Review Article

Physiopathogenetic Interrelationship between Nocturnal Frontal Lobe Epilepsy and NREM Arousal Parasomnias

Péter Halász, Anna Kelemen, and Anna Szücs

1 Institute of Experimental Medicine, Budapest, Hungary
2 Department of Neurology, National Institute of Neuroscience, Budapest, Hungary

Correspondence should be addressed to Péter Halász, halasz35@gmail.com

Received 29 November 2011; Accepted 18 January 2012

Aims. To build up a coherent shared pathophysiology of NFLE and AP and discuss the underlying functional network. Methods. Reviewing relevant published data we point out common features in semiology of events, relations to macro- and microstructural dynamism of NREM sleep, to cholinergic arousal mechanism and genetic aspects. Results. We propose that pathological arousals accompanied by confused behavior with autonomic signs and/or hypermotor automatisms are expressions of the frontal cholinergic arousal function of different degree, during the condition of depressed cognition by frontodorsal functional loss in NREM sleep. This may happen either if the frontal cortical Ach receptors are mutated in ADNFLE (and probably also in genetically not proved nonlesional cases as well), or without epileptic disorder, in AP, assuming gain in receptor functions in both conditions. This hypothesis incorporates the previous “liberation theory” of Tassinari and the “state dissociation hypothesis” of Bassetti and Terzaghi. We propose that NFLE and IGE represent epileptic disorders of the two antagonistic twin systems in the frontal lobe. NFLE is the epileptic facilitation of the ergotropic frontal arousal system whereas absence epilepsy is the epileptic facilitation of burst-firing working mode of the spindle and delta producing frontal thalamocortical throphotropic sleep system. Significance. The proposed physiopathogenesis conceptualize epilepsies in physiologically meaningful networks.

1. Concept of Nocturnal Frontal Lobe Epilepsy (NFLE)

From the eighties several observations had been published reporting on events characterized by a storm of dystonic/dyskinetic movements involving both sides of the body, accompanied by bizarre vocalisation, arising from sleep. Patients preserved consciousness during or retained it immediately after the attacks which were preceded usually by EEG/polygraphic microarousals appearing during NREM sleep in clusters. Since interictal and even ictal EEG was meager in epileptiform signs, at the beginning it was held to be a sleep disorder named “nocturnal paroxysmal dystonia” [1, 2]. It was recognized from the beginning that the attacks exhibited a variation in degree of motor components from “minimal” to “major” symptomatology.

Later it turned out that several patients with similar symptoms have MRI lesions in the frontal lobe [3] and both the scalp EEG data and the data derived from intracerebral studies pointed to frontomedial or orbitofrontal origin [4, 5]. The spectrum of symptoms of these surgical cases compared to unlesional ones proved to be similar [6]. Lastly intracerebral stereo-EEG data showed the presence of ictal epileptic discharges during even the minimal motor events provided direct proof of the epileptic nature of the disorder [7].

Functional neuroimaging data have provided further support of the frontal origin in these patients. SPECT studies have found frontopolar and orbitofrontal seizure onset zones [8] and PET studies interictal frontal hypometabolic areas [9]. In one study singular hyperperfusion zone was described with ictal SPECT [10]. Further surgical interventions targeted to frontal lobe areas confirmed good results resolving this type of seizures [11].

However it has been reported that sleep-related hypermotor seizures can originate in temporal lobe [12–15] and later congruent reports have been described a possible insular-opercular origin [16–18] activating probably the same
network as in NFLE. Several works [16, 18, 19] have shown that extrafrontal resective surgery provides excellent results in these cases.

A familiar clustering of cases have been observed long ago and in the middle of the nineties [20] described the familial variant of the disorder (Autosomal Dominant Nocturnal Frontal Lobe Epilepsy—ADNFLE) with autosomal dominant inheritance. The underlying cause was mutation of the nicotinic acetylcholine receptor a4 (CHRNA4) and b2 (CHRNBB2) subunit on the 20q13 and 15q24 chromosome. The familial cases proved to exhibit the same spectrum of seizure symptoms as the sporadic patients. The ictal hyperperfusion in ictal SPECT studies showed identical localisation in different seizures within a patient, but may have different localisation in different patients even within the same family [21].

