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Isolated paroxysmal arousals as focal epilepsy

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ABSTRACT – Paroxysmal motor phenomena and arousals during sleep are frequent. The differential diagnoses between benign hypnic transient events, epileptic and non-epileptic seizures represent a common clinical problem. Video-EEG monitoring during sleep, recording several episodes in the same patient, is essential in order to characterize these phenomena. It offers the possibility to compare electro-clinical data, to demonstrate the eventual stereotyped pattern of motor phenomena and their progression in time, and to study EEG-polygraphic correlates. The recently described double split-screen synchronized display (DSSSD) technique represents a useful tool for comparing particular clinical patterns of epileptic seizures when dealing with complex, hypermotor phenomena observed in frontal lobe epilepsy. We reviewed the data of 24 patients admitted during a two-year period (2002-2003) to our epilepsy sleep unit for isolated paroxysmal sleep motor events. Four patients presented with very brief paroxysmal arousals without daytime fits. Three of our patients presented isolated paroxysmal arousals, whereas in one, the events were associated with hypermotor seizures. We present a simplified variant of the DSSSD method (modified DSSSD) that can be used to study episodes of paroxysmal arousals in order to confirm their stereotyped motor pattern. The clinical aspects and the EEG-polygraphy patterns were informative, with the absence of asymmetrical tonic or dystonic posturing of the limbs. Scalp EEG alone does not usually provide much information in patients with isolated paroxysmal arousals. Coupled to the modified DSSSD technique, it may allow confirmation of the diagnosis of frontal epilepsy, as was the case in our four patients.
[Published with video sequences]

Key words: motor phenomena during sleep, paroxysmal arousals, nocturnal frontal lobe epilepsy, frontal lobe seizures

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Arousals during sleep represent physiological, transient cyclic events, characterized by motor and autonomic activation related to sleep architecture, and leading to the transition from different stages of sleep to wakefulness. A large number of paroxysmal motor phenomena during sleep represent a diagnostic dilemma. Based on the patient's history and description alone, it is often difficult to differentiate between benign sleep transient events, movement disorders during sleep, and epileptic and non-epileptic phenomena.

Paroxysmal arousals (PAs) correspond to repetitive, sudden arousals originating from a "stable state" of 2-3 NREM

sleep, usually brief (lasting < 20 sec), clinically stereotyped (Montagna *et al.* 1990). A considerable variability in "intensity" of these phenomena has been reported, ranging from only brief motor and autonomic patterns (tachycardia, tachypnea) associated with brief "extrapyramidal motor" phenomena, to "full attacks" characterized by more complex and prolonged abnormal motor phenomena with more or less prolonged dystonic often lateralized limb posturing, corresponding to the so- called "nocturnal paroxysmal dystonia (NPDs)". Even if ictal EEG is often considered normal, the epileptic origin of paroxysmal arousals has been widely discussed in the literature, on the basis of their paroxysmal onset, stereotyped clinical features, repetition, and good response to antiepileptic drugs (Montagna *et al.* 1990, Lugaresi *et al.* 1981, Hirsch *et al.* 1994, Montagna *et al.* 1992). Moreover, in the report of a large series of 100 patients with nocturnal frontal lobe epilepsy (NFLE) (Provini *et al.* 1999), the authors suggested that the different subtypes of paroxysmal motor events, of variable "intensity", during sleep (paroxysmal arousals; nocturnal paroxysmal dystonia; epileptic nocturnal wanderings), may often coexist in the same patient, suggesting a clinical spectrum of NFLE. In this series (Provini *et al.* 1999), the patients having isolated paroxysmal arousals were rare (9%) and EEG tracings were normal. Brief, unilateral choreoathetoid or dystonic postures, associated with a frightened expression and sudden jerks of the upper limbs and the trunk, were often present in stereotyped motor patterns characterizing paroxysmal arousals.

Double split-screen synchronized display (DSSSD), recently described by Tinuper *et al.* (2004), represents a useful technique for comparing clinical patterns of epileptic seizures, particularly when dealing with complex hypermotor seizures in frontal lobe epilepsy.

We used a simplified variant of the DSSSD technique (m DSSSD) to compare two or more episodes in four patients with paroxysmal arousals, selected from among 24 patients admitted to our epilepsy sleep unit for isolated paroxysmal sleep motor events. The mDSSSD allows us to demonstrate the strongly stereotyped motor pattern and its progression over time.

