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Pure sleep seizures: risk of seizures while awake

Lorena Benavente Fernández, Javier Salas-Puig

Department of Neurology, Hospital Universitario Central de Asturias, Oviedo, Spain

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ABSTRACT – *Purpose.* To estimate the risk of seizures while awake in pure sleep epilepsies - a long follow-up study.
Methods. Fifty five patients (60% male), with pure sleep epilepsy were followed up for at least ten years. Patients younger than 18 years of age were excluded. The primary endpoint was the occurrence of seizures while awake, after a period of 10 years or longer suffering from pure sleep seizures.
Results. The duration of the pure sleep seizures ranged from 10 to 67 years (median 22). The patients had been followed in our Department for a mean of 12 years. Patients' ages ranged from 18 to 88 years (median 50); 44% of patients suffered from apparently generalized seizures. Epilepsy was considered undetermined in 38.2%, focal cryptogenic in 38.2%, and focal symptomatic in 21.8%. There was a single case of idiopathic generalized epilepsy. In the last evaluation, 35 patients were on monotherapy and two were not receiving treatment. Seizure frequency was < 1/year in 65.5%; 1-10/year in 14.5%; > 1/month in 9.1%. Seventeen patients (30.9%) had suffered one or more seizures while awake. Multivariate analysis showed that sudden withdrawal of treatment ($p < 0.032$) and polytherapy ($p < 0.18$) were associated with an increased risk of seizures while awake.
Conclusions. In spite of a small number of seizures and good response to monotherapy, a third of the patients studied suffered seizures while awake. The significant risk factors were sudden withdrawal of treatment and polytherapy.

Key words: sleep, seizure, risk of seizure, epilepsy and sleep

Pure sleep seizures are difficult to classify into epilepsy syndromes according to the Classification of the International League Against Epilepsy (ILAE 1989). Because of their heterogeneous characteristics, they are included in the section of "Epilepsies and syndromes undetermined whether focal or generalized", due to lack of unequivocal generalized or focal features. Epilepsy with seizures occurring almost exclusively during sleep certainly has an important impact on quality of life with possible medico-legal issues. We analyzed the long-term follow-up of patients diagnosed as suffering from epilepsy during sleep, to better determine the risk of seizures while awake.

Methods

Patients were retrospectively recruited from the neurology department of a university hospital. Ninety six patients with seizures during sleep were studied. On the basis of the following four criteria, 55 patients were retained for analysis: (a) over eighteen years of age; (b) seizures exclusively during sleep over a period of ten years or more; (c) a history of at least three, pure sleep seizures; (d) patients suspected of having had, at epilepsy onset, focal seizures; absences or myoclonus while awake were excluded.
Antiepileptic drugs used depended on the type of epilepsy.

Correspondence:
Dr Javier Salas-Puig
Department of Neurology
Hospital Universitario Central de Asturias
Julian Claveria s/n
33066 Oviedo
Spain
Fax: (+ 00 34) 985273657
<jsalasp@meditex.es>

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Table 1. Main characteristics of 55 patients with pure sleep seizures over a mean period of 23.8 years (10-67 y).

Age	52.6 years (18-88)
Sex	33 (60%) male/22 (40%) female
Age-at-onset	25.2 years (5-75)
Seizure type	43.6% generalized seizures 25.5% partial seizures 7.3% partial secondary generalized seizures 23.6% unclassified seizures
EEG	13 T; 1 F; 3 FT; 3 O; 1 generalized spike-waves
Sleep-EEG	6 T; 2 F; 7 FT; 1 O; 1 generalized spike-waves
Neuroimaging	3 ischemic lesions involving cortex 2 gliosis 2 disorders of cortical development 7 other causes: 2 calcifications, 2 angiomas, 1 meningioma, 1cerebellar atrophy, 1 hydrocephalus 5 diffuse atrophy 6 small subcortical ischemic lesions
Epileptic syndrome	21 (38.2%) undetermined 21 (38.2%) focal cryptogenic 12 (21.8%) focal symptomatic 1 (2.8%) idiopathic generalized
Relapses	52.7% withdrawal of therapy 10.3% free of seizures 89.7% relapsing

EEG focus: F = frontal; T = temporal; FT = fronto-temporal; O = occipital.

Seizures while awake were defined as those occurring out of any period of sleep or sleep-related situation. Forty one patients were excluded because of the following reasons: rare possibility of seizures while awake at epilepsy onset (12 patients); shorter than 10 years' follow-up with pure sleep seizures (29 patients).