The clinical features of NFLE have been described under different headings as nocturnal paroxysmal dystonia [1, 2], paroxysmal awakenings or arousals [22, 23], paroxysmal periodic motor attacks [24], episodic or epileptic nocturnal wanderings [25–28] and in childhood as mesial frontal lobe epilepsy [29] and hypnic tonic postural seizures in children [30].

The seizures described in these studies contained a spectrum of symptoms: assumption of postures, rhythmic and repetitive movements of arms and legs, rapid uncoordinated movements, with dystonic or dyskinetic components, complex motor activities (pelvic thrusting, wandering), and sudden elevation of the trunk and head associated with expression of fear and vocalisation). Seizures are accompanied by major autonomic manifestations involving heart rate, breathing, vasomotor tone, and sympathetic skin response. Among them tachycardia is the most prominent.

Provini et al. [31] created three subgroups of manifestations: (1) paroxysmal arousals: brief (<20 s) episodes characterized by sudden eye opening, head raising, or sitting up in bed, often with frightened expression and sometimes vocalisation, (2) nocturnal paroxysmal dystonia: episodes of 20 s–2 min duration, characterized by wide, often ballistic movements, dystonic posturing, or choreoathetoid movements of head, trunk, limbs, and vocalization, (3) episodic nocturnal wanderings: episodes of longer duration (1–3 min) with stereotyped paroxysmal ambulation, accompanied by screaming and bizarre, dystonic movements.

The three groups frequently occur in the same patient and seem to be different degree expression of a continuum.

Based on studies evaluating higher number of patients, during wake state interictal epileptiform activity has been reported rarely and even in sleep not more than 50% of the patients. Frontobasal discharges may project to the anterior temporal leads and frontomedial ones to the midline electrodes, raising difficulties to establish proper localization. Typical ictal pattern has been observed also rarely. In not more than 50% of registered seizures some kind of ictal changes as rhythmic theta sometimes delta pattern or flattening was described.

About one-third of the patients report seizures also during wake state and one part of them suffer rarely occasional generalized tonic-clonic seizures as well. The seizures start usually in childhood where they were prolonged and more frequent and tend to decrease both in frequency and complexity during adulthood, but they rarely disappear. According to the most publication the seizures respond well to carbamazepine, but cca 30% is therapy resistant [31, 32]. We have some anecdotal evidence for beneficial effect of acetazolamide [33] and nicotine patch [34].

2. Relation to NREM Sleep
Macro- and Microstructure

One of the most characteristic feature of the syndrome is the relation to sleep macro- and micro-structure. The attacks are related to NREM sleep [32]. Studying 40 patients the Parmar group recently [35] found that majority of motor events occur from slow wave (72%) and 28% from stage 2 sleep. However, this is not in agreement with the findings [36, 37] who found majority of NFLE paroxysmal events during stage 2.

Seizure manifestations have been reported to preceded by K-complexes [38], spindles [39]. This fits into a more global interrelationship with Cyclic Alternating Pattern (CAP) [24, 40]. Thus probably CAP is the essential provocative factor in NFLE.

The recent Parrino study [35] found that almost all events occur in association of phase A and their distribution throughout sleep cycles was highest in the first cycles and followed the homeostatic decay of slow wave sleep across the night. CAP time, CAP rate, number of CAP cycles, duration of CAP sequences, and especially CAP A1 rate were all elevated in NFLE patients compared to normal controls. The precise relationship with CAP A phases according to the A1-2-3 subtypes is not quite clear, since the Terzano group reported strong relationship in two studies with A1-2 types: (70–30% [40] and 72–28% [35] compared to A3 type), whereas according to the Zucconi et al. [41] study most frequent relationship was found with A2 (and A1) type. These microstructural features of sleep of NFLE patients point to a continuous higher level of arousal activity during NREM sleep, besides the overt arousal-related motor seizure elements. Interestingly, slow wave sleep duration was maintained or even increased (power spectra were not calculated) in the patients [35]. Probably as a consequence of increased microarousal activity the compensatory slow wave production in CAP A1 and A2 phases is which contributes and maintains the slow wave production and prevents sleep fragmentation.