Materials and methods

During a two year period (2002-2003), we performed EEG-video-polysomnography in 24 patients referred for paroxysmal motor events during sleep, and daytime tiredness. A detailed family and personal medical history (with particular attention to family history of sleep disorders or epilepsy), neurological and neuropsychological examination were performed. Neuroradiological (high resolution MRI) findings were obtained for all patients. They underwent awaking and sleep, prolonged video- EEG monitoring, (using the International 10-20 System electrodes), including EKG, muscle, and EOG electrodes. The nocturnal motor activity recorded in each patient was carefully analyzed and classified in two subtypes, on the basis of duration, semiology and complexity of motor pattern: i) cyclic transient motor events, with or without arousal, and ii) repetitive paroxysmal arousals, with more complex motor activity and autonomic signs.

Analysis of the paroxysmal events was performed using the modified double split-screen synchronized display (mDSSSD) technique: analogue video sequences (recorded on S-VHS cassettes, currently used during video-EEG monitoring), were digitalized on a Pentium II computer under the Windows NT operative System using Videocap software (version 7.0 Pack 5). The double-SSSD technique consisted of first digitizing the motor events, calibrated for the same duration (5 sec) before onset of the motor phenomena, and up to the post-ictal phase. Video timing was performed using Quick Time Player® software (version 6.0). Video-sequences were animated using Microsoft® Powerpoint® 2000 SR-1. The first video was run manually, without a compilation effect, the other(s) automatically following the first one.

Two or more clinical events recorded for the same patient were then synchronized onto a double-split-screen, in order to observe the eventual stereotyped motor pattern.

Results

Four patients had isolated PAs. In patients 1 and 2 (*table 1*) a family history of parasomnias in a first degree relative, and a personal history of sleepwalking and sleep terrors were reported.

Results of clinical, electrophysiological and neuroradiological investigations are summarized in *table 1*. Cerebral MRIs were normal in all patients.

Detailed analysis of sleep architecture, and of electroclinical findings showed, in all patients: i) cyclic motor events, associated or not with modification of the vigilance level, which were non-stereotyped, suggesting posturing changes and physiological sleep phenomena; ii) repetitive paroxysmal arousals, associated with more complex motor activity and autonomic signs, which were strongly stereotyped.

Analysis using the mDSSSD technique, comparing different episodes in the same patient, showed an identical semiology and the same time progression of the motor phenomenology, suggesting an epileptic origin. From a clinical point of view, arousals were characterized by a sudden awakening, opening of the eyes, elevation of the trunk and adduction of the upper or all four limbs, sometimes associated with brief vocalization. No sign of head lateralization was observed, nor post-ictal aphasia.

Interictal EEG demonstrated isolated spikes and waves on frontal regions in all *(figure 1)*. EEG correlates during the episodes showed a clear-cut, rhythmic delta frontal activity, followed by muscular artifacts at arousal *(figure 2)*.

Table 1. Clinical, electrophysiological, neuroradiological findings and treatment.

Cases	Gender /age	PA onset	Hypermotor seizures	Interictal EEG awake and asleep	Ictal EEG	MRI	Treatment
1	male 39 years	14 years	no	Bilateral frontal spikes and waves and delta activity	Bilateral, delta activity predominant in frontal regions	Normal	CBZ
2	male 36 years	26 years	no	Right frontal theta and spikes and waves	Bilateral frontal spikes and waves	Normal	CBZ
3	male 73 years	63 years	no	Normal	Bilateral frontal polyspikes and waves, followed by delta activity	Diffuse vascular lesions of white matter	CBZ
4	male 28 years	4 months	yes	Normal	Bilateral frontal spikes and waves	Normal	PB; CBZ

PA: paroxysmal arousal.

Polygraphic recording of muscle activity in the upper limbs confirmed the absence of tonic or dystonic posturing *(figure 2)*. PAs were very brief (a few seconds), and very frequent (an average of seven per night) in the same patient, always occurring during NREM stage 2 sleep, and inducing a very important fragmentation of sleep architecture *(figure 3A)*. At follow-up, following introduction of anti-epileptic drug therapy, the electro-clinical findings confirmed a significant reduction of arousal episodes *(figure 3B)*.

