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The role of the nicotinic acetylcholine receptors in sleep-related epilepsy

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ABSTRACT

The role of neuronal acetylcholine receptors (nAChRs) in epilepsy has been clearly established by the finding of mutations in a subset of genes coding for subunits of the nAChRs in a form of sleep-related epilepsy with familial occurrence in about 30% of probands and dominant inheritance, named autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE). Sporadic and familial forms have similar clinical and EEG features. Seizures begin in middle childhood as clusters of sleep-related attacks with prominent motor activity, and sustained dystonic posturing. In addition to nocturnal seizures, psychosis or schizophrenia, behavioral disorders, memory deficits and mental retardation were described in some individuals. Although over hundred families are on record, only a minority of them have been linked to mutations in the genes coding for the α4, α2 and β2 (*CHRNA4*, *CHRNA2*, and *CHRNB2*) subunits of the nAChRs, indicating that ADNFLE is genetically heterogeneous despite a relatively homogeneous clinical picture. Functional characterization of some mutations suggests that gain of the receptor function might be the basis for epileptogenesis. *In vitro* and *in vivo* studies have shown high density of nAChRs in the thalamus, over activated brainstem ascending cholinergic pathway and enhanced GABAergic function, reinforcing the hypothesis that cortico-subcortical networks, regulating arousal from sleep, play a central role in seizure precipitation in ADNFLE.

1. Introduction

Whilst the idiopathic generalized epilepsies have always been regarded as genetic in origin, focal epilepsies have generally been considered as acquired. However, recent findings demonstrate that some focal epilepsies have a predominant genetic component and specific gene mutations have been identified in a few syndromes of focal epilepsy [1–4]. These mendelian epilepsies are mainly associated with mutations in the genes coding for subunits of voltage-gated and ligand-gated ion channels [5]. In particular, mutations in genes coding for subunits of the ligand-gated nAChRs, associated with a

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Abbreviations: ACh, acetylcholine; ADNFLE, autosomal dominant nocturnal frontal lobe epilepsy; AEDs, antiepileptic drugs; CBZ, carbamazepine; *CHRNA4*, α4 subunit of the neuronal acetylcholine receptor gene; *CHRNA2*, α2 subunit of the neuronal acetylcholine receptor gene; *CHRNB2*, β2 subunit of the neuronal acetylcholine receptor gene; GABA, gamma-aminobutyric acid; EEG, electroencephalogram; nAChRs, neuronal nicotinic acetylcholine receptors; NFLE, nocturnal frontal lobe epilepsy; NPD, nocturnal paroxysmal dystonia; NREM, non-rapid eye movement; NW, nocturnal wanderings; PA, paroxysmal arousals; PET, positron emission tomography; SPECT, single-photon emission computed tomography; TM2, transmembrane domain 2; TM3, transmembrane domain 3

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form of inherited nocturnal frontal lobe epilepsy (ADNFLE), have clearly established a causative relationship between nAChRs dysfunction and epilepsy.

2. Autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE)

2.1. The phenotype

ADNFLE is a peculiar form of focal epilepsy with about 70% penetrance [6]. More than a hundred families have been reported to date [7]. Seizures typically start in middle childhood, usually between 8 and 11.5 years, but can begin anytime from infancy to the sixth decade, with clusters of attacks arising from sleep [6,7]. Each cluster features a mean of six attacks but patients with up to 70 seizures per cluster have been described [6]. Seizures usually occur very soon after falling asleep or during the early morning hours. About half of the patients wake up from sleep, experience an aura that is commonly described as generalized tingling or shiver, fear, breathless feeling or auditory hallucinations and remain aware throughout the attack [6]. Bizarre vocalization, moaning, gasping or grunting at seizure onset are also common features. Seizures are clinically characterized by prominent motor activity such as hyperkinetic thrashing movements with bipedal and bimanual automatisms, tonic contraction and, sustained dystonic posturing with forced hyperextension [6–9]. In some patients motor activity can be so bizarre and violent to cause them falling out of bed. Conversely, some patients might have very mild cramp-like motor manifestations during sleep or very brief attacks with a dystonic component.

Provini et al. performed a video-polysomnographic study of a large series of patients with nocturnal attacks, and according to duration, semiology and complexity of the motor behavior classified them into: paroxysmal arousals (PA), nocturnal paroxysmal dystonia (NPD) and nocturnal wanderings (NW) [9]. These authors also showed that PA, NPD, NW can occur in a single patient to suggest that they represent a continuum of the same seizure where the more complex motor behavior might be explained by the spreading of the epileptic discharge to progressively wider areas of the brain [9].

