Nocturnal paroxysmal dystonia

E LUGARESI, F CIRIGNOTTA, P MONTAGNA

From the Institute of Neurology, University of Bologna, Italy

SUMMARY Sleep-related seizures characterised by choreoathetoid, dystonic and ballistic movements occurred in 12 patients, repeatedly each night and over a period of years. The nocturnal attacks were short-lasting, responded well to carbamazepine and were sometimes associated with clearly or possibly epileptic seizures during night- or daytime. They resembled the paroxysmal kinesigenic dystonias of wakefulness. Similar dystonic-dyskinetic attacks, but of long duration and unresponsive to medication, were also observed in two other patients, in one 20 years before the onset of clinically apparent Huntington's chorea. Nocturnal paroxysmal dystonia represents a syndrome of sleep-related motor attacks which comprises two variants, respectively characterised by short and long-lasting seizures. Its precise nosological definition still awaits elucidation.

Polysomnographic monitoring under audiovisual control allows the differential diagnosis of many paroxysmal abnormal movements arising during sleep, and may be particularly helpful in differentiating epileptic seizures from the so-called arousal disorders or parasomnias (sleep terrors, sleep-walking etc).^{1–3} We studied by repeated polysomnographic investigations several patients displaying nocturnal seizures characterised by stereotyped dystonic and/or ballistic movements, which did not fit, however, into any of the usual clinical categories of sleep-related motor attacks.² The uniformity of their clinical and polysomnographic features led us to outline a distinct syndrome for which we proposed the term nocturnal paroxysmal dystonia.^{4,5} In recent years we have had the chance to study more patients with nocturnal paroxysmal dystonia, and have performed repeated polysomnographic and pharmacological studies. Follow-up and clinical analysis of differential features in our material have convinced us that different sub-types of such dystonic-dyskinetic attacks arise during sleep. Thus our patients can be subdivided into at least two variants, the more common one characterised by attacks of rather short duration and responsive to carbamazepine, the rarer by more protracted motor seizures, unaffected by any treatment. We detail here the clinical and polygraphic features of our patients and discuss their relationship to epilepsy and to other paroxysmal motor attacks such as the paroxysmal choreoathetosis of wakefulness.

NOCTURNAL PAROXYSMAL DYSTONIA WITH SHORT-LASTING ATTACKS

We have been able to study four males and eight females displaying short-lasting attacks of nocturnal paroxysmal dystonia (table). Age at observation varied between 6 and 74 years. Both family and personal histories were irrelevant in each case. The nocturnal attacks began between 3 and 47 years of age (mean 21.8 years), the duration of the illness from onset to age at observation varied between 1 and 34 years and frequency of the attacks ranged from 1–2 to 20 per night; in eight patients the attacks recurred every night, and in the remaining four patients from 20 to 25 nights in a month. In all cases the duration of the attacks varied between 15 and 50 seconds.

Repeated EEG recordings, run during both wakefulness and spontaneous sleep, always remained normal in all patients. On polysomnography, the attacks were never associated with EEG activity suggestive of epilepsy. The attacks always appeared with a sudden EEG arousal during NREM sleep. The patient then opened his/her eyes, and, immediately or after a few seconds, showed wide and disordered purposeless movements, which assumed a choreoathetoid and/or ballistic aspect (figs. 1, 2, 3). Such movements tended to occur in a stereotyped fashion in each patient, sometimes accompanied by prolonged vocalisation. Dystonic posturings, localised to only one limb or involving the entire trunk and all limbs, were usually associated or alternated with the dyskinetic movements. At the end of the attack, the patients appeared clear-headed and well orientated and, left alone, soon went back to sleep. On awakening in the morning, they were able to report the motor attacks of the night. Neurological examination and laboratory tests including brain CT were normal in all patients.

The following selected case histories typify the clinical features of nocturnal paroxysmal dystonia with short-lasting attacks:

Case 12 An 11-year-old girl had normal personal and family history until age 9, when sudden episodes lasting a few

Address for reprint requests: Prof. Elio Lugaresi, Clinica Neurologica, Via Ugo Foscolo 7, 40123 Bologna, Italy.