Application of the mDSSSD technique is shown in video sequences A and B (patients 1 and 4).

Discussion

Several types of nocturnal paroxysmal abnormal movements may occur during rapid eye movement (REM) and non-REM sleep. On the basis of clinical semiology (motor patterns) and duration, several repetitive sleep motor events have been described under different terms in the literature: hypnogenic or nocturnal paroxysmal dystonia (Lugaresi *et al.* 1981, Hirsch *et al.* 1994, Tinuper *et al.* 1990); episodic or epileptic nocturnal wanderings (Pedley and Guilleminault 1977, Plazzi *et al.* 1995). "Minimal motors attacks" during sleep have been described as paroxysmal awakenings (Peled and Lavie 1986) and paroxysmal arousals (Montagna *et al.* 1990).

Differentiation between the various subtypes of paroxysmal sleep motor phenomena, on the basis of clinical semiology, is not easy, even when video EEG recording is available. By definition, "minor events" (such as PAs) are clinically characterized by repetitive, stereotyped sudden arousals from a "stable state" of 2-3 non-REM sleep, they are brief (< 20 sec) or ultrabrief (2-3 sec), associated with a terrified expression. Motor activity is described as brief unilateral choreoathetoid or dystonic posturing and sudden jerks of the upper limbs and the trunk, occasionally associated with a brief vocalization. Autonomic signs are often present (tachycardia and tachypnea). In nocturnal paroxysmal dystonia, motor phenomena, particularly tonic or dystonic limb posturing, are more complex and prolonged, sometimes with superimposed clonic jerks. Episodic or epileptic nocturnal wanderings are usually defined as a violent and elaborated motor activity, with trunk and pelvic movements, while the patient is sitting, or possibly running around the bed. The duration is longer (1 min) than paroxysmal arousals and there is no impairment of consciousness.

When the epileptic origin of these events was suggested (Montagna *et al.* 1990, Lugaresi *et al.* 1981, Hirsch *et al.* 1994, Montagna *et al.* 1992), the authors reported a considerable variability in "intensity" of these phenomena, coexisting in the same patient, and ranging from only brief motor behaviors to "full events" characterized by more complex and prolonged motor activity. Frequency, stereotyped clinical semiology, and good response to antiepileptic drugs suggest that these motors events during sleep may correspond to the same clinical spectrum of focal epileptic seizures involving the frontal lobe, in which the increasing duration and complexity of the motor activity may reflect different patterns of ictal discharge spread.

However, because interictal or ictal EEG abnormalities are usually absent or not easily identifiable, the epileptic versus non-epileptic nature of such phenomena was debated in the literature (Lee *et al.* 1985, Oswald 1989).

Interictal and particularly ictal scalp EEG data in "minor motor attacks" during sleep (paroxysmal arousals, nocturnal paroxysmal dystonia) are often inconclusive, because EEG activity modifications are not easily detectable.

The use of semi-invasive EEG recordings (such as subdural grids or sphenoidal electrodes) in some patients with frequent episodes, supported the epileptic origin of these events (Tinuper *et al.* 1990, Lombroso 2000).

Moreover, a stereo-electroencephalographic study in one patient presenting "brief motor attacks" during sleep, clinically corresponding to PAs coexisting with nocturnal