Seizures are stereotyped and usually brief, lasting less than a minute, occasionally evolving into secondarily generalized tonic-clonic seizures, and only rarely occurring during wakefulness [6,9]. Seizures often persist through adult life, although they tend to peter out in adulthood. There is intra and inter familial variability in severity. In most patients seizures are mild and respond to carbamazepine treatment. About a third of patients are refractory, although seizures are usually confined to sleep.

Neurological examination and neuroimaging studies are usually normal. In addition to nocturnal seizures, however, psychosis or schizophrenia, behavioral disorders, distinct memory deficits and mental retardation have been reported in some individuals with familial ADNFLE [10–12].

Because attacks manifest during sleep and often have bizarre motor or affective semiology, they are usually misdiagnosed as sleep disorders [6]. Based on careful analysis of clinical features combined with the use of video-polysomnography, some authors have proposed clinical guidelines and scales, that might be useful for the diagnosis of sleep-related events [13,14].

2.2. Family history

The term ADNFLE implies a family history of seizures with segregation of the disorder consistent with autosomal dominant inheritance. Sleep studies have shown that among patients with idiopathic nocturnal frontal lobe epilepsy (NFLE) only a third have a family history of the disorder [9]. Attacks have very similar semiology in sporadic and familial cases. In the study of Provini et al., family history showed that about 40% of patients have at least one first degree relative with probable primary parasomnias [9]. Moreover, 34% of NFLE patients had a history of sleep disorders in childhood with 1–30 years gap between the last parasomnic manifestation and the onset of seizures [9]. This finding might be coincidental since parasomnias are common in the general population or result from bias due to patients' recollection of nocturnal episodes of any nature. However, it may also suggest a common pathophysiological and etiological background between non-epileptic and epileptic sleep phenomena.

Tassinari et al. [15] have hypothesized that motor phenomena of nocturnal frontal lobe seizure are produced by the release of the central pattern generators allowing innate motor behaviors to emerge [15]. Therefore, any trigger, either an epileptic phenomenon or a sleep-related dysfunction, would cause a motor event with similar semiology, consisting in the activation of repetitive motor patterns, which represent innate motor behavior(s) [15].

2.3. EEG and neuroimaging findings

Interictal EEG recordings fail to disclose abnormalities in over 50% of patients with ADNFLE. Ictal EEGs show that seizures occur predominantly in stage 2 NREM sleep, but because of prominent motor activity, recordings are often obscured by movement artifacts. Artifact-free recordings show epileptiform discharges in the anterior regions, often bilaterally. Lack of epileptiform activity may reflect the inaccessibility of the focus to scalp EEG recordings. Therefore, the localization of the epileptic foci to the frontal regions – mesial or fronto-orbital – in ADNFLE patients rested initially on the clinical features [6].

Invasive and semivasive recordings with subdural grids and sphenoidal or zygomatic electrodes, confirmed this hypothesis [16,17]. Investigations with functional neuroimaging using interictal positron emission tomography (PET) and ictal single-photon emission computed tomography (SPECT) were also consistent with frontal origin of seizures in a family with *CHRNA4* mutation [18]. However, intracranial EEG recordings and SPECT studies have shown that seizures with predominant motor activity might also arise from the temporal lobe and from the anterior cingulated gyrus [19–21].

3. ADNFLE: molecular genetic

ADNFLE was the first human idiopathic focal epilepsy for which specific gene mutations were described [3]. In 1995, a

Table 1 – Summary of the clinical features of ADNFLE families with known gene defects