Parasomnias characteristically arose from deep NREM sleep, usually at the turning point of one of the first sleep cycles (at the end of the first or second stage 3–4), preceded by delta hypersynchrony [42]. Some observation describes an EEG dissociation pattern with anterior delta and posterior alpha activity [37].

3. Arousal Parasomnias and Their Relationship to NFLE

During the development of NFLE concept the main challenge was to differentiate the disorder from parasomnias.
Paradoxically nowadays the peculiar link between these two disorders became the centre of interest.

Parasomnias are classically grouped to NREM parasomnias or arousal parasomnias, REM parasomnias, and parasomnias having no sleep state preference. The NREM parasomnias are held to be arousal disorders since the classical work of Broughton [43], representing a dissociated condition between NREM and wake state, and divided in contemporary categorization [44] to three forms: “Confusional Arousals,” “Sleepwalking,” or “Somnambulism” and Sleep Terrors.

Recently Derry et al. [37] reinvestigated the semiology of arousal parasomnias in video-EEG, detected 57 events, and compared them with 63 NFLE seizures.

They identified three fundamental patterns, but 79% of the registered events comprised a composite of more than one pattern. The basic patterns were as follows.

1. “Arousal behavior” which was the first (or only) element in 92% of all events: simple arousal behavior including eye opening, head elevation, staring and face rubbing, yawning, stretching, moaning, and mumbling.

2. “Non-agitated motor behavior” (present in 72%) sitting forward, manipulation of nearby objects and searching (orienting) behavior. Standing and walking was only occasionally registered (patients were mounted with electrodes). Facial expression was impassive or perplexed and coherent speech fragments were also common.

3. “Distressed emotional behavior” (51%): behavior of fear and anguish indicated by the facial expression and speech content. Patients were sitting or standing up, screaming, and expressing frantic behavior. Attempts of restrain evoked aggressive response.

Comparison of NFLE and AP in the Derry study [37] showed that 79% of AP the events began with arousal behaviour and in 65% of the events followed by more dramatic manifestations, NFLE seizures were preceded also in 49% by arousal behaviour. In 51% of NFLE patients the start was abrupt (without arousal behaviour) and it was indistinguishable from that seen in 21% of parasomnia cases. Tachycardia was prominent feature in both groups.

The events were in 39% triggered by an external (noise) or internal (cough or snore) stimulus in the parasomnia group whereas in the IFNLE group trigger stimulus was identifiable only in 8%.

In the NFLE group environmental interactions were present only in 11% of seizures and coherent speech was rare, if present frenetic and not interactive type.

Parasomnias terminated in 74% with NREM sleep or with wakefulness (26%), while NFLE seizures awakened the patients in 88%.

4. Genetic Aspects Connecting AP and NFLE

The familial nature of parasomnias is long ago recognised [45] but the genetic background was not known. Twin studies have shown higher concordance for sleep walking in monozygotic than dizygotic twins [46]. Recently Licis et al. [47] based on the study of a 4-generation family, by genomewide multipoint parametric linkage analysis, described the first genetic locus for sleepwalking at chromosome 20q12-q13.12. According to their findings sleepwalking may be transmitted as an autosomal dominant trait with reduced penetrance.

Provini et al. [31] in a survey of 100 cases of NFLE showed that 39% of the patients reported a family history and in 34% a personal history positive for parasomnias. Bisulli et al. [48] compared 33 NFLE patients and 200 relatives of the probands with 31 age, sex, education, and residence area matched controls and 194 relatives, for the occurrence rate of arousal parasomnias. The lifetime prevalence of arousal disorders (and nightmares) was more frequent among NFLE patient’s relatives compared to the relatives of the controls. Arousal disorders (and bruxism) were more frequent among NFLE patients than controls. It was significant for sleep walking and showed only tendency in other arousal parasomnias as confusional arousals and sleep terrors.