For each patient, the following clinical and prognostic variables were recorded at the time of inclusion: age, sex, age-at-onset of epilepsy, history of febrile seizures, family history of epilepsy, frequency of seizures before and after beginning any AED treatment, AEDs in the past and at inclusion.

All the patients underwent standard EEG, with 33 (60%) undergoing sleep-EEG during a nap period. The following EEG parameters were retained for analysis: normal; with diffuse background non-specific abnormalities; generalized epileptiform discharges; temporal, frontal, fronto-temporal, parietal or occipital foci. All patients included had had a brain CT scan, an MRI or both. We looked for: normal neuroimaging; diffuse brain atrophy; a focal lesion such as ischemia, gliosis, tumour, abnormal cortical development or vascular malformation.

Seizures were classified on the basis of eyewitness evidence as generalized, focal, focal with secondary generalization or undetermined. On the basis of all the above data, the epilepsy type was defined as: *cryptogenic focal epilepsy* if the EEG showed a focus, but neuroimaging was normal; *symptomatic focal epilepsy* when neuroimaging demonstrated some abnormality, with a normal or abnormal EEG; *undetermined*, when both EEG and neuroimaging were normal; and *generalized epilepsy*, in the presence of generalized spike-wave EEG discharges and normal neuroimaging (one patient). Prolonged video-EEG monitoring was not performed.

The PC/SPSS version 8 for Windows was used for data analysis. The mean was compared with one-way ANOVA and parametric and non-parametric Tests (Chi^2 and Test de Mann-Whitney) were used depending on the characteristics of the various variables.

Results

A total of 55 patients [33 males (60%) and 22 females (40%)] were included (*table 1*). Age-at-onset of epilepsy ranged from five to 75 years (mean 25.2, median 17). At inclusion, patients' ages ranged from 18 to 88 years (mean 52.6, median 50). Time from onset of the epilepsy to the inclusion period ranged from 10 to 67 years (mean 23.8, median 22) with a mean follow-up of 12 years (0-35 years). The follow-up in our Department started at different times during the patients' epilepsy history.

A family history of epilepsy was present in 31% of the patients included, and neurological antecedents were reported in 38% (cranial trauma in 14; perinatal anoxia in four; febrile seizures in two; and brain ischemia in one). Twenty-four patients (43.6%) suffered from generalized

seizures, fourteen (25.5%) had focal seizures, four (7.3%) experienced focal seizures with secondary generalization and thirteen (23.6%) were classified as having an undetermined type of seizure. Standard EEG showed epileptiform discharges in 22 patients (40%): 20 had focal interictal epileptiform discharges (13 temporal, one frontal, three fronto-temporal, three occipital), one patient had diffuse background, non-specific abnormalities, and one patient had generalized spike-wave discharges. Sleep-EEG during a nap period was performed in 33 patients, revealing epileptiform discharges in 17 (51.5%): one with generalized spike-wave discharges; six with a temporal focus; two with a frontal focus; seven with a fronto-temporal focus; one with an occipital focus.

Focal brain lesions at CT/RM imaging were detected in 14 patients: three ischemic lesions; two gliotic scars; two focal abnormalities of cortical development, and seven with various other cortical lesions (calcifications, cavernoma and primary cerebral tumours). Five patients had diffuse atrophy, and six others had small subcortical ischemic lesions. Neuroimaging was interpreted as normal in 30 patients.

According to the type of seizures, EEG characteristics and neuroimaging, the patients were classified as follows: 21 (38.2%) had undetermined epilepsy; 21 (38.2%) had focal cryptogenic epilepsy; 12 (21.8%) had focal symptomatic epilepsy and one patient had idiopathic generalized epilepsy.

The mean seizure frequency before treatment was less than one per year in 25.5%, one to 10 seizures per year in 45.5% and more than one per month in 29.1%. After receiving AED treatment, the mean seizure frequency was less than one per year in 65.5%, one to 10 seizures per year in 14.5% and more than one per month 9.1%. Five patients (9.1%) were seizure-free under treatment.

At the end of follow-up, two patients were not receiving any treatment. 35 patients were on monotherapy, 17 were on two AEDs and one patient was receiving three drugs.