Family origin	Gene AA change	Age sz onset (yrs)	Semiology highlights	Epilepsy severity/outcome	Authors
1. Australian (27 affected)	*CHRNA4 Ser248Phe*	8.5 (range 0.2–52)	Aura (70%); vocalization; retained awareness (70%); frightening sensation (33%); breathing difficulty (61%)	Intrafamilial variability, CBZ effective	[3]
2. Norwegian (11 affected)	*CHRNA4* Ser248Phe	8.6 (range 4–13)	Arousal, tongue automatisms, nocturnal wandering	Intrafamilial variability	[25]
3. Scottish (6 affected)	*CHRNA4* Ser248Phe	11.3	Typical NFLE sz with breathless sensation	Good control on AEDs	[27]
4. Spanish (11 affected)	*CHRNA4* Ser248Phe	7.6 (range 3–12)	No diurnal attacks, sudden awakening, malaise and suffocation, retained awareness	Intrafamilial variability	[24]
5. Norwegian (10 affected)	*CHRNA4* 776insGCT	8 (range 1–11)	Aura (20%), mostly complex partial sz with impaired consciousness	40% sz only in childhood, 40% sz-free on AEDs; good response to CBZ	[22]
6. Japanese (5 affected)	*CHRNA4* Ser252Leu	8.7 (range 0.4–30)	Mild mental retardation & hyperactive behavior (60%); very early onset < 1 year and sz provoked by sound or movement	60% sz-free on AED	[23,36]
7. Lebanese (2 affected)	*CHRNA4* Ser252Leu	2 and 0.8	Typical NFLE sz preceed by aura, low intellect	Sz not controlled by AEDs	[26]
8. Polish (3 affected)	*CHRNA4* Ser252Leu	0.6, 5 and 2	Sz with puffing out of cheeks, verbal manifestations, motor acts, ±provoked by sound or movement	CBZ was ineffective	[28]
9. Korean (9 affected)	*CHRNA4* Ser252Leu	11	Arousal, loss of consciousness, lip smacking; unintelligible speech, mild/moderate mental retardation	67% poor response to AEDs	[29]
10. German (2 affected)	*CHRNA4* Thr265Iso	15–20	Typical NFLE sz with loss of consciousness	CBZ alone was ineffective	[30]
11. Italian (8 affected)	*CHRNB2* V287L	9 (range 8–12)	Typical NFLE sz with aura, retained awareness, triggers: stress and fatigue; no diurnal sz,	Intrafamilial variability	[4]
12. Scottish (10 affected)	*CHRNB2* Val287Met	NA	Typical 'very mild' NFLE sz	Sz controlled by CBZ	[31]
13. MZ-Twins	*CHRNB2* I312M	7	Typical NFLE sz + specific problems with verbal memory tasks	Sz not controlled	[12]
14. Italian (10 affected)	*CHRNA2* I279N	10 (range 4–29)	Vocalization, fear sensation, tongue movements, nocturnal wanderings, triggers: sudden noise, hot weather, nicotine, coffee	Sz more severe and frequent at onset	[32]

AEDs: antiepileptic drugs; CBZ: carbamazepine; yrs: years; NA: not available; NFLE: nocturnal frontal lobe epilepsy; sz: seizures.

large Australian family was linked to chromosome 20q and a genetic defect was identified in the α4 subunit of the neuronal acetylcholine receptor gene (*CHRNA4*) [3] (Table 1). The causative role of *CHRNA4* in ADNFLE was further supported by the observation of mutations in a few other families (Table 1) [22–30]. Few years later, mutations in the gene coding for the β2 subunit of the neuronal acetylcholine receptor (*CHRNB2*) were identified in two families of Italian and Scottish origin (Table 1) [4,31].

In 2006 a molecular genetic study of a large Italian family revealed a heterozygous missense mutation resulting in an aminoacid substitution in the M1 domain of the nAChRs α2-subunit gene (*CHRNA2*) (Table 1) [32]. This recent finding strongly reinforces the link between nocturnal frontal lobe epilepsy and neuronal nicotinic receptors.

However, *CHRNA4*, *CHRNB2* and *CHRNA2* mutations remain a rare cause of ADNFLE as the majority of families, and nearly all sporadic cases were negative for these mutations [8,33–35]. Other loci have been reported including a locus on chromosome 15q24, which harbors other subunits of the nAChRs [33], and 2 loci on chromosomes 3p22-p24 and 8q11.2-q21.1 [35] but specific gene defects have not yet been found.

3.1. *Phenotype-genotype correlations*

Phenotypic comparison of ADNFLE families with known mutations might be helpful to understand whether a variation in the clinical picture is associated with mutations in different subunits. Table 1 summarizes some of the peculiar clinical features of ADNFLE families with known gene defects. The limited number of families with a defined genetic cause so far published, makes phenotype-genotype correlations difficult. Age at onset, nocturnal clusters of hyperkinetic/dystonic seizures, tendency to remit or improve after puberty and favorable response to carbamazepine, are some of the phenotypic similarities of families with known gene defects, suggesting that mutations in the genes coding for subunits of the nAChR are major factors determining the phenotype. The presence or absence of an initial aura, of simple partial seizures with preserved awareness or complex partial seizures with unresponsiveness and of diurnal seizures are some of the slight differences observed amongst ADNFLE families, but no clear association with a specific genotype is apparent.

