Nocturnal frontal lobe epilepsy

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Summary

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The paroxysmal motor events during sleep are certainly common. The systematic use of nocturnal video-polysomnography has largely improved the diagnostic yield in patients with clusters of nocturnal motor events. Two broad nosological categories have been identified: parasomnias (sleep terror and sleep-walking), which are thought to represent disorders of arousal during sleep, and the epileptic seizures arising from sleep (nocturnal epilepsy). In recent years, particular attention has been devoted to those seizures arising from epileptic foci located within the frontal lobe or within the temporal lobe with early involvement of the frontal lobe: so-called nocturnal frontal lobe epilepsy (NFLE). Also in recent years the clinical, neuroradiological and neurophysiological profile of NFLE has clearly been delineated: up to 40% of patients with NFLE had at least one first-degree relative with a probable primary parasomnia; about 20% of patients had a family history of epilepsy; 5 to 10% had NFLE, with nocturnal seizures quite similar to those of the proband; the age at onset of seizures ranged from 1 to 65 years; the mean frequency of seizures was 15–20 per month; patients often complained of nocturnal sleep disruption (about one half of them reported excessive daytime sleepiness); one third of patients also had occasional seizures during wakefulness, usually in childhood; the seizures had a stereotypic motor pattern, of various complexity; traditional neuroradiological examinations showed abnormalities in about 10% of cases; there was a wide intra-familial variation in the severity of seizure disorder. There was also considerable intra-individual variation in severity during the different periods of life, with an age-dependent degree of severity; ictal EEG abnormalities were found in 30 to 60% of patients; the EEG during sleep showed interictal focal epileptiform abnormalities in about 50% of patients; in about two third of patients carbamazepine, clonazepam or their association were able to greatly reduce nocturnal seizures in frequency and complexity and, in some cases, to completely control them. The differential diagnosis between sporadic (and familial) NFLE from benign parasomnias is difficult from the history alone.

A full video-polysomnographic study should be proposed to all the patients complaining of repeated nocturnal motor, autonomic and behavioural episodes, in order to provide a correct diagnosis.

Keywords: nocturnal frontal lobe epilepsy; video-polysomnography

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Introduction

The relationship between epilepsy and sleep has been recognised since antiquity: both Hippocrates and Aristotle observed the occurrence of epileptic seizures during sleep. However, the reciprocal influence between sleep and epilepsy has not been investigated until the end of the 19th century when Gowers studied the effect of sleep/wake cycle on "grand mal" epilepsy [1]. Several years later a study described, on the basis of clinical observations, two peaks of the time of occurrence of nocturnal seizures: the first peak occurred approximately two hours after bedtime and the second was between 4 and 5 in the morning [2]. The same study also found that daytime seizures occurred predominantly in the first hour after awakening.

After the discovery of the human EEG [3] and its application in medical practice, the relationship of sleep and epilepsy was better defined. Gibbs and Gibbs [4] observed an increase in the interictal epileptiform activity (IEA) during sleep compared

to the frequency of the interictal epileptiform activity during the waking state.

Some authors have classified seizures according to the time of seizure occurrence in relation to sleep/wake cycle [1, 2, 5]. Three distinct groups were identified: (a) seizures restricted to sleep (sleep epilepsy); (b) seizures occurring only in wake state (waking epilepsy); (c) seizures occurring in both sleep and waking state (diffuse epilepsy). In the early clinical observations [1, 2, 6] it was found that about 45% of epileptic patients had "waking epilepsy", about 20% presented "sleep epilepsy" and 35% had "diffuse epilepsy".

The two neurophysiological states that characterise sleep (NREM and REM) have opposite consequences on interictal abnormalities and critical manifestations. According to most studies, generalised discharges and clinical seizures mainly occur in NREM sleep, which may be considered a natural "convulsive agent" [7]. The majority of EEG discharges are found in stage-2 NREM whereas REM sleep, with its asynchronous cell discharge patterns and atonia, is resistant to propagation of epileptic EEG potentials [8]. NREM sleep activates interictal epileptiform discharges in both partial and generalised syndromes [9]. Montplaisir et al. [10], by studying patients with deep electrodes, proposed that REM sleep limits the diffusion of epileptic discharges outside the area of seizure onset: this suggests that REM sleep allows the localisation of the primary epileptogenic area. However, in most patients with partial epilepsy the seizures are more common during NREM sleep than during REM sleep [11]. The activating role of NREM sleep on the epileptic cortex has been attributed to increased neuronal synchronisation within thalamocortical projection neurons [12].