The parasomnias of childhood were found to be substituted by NFLE later in life in predisposed subjects [31, 49].

Summing up arousal parasomnias and NFLE share similarities and overlap in the semiology of paroxysmal events and probably in genetic background. Further common features are their relation to NREM sleep and to the mechanism of cholinergic arousal during sleep.

5. The Cholinergic Arousal Mechanism in NREM Physiology and in Paroxysmal Sleep Pathologies

There is a considerable body of evidence indicating that acetylcholine plays an important role in cortical activation during arousal especially in sleep and in the frontal cortex [50–52]. Thalamus and cortex are important structures being rich in cholinergic fibers, originating from the nucleus basalis (Meynert) providing the most robust cholinergic input. It is important to know that not only the trans-synaptic, but the nonsynaptic release Ach should be taken into consideration [53].

Increasing lines of evidence support that the dynamic structure of sleep cyclcity is shaped by the continuously changing balance of two reciprocal antagonistic twin systems: the multibraided Ascending Reticular System of the brainstem and posterior hypothalamus and the anterior hypothalamic Sleep Promoting System [54, 55]. The recognition of the so-called “microarousals” (MAs) during NREM [56] sleep provided strong evidence of the presence and shaping role of an arousal activity during NREM sleep. Revealing the arousal-related “micro-structure” of NREM sleep led to the recognition of Cyclic Alternating Pattern (CAP) [57], a homeostatic control system defending sleep against perturbations and description of arousal regulation of NREM sleep [58].
6. Pathophysiology of NFLE and Arousal Parasomnias

Because ADNFLE provides a model for the more common sporadic NFLE and because ADNFLE is characterised by increased receptor sensitivity in the nicotinic cholinergic system [59, 60], we can assume that the cholinergic arousal system might be pathological in these patients [36]. The alpha 4 and beta 2 nAChrs mutations revealed in ADNFLE are preferentially expressed in the thalamus and mesencephalic tegmentum belonging to the Ascending Arousal System [61], and in the frontal cortex.

Within the thalamocortical interplay two circuits with opposite actions can be differentiated. The positive loop activating the cortex via thalamocortical connections and the negative loop by which cortical innervation of the reticular thalamic nucleus provide recurrent inhibition of the thalamic relay cells. Itier and Bertrand [59] proposed that in ADNFLE the increased receptor sensitivity due to the mutation of the alpha 4 and beta 2 subunits shifts the balance of these two loops toward more cortical cholinergic activation.

Léna et al. [62] using knockout mice of the nAChRs beta 2 subunit gene showed that beta 2 nicotinic receptors contribute to the organisation of sleep regulating MAs. In the knockout animals the frequency of MAs in NREM decreased, particularly before REM periods. We also know that MA analogue CAP phase A2-3 episodes show the same distribution pattern (elevation before REMs) [63] and these CAP elements were found just before NFLE events recurring with 20–40 s intervals similarly to the periodicity of physiological CAP sequences [24].

7. Common Mechanisms of Paroxysmal Sleep Events in NFLE and Arousal Parasomnias? Which One: Liberation, Dissociation, or Pathological Arousal?

The symptomatological similarities of the two continuums of paroxysmal nocturnal events in NFLE and arousal parasomnias (AP), the common relationship with the sleep process, and the genetic relationship between the two conditions led to look for a common pathomechanism [36].