The most interesting phenotypic difference is the presence of mental retardation in two of three children of a Japanese family [36] and in all affected individuals of a Korean kindred [29]. Both families harbored the *CHRNA4* – Ser252Leu mutation [29,36]. The proband of a Lebanese family with the same Ser252Leu mutation also had low intellect, although neuropsychological testing was not performed [26]. Cognitive deficits have not been reported in ADNFLE families with other *CHRNA4*, *CHRNB2* and *CHRNA2* mutations. Therefore, cognitive impairment might be a distinctive clinical feature of families with Ser252Leu mutation. The connection between ADNFLE and mental retardation could be just a coincidence since two family members of the Japanese family [36] and the affected individuals of a Polish family [28] with the same Ser252Leu mutation were of normal intelligence. An alternative hypothesis is that mental retardation is subsequent to frequent uncontrolled nocturnal seizures. Indeed, the Lebanese, Korean and Japanese individuals carrying the mutation had poor seizure control on AEDs [26,29,36]. The report of the Polish family with Ser252Leu mutation in whom affected individuals had refractory seizures but normal intelligence is against this hypothesis [28]. A third plausible explanation is that epilepsy and mental retardation are fully associated, and both phenomena are primarily caused by the Ser252Leu mutation. The nAChRs are widely distributed in the brain and influence a wide range of physiological functions such as sleep, arousal, anxiety, fatigue and cognitive functions [37]. Studies of ADNFLE have so far focused on seizures, therefore other neurological signs might have been underestimated. Further studies are warranted to clarify whether mutations of acetylcholine receptors subunit genes, in addition to seizures, have a causal relationship with other clinical manifestations including cognitive impairment, memory deficits or psychiatric disorders. This possibility is further supported by the observation that three of ten individuals of a Norwegian ADNFLE family harboring the 776ins3 had psychiatric symptoms [10] and that memory deficits occurred in ADNFLE patients with *CHRNB2*- I312M mutation [12].

4. The neuronal nicotinic acetylcholine receptors (nAChRs)

Most of the current knowledge about the structure and function of nAChRs comes from studies in rodents and chicks, and information concerning human nicotinic receptors is still incomplete. Nevertheless, it is known that the nAChRs are membrane proteins with four transmembrane domains, and comprise an assembly of five subunits. So far, 12 nAChRs subunits have been identified (α2–α10 and β2–β4) [38]. Based on subunits composition, there are several different nAChRs, all of which have their own unique biochemical, pharmacological and biophysical characteristics [38,39]. The main functional nAChRs in the brain is a pentamer comprised of two α4 and three β2 [40]. The receptors are ligand-gated channels involving calcium. Transmembrane domain 2 (TM2) segment and the TM2-TM3 loop of the nAChR subunits take part in the ion gate constitution, thereby controlling channel activity [41].

Neuronal AChRs seem to be expressed preferentially in the presynaptic surface [42] thus regulating the release of acetylcholine or other neurotransmitters such as GABA and glutamate [43]. However, postsynaptic receptors also play important roles [44]. *In vitro* studies have demonstrated the coexistence in the same brain nuclei, and even the same neuron, of different nAChRs subtypes, making *in vivo* study of the properties of individual receptor subtypes extremely difficult [37].

In vitro studies with subunit-specific-antibodies and *in vivo* mapping using PET have shown that nAChRs are widely distributed in the human brain with the highest expression in the thalamus, neocortical and striatal regions [45,46]. Through pre- and postsynaptic actions nAChRs play an important role in various complex cognitive functions such as attention, memory consolidation, arousal, sensory perception and in the control of locomotor activity, pain perception and body temperature regulation [37]. High density of neuronal ACh

receptors in fetal life at very early stages suggest that they also play a particular role in brain development [47,48]. Neuronal AChRs display a steady and progressive spontaneous reduction throughout life in the frontal lobe [49]; changes of this regional density over time well explains the spontaneous reduction in seizure frequency or remission with advancing age often observed in ADNFLE.

5. How mutations in nAChRs can cause ADNFLE?

Molecular genetic studies have clearly shown the determinant role of nAChRs in ADNFLE. The first step toward understanding the basic mechanisms underlying epileptogenesis in ADNFLE is to examine the functional properties of mutated nAChRs.

5.1. *In vitro studies*

Functional studies of reconstituted receptors obtained by expression in *Xenopus* oocytes offered the first possibility to examine how ADNFLE mutations alter nAChR properties. However, initial experiments were not performed under comparable conditions, making interpretation of their results difficult. For example, initial analysis of the first S248F *CHRNA4* mutant, simulating the homozygous state, revealed that these receptors display a marked desensitization and lower ACh-evoked current amplitude with respect to controls [50–52]. Based on these data, it was hypothesized that seizures were somehow caused by loss of receptor function. In contrast, co-expression of the normal and mutant receptors, to simulate the heterozygous state, showed that ACh-evoked currents had the same amplitude, but there was a significant increase in sensitivity to ACh in the heterozygous mutant receptors [39,53]. These data illustrate the necessity of obtaining the closest possible correlation with *in vivo* conditions before drawing any conclusion about the mechanisms underlying epileptogenesis.

In the heterozygous condition, the only common electrophysiological finding for seven studied mutations was an increased ACh sensitivity of mutant receptors [30–32,39,53]. Another mutation, the *CHRNB2* V287L, showed a retardation of channel desensitization causing a dominant effect [4]. A reduction of the Ca+ dependence of the ACh response could be an alternative common mechanism [54]. In conclusion, although electrophysiological studies suggest an increased gain in the function of the mutant receptors, the precise mechanism behind seizures in ADNFLE remains unknown.