In recent years, some papers [13, 14] have shown that specifically arranged phasic EEG events, closely related to a transient lightening of sleep depth, may provide crucial information on the dynamic characteristics of the sleep process. Studies concerning the aggregation of the arousal-related phasic events within the non-rapid eye movements (NREM) sleep stages have led to the identification of a double modality of arousal control: (a) the cyclic alternating pattern (CAP), which corresponds to a prolonged oscillation of the arousal level; (b) the complementary condition, non-CAP, closely related to a degree of stability in sleep depth.

CAP is organised in sequences of CAP cycles; each CAP cycle consists of a phase A and a phase B, each lasting between 2 and 60 s. Phase A is the expression of a transient activation of the arousal level, while phase B is the recovery of background activities. Variations during CAP involve muscle tone, heart rate and respiratory activity, which increase during phase A and decrease during phase B. On the basis of the information derived from EEG activities, muscle tone and neurovegetative responses, three subtypes of phase A may be distinguished:
– *Subtype A1* = synchronised EEG pattern;
– *Subtype A2* = desynchronised EEG pattern preceded by or mixed with slow high-voltage waves, linked with a moderate increase of muscle tone and cardiorespiratory rate;
– *Subtype A3* = desynchronised EEG pattern, coupled with a remarkable increase in muscle tone and cardiorespiratory rate.

The A1 subtypes prevail in the build-up and maintenance of deep NREM sleep, while the A2 and A3 subtypes dominate in light NREM sleep that precedes the onset of REM sleep [15].

Epileptiform discharges appear to be activated in the CAP-phase A. In particular, it has been observed that in idiopathic generalised epilepsy 70% of epileptiform discharges were in phase A1, 24% in phase A2 and 6% in phase A3 [16].

Focal motor seizures occurring in NREM sleep have been reported to arise predominantly from the CAP-phase A, 41 of 43 seizures in a study by Terzano et al. [17].

Confusion over sleep deprivation, disparities between evidence and recommendations and inconsistent practices have been reported in a recently published survey [18]. However, many studies report an increased epileptiform discharge activity following sleep deprivation. It is well known that sleep itself activates epileptiform discharges in partial as well as generalised epilepsies. Nevertheless, there is no general agreement whether the activating effect of sleep deprivation is merely caused by the sleep or whether there is an independent genuine provocative effect of sleep deprivation "per se" [19]. The main arguments in favour of a genuine activating effect of sleep deprivation are the presence of activation not only in sleep but in the awake state after sleep deprivation [20], as well as the activation after sleep deprivation in sleep in those patients who had no activation in sleep without sleep deprivation in previous recordings [21]. In a recent study, Halasz et al. [22] have investigated the effect of sleep and sleep deprivation on spike-wave discharges in idiopathic generalised epileptic patients by continuous EEG monitoring for 4×24 h (sleep was deprived during the second 24 h). This study showed that sleep had an activating effect being the highest during stages 1 and 2 NREM; there was

an increase of interictal EEG discharges in all vigilance states after sleep deprivation, but the epileptiform EEG activity remained the highest in light NREM sleep. These results support the view that sleep-dependent rather than sleep-independent mechanisms cause EEG activation after sleep deprivation in generalised epilepsy. However, an increased epileptiform discharge activity has been observed by Halasz et al. in the awake state after sleep deprivation. It is known that power spectrum of awake state EEG after sleep deprivation contains more theta elements than awake state before sleep deprivation [23]: this suggests that awake state after sleep deprivation may contain some sleep elements and, thus, the high rate of vigilance level fluctuations is essential in promoting epileptiform discharges.

Concerning the vigilance levels fluctuations, Parrino et al. [24] found that CAP rate was significantly higher in morning sleep after sleep deprivation, due to the outcome of two opposite tendencies of high sleep pressure (homeostatic influence) and propensity to wakefulness (circadian influence). The higher arousal instability in sleep after sleep deprivation, compared with sleep without sleep deprivation, may determine the activating EEG effect. According to CAP findings of Parrino et al. [24], the EEG recording after sleep deprivation should be performed in the morning and not in the early afternoon. This methodological aspect could ameliorate the results obtained by Peraita-Adrados et al. [25] who observed interictal/ictal EEG discharges during nap recording (in the early afternoon) after sleep deprivation in 40.4% of 686 epileptic patients with normal EEG during wakefulness.