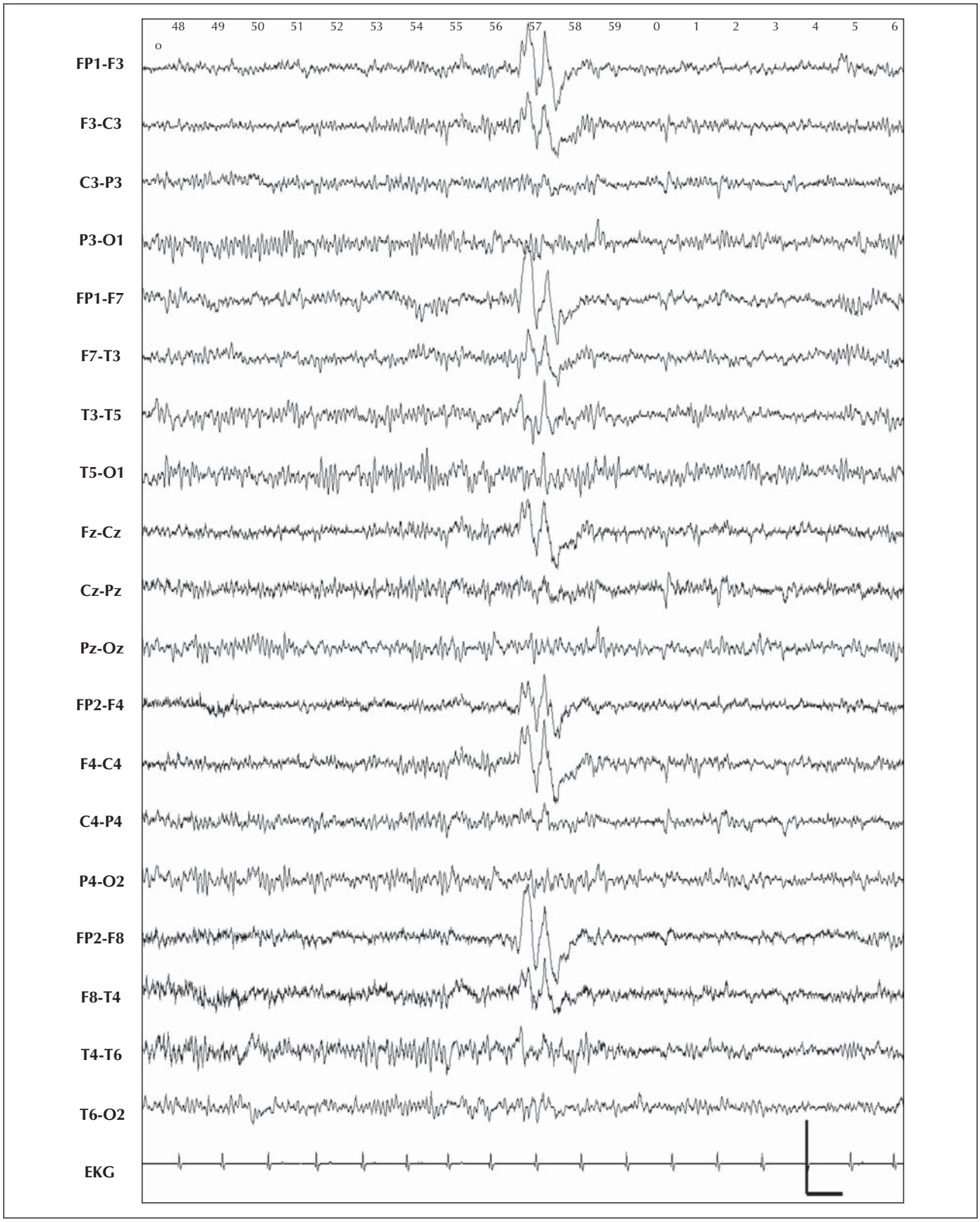

Figure 1. Interictal EEG findings of case 1 *(table 1). Bilateral isolated spike and waves in frontal regions. Scale (1 sec. 100µv).*