5.2. *In vivo studies*

Experimental animal models bearing the mutations homologous to either *CHRNA4*, *CHRNB2* and *CHRNA2* human mutations are expected to facilitate the understanding of pathogenetic mechanisms underlying ADNFLE. Klaassen et al., genetically engineered two mice strains harboring two Chrna ANDFLE mutations [55]. Heterozygous ADNFLE mutant mice showed abnormal EEG patterns, interictal spiking, and recurrent seizure activity [55]. In addition, mice were considerably more sensitive to nicotine-induced seizures, suggesting that in ADNFLE seizure origin and EEG paroxysmal activity may involve an increased response to ACh [55] and confirming the electrophysiological findings of *in vitro* studies [39]. The mice model also provided compelling evidence for enhanced GABAergic function in ADNFLE [55].

PET represents the most useful non-invasive technique for studying *in vivo* localization and functional activity of nAChRs in humans. Picard et al. recently performed a PET study in a group of ADNFLE patients with known mutations and showed significant regional changes in brain nAChRs density [56]. Such findings point towards an over activated cholinergic pathway ascending from the brainstem [56]. An additional finding of this study was a decrease of receptor density in the prefrontal cortex, which was hypothesized to reflect progressive neuronal loss caused by seizure activity [56].

6. Therapeutic implications of nAChRs in epilepsy

Some pieces are still missing in the puzzle of how nAChRs dysfuntion causes the ADNFLE phenotype and new therapeutic strategies arising from such knowledge are very far behind.

Carbamazepine (CBZ) is certainly the most effective antiepileptic drug in some ADNFLE patients, and an increased sensitivity of mutant nAChRs to CBZ might be the hypothetical underlying mechanism [57]. CBZ-binding through an inhibition of the hyperfunctional mutated nAChRs may lead to a reduction in seizure frequency in ADNFLE.

There have been some clinical data that chronic use of nicotine influences seizures susceptability in ADNFLE [58,59]. The underlying mechanism is most likely related to progressive desensitization of nAChRs produced by chronic exposure to nicotine. Thus, it can be hypothesized that increased sensitivity to ACh of mutant nAChR can be counteracted by nicotine. Prospective studies in larger samples of patients might further clarify the relationship between nicotine and seizures in ANDFLE and the use of transdermal nicotine administration.

7. Conclusions

The mutations identified in the *CHRNA4*, *CHRNB2* and *CHRNA2* genes in ADNFLE families strongly establish to role of the cholinergic system in this inherited epilepsy. Functional characterization of known mutations suggests that increased gain of the receptor function is at the origin of seizures. *In vitro* and *in vivo* studies have demonstrated a high density of nAChRs in the thalamus [32,56] and an over activated cholinergic pathway, reinforcing the hypothesis that cortico-subcortical networks, regulating arousal from sleep, play a central role in the epileptogenesis of ADNFLE. The mouse model with chrna4 mutations supports the hypothesis of an increased response to ACh behind nocturnal frontal lobe seizures and also provides compelling evidence for enhanced GABAergic function in ADNFLE.

Only a small number of ADNFLE families carry mutations in the three known genes, indicating that ADNFLE has genetic

heterogeneity despite a relatively homogeneous clinical picture. Other mutated genes causing familial ADNFLE are yet to be found and the puzzle of whether sporadic cases also have a genetic etiology is yet to be solved. At present only two '*de novo*' mutations have been reported [12,26].

The increasing number of ADNFLE families with known mutations is also providing evidence that mutant nAChRs are associated with a more complex phenotype than initially expected where, in addition to seizures, cognitive or behavior deficits can cooccur. A conclusive picture on the role of nAChRs in the human brain and in epileptogenesis might emerge from the discovery of mutations in other ANDFLE families and from further *in vivo* studies.

REFERENCES

[1] Scheffer IE, Harkin LA, Grinton BE, Dibbens LM, Turner SJ, Zielinski MA, et al. Temporal lobe epilepsy and GEFS+ phenotypes associated with SCN1B mutations. Brain 2007;130(Pt 1):100–9.

[2] Kalachikov S, Evgrafov O, Ross B, Winawer M, Barker-Cummings C, Boneschi FM, et al. Mutations in LGI1 cause autosomal-dominant partial epilepsy with auditory features. Nat Genet 2002;30(3):335–41.

[3] Steinlein OK, Mulley JC, Propping P, Wallace RH, Phillips HA, Sutherland GR, et al. A missense mutation in the neuronal nicotinic acetylcholine receptor alpha 4 subunit is associated with autosomal dominant nocturnal frontal lobe epilepsy. Nat Genet 1995;11(2):201–3.