The mean age-at-onset of the epilepsy for patients on monotherapy was 30 years while it was clearly less (18 years old) for those treated with more than one AED. Patients with a lower seizure frequency when on treatment were older, which may suggest benign forms of epilepsy. Although our analysis did not show a statistical significance ($p = 0.18$ ANOVA one way), it is worth mentioning that patients on monotherapy or with no treatment had a better response, being either seizure-free or experiencing a mean seizure frequency of less than one seizure per year. Patients on two or three drugs had more than one seizure per year ($p = 0.046$, Chi^2 Pearson).

Discontinuation or reduction of AED medication was tried in 29 patients (52.7%), but only three (10.3%) of them remained free of seizures, two without any treatment and one on monotherapy following withdrawal of the second drug. Twenty patients (69%) had a relapse of seizures, three patients (10.3%) had two relapses, two patients (6.9%) had three relapses and one patient (3.5%) had five relapses. Patients with more than one relapse after withdrawal of AEDs were those who had stopped the treatment on their own. This is a very important aspect as regards prognosis, as the relapses after withdrawal of therapy are significantly associated with the occurrence of seizures while awake ($p < 0.032$ Mann-Whitney test or $p < 0.006$ ANOVA one way).

Occurrence of seizures while awake was reported in seventeen patients (30.9%) (*table 2*): Four patients (7.3%) had one seizure while awake; four (7.3%) experienced two seizures; three (5.5%) had three seizures; two (3.6%) had four; one patient (1.8%) had five and three (5.5%) had more than ten seizures while awake. The majority of the patients with seizures while awake had focal seizures.

A further feature observed in the group of patients with seizures while awake is related to the number of ongoing AEDs. Most of these patients were on at least two drugs, suggesting a more resistant form of epilepsy. It is to be noted that the introduction of a second AED was not related to the appearance of seizures while awake. In *table 2*, we also present the seizures while awake that occurred during medication withdrawal and the time to a first seizure while awake following AED withdrawal.

Discussion

This study attempts to assess the risk of occurrence of a seizure while awake among patients with a long-term evolution of pure sleep seizures. This is an important issue with significant consequences for social integration, such as type of employment, social activities, and obtaining a driving licence. Our inclusion criteria were very strict, as we included patients with an at least ten-year history of exclusively sleep-related seizures. Children with rolandic epilepsy were excluded because of the low seizure frequency naturally observed in this epilepsy syndrome. We also excluded patients with sleep disorders that could have been erroneously diagnosed as epilepsy.

The International Classification of Epilepsies and Epileptic Syndromes considers pure sleep seizures as "epilepsies and syndromes undetermined whether focal or generalized". It is obvious that based mainly on eyewitness descriptions, a number of secondarily generalized seizures may be misdiagnosed as generalized tonic-clonic seizures from onset. Our analysis also took into account EEG and neuroimaging findings, to conclude that for nearly 60% of our patients we had sufficient information to diagnose focal epilepsy.

Several published studies reported on classification and prognosis of pure sleep seizures. In 1962, Janz had already studied the incidence of sleep epilepsy (30-45% of patients with *grand mal*) and had noticed that this kind of seizures could spread according to the circadian rhythm [1].

Table 2. Patients (n = 17) who suffered seizures while awake.

Seizures while awake	Standard EEG	Sleep EEG	Neuroimaging	Epilepsy syndrome	Pure sleep seizure evolution	Relapses	Seizures while awake during AED withdrawal	Time to seizures while awake following AED withdrawal
4	T	T	N	Focal cryptogenic	22	2	Yes	1 year
10	N	N	N	Undetermined	10	5	Yes	Days
5	FT	FT	Ischemic lesion	Focal cryptogenic	67		Yes	Months
1	N		N	Undetermined	22		No	
1	O	N	Diffuse atrophy	Focal cryptogenic	37	1	Yes	Months
1	N	N	N	Undetermined	17		No	
10	T		Others	Focal cryptogenic	32		No	
2	N		N	Undetermined	33		No	
1	N	F	N	Focal cryptogenic	10	1	No	
2	N	FT	Diffuse atrophy	Focal cryptogenic	25		Yes	Months
10	T	N	N	Focal cryptogenic	10		Yes	Months
4	N	FT	Gliosis	Focal cryptogenic	23	1	Yes	Days
2	N	N	Ischemic lesion	Undetermined	15		No	
3	N		Others	Focal cryptogenic	10	2	Yes	Months
3	T		Ischemic lesion	Focal cryptogenic	43		Yes	Days
3	N	FT	Others	Focal cryptogenic	30		No	
2	N	FT	N	Focal cryptogenic	13	3	Yes	Days

EEG focus: F = frontal; T = temporal; FT = fronto-temporal; O = occipital; N = normal.