Sleep and frontal lobe seizures

It is well known that seizures originating from the frontal lobe show a tendency to occur preferentially during sleep. They tend to have prominent motor manifestations and are likely to be recognised by the parents or bed partners. Three major clinical forms of frontal lobe epilepsy may be distinguished:
a   benign focal epilepsy of childhood,
b   supplementary sensorimotor area epilepsy,
c   nocturnal frontal lobe epilepsy (NFLE).

Benign focal epilepsy of childhood

This syndrome, also referred to as benign rolandic epilepsy or benign childhood epilepsy with centro-temporal spikes, is a common form accounting for 15–25% of childhood epilepsy [26]. The children are of normal intelligence and have a normal neurological examination. Approximately 75% of the seizures occur during sleep [27]. The seizures are unilateral focal motor (usually involving the face and arm), present with oropharyngeal sensorimotor phenomena or are generalised tonic-clonic in nature. The oropharyngeal seizures manifest as hypersalivation, guttural sounds and mouth movements and at times sensations in the mouth (dryness or prickling tongue sensation).

The characteristic interictal discharges are typically distributed in the centro-temporal region but may occur in any region. The discharges may be unifocal, bifocal or multifocal in distribution. The sharp waves have a stereotyped morphology and are typically infrequent during the wake state.

Supplementary sensorimotor area (SSMA) epilepsy

This form refers to epilepsy originating from the SSMA on the mesial aspect of the superior frontal gyrus (area 6) and extending onto the dorsal aspect of the convexity. The typical seizures are characterised by abrupt tonic posturing of the extremities. The upper extremities are usually asymmetrically involved with the abduction at the shoulders, flexion of the elbow on one side and the extension in the other extremity. The head is turned to one side as though looking toward the flexed arm ("fencing posture"). The lower extremities are involved in the tonic posture with abduction at the tips and flexion or extension at the knees. There may be associated vocalisation and kicking with preserved responsiveness. Somatosensory (lateralised or diffuse) symptoms may precede the tonic contraction and consist of a feeling of pulling or heaviness, or a limb sensation of moving [28].

The seizures tend to occur predominantly during sleep. Interictal sharp waves are usually found at the midline, maximum at the vertex or just adjacent to the midline in the fronto-central region. It is fundamental to distinguish epileptiform discharges from the vertex sharp transients of sleep. The appearance of sharp waves during the waking state allows the discrimination.

The ictal EEG pattern is characterised by a high amplitude slow transient or sharp wave at the vertex, followed by low amplitude fast activity or an electrodecremental pattern [28, 29]. Following this pattern, there is a high amplitude slowing in the fronto-central regions distributed bilaterally.

Nocturnal frontal lobe epilepsy (NFLE)

In the last years a distinct form of clear-cut attacks originating from epileptic foci located in the frontal lobe (in particular in mesial and orbital cortex) and emerging almost exclusively from sleep has been described [30–33]. Seizures are characterised by a wide spectrum of clinical features: assumption of postures, rhythmic and repetitive movements of arms and legs, rapid uncoordinated movements, with dystonic or dyskinetic components, complex motor activities (deambulation, wandering, pelvic thrusting), sudden elevation of the trunk and head associated with expression of fear and vocalisation. In a series of 100 consecutive patients with NFLE Provini et al. [34] emphasised the usefulness of a clinical distinction of motor manifestations into three subgroups: (a) *paroxysmal arousals:* brief (<20 s) episodes characterised by sudden eye opening, head raising or sitting up in bed, often with a frightened expression and sometimes vocalisation; (b) *nocturnal paroxysmal dystonia:* episodes of intermediate duration (20 s – 2 min) characterised by wide, often ballistic movements, dystonic posturing or choreoathetoid movements of head, trunk and limbs and vocalisation; (c) *episodic nocturnal wandering:* episodes of longest duration (1–3 min) with stereotyped, paroxysmal ambulation, accompanied by screaming and bizarre, dystonic movements. All three types of seizures frequently occur in the same patients.