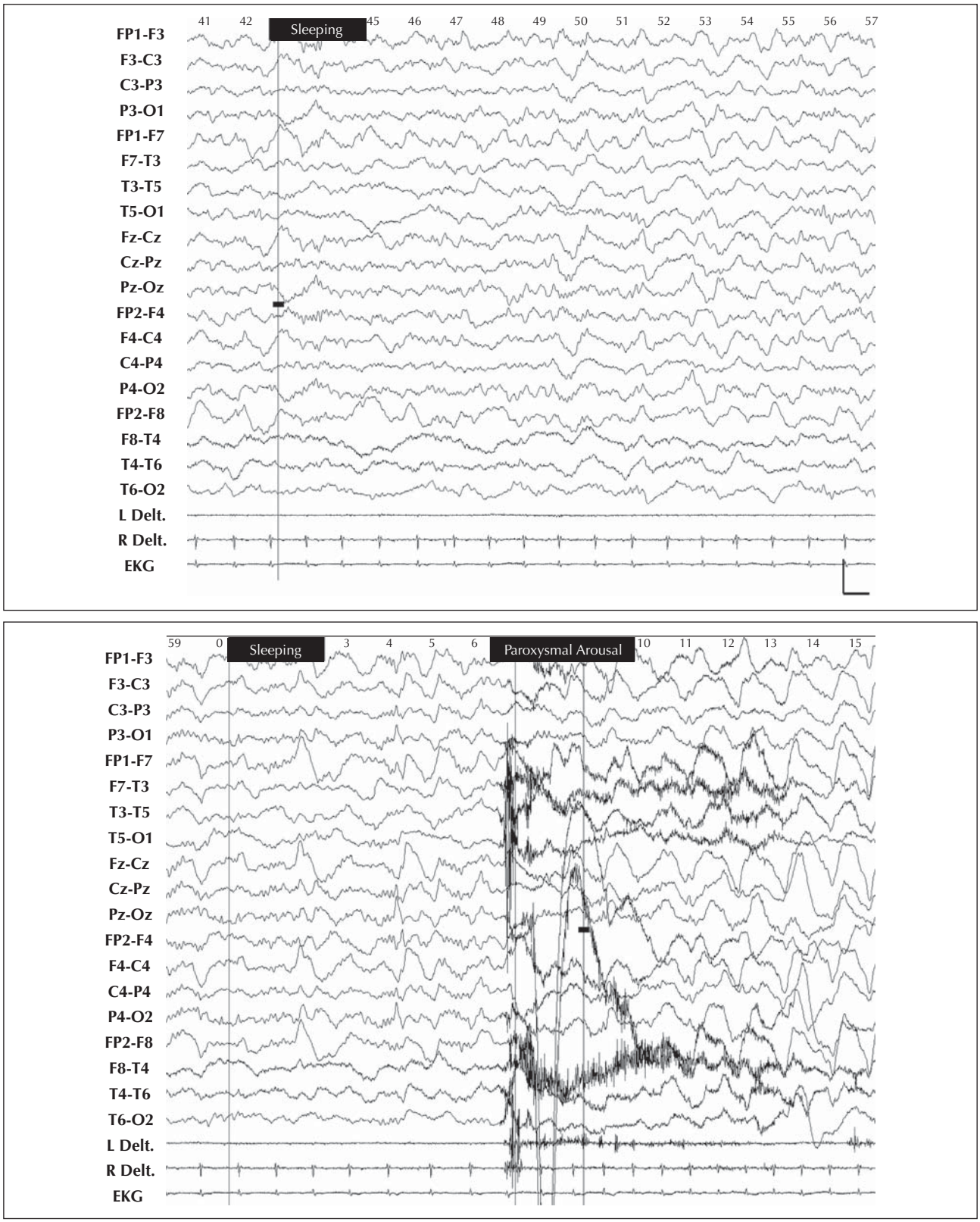

Figure 2A et B. Ictal EEG findings in case 1 *(table 1).* ***A****) Pre-ictal phase with normal background of 2 NREM sleep stage.* ***B****) Ictal phase. Muscular artifacts, superimposed over bifrontal delta activity.*