Received 28 June 1985. Accepted 3 August 1985

Table Clinical features of nocturnal paroxysmal dystonia

N	1	2	3	4	5	6	7	8	9	10	11	12
Sex	F	F	F	F	M	M	M	M	F	F	F	F
Age yr	6	7	10	24	37	40	50	74	29	38	34	11
Onset of nocturnal paroxysmal dystonia, yrs	3	5	7	18	35	26	47	40	12	26	33	10
Frequency of nocturnal paroxysmal dystonia (nights per month)	30/30	30/30	30/30	20/30	30/30	25/30	30/30	25/30	30/30	20/30	30/30	30/30
Attacks per night	2-3	4-7	3-4	2-3	1-2	4-20	10-15	2-3	5-7	2-15	14-15	2-3
Nocturnal paroxysmal dystonia seizures also during wakefulness	0	0	Once	0	0	+	0	0	0	0	0	0
Other seizures epileptic or suggestive of epilepsy	0	+	0	+	+	0	+	0	+	+	+	+

* = Grand mal.

seconds and characterised by a feeling of suffocation and inability to swallow occurred 2-4 times a week during classes, without any onlookers noticing anything abnormal. They spontaneously ceased a few months later. In the last 6 months the child has had nocturnal attacks, usually 2-3 times per night, when she would suddenly sit upright in her bed, show some respiratory distress and disordered movements of the arms and trunk for a few seconds. Carbamazepine 100 mg/day abolished the attacks almost completely.

Case 10 A 38-year-old woman reported nocturnal attacks since age 26 years, in which she would wake up with a sensation of "tightness" around her head, sit up in her bed, stare intently into the void and show dystonic purposeless move-

ments of both arms and legs for 15 s, vocalising all the while. The seizures occurred several times per night 4-5 nights a week. A few years later seizures also appeared during the daytime characterised by a cry, flexion of arms and a feeling of being unable to move for 10-15 s. In the last 3 years the daytime attacks have ceased. Carbamazepine 200 mg/day totally suppressed the nocturnal seizures.

Case 7 A 50-year-old man had had 1-2 grand mal seizures per year since age 12. At 47 years of age, when the patient was still under treatment (phenytoin 300 mg + phenobarbitone 200 mg/day) nocturnal attacks began characterised by violent ballistic movements of all limbs, associated with dystonic posturing of arms and trunk and lasting 40-50 seconds. The attacks initially occurring once every 3-4 nights,

Fig 1 Polygraphic recordings of a short-lasting seizure of nocturnal paroxysmal dystonia. The seizure occurred in stage 3-4 NREM sleep with initial changes of electrodermogram (EDG) and photoplethysmogram (Photopleth), associated with an increase in chin muscle tone (Myo). These changes were immediately followed by an EEG arousal and by tachycardia (ECG), slight opisthotonus and dystonic posturing with torsion of the trunk concomitant with pseudo-automatic purposeless movements of the upper limbs.

Fig 2 Polygraphic recordings of a short-lasting seizure of nocturnal paroxysmal dystonia, occurring during stage 2 NREM sleep. The onset was characterised by vegetative changes represented by marked and progressive bradycardia (EKG) and by a central apnea (Resp), later followed by an arousal lasting a few seconds and associated with an increased muscle tone (Mylo EMG). After a few seconds, the patient exhibited motor agitation, characterised by head rotation, extension of the trunk, dystonic arm postures and violent disordered ballistic movements involving both upper and lower limbs (see also fig 3).

reached a frequency of 10–15 per night every night. Carbamazepine 400 mg totally abolished the nocturnal attacks for the following 3.5 years.

Other types of seizures

Eight patients reported what appeared to be sporadic partial sensory-motor seizures also during the daytime, characterised by variable features as for instance: sudden pain, soon followed by stiffening in the right leg and facial redness (case no 2); a sudden feeling of "something ascending from the stomach", associated with suffocation, salivation and inability to speak (case no 4); a sudden urge to start walking, associated with swallowing (case no 9), or, on the contrary, a feeling of being unable to start moving (case no 10).

Four patients had sporadic grand mal seizures during sleep. Two patients reported nocturnal paroxysmal dystonia (dystonic-dyskinetic) attacks during both day and nighttime, even though the day-time attacks always remained exceptional or sporadic.

