (see Introduction), one could suspect that the decrease in dopamine treatment, carried out in the pre-operative period in our patient, could be a precipitating factor. However, no case similar to ours has been described in relation with operation for PD, a situation where pre-operative decrease in dopaminergic agents is usual.

The basic neuronal machinery responsible for REM sleep is located in the mesopontine tegmentum. It consists of two groups of nuclei, one silent (REM-off regions), the other active (REM-on regions) during REM sleep [9]. REM-off areas (ventrolateral part of the periaqueducal grey matter and the lateral pontine tegmentum in the rat) and REM-on areas [the sublaterodorsal nucleus (SLD) and the precoeruleus region (PC) in the rat] inhibit each other mutually. REM-off regions are submitted to the influence of two hypothalamic inputs: orexin (or hypocretin) neurons in the lateral hypothalamus excite them, neurons of the extended part of the ventrolateral preoptic nucleus inhibit them [9]. Among the REM-on regions, the PC nucleus is responsible for REM EEG phenomena whereas the ventral part of the SLD nucleus is responsible for atonia [9].

Selective damage to the SLD in the rat [9] or to the equivalent nuclei in cats [10–12] and in humans [13] may cause REM sleep without atonia. However, the RBD episode observed in our patient cannot have a similar origin as his lesion was located at a higher level, in the midbrain. One possible cause could be that the lesion concerned some fiber tract providing input to the structures of the mesopontine tegmentum responsible for REM sleep. However, because the loss of orexin neurons causes narcolepsy in which fragments of REM sleep and muscle atonia occur suddenly against a background of wakefulness [14–16], a lesion of the descending input from orexin neurons to the mesopontine region could explain the sudden induction of REM sleep in our patient but not the absence of concomitant atonia. As another possibility, our observation of an RBD episode triggered by a lesion in the substantia nigra could also be considered as additional evidence supporting the hypothesis that RBD is a dopaminergic deficiency disorder [6].

Acknowledgment

We thank Christiane Busson for realizing the illustration and Ramona Shelby for correcting the English.

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