One of the proposed mechanisms is “liberation” due to functional inactivation of an inhibitory structure. It is a classical mechanism introduced in neurology by Jackson [64] in his pioneering work. The work of Tassinari et al. [65] is a powerful exponent of this view. They use a poetical analogy speaking about a musical box which plays always the same melody whatever force is opening the cover of the box. Here opening the cover of the box means eliminating the inhibition exerted by the frontal lobes on subcortical ancient “motor-pattern generators.” The functional inactivation of the frontal lobe (especially the frontotemporal convexity) is given during NREM sleep in both conditions. The “melody” is the hypermotor (and autonomic) atomatisms released by the activation of basal ganglia as we have several examples for this mechanism in the animal world under the term “fixed action patterns” (FAPs) [66]. Very similar motor automatism can be observed in newborns and infants in early or delay stage of telencephalisation, giving rise to the erroneous suspicion of an epileptic condition [67].

Another mechanism offering good explanation for the nocturnal events in NFLE and APs is “state dissociation.” Nowadays our concepts about the nature of sleep are very much changing: two basic assumptions have been challenged in the last years. One is connected with the local/regional nature of sleep (and wake) states. Particularly in some of the brain diseases elements of different vigilance states can occur simultaneously. For example, in “REM behavior disorder” (connected often to Parkinson’s disease) motor actions occur during REM sleep. The recognition of these “mixed states” led to term “status dissociatus” [68]. APs are fitting into “mixed state” concept exhibiting Janus faced, partially awake and partially sleeping behavior. The other basic assumption challenged from several aspects is the global nature of sleep. One is the experience of local sleep differentiating the state of the different cortical columns [69], another approach showing local changes of delta power after local utilisation of body functions during the previous day [70]. Alternating sleep of the two hemispheres discovered in dolphins and other aquatic mammals [71, 72] pushed thinking also toward the possibility of simultaneous mixed, awake- and sleep-like regions in the brain during certain sleep conditions.

In the last years two publications have provided congruent objective lines of evidence for such dissociated conditions in APs patients. Bassetti et al. [73] reported a single-photon emission computed tomography (SPECT) study in a man with AP. Their findings suggest a clear state dissociation: activation of thalamo-cingulate pathways and persisting deactivation of other thalamocortical arousal systems during a nocturnal episode.

Almost the same was demonstrated by Terzaghi et al. [74] in a patient under invasive presurgical evaluation for epilepsy who had a history of AP episodes and they were lucky to observe one event with implanted electrodes. During this episode in NREM sleep the frontal convexity showed the usual slow wave activity, but the singular gyrus emanated wake-like activity.

A third possibility is that the pathological arousals accompanied by confused behavior with autonomic signs and hypermotor automatisms are expressions of a different degree alarm like behavior activated by the frontal cholinergic arousal system during the condition of depressed cognition in NREM sleep. This may happen either if the frontal cortical Ach receptors are mutated in NFLE or, without epileptic disorder in AP, assuming gain in receptor functions.

This explanation amalgamates the two previous hypotheses and seems to be congruent with other features of the two conditions as well. The high frequency of the different degree of events probably reflects the highly facilitated arousal system in NFLE. In AP patients this degree of facilitation is not reached. Therefore the constellation for the state dissociation is present only in special suitable circumstances during the night. This would explain why are the events in AP rare, usually single in a night and coincide with the first
(or second) turn of cycles. AP is usually preceded by a characteristic arousal (typically accompanied by muscle activity or body turn) at the end of the trough of the cycle, when the ascending slope of the cycle is beginning. This fast change in the tendency from deep sleep to sudden turnig toward more superficial level, or REM sleep, together with genetic origin sensitization of the Ach receptors, offers reasonable basis for a dissociational event.

8. Relation with the Network Concept of Epilepsy

The most essential feature of the epileptic network concept is that epileptic networks exaggerate the functions of certain physiological networks [75, 76]. This connection between the physiological networks and epilepsy is twofold. On one hand epileptic activation of the physiological network functions produces epileptic symptoms specific to the network that anchors it. On the other hand the activation of the physiological network functions simultaneously activates the epilepsy embedded into the system. For example, limbic network epilepsy may show emotional activation characteristic for the limbic system and photic stimulation activates occipital epileptic manifestation due to epileptic facilitation of the visual cortex.