Surface EEG during the attacks and interictally is often normal, uninformative or not interpretable because of the presence of muscular artefacts [35]. Only deep (intracranial, sphenoidal) electrode recordings can help to identify ictal and/or interictal discharges [30, 36, 37]. Various ictal EEG patterns may be observed: background flattening, rhythmic theta/delta activity, sharp wave on the frontal regions.

NFLE has been described as sporadic and familial form. Autosomal dominant NFLE (ADNFLE) was first described by Scheffer et al. [38] in 1994: the authors collected six families with 39 affected individuals in Australia, the United Kingdom and Canada and were able to demonstrate monogenic inheritance with an autosomal dominant transmission pattern. In the last years more families, mostly of Caucasian descent, have been described [39–41]. The first gene found to be responsible for ADNFLE was identified by Phillips et al. [42] in a large Australian kindred and mapped to chromosome 20q13.2–q13.3. Steinlein et al. [43] discovered a corresponding missense mutation in the neuronal nicotinic acetylcholine receptor (nAchR) alpha-4 subunit (CHRNA4), resulting in a substitution of serine with phenylalanine. Other new CHRNA4 mutations have more recently been reported in other families [44, 45] and three loci have been associated with ADNFLE: the ENFLE1 locus on chromosome 20q13.2, the ENFLE2 on chromosome 15q24, the ENFLE3 on chromosome 1q21. Our recent paper indicates the existence of at least a fourth locus for ADNFLE which should not belong to the nAchR gene family [46]. In fact, we investigated in four unrelated ADNFLE Italian families the possible involvement of all genes coding for brain-expressed nAchR subunits, with known chromosome localisation; linkage and mutation analyses were performed. In none of the Italian families was a linkage between ADNFLE and the analysed chromosome regions detected.

Electroclinical profile of NFLE
In recent years the clinical, neuroradiological and neurophysiological profile of NFLE has clearly been delineated [30–41].

Clinical data: Up to 40% of patients with NFLE had at least one first-degree relative with a probable primary parasomnia (sleep-talking; sleep-walking; sleep terrors; primary enuresis; bruxism). About 20% of patients had a family history of epilepsy; 5 to 10% had NFLE, with nocturnal seizures quite similar to those of the proband. In these cases, the autosomal dominant transmission allowed the diagnosis of ADNFLE. The age at onset of the seizures ranged from one to 65 years (mean age between 8 and 14 years). Patients reported a mean frequency of seizures about 15–20 per month. The most common triggering factor (in 15 to 25%) was psychological stress. Patients often complained of nocturnal sleep disruption. About one half of them reported excessive daytime sleepiness. One third of patients also had occasional seizures during wakefulness, usually in childhood.

Neuroimaging data: Traditional neuroradiological examinations (CT and MR scans) showed abnormalities in about 10% of cases: frontal vascular malformations; ischaemic lesions; frontobasal arachnoid cyst; frontal cortical dysplasia; temporal and/or frontal gliosis. Magnetisation transfer imaging and diffusion-weighted imaging showed subtle and widespread abnormalities related to intra- and extracellular distribution and motion of water in the brains of patients with NFLE [47]. Using single-photon CT some authors have recently found a hyperperfusion of the cingulate gyrus both during the ictal phase of the so-called nocturnal paroxysmal dystonia (a semeiological manifestation of NFLE) [48] and during episodes

Figure 1 Beginning of a major attack (shown in sequence of photos, 1 to 4) arising from delta sleep. Absence of clear-cut epileptiform abnormalities.

Sequence of photos, 1 to 4 (major attack): sudden elevation of head and trunk, assumption of sitting position, dystonic movements of arms, fearful expression and panic sensation.

of sleep-walking [49]. The cingulate gyrus seems to be a brain region highly involved, both primarily and secondarily, in the generation of complex motor behaviours during sleep.

Video-polysomnographic data: The seizures had a stereotypic motor pattern of various complexity; we summarised the possible motor attacks in:

– *Minimal:* Simple motor acts of body touching (such as scratching or rubbing the nose or head), limb flexion, chewing, facial grimacing, vocalisation, moaning or simple body movements; duration of 3–10 seconds.
– *Minor:* Motor acts with the involvement of more body segments, with purposeful or semi-purposeful behaviour, such as gross body movements, change in body position and/or rhythmic movements; duration of 10–30 seconds.
– *Major:* Sudden and abrupt body or segmental movements such as elevation of head and trunk, hyperextension of arms and trunk accompanied by dystonic or clonic movements, fearful expression and panic sensation; duration of 5–30 seconds (see figure 1, sequence of photos 1 to 4).
– *Prolonged:* Complex motor behaviour with tonic-dystonic posture, bimanual and bipedal activity, axial movements, shouting, laughing and deep breathing; duration of more than 1 minute.