In another series of 2825 patients with *grand mal* epilepsy, Janz (1974) found 44% of patients having seizures while asleep, who could evolve to a mixed epilepsy with seizures both while asleep and awake. Gibberd and Bateson (1974) found that 16 patients out of 64 followed-up for three years, developed at least one seizure while awake and that after this time frame the risk of seizures while awake diminished. They concluded that a three-year follow-up was sufficient to establish the prognosis of sleep seizures. However, some of their patients had had seizures while awake many years before, and rolandic epilepsy patients were not excluded from their study. A number of other studies, involving a rather small number of patients and a short follow-up have been published (Billiard 1982, Autret *et al.* 1982, D'Allesandro *et al.* 1983, Young *et al.* 1985). D'Allesandro *et al.* found that 11.7% of 34 epilepsy patients with generalized tonic-clinic sleep seizures developed a seizure while awake during a two-year follow-up. Similarly, Young *et al.* (1985), found that pure sleep seizures were usually generalized tonic-clonic and of unknown aetiology. Those of their patients who also experienced some seizures while awake usually presented with focal epilepsy, an abnormal EEG, a positive family history and a poor response to drugs.

Autret *et al.* (1987) reported on the EEG findings in 236 patients, which showed that there was no correlation between the seizure timetable and activation on the EEG, and concluding that pure sleep seizures could not be classified as a separate epilepsy syndrome.

Basim *et al.* (1994, 1997), classified 66% (42/64) of their patients, according to the International League Against Epilepsy, and found that 79% had had partial seizures and 94% were seizure-free on monotherapy after 2 years of follow-up. According to these arguments, they suggested that pure sleep seizures can be considered a new form of epilepsy syndrome. A similar suggestion was made by Mauri *et al.* (1996), following a study of 20 patients with pure sleep seizures with a three-year follow-up. All were seizure-free on monotherapy, but relapsed after discontinuation of AEDs. More recently, Park *et al.* (1998) reported that 19% (12/63) of patients with pure sleep epilepsy developed a seizure while awake within two years of onset. In that particular study, as well as previous ones, the risk was greater among patients with partial seizures with or without secondarily generalization, a longer history of epilepsy and a greater frequency of seizures.

In a recent study, D'Allesandro *et al.* (2004) found that during the first two years of follow-up, 7.5% of patients suffered a seizure while awake, with a slight decrease in risk in the following years. The risk was greater in patients with a baseline seizure frequency of more than six seizures per year and if AED discontinuation was performed abruptly. None of their patients who followed a planned gradual therapy withdrawal had a seizure while awake. Their patients had mainly generalized seizures (85%), according to eyewitness accounts. If we adopted the same criteria we would have 43.6% (24) of our patients with this type of seizure. A focal onset was recognised in 58.2% of our patients according to EEG and neuroimaging criteria.

In our series, the estimated risk of experiencing a seizure while awake, after a period of at least 10 years with pure sleep epilepsy, was 30.9%. This figure is in contrast with previous studies (Billiard M. 1982, Autret *et al.* 1982, D'Allesandro *et al.* 1983, Young *et al.* 1985, D'Allesandro *et al.* 2004), where the estimated risk was around 10%, possibly because of a shorter follow-up.

Another prognostic factor, according to our findings is the withdrawal of therapy, both abrupt and gradual. In this respect, we obtained statistical significance ($p = 0.006$ ANOVA one way; $p = 0.32$ U-Mann-Whitney Test). Twenty-nine of our patients (52.7%) tried to withdraw treatment, but only 10.3% (3 patients) remained seizure-free. The more optimistic data from previous studies may be explained by a shorter follow-up.

Despite the risk of recurrence, our data support the overall good prognosis of pure sleep epilepsies, because of the rarity of seizure occurrence. Furthermore, 63.7% of our patients were on monotherapy and 65.5% had one or fewer seizures per year, likewise 9.1% became seizure-free if the treatment was followed properly. In contrast with others (Janz 1974, Montplaisir *et al.* 1987, Bazil 2000, Bazil 2002) the risk of seizures while awake was not found to be any greater among patients with partial seizures with or without secondarily generalized tonic-clonic sleep seizures ($p = 0.28$ Chi^2). Basim *et al.* 1994, 1997; ILEA, 1989. □

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