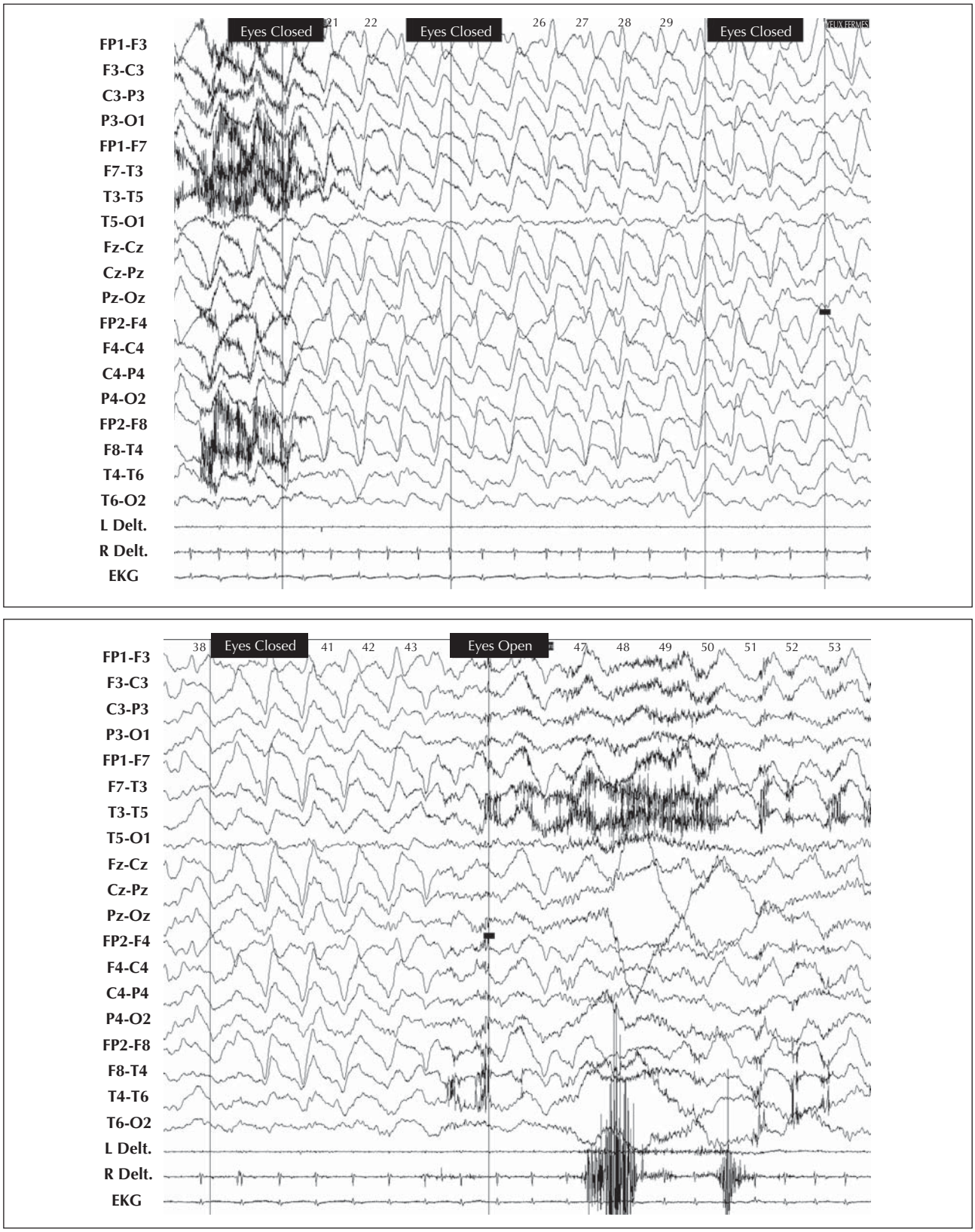

Figure 2C, D. Post-ictal phase. Prolonged diffuse delta activity, predominant bilaterally in anterior regions. Scale (1 sec. 100μv).