There was a wide intra-familial variation in the severity of seizure disorder. And there also was considerable intra-individual variation in severity during the different periods of life, with an age-dependent degree of severity. The seizures were prolonged and frequent in childhood and adolescence and tended to decrease in complexity and frequency during adulthood, although they rarely disappeared.

Ictal EEG abnormalities were found in 30 to 60% of patients (diffuse or focal flattening of background activity; focal theta activity; rhythmic delta activity; spikes and spikes-and-wave activity). While the daytime EEG was often (65 to 90%) normal, the EEG during sleep showed interictal focal epileptiform abnormalities in about 50% of patients.

Autonomic modifications were remarkable in most of the cases. In particular, tachycardia appeared synchronously with seizure onset in about 90% of patients.

In about two third of patients carbamazepine, clonazepam or their association were able to greatly reduce nocturnal seizures in frequency and complexity, and, in some cases, to completely control them.

Differential diagnosis

Recently we studied a large sample of patients with abnormal motor activity during sleep: among the consecutive patients evaluated in our Sleep Disorders Centre during a five-year period, all the subjects complaining of repeated nocturnal motor and/or behavioural episodes underwent physical and neurological examinations; detailed sleep interview with parents or the bed partner; electroencephalographic studies during wakefulness; neuroradiological (computer tomography and/or magnetic resonance imaging) examinations; nocturnal video-polysomnography (after an adaptation night to the laboratory) including EEG monitoring (at least eight bipolar leads positioned according to the International 10–20 System), electrooculogram, submental electromyography, EKG and, in most cases, electromyography of arms and legs and abdominal and/or thoracic respiratory movements.

During the entire night the patients had a video monitoring (split-screen system) and the recordings were analysed for abnormal behaviour and/or motor activity. The nocturnal repetitive motor activity was carefully analysed and classified into the four classes mentioned above: minimal, minor, major and prolonged, according to duration, semeiology and complexity of motor behaviour. Sleep was scored according to international criteria [50].

We selected 147 patients (35 with parasomnias, 67 with NFLE and 45 with ADNFLE). The age at evaluation ranged from 4 to 49 years. There were some differences in clinical features between parasomnias and NFLE, both sporadic and familial forms. These differences are summarised in table 1.

Concerning the epileptic attacks, there was no difference between sporadic and familial forms of NFLE. The clinical and neurophysiological data are summarised in tables 2 and 3.

The seizures began in childhood, usually persisting throughout adult life. There was a wide spectrum of complexity and severity, ranging from urinary incontinence to violent behaviour.

About one third of the patients reported some seizures also during wakefulness. Almost one half of the patients reported daytime complaints as difficulty in waking, morning tiredness and/or excessive daytime sleepiness.

The video-polysomnographic recordings showed a wide spectrum of episodes, ranging from repeated stereotypic brief motor attacks (classified as minimal and minor episodes) to prolonged attack, with complex and bizarre behaviour, assumption of abnormal posture, dystonic bipedal

Table 1   Differences between NFLE and parasomnias.

	NFLE	parasomnias
age at onset (years)*	11.8 ± 6.3	usually <10
attacks/month (number)*	36 ± 12	<1 to 4
clinical course	increasing or stable	decreasing/disappearing
movement semiology	stereotypic	polymorphic
onset of attacks	any time during the night	first third of the night
distribution of attacks	2 non-REM (65%)	slow-wave sleep

* mean ± SD

and/or bimanual movements, shouting and/or unintelligible mumbling.

The recorded episodes occurred during non-rapid eye movements sleep, both stage 2 and stage 3–4 (see fig.1). The patients showed a normal sleep profile. In any case, no difference was found between sporadic and familial cases in all sleep parameters.