Treatment

Many patients were referred to us for evaluation after a long history of usually ineffective medication, which included neuroleptic drugs, benzodiazepines and sometimes anti-convulsants such as phenytoin, phenobarbitone or primidone. However we found that the attacks responded favourably to the administration of carbamazepine at dosages of 1.5–11.1 mg/kg/day. The drug was occasionally

effective also at very low levels (plasma levels below 3.5 µg/ml). Follow-up observation periods of 6 months to 4.5 years showed that the attacks were completely or partially suppressed by carbamazepine in all patients who received the drug. In one case the attacks recurred despite treatment after 2 years of complete control, in 2 cases voluntary withdrawal of carbamazepine led to the subsequent reappearance of the nocturnal attacks, which were however again suppressed after resumption of treatment with carbamazepine. Finally, in one case which had already obtained total relief from the dystonic-dyskinetic attacks with carbamazepine, we recorded an isolated nocturnal grand mal seizure during polysomnography.

NOCTURNAL PAROXYSMAL DYSTONIA WITH LONG-LASTING ATTACKS

Prolonged attacks of motor agitation with dystonic and dyskinetic features were observed in two patients.

Case 1 A 44-year-old man, whose father had had Huntington's chorea, reported his first nocturnal attack of motor agitation at 23 years of age. Initially the attacks occurred every 1–2 months, but later on they became more frequent and prolonged, occurring up to 10 or more times per night. The attacks were characterised by dystonic posturing of all four limbs and trunk, associated with choreic and ballistic movements. They could last only a few minutes or more than half an hour, and only appeared during sleep. It should be noted that the patient remained free of other symptoms

Fig 3 Video pictures of a short-lasting attack of nocturnal paroxysmal dystonia (the polygraphic recordings of this seizure are illustrated in fig 2). The attack started with rotation of head and trunk to the right, slight opisthotonus and dystonic arm posturing, subsequently followed by disordered and violent movements of both upper and lower limbs, resembling ballismus. The seizure ended after 40 s with the patient going back to sleep.

until the age of 43 years, when slowly worsening continuous choreic movements and cognitive impairment appeared, which eventually established a diagnosis of Huntington's disease.

Polysomnographic recordings run during several different nights showed that repeated (5–7 per night) episodes of generalised motor agitation, with ballistic and choreoathetoid features and dystonic postures occurred during sleep, lasting 30 to 60 min. All the attacks but one occurred during NREM sleep, especially light sleep stages. Sleep was fragmented by repeated awakenings and deep NREM and REM sleep stages were short. Ictal and interictal EEG however always remained normal during both sleep and wakefulness. Treatment with benzodiazepines, anticonvulsant and phenothiazines remained ineffective; haloperidol alone, given after the onset of Huntington's chorea, slightly reduced the frequency and duration of the nocturnal attacks.

Case 2 A 44-year-old woman, with no relevant family or personal history, experienced nocturnal motor attacks at 22 years of age. The attacks lasted from 2 to 50 minutes and recurred many times during sleep sometimes followed by awakening and anxiety. Since their first appearance 20 years earlier these nocturnal attacks had occurred once or more every night. Neurological examination was normal. Repeated polysomnographic recordings under audiovisual control showed the onset of attacks during NREM sleep, lasting 2–40 minutes and characterised by motor agitation with disordered purposeless movements of the trunk and limbs, repeated in a stereotyped fashion. Ictal and interictal EEG however was always normal during both wakefulness and sleep. Tranquillisers, anticonvulsants, tricyclic antidepressants and phenothiazines all remained ineffective. The patient, whom we have followed for over 15 years, leads a normal family and social life. Only in recent years has she developed some reactive depressive traits.