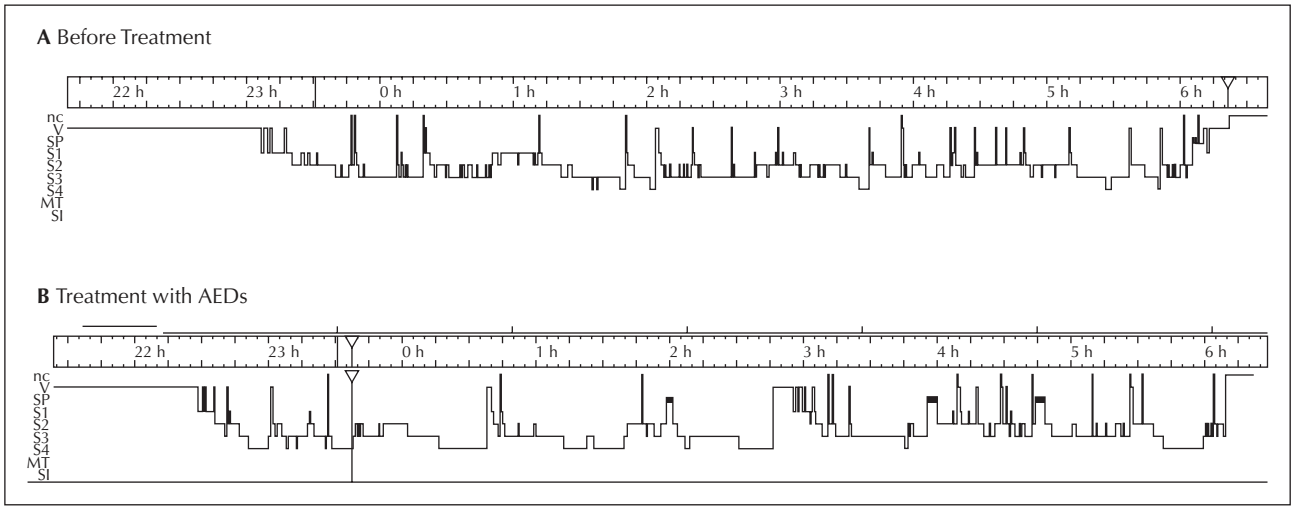

Figure 3. Hypnogram before treatment (**A**) and after treatment (**B**). V (awakening), SP (REM sleep), S 1-4 (NREM sleep stages).

paroxysmal dystonia, confirmed the epileptic origin of the events. The ictal discharge involved the supplementary motor area and the cingulate gyrus, suggesting that the increasing complexity and duration of the motor semiology may reflect a variable, progressive spread of the ictal discharge from the primary epileptogenic zone to contiguous regions. The paroxysmal events stopped after complete resection of the epileptogenic zone, corresponding to a Taylor-type dysplasia (Nobilie *et al.* 2003).

Our four patients presented with nocturnal paroxysmal events, characterized by sudden arousal with eye opening, terrified facial expression and brief elevation of the trunk, sometimes associated with a sigh. There was no impairment of consciousness, or aphasia. Autonomic signs were present, and a subjective recall of a bad dream (videosequences A, B). Arousals during the same night were very frequent, resulting in an important fragmentation of sleep architecture and diurnal sleepiness. In three cases, PAs were isolated, and were not associated with more elaborated ictal events.

Although usually scalp EEG findings in PAs are inconclusive, in our cases interictal EEG activity showed bilateral frontal abnormalities, with isolated spikes and waves in frontal regions *(figure 1)*. The ictal activity suggested a frontal involvement, with a post-ictal bilateral delta rhythmic activity on frontal regions, following muscular artifacts due to arousals. They were prolonged in one case *(figure 2)*. This EEG pattern could be compared to the "mitten EEG pattern" described in patients presenting with cerebral tumor and psychosis (Gibbs and Gibbs 1963). As previously reported (Tinuper *et al.* 1990) PAs always occurred during the 2 non-REM sleep stage, following a K-complex.

The double-split-screen synchronized display (DSSSD) described recently (Tinuper 2004), represents a useful technique for comparing clinical patterns of hypermotor seizures involving the frontal lobe. Stereotyped semiology regarding the onset of the events and the identical progression of motor activity over time when comparing different events in the same patient, supports the epileptic origin of these events.

Using a simplified DSSSD method we were able to compare isolated, sudden, ultrabrief PAs in four patients, representing, for three, the only paroxysmal phenomena.

Frequency and identical clinical semiology of different episodes in the same patient (associated with concomitant EEG bilateral frontal abnormalities), suggested that these motor events during sleep correspond to focal seizures involving, initially or secondarily, the frontal lobe. Good response to antiepileptic drugs, inducing a reduction in frequency of arousals (documented by video EEG follow-up), and a subjective improvement of diurnal daytime tiredness, are also evidence of an epileptic origin.

Conclusion

Differentiation between physiological or pathological brief motor events during sleep, particularly when isolated, represents a common clinical dilemma. Our cases of PAs, without tonic or dystonic unilateral motor phenomena, associated with clear-cut interictal and ictal EEG abnormalities, suggest that isolated PAs may correspond to focal seizures. The use of the modified DSSSD technique was of great help in identifying the stereotyped pattern of the events, thus further supporting the hypothesis that we were dealing with epileptic phenomena. □

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Legends for video sequences

Video sequence A

PA in case 1 (*table 1*). Stereotyped sudden awakening, opening eyes and terrified expression, elevation of trunk and adduction of superior limbs, associated with a sigh or a brief vocalization. Absence of tonic or dystonic lateralized phenomena.

Video sequence B

PA in case 4 (*table 1*). Stereotyped sudden arousal, associated with axial hypertonia and elevation and adduction of four limbs, followed by adjust posturing. Absence of tonic or dystonic lateralized phenomena.

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