Looking for a physiological system where the NFLE should be embedded the best candidate seems to be the frontal cholinergic arousal system, serving different functions from maintaining wakefulness and targeted attention in wake state to arousal in sleep. The question is, why we have nocturnal predisposition of the events, if the mechanism is in the genetically altered (toward a gain in function) Ach-erg arousal system? Arousal has an important physiological regulatory role, being inherently and continuously present during NREM sleep [58]. The symptomatology of NFLE seizures reflects a continuum from confused arousal (automatic motor manifestations of normal arousal) through classical hypermotor seizures to agitated behaviour with expressions of fear, automatic fight-flight behavior, and marked autonomic activation. The later are probably secondary consequences of arousal without cognition (due to the frontal deactivation of NREM sleep), eliciting self perpetuating escape or fight (with non existing enemies) reactions. In this regard the observations of the Australian group [37], that attempts of restrain of motor behavior evoked aggressive response, are especially relevant.


Overlapping clinical and physiopathological features between NFLE, characterized by different degrees of arousal, hypermotor and agitated behaviour and NREM parasomnias, with a proven genetic and pathophysiological relationship were detailed above.

We have growing lines of evidence about the role of frontal lobe in IGE through the burst-firing working mode of the thalamocortical system which is the main player in the development of NREM sleep phenomena. Absence seizures, the hallmark of IGE, are considered to be an epileptic exaggeration of the burst-firing in the thalamocortical system, which is the characteristic working mode in physiological sleep. Arousing sensory stimulation in absence epilepsy is a strong inhibitory factor. On the contrary, the lack of bilateral spike-wake activity in NFLE is a strong argument against the involvement of the thalamocortical inhibitory system.

Rudolf Hess the Swiss neurophysiologist in his Nobel Prize winner work [77] showed that electrical stimulation of the diencephalon of cats delineates two areas with antagonistic effect on autonomic functions and holistic behaviour of the animal.

The first one provides the organization of all mechanisms for an externally directed behavior of the animal, for example, as fight or flight. This function was named as “ergotropic” and the system subserving it as “ergotroph” system. He showed that autonomic part of this type of behavior is mainly mediated by sympathetic nervous system.

The second area serves functions of restitution, avoiding overstrain and exhaustion, provides protective mechanisms for rest and sleep, and is connected with the buildup of the organism. It is a necessary counterpart (a twin system) of the first and named as “trophotropic-endophylactic” system; the autonomic part of it is the parasympathetic nervous system.

The antagonistic twin functions of the arousal and sleep promoting systems are probably represented on different levels of the brain. As described previously the thalamocortical system also contains antagonistic loops supporting the balance between sleep and wakefulness [59]. This balance became shifted toward the cholinergic arousal functions in NFLE, due to the gain of function in the cholinergic receptors, and toward sleep in absence epilepsy due to epileptic facilitation of the reticulothalamic inhibition, fueling the burst-firing working mode.

Full-blown manifestations of NFLE might be interpreted as an emergency reaction—a typical ergotropic function—executed by an ancient arousal/alarm system (when a cholinergic arousal is extended into an presumably adrenergic activation), ensuring escape in the situation of an attack while sleeping. One of the subgroups of arousal parasomnias, night terror, proved to be in several ways related to NFLE and exhibits similar behavior with extreme nocturnal alarm manifestations.

On the other hand, in absence epilepsy, the balance shifts to the opposite direction by the epileptic augmentation of the burst-firing working mode of the thalamocortical system, transforming physiological spindling and slow oscillation to spike-wave paroxysms. Therefore absence epilepsy is strongly related to sleep—a prototype of trophotropic-endophylactic activity [78].

We propose here that NFLE and IGE are epileptic disorders of the two antagonistic biological twin systems.

This hypothesis fits into the endeavour to conceptualize epilepsies in physiologically meaningful networks.


[74] M. Terzaghi, I. Sartori, L. Tassi et al., “Evidence of dissociated arousal states during nrem parasomnia from an intracerebral...