Discussion

Either sporadic or familial NFLE are disorders often difficult to diagnose because their clinical manifestations are usually limited to brief motor seizures during sleep. The differential diagnosis from benign parasomnias is difficult from the history alone. Moreover, in these patients the EEG studies during wakefulness (and often also during sleep) are usually normal. On the other hand, a full nocturnal video-polysomnographic study, although expensive and needing specific rooms and trained technical-medical staff, is diagnostic in a large part of cases.

In any case, a full video-polysomnographic study should be proposed to all the patients complaining of repeated nocturnal motor, autonomic and behavioural episodes, in order to provide a correct diagnosis: in particular, NFLE should be suspected in presence of paroxysmal nocturnal motor attacks characterised by abrupt onset, stereotypy, high frequency in the same night and persistence into adulthood. In these patients with NFLE it is of utmost importance to provide a correct diagnosis because an anti-epileptic therapy usually controls both nocturnal and diurnal seizures as it does on daytime somnolence.

Moreover, there seems to be no difference in clinical and neurophysiological data between familial and sporadic cases of NFLE. Familial cases of NFLE seem to represent a valid model of idiopathic epilepsy. In the last few years, considerable progress has been made in the field of genetics of epilepsy. The candidate gene approach and subsequent molecular genetics studies demonstrated the role of ligand and voltage-gated ion channels in the aetiology of idiopathic epilepsies, which therefore appear, at least in part, as ion channel disorder [51]. Three loci, ENFL1 (MIM#600513), ENFL2 (MIM*603204) and ENFL3 (MIM#605375), have been associated with ADNFLE. As far as ENFL1 locus is concerned, three different mutations in the CHRNA4 gene, coding for the α4 subunit of the neuronal nicotinic acetylcholine receptor (nAchR) and located on chromosome 20q13.2 have been found in a few families (for review see [51]). The ENFL2 locus has been mapped by linkage analysis in a single family to chromosome 15q24 region, close

Table 2   Clinical profile in patients with NFLE and ADNFLE.

	NFLE	ADNFLE
male/female ratio	2.3	1.7
age at evaluation (mean, years)	26.4	23.8
age at onset (mean, years)	13.7	11.8
patients with persistence of seizures throughout adult life (%)	100	93.8
patients with seizures also during wakefulness* (%)	30.6	36.8
patients with daytime complaints* (%)	38.5	57.9

* excessive daytime sleepiness and/or fatigue

Table 3   EEG findings in patients with NFLE and ADNFLE.

	NFLE	ADNFLE
patients with epileptiform abnormalities during daytime EEG (%)	6.2	11.8
patients with interictal epileptiform abnormalities over frontal areas (%)	36.4	50.0
patients with ictal epileptiform abnormalities over frontal areas (%)	21.8	31.6
patients with ictal rhythmic slow activity over frontal areas (%)	36.8	47.4
patients with ictal diffuse background flattening (%)	7.5	10.5

to the CHRNA5/A3/B4 cluster, coding for the α3, α5 and β4 subunits of the nAchR [44]. However, neither the gene nor the mutation involved has been identified. More recently, a third locus for ADNFLE, ENFL3, has been identified on chromosome 1q21 [52]. Two different mutations, affecting the same aminoacid residue, were found in the CHRNB2 gene, coding for the β2 subunit of the nAchR [53, 54]. All the identified mutations in CHRNA4 and CHRNB2 are located in the second transmembrane domain (M2) of the nAchR subunits, which lines the cationic channel pore of the receptor. Mutations in CHRNA4 and CHRNAB2 only account for a minority of ADNFLE cases [52–55] and, in most families, the mutated gene remains unknown. Thus, additional nAchR subunit genes expressed in the brain are candidates for being the cause of epilepsy. Chromosome localisation is known for nine subunit genes: 1q21, β2; 8p21, α2; 8p11.1, α6 and β3; 15q14, α7; 15q24, α5/α3/β4 and 20q13.2, α4. We studied the involvement of the above-mentioned chromosome regions in ADNFLE in four unrelated Italian families [46]. In none of the families was a linkage between ADNFLE and the analysed chromosome regions detected. These findings support the hypothesis that genes different from those coding for α2–α7 and β2–β4 neuronal nAchR subunits could be responsible for ADNFLE. The fact that neuronal nAchR subunit genes do not appear as major loci for the disease opens new frontiers in the study of ADNFLE and idiopathic epilepsies in general.

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