SHORT REPORT

Bilateral paramedian thalamic syndrome: abnormal circadian wake-sleep and autonomic functions

P Montagna, F Provini, G Plazzi, R Vetrugno, R Gallassi, G Pierangeli, M Ragno, P Cortelli, D Perani

J Neurol Neurosurg Psychiatry 2002;**73**:772–774

Objectives: To describe wake-sleep and body core temperature (t°) rhythm abnormalities in two patients with bilateral paramedian thalamic calcifications.

Methods: Patients underwent (18F)FDG PET scans and 24 hour polygraphic recordings of wake-sleep and t° .

Results: PET showed bilateral thalamic hypometabolism in both patients with additional basal ganglia or mesiolateral frontal and cingular hypometabolism. Wake-sleep studies showed abnormal sleep organisation and in the case with frontal and limbic PET hypometabolism, pre-sleep behaviour associated with "subwakefulness" EEG activities, lack of EEG spindles and K complexes, and features of status dissociatus. The t° rhythms showed increased mesor in both (37.4°C and 37.75°C) and inverted rhythm in one patient.

Conclusions: Paramedian thalamic structures and interconnected, especially frontal and cingular, areas play a part in the organisation of the wake-sleep cycle and attendant autonomic functions.

Chronic bilateral vascular paramedian thalamic lesions cause "subwakefulness" behaviour associated with slowing of EEG background activity with intermixed alpha/theta activities, and a lack of both deep sleep and alert wakefulness EEG activities.^{1,2} Similar behavioural and EEG patterns are seen in fatal familial insomnia (FFI), a prion disease with prominent involvement of the medial and anterior thalamic nuclei and limbic cortex.³ Circadian autonomic functions have not been explored in paramedian thalamic syndromes other than FFI. We recorded EEG and t° in two patients with non vascular bilateral paramedian thalamic lesions, exploring the relation between thalamic structures and circadian wake-sleep and vegetative functions.

METHODS

Two patients with bilateral paramedian thalamic calcifications underwent (18-FDG) PET scans on a GE-Advance PET tomograph. Regional cerebral glucose metabolism was measured and images reconstructed and analysed with statistical parametric mapping. Regional cerebral activity of individual patients was compared with the regional activity of a group of 19 controls.⁴

Cognitive functions were assessed by Mini Mental Status Examination, the Brief Battery for Mental Deterioration,⁵ and computerised tests exploring psychomotor performance.

Patients underwent recording of EEG, ECG, eye movements, and chin and tibial anterior EMG by means of Vitaport. The 24 hour t° was analysed by means of a Mini-Logger 2000 rectal probe. Plasma growth hormone, melatonin, prolactin and cortisol were analysed in patient 2 during 24 hour polysomnography.

RESULTS

Patient 1

A 63 year old woman with ataxia and dysarthria since she was 58 years old, had calcifications of the medial thalami and quadrigeminal tubercles extending into the right lenticular nucleus. PET revealed hypometabolism in the thalamus and caudate bilaterally, and the right putamen and insula (fig 1A). Neuropsychological tests demonstrated only deficits of attention in acoustic and visual tasks and motor slowing in manual

Figure 1 (18-FDG) PET showing regions of significant hypometabolism bilaterally in the thalamus and caudate and right insula and putamen in patient 1 (A), and bilaterally in the thalamus and left mesial and lateral frontal cortex in patient 2 (B).

Figure 2 The 24 hour t° rhythm (upper panels) and concomitant wake-sleep histograms (lower panels) in patient 1 (A, second day) and patient 2 (B). The x axis bar denotes the dark period. NW-NS = non-wake–non-sleep activity; A-NREM = atypical NREM sleep.

dexterity. The 48 hour polygraphic recordings showed normal wake/sleep EEG activities. During the daytime, the patient napped repeatedly, reaching stage 2 twice and REM sleep once. Night sleep showed prevalent light sleep stages, and protracted awakenings (fig 2A). All sleep stages were however evident, with normal EEG sleep figures and physiological REM sleep atonia. Total sleep time was reduced (3 h 26 min), and sleep efficiency decreased (52%–55%, normal $\geq 85\%$).

The 24 hour t° oscillation was present but with a mesor at 37.4°C, significantly higher than 15 normal controls (mean (SD) 37.05 (0.17°C); t° rhythm amplitude, 0.47°C, was normal; the rhythm was however inverted, as the nadir was in the afternoon, whereas acrophase was at 05:52 during sleep (acrophase in 15 normal controls, mean (SD) 16:16 (1:20) h:m) $^{\circ}$ and the physiological decrease in t° during sleep was absent (fig 2A).