Discussion

The rather uniform clinical features and polysomnographic patterns in our patients with short-lasting nocturnal paroxysmal dystonia suggest that we are dealing with a distinct nosological entity, which we proposed to term hypnogenic or nocturnal paroxysmal dystonia.^{4,5} We would summarise its clinical aspects as follows: short-lasting (about one minute or less) attacks of ballistic and/or choreoathetoid movements arising during NREM sleep, often preceded by EEG signs of arousal; they may occur many times per night, without spontaneous improvement over the years; there is no sex or age preference and no family predisposition; patients may or may not report similar sporadic day-time attacks, or occasional fits of epileptic origin; the attacks respond favourably to carbamazepine, often at very low dosages. Nocturnal motor attacks have previously been reported by Boller *et al*⁶ and by Pedley and Guilleminault⁷ but these were characterised by pacing around and ambulation, complex activities which were always absent in our patients. Sleep-related axial tonic flexion spasms were later reported

by Rajna *et al*⁸ in a patient with a cingular cortex focus on stereo-EEG, whereas Lee *et al*⁹ recently reported dystonic spasms related to NREM sleep, which were, however, atypical because of their familial occurrence as an autosomal dominant trait and the poor or absent response to carbamazepine. As far as pathogenesis is concerned, in the absence of positive EEG findings, three hypotheses can be entertained: that the attacks fall within the category of parasomnias, for example pavor nocturnus; that instead they represent epileptic phenomena; or, finally, that they are related to the paroxysmal choreoathetosis of wakefulness. Because of the short duration, the characteristic and stereotyped motor phenomena, their high frequency and good response to carbamazepine with no response to benzodiazepines, we consider the first hypothesis rather unlikely. The epileptic origin of nocturnal paroxysmal dystonia with short-lasting attacks is suggested by the peculiar efficacy of carbamazepine treatment and secondly, by the not uncommon association of nocturnal paroxysmal dystonia with day- or night-time sporadic seizures surely epileptic in nature. The normal ictal and interictal EEG during both sleep and wakefulness, however, prevent definite confirmation of the epileptic nature of the attacks. On the other hand, the selective and peculiar effectiveness of carbamazepine itself cannot be taken as a univocal diagnostic point, since it is well known that other non epileptic "seizures" may respond to carbamazepine, for instance dysarthric-ataxic fits in multiple sclerosis, tic douloureux etc.¹⁰ Furthermore, the clinical features of nocturnal paroxysmal dystonia pertain mainly, if not exclusively, to the extrapyramidal system, which is conspicuously unaffected during seizures of epileptic origin. The existence of a so-called "extrapyramidal, choreic or choreoathetoid epilepsy" was recognised in the old neurological literature,¹¹ but, with the advent of clinical electroencephalography, only those seizures associated with an electrical discharge have been considered epileptic. As a consequence, the so-called "extrapyramidal seizures" have been excluded from the classification of epileptic manifestations, and now fall probably under the heading of paroxysmal choreoathetosis. According to Lance, paroxysmal choreoathetosis can be divided into two types: (a) paroxysmal kinesigenic dystonia, characterised by short attacks and having clear similarities with epilepsy, and (b) paroxysmal dystonic choreoathetosis related to stress or to alcohol or drug abuse, and characterised by prolonged attacks. In both types paroxysmal attacks are triggered by disturbances of the cortical control of the neostriatum and its thalamic connections, either transiently, as an epileptic phenomenon, or prolonged, as in paroxysmal dystonic choreoathetosis.¹² A similar

mechanism, but restricted to sleep, could be at work in our patients with short-lasting nocturnal paroxysmal dystonia. And, in effect, the nocturnal occurrence of nocturnal paroxysmal dystonia suggests that the functional state of the basal ganglia may vary during the sleep-wake cycle; consistent with this hypothesis are some clinical observations of Segawa, who has identified a peculiar form of hereditary dystonia with marked diurnal fluctuations¹³ and of Marsden *et al*, who commented on the "sleep benefit" observed in Parkinsonian patients.¹⁴ We observed a similar "sleep benefit" in patients with Meige syndrome and in one patient with Wilson's disease (unpublished observations). Moreover, the short attacks of paroxysmal kinesigenic dystonia respond favourably to carbamazepine¹⁵ like our cases of short-lasting nocturnal paroxysmal dystonia.