[4] De Fusco M, Becchetti A, Patrignani A, Annesi G, Gambardella A, Quattrone A, et al. The nicotinic receptor beta 2 subunit is mutant in nocturnal frontal lobe epilepsy. Nat Genet 2000;26(3):275–6.

[5] Mulley JC, Scheffer IE, Petrou S, Berkovic SF. Channelopathies as a genetic cause of epilepsy. Curr Opin Neurol 2003;16(2):171–6.

[6] Scheffer IE, Bhatia KP, Lopes-Cendes I, Fish DR, Marsden CD, Andermann E, et al. Autosomal dominant nocturnal frontal lobe epilepsy. A distinctive clinical disorder. Brain 1995;118:61–73.

[7] Picard F, Scheffer IE. Recently defined genetic epilepsy syndromes. In: Roger JBM, Dravet C, Genton P, Tassinari CA, Wolf P, editors. Epileptic syndromes in infancy, childhood and adolescence. Mountrouge: John Libbey Eurotext; 2005. p. 519–35.

[8] Oldani A, Zucconi M, Asselta R, Modugno M, Bonati MT, Dalpra L, et al. Autosomal dominant nocturnal frontal lobe epilepsy. A video-polysomnographic and genetic appraisal of 40 patients and delineation of the epileptic syndrome. Brain 1998;121(Pt 2):205–23.

[9] Provini F, Plazzi G, Tinuper P, Vandi S, Lugaresi E, Montagna P. Nocturnal frontal lobe epilepsy. A clinical and polygraphic overview of 100 consecutive cases. Brain 1999;122(Pt 6):1017–31.

[10] Magnusson A, Stordal E, Brodtkorb E, Steinlein O. Schizophrenia, psychotic illness and other psychiatric symptoms in families with autosomal dominant nocturnal frontal lobe epilepsy caused by different mutations. Psychiatr Genet 2003;13(2):91–5.

[11] Khatami R, Neumann M, Schulz H, Kolmel HW. A family with autosomal dominant nocturnal frontal lobe epilepsy and mental retardation. J Neurol 1998;245:809–10.

[12] Bertrand D, Elmslie F, Hughes E, Trounce J, Sander T, Bertrand S, et al. The CHRNB2 mutation I312M is associated with epilepsy and distinct memory deficits. Neurobiol Dis 2005;20(3):799–804.

[13] Derry CP, Davey M, Johns M, Kron K, Glencross D, Marini C, et al. Distinguishing sleep disorders from seizures: diagnosing bumps in the night. Arch Neurol 2006;63(5): 705–9.

[14] Tinuper P, Provini F, Bisulli F, Vignatelli L, Plazzi G, Vetrugno R, et al. Movement disorders in sleep: guidelines for differentiating epileptic from non-epileptic motor phenomena arising from sleep. Sleep Med Rev 2007.

[15] Tassinari C, Gardella E, Meletti S, Rubboli G. The neuroethological interpretation of motor behaviours in 'nocturnal-hyperkinetic-frontal-seizures': emergence of 'innate' motor behaviours and role of central pattern generators. In: Beaumanoir A, Andermann F, Chauvel P, Mira L, Zifkin B, editors. Frontal lobe seizures and epilepsies in children. John Libbey; 2003. p. 43–5.

[16] Tinuper P, Cerullo A, Cirignotta F, Cortelli P, Lugaresi E, Montagna P. Nocturnal paroxysmal dystonia with short-lasting attacks: three cases with evidence for an epileptic frontal lobe origin of seizures. Epilepsia 1990;31:549–56.

[17] Lombroso CT. Pavor nocturnus of proven epileptic origin. Epilepsia 2000;41(9):1221–6.

[18] Hayman M, Scheffer IE, Chinvarun Y, Berlangieri SU, Berkovic SF. Autosomal dominant nocturnal frontal lobe epilepsy: demonstration of focal frontal onset and intrafamilial variation. Neurology 1997;49(4):969–75.

[19] Nobili L, Cossu M, Mai R, Tassi L, Cardinale F, Castana L, et al. Sleep-related hyperkinetic seizures of temporal lobe origin. Neurology 2004;62(3):482–5.

[20] Schindler K, Gast H, Bassetti C, Wiest R, Fritschi J, Meyer K, et al. Hyperperfusion of anterior cingulate gyrus in a case of paroxysmal nocturnal dystonia. Neurology 2001;57(5):917–20.

[21] Ryvlin P, Minotti L, Demarquay G, Hirsch E, Arzimanoglou A, Hoffman D, et al. Nocturnal hypermotor seizures, suggesting frontal lobe epilepsy, can originate in the insula. Epilepsia 2006;47(4):755–65.