Patient 2

A 57 year old woman developed depression, memory loss, and hypersomnia at 46 year of age and, at 52 years, visual hallucinations. At 55 years of age there began episodes of screaming and terrifying dreams during sleep, sometimes associated with jumping out of bed. At age 56 years, she became voracious and developed compulsive behaviours, urgency, and faecal incontinence. Sleep episodes would occur throughout

the daytime, during which the patient did not respond to callings. Examination disclosed snout and brisk deep reflexes, and slow gait with retropulsion. Computed tomography demonstrated calcifications in the medial thalami and in the mesencephalon. Low blood calcium with normal parathormone and the brain changes led to the diagnosis of pseudo-hypoparathyroidism. PET showed a bilateral hypometabolism in the thalamus, the hippocampal structures, the orbito-frontal, the mesial frontal, and the cingulate cortices; the dorsolateral, especially left frontal cortex was also involved (fig 1B). Neuropsychological tests showed impaired long term and short-term verbal memory, increased false alarms during visual attention tests, reduced verbal fluency, inadequate vigilance with difficulties in maintaining concentration and attention, and psychomotor slowing. Four days of continuous Vitaport showed daytime periods of reduced motor activity associated with EEG alpha/theta activity; this occupied 17%–63% of day and 7%–17% of night time. Non-REM sleep was characterised by a continuous theta/delta activity, and by the complete absence of sleep spindles and K complexes. REM sleep was slightly reduced (15%–22%, normal 25%) (fig 2B). There were significant ($p < 0.001$) circadian oscillations of t° , but mesor was significantly increased (37.75 (0.06)°C); rhythm amplitude was normal (0.45 (0.06)°C). The t° decreased

normally during the night and acrophase occurred normally at 15:00±00:02 h:m (fig 2B). Melatonin secretion and the circadian rhythmicity of cortisol, GH, and prolactin were normal.

DISCUSSION

In our patients, (18-FDG) PET demonstrated bilateral hypometabolism of the thalamus and caudate, extending to the right putamen and insula in patient 1. Patient 2 had additional involvement of the hippocampus, the orbitofrontal and mesial and lateral frontal cortices. Circadian studies exploring concomitant alterations of sleep and autonomic functions demonstrated milder disturbances in patient 1, with daytime sleep episodes, nocturnal awakenings, decreased total sleep time on the second night, and reduced sleep efficiency; τ° patterns were characterised by increased mesor at 37.4°C and inversion of the rhythm without the physiological decrease during sleep. Patient 2 displayed impaired alertness with sub-wakefulness daytime EEG activities, and prominent sleep abnormalities, with lack of EEG spindles and K complexes, and alpha/theta activities intermixed with continuous theta/delta activity during NREM. These abnormalities fulfilled the description of “status dissociatus”.⁷ The wake-sleep changes were more prominent in patient 2 probably because of the additional involvement of the limbic areas, shown by PET. Our observations confirm previous reports^{1,2} of daytime drowsiness and “subwakefulness” patterns, sometimes reaching “status dissociatus”, in chronic paramedian thalamic lesions, and emphasise that changes may extend to autonomic functions such as τ° . Abnormalities seem particularly evident when the frontal and limbic areas are involved in addition to the thalamus. In such cases, the clinical features mimic those of FFI and “Agrypnia Excitata”, a syndrome related to dysfunction of the thalamolimbic system.⁸

ACKNOWLEDGEMENTS

Ms A Collins revised the English text and Ms A Laffi helped with the typescript. Supported by MURST COFIN ex-40% 1999 prot. 9906037938, 2000 prot. MM06244347 and CNR no 96.05253.ST74.115.29454 grants.

.....

Authors' affiliations

P Montagna, F Provini, G Plazzi, R Vetrugno, R Gallassi, G Pierangeli, P Cortelli, Institute of Clinical Neurology, University of Bologna Medical School, Bologna, Italy
M Ragno, Department of Neurology, Hospital of Ascoli Piceno, Milan, Italy
D Perani, Institute of Neuroscience and Bioimaging, CNR, University Vita-Salute HRS, Scientific Institute, H San Raffaele, Milan, Italy

Correspondence to: Professor P Montagna, Dipartimento di Scienze Neurologiche, dell'Università di Bologna, Via Ugo Foscolo 7, 40123 Bologna, Italy; pmontagn@neuro.unibo.it

Received 23 April 2002

In revised form 31 July 2002

Accepted 15 August 2002

REFERENCES

- 1 **Guilleminault C**, Quera-Salva MA, Goldberg MP. Pseudo-hypersomnia and pre-sleep behaviour with bilateral paramedian thalamic lesions. *Brain* 1993;**116**:1549–63.
- 2 **Baschetti C**, Mathis J, Gugger M, et al. Hypersomnia following paramedian thalamic stroke: a report of 12 patients. *Ann Neurol* 1996;**39**:471–80.
- 3 **Montagna P**, Cortelli P, Gambetti P, et al. Fatal familial insomnia: sleep, neuroendocrine and vegetative alterations. *Adv Neuroimmunol* 1995;**5**:13–21.
- 4 **Signorini M**, Paulesu E, Friston K, et al. Rapid assessment of [18F]FDG PET brain scans in individual patients with Statistical Parametric Mapping. A clinical validation. *Neuroimage* 1999;**9**:63–80.
- 5 **Gallassi R**, Lenzi P, Stracciari A, et al. Neuropsychological assessment of mental deterioration: purpose of a brief battery and a probabilistic definition of “normality” and “non-normality”. *Acta Psychiatr Scand* 1986;**74**:62–7.
- 6 **Pierangeli G**, Provini F, Maltoni P, et al. Nocturnal body core temperature falls in Parkinson's disease but not in multiple system atrophy. *Mov Disord* 2001;**16**:226–32.
- 7 **Mahowald MW**, Schenck CH. Status dissociatus—a perspective on states of being. *Sleep* 1991;**14**:69–79.
- 8 **Montagna P**, Lugaresi E. Agrypnia Excitata: a generalized overactivity syndrome and a useful concept in the neurophysiopathology of sleep. *Clin Neurophysiol* 2002;**113**:552–60.