Nocturnal paroxysmal dystonia with long lasting seizures should instead be set clearly apart and because of the clinical features, duration of attacks, complete inefficacy of anticonvulsant drugs and normal EEG, a possible epileptic origin is not at all tenable. The fact that the first patient we studied went on to develop Huntington's chorea, albeit 20 years later, rather suggests that a sleep-related biochemical disequilibrium at the level of the basal ganglia underlies these long-lasting attacks.

In conclusion, we feel justified in proposing the division of nocturnal paroxysmal dystonia into two variants of sleep-related motor disturbances, with short and long-lasting attacks respectively. The former shows many similarities with paroxysmal kinesigenic dystonia, having in common the short duration of the attacks, the responsiveness to carbamazepine and the common occurrence of sporadic seizures of a definite epileptic nature. Nocturnal paroxysmal dystonia with long-lasting attacks instead has many similarities with paroxysmal dystonic choreoathetosis, because of the long duration of the attacks, the inefficacy of drug treatments and the absence of epileptic antecedents. Further studies are however needed in order to better clarify the issue of nocturnal paroxysmal dystonia and to try and delineate a reliable classification of sleep-related motor attacks. Sleep dystonias represent just one example of the nosographic problems that arise from systematic approaches to the neglected field of motor control during sleep.

References

- ¹ Broughton RJ. Sleep disorders: disorders of arousal? *Science* 1968;**159**:1070-8.
- ² ASDC-APSS. Diagnostic Classification of Sleep and Arousal Disorders. *Sleep* 1979;**2**:5-122.
- ³ Broughton RJ. Pathophysiology of enuresis nocturna, sleep terrors and sleep walking: current status and the Marseilles contribution. *Electroencephalogr Clin Neurophysiol* 1982;**Suppl**, **35**:401-10.
- ⁴ Lugaresi E, Cirignotta F. Hypnogenic Paroxysmal Dystonia: Epileptic Seizures or a New Syndrome? *Sleep* 1981;**4**(2):129-38.
- ⁵ Lugaresi E, Cirignotta F. Two variants of nocturnal paroxysmal dystonia with attacks of short and long duration. In: Degen R, Niedermeyer E, eds. *Epilepsy, Sleep and Sleep Deprivation*, Amsterdam: Elsevier 1984:169-73.
- ⁶ Boller F, Wright DG, Cavalieri R, Mitsumoto H. Paroxysmal nightmares. Sequel of a stroke responsive to diphenylhydantoin. *Neurology (Minneapolis)* 1975;**25**:1026-8.
- ⁷ Pedley TA, Guilleminault C. Episodic nocturnal wanderings responsive to anticonvulsant drug therapy. *Ann Neurol* 1977;**2**:30-5.
- ⁸ Rajna P, Kundra O, Halász P. Vigilance level-dependent tonic seizures: epilepsy or sleep disorder? A case report. *Epilepsia* 1983;**24**:725-33.
- ⁹ Lee BI, Lesser RP, Pippenger CE, *et al*. Familial paroxysmal hypnogenic dystonia. *Neurology (Cleveland)* 1985;**35**:1357-60.
- ¹⁰ Johnson RT. *Current Therapy in Neurological Disease*. Philadelphia, BC Decker Inc., 1985:1-425.
- ¹¹ Marchand L, Ajuriaguerra J de. *Epilepsies, leurs Formes Cliniques, Leurs Traitements*. Paris, Desclée de Brouwer, 1984.
- ¹² Lance JW. Familial paroxysmal dystonic choreoathetosis and its differentiation from related syndromes. *Ann Neurol* 1977;**2**:285-93.
- ¹³ Segawa M, Hosaka A, Miyagawa F, Nomura Y, Imai H. Hereditary Progressive Dystonia with Marked Diurnal Fluctuation. In: Eldridge P, Fahn S, eds. *Advances in Neurology*, Vol 94, New York: Raven Press, 1976: 215-33.
- ¹⁴ Marsden CD, Parkes JD, Quinn N. Fluctuations of disability in Parkinson's disease-clinical aspects. In: Marsden CD, Fahn S, eds. *Movement Disorders*, London: Butterworth 1981:96-122.
- ¹⁵ Kato M, Araki S. Paroxysmal kinesigenic choreoathetosis. Report of a case relieved by carbamazepine. *Arch Neurol* 1969;**20**:508-13.