[22] Steinlein OK, Magnusson A, Stoodt J, Bertrand S, Weiland S, Berkovic SF, et al. An insertion mutation of the *CHRNA4* gene in a family with autosomal dominant nocturnal frontal lobe epilepsy. Hum Mol Genet 1997;6:943–8.

[23] Hirose S, Iwata H, Akiyoshi H, Kobayashi K, Ito M, Wuda K, et al. A novel point mutation of the neuronal nicotinic acetylcholine receptor a4 subunit (*CHRNA4*) gene in a Japanese family with autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE). Epilepsia 1999;40(Suppl. 7):236.

[24] Saenz A, Galan J, Caloustian C, Lorenzo F, Marquez C, Rodriguez N, et al. Autosomal dominant nocturnal frontal lobe epilepsy in a Spanish family with a ser252phe mutation in the CHRNA4 gene. Arch Neurol 1999;56: 1004–9.

[25] Steinlein OK, Stoodt J, Mulley JC, Berkovic SF, Scheffer IE, Brodtkorb E. Independent occurence of the CHRNA4 Ser248Phe mutation in a Norwegian family with nocturnal frontal lobe epilepsy. Epilepsia 2000;41(5):529–35.

[26] Phillips HA, Marini C, Scheffer IE, Sutherland GR, Mulley JC, Berkovic SF. A de novo mutation in sporadic nocturnal frontal lobe epilepsy. Ann Neurol 2000;48:264–7.

[27] McLellan A, Phillips HA, Rittey C, Kirkpatrick M, Mulley JC, Goudie D, et al. Phenotypic comparison of two Scottish families with mutations in different genes causing autosomal dominant nocturnal frontal lobe epilepsy. Epilepsia 2003;44:613–7.

[28] Rozycka A, Skorupska E, Kostyrko A, Trzeciak WH. Evidence for S284L mutation of the CHRNA4 in a white family with autosomal dominant nocturnal frontal lobe epilepsy. Epilepsia 2003;44(8):1113–7.

[29] Cho YW, Motamedi GK, Laufenberg I, Sohn SI, Lim JG, Lee H, et al. A Korean kindred with autosomal dominant nocturnal frontal lobe epilepsy and mental retardation. Arch Neurol 2003;60(11):1625–32.
[30] Leniger T, Kananura C, Hufnagel A, Bertrand S, Bertrand D, Steinlein OK. A new Chrna4 mutation with low penetrance in nocturnal frontal lobe epilepsy. Epilepsia 2003;44(7): 981–5.
[31] Phillips HA, Favre I, Kirkpatrick M, Zuberi SM, Goudie D, Heron SE, et al. CHRNB2 is the second acetylcholine receptor subunit associated with autosomal dominant nocturnal frontal lobe epilepsy. Am J Hum Genet 2001;68(1):225–31.
[32] Aridon P, Marini C, Di Resta C, Brilli E, De Fusco M, Politi F, et al. Increased sensitivity of the neuronal nicotinic receptor alpha 2 subunit causes familial epilepsy with nocturnal wandering and ictal fear. Am J Hum Genet 2006;79(2):342–50.
[33] Phillips HA, Scheffer IE, Crossland KM, Bhatia KP, Fish DR, Marsden CD, et al. Autosomal dominant nocturnal frontal lobe epilepsy: genetic heterogeneity and a probable second locus at 15q24. Am J Hum Genet 1998;63(4):1108–16.
[34] De Marco EV, Gambardella A, Annesi F, Labate A, Carrideo S, Forabosco P, et al. Further evidence of genetic heterogeneity in families with autosomal dominant nocturnal frontal lobe epilepsy. Epilepsy Res 2007;74(1): 70–3.
[35] Combi R, Ferini-Strambi L, Montruccoli A, Bianchi V, Malcovati M, Zucconi M, et al. Two new putative susceptibility loci for ADNFLE. Brain Res Bull 2005;67(4): 257–63.
[36] Ito M, Kobayashi K, Fujii T, Okuno T, Hirose S, Iwata H, et al. Electroclinical picture of autosomal dominant noturnal frontal lobe epilepsy in a Japanese family. Epilepsia 2000;41(1):52–8.
[37] Gotti C, Fornasari D, Clementi F. Human neuronal nicotinic receptors. Prog Neurobiol 1997;53(2):199–237.
[38] Gotti C, Clementi F. Neuronal nicotinic receptors: from structure to pathology. Prog Neurobiol 2004;74(6): 363–96.
[39] Bertrand D, Picard F, Le Hellard S, Weiland S, Favre I, Phillips H, et al. How mutations in the nAChRs can cause ADNFLE epilepsy. Epilepsia 2002;43(Suppl. 5):112–22.
[40] Cooper E, Couturier S, Ballivet M. Pentameric structure and subunit stoichiometry of a neuronal nicotinic acetylcholine receptor. Nature 1991;350:235–8.
[41] Campos-Caro A, Sala S, Ballesta JJ, Vicente-Agullo F, Criado M, Sala F. A single residue in the M2-M3 loop is a major determinant of coupling between binding and gating in neuronal nicotinic receptors. Proc Natl Acad Sci USA 1996;93(12):6118–23.
[42] de la Garza R, Bickford-Wimer PC, Hoffer BJ, Freedman R. Heterogeneity of nicotine actions in the rat cerebellum: an in vivo electrophysiologic study. J Pharmacol Exp Ther 1987;240(2):689–95.
[43] Alkondon M, Pereira EF, Eisenberg HM, Albuquerque EX. Nicotinic receptor activation in human cerebral cortical interneurons: a mechanism for inhibition and disinhibition of neuronal networks. J Neurosci 2000;20(1):66–75.
[44] Jones S, Sudweeks S, Yakel JL. Nicotinic receptors in the brain: correlating physiology with function. Trends Neurosci 1999;22(12):555–61.
[45] Nordberg A. Clinical studies in Alzheimer patients with positron emission tomography. Behav Brain Res 1993;57(2):215–24.
[46] Rubboli F, Court JA, Sala C, Morris C, Chini B, Perry E, et al. Distribution of nicotinic receptors in the human hippocampus and thalamus. Eur J Neurosci 1994;6(10): 1596–604.
[47] Cairns NJ, Wonnacott S. [3H](-)nicotine binding sites in fetal human brain.. Brain Res 1988;475(1):1–7.
[48] Court JA, Perry EK, Spurden D, Griffiths M, Kerwin JM, Morris CM, et al. The role of the cholinergic system in the development of the human cerebellum. Brain Res Dev Brain Res 1995;90(1/2):159–67.
[49] Nordberg A, Alafuzoff I, Winblad B. Nicotinic and muscarinic subtypes in the human brain: changes with aging and dementia. J Neurosci Res 1992;31(1):103–11.
[50] Bertrand S, Weiland S, Berkovic SF, Steinlein OK, Bertrand D. Properties of neuronal nicotinic acetylcholine receptor mutants from humans suffering from autosomal dominant nocturnal frontal lobe epilepsy. Br J Pharmacol 1998;125:751–60.
[51] Kuryatov A, Gerzanich V, Nelson M, Olale F, Lindstrom J. Mutation causing autosomal dominant nocturnal frontal lobe epilepsy alters Ca^{2+} permeability, conductance, and gating of human alpha4beta2 nicotinic acetylcholine receptors. J Neurosci 1997;17(23):9035–47.
[52] Weiland S, Witzemann V, Villarroel A, Propping P, Steinlein O. An amino acid exchange in the second transmembrane segment of a neuronal nicotinic receptor causes partial epilepsy by altering its desensitization kinetics. FEBS Lett 1996;398(1):91–6.
[53] Moulard B, Picard F, le Hellard S, Agulhon C, Weiland S, Favre I, et al. Ion channel variation causes epilepsies. Brain Res Brain Res Rev 2001;36(2/3):275–84.
[54] Rodrigues-Pinguet N, Jia L, Li M, Figl A, Klaassen A, Truong A, et al. Five ADNFLE mutations reduce the Ca2+ dependence of the mammalian alpha4beta2 acetylcholine response. J Physiol 2003;550(Pt 1):11–26.
[55] Klaassen A, Glykys J, Maguire J, Labarca C, Mody I, Boulter J. Seizures and enhanced cortical GABAergic inhibition in two mouse models of human autosomal dominant nocturnal frontal lobe epilepsy. Proc Natl Acad Sci USA 2006;103(50):19152–7.
[56] Picard F, Bruel D, Servent D, Saba W, Fruchart-Gaillard C, Schollhorn-Peyronneau MA, et al. Alteration of the in vivo nicotinic receptor density in ADNFLE patients: a PET study. Brain 2006;129(Pt 8):2047–60.
[57] Picard F, Bertrand S, Steinlein OK, Bertrand D. Mutated nicotinic receptors responsible for autosomal dominant nocturnal frontal lobe epilepsy are more sensitive to carbamazepine. Epilepsia 1999;40(9):1198–209.
[58] Willoughby JO, Pope KJ, Eaton V. Nicotine as an antiepileptic agent in ADNFLE: an N-of-one study. Epilepsia 2003;44(9):1238–40.
[59] Brodtkorb E, Picard F. Tobacco habits modulate autosomal dominant nocturnal frontal lobe epilepsy. Epilepsy Behav 2006;9(3):515–20.