

Case Report

Identification of a novel SNAP29 mutation in a patient with nocturnal frontal lobe epilepsy with long interictal and ictal phases: a case report

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Abstract: *Background:* Nocturnal frontal lobe epilepsy is a rare type of focal epilepsy in which seizures occur almost exclusively during sleep. It can be sporadic or autosomal dominant; the familial form has been linked to mutations in the genes coding for the subunits of the neuronal acetylcholine receptors and novel gene mutations (*KCNT1*, *DEPDC*). The clinical features and pathogenetic variants nocturnal frontal lobe epilepsy are not well-characterized. *Case report:* We describe a 32-year-old woman who presented with a 4-year-long history of epileptic seizures. The seizures manifested as episodes of convulsions, rigidity and pain in the right extremities, accompanied by a sense of fear. Each episode lasted for several seconds. Loss of consciousness and urinary incontinence seldom occurred. The interictal period was 3 months, and the ictal period reached up to 1 month. During the ictal period, clusters of seizures occurred every night. Treatment with carbamazepine was effective. Exome sequencing analysis disclosed a novel heterozygous mutation (c.766C>T) in the *SNAP29* gene. *Conclusion:* Nocturnal frontal lobe epilepsy with long interictal and ictal phases is an extremely rare disease. The detected mutation (c.766C>T) in chr22:21242113 loci has never been reported previously. Our findings will add to the current understanding as well as the genetic profiles of nocturnal frontal lobe epilepsy.

Keywords: Nocturnal epilepsy, frontal lobe epilepsy, long interictal phase, long ictal phase, exome sequencing

Introduction

Nocturnal frontal lobe epilepsy is a specific type of focal epilepsy characterized by nocturnal seizures that occur almost exclusively during sleep [1, 2]. It is an extremely rare condition; however, owing to the advances in electroencephalography (EEG), the condition is being increasingly identified [3]. Nocturnal frontal lobe epilepsy is characterized by clusters of motor seizures that occur during non-REM sleep; the ictal phase is typically transient [3]. It can be sporadic, or occur as an autosomal dominant form, which is also known as autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE). Previously reported pathogenetic variants have included mutations in the genes coding for the subunits of the neuronal acetylcholine receptors (nAChR), and some novel gene mutations (such as those of *KCNT1* and *DEPDC*).

Herein, we report a case of nocturnal frontal lobe epilepsy with long interictal and ictal phases, whose clinical features mimicked ADNFLE. On exome sequencing analysis, a novel heterozygous mutation (c.766C>T) in the *SNAP29* gene was detected.

Case report

A 32-year-old woman presented to us in Jan 2015 with a 4-year-long history of epileptic seizures. In Jan 2011, she experienced the first episode of seizures soon after she fell asleep at night. The seizures manifested as convulsions, rigidity and pain in the right extremities; a sense of fear and muscle twitches were particularly notable. The episode lasted for several seconds. There was no loss of consciousness or urinary incontinence. There were multiple seizures, and she was not able to fall asleep. During these four years, the interictal period

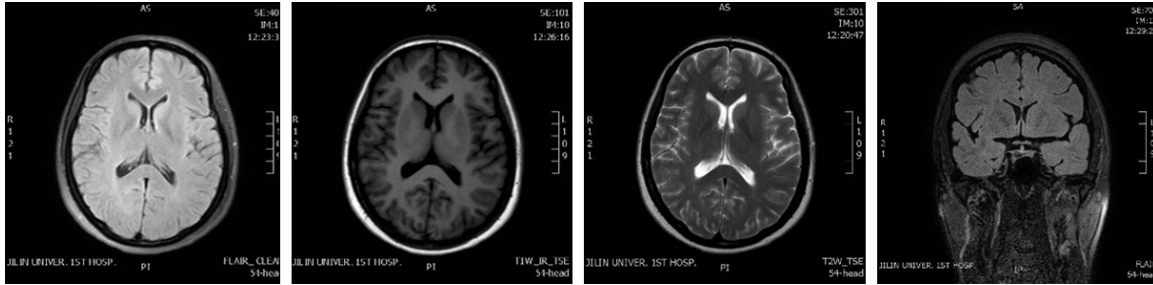


Figure 1. Brain magnetic resonance imaging during the ictal phase was normal.

was approximately 3 months; the ictal period could last up to one month. The seizures occurred exclusively during sleep; during the ictal period, the seizures occurred during daytime sleep as well. There was seldom loss of consciousness or urinary incontinence. She denied any history of febrile convulsions, head injury, intracranial infection or family history of epilepsy. Physical examination was unremarkable.

Brain magnetic resonance imaging during the ictal phase was normal (**Figure 1**). 24-hour EEG showed normal background activity (**Figure 2A**); several clinical seizures were monitored in the non-REM II phase, during which the patient developed convulsions and rigidity in the right extremities (symptoms were more significant in the right lower extremity) with a suffering expression; real-time EEG showed low-amplitude fast wave activities and several muscle artifacts which tended to alleviate as the seizure relieved (**Figure 2B, 2C**); during the REM-sleep stage, slow waves were noted in the left frontal area (**Figure 2D**).

The hepatorenal function, blood routine investigations including serum electrolytes and electrocardiogram were normal. For genetic analysis, we performed DNA sequencing for 527 known epilepsy-related genes, and found a novel heterozygous nonsense mutation (c.766-C>T) in the SNAP29 gene (**Figure 3**). This single-stranded mutation was predicted to cause a premature termination codon at nucleotides (NTs) 766 to 768 to generate a truncated protein of 255 amino acids. Initially, levetiracetam was administrated (500 mg twice daily), but the seizures were not relieved. Three months later, we shifted the patient to carbamazepine (200 mg twice daily), and the seizures were well controlled. During the follow-up period of half a year, no epileptic seizure occurred.

Discussion

Frontal lobe epilepsy is the second most common form of focal epilepsy after temporal lobe epilepsy. Due to the complex anatomical and functional features of the frontal lobe, the clinical manifestations of frontal lobe epilepsy tend to show considerable variability. Epileptic aura, especially fear aura, has been frequently reported in patients with frontal lobe epilepsy [4]. Ictal presentations of frontal lobe epilepsy are characterized by remarkable motor behavior or sustained asymmetric dystonic posture, such as posturing tonic seizure, focal clonic activity, agitation of hands and semi-purposeful motor automatism, which suggests the involvement of supplementary motor area (SMA) and premotor cortex in the frontal lobe [5].

Frontal lobe epilepsy usually manifests as clusters of transient seizures which last for less than one minute [6-8], and these occur more frequently in the nighttime. Though the long interictal phase alternating with long ictal phase can be common in frontal lobe epilepsy, the longest interval has not yet been systematically studied.

The seizures associated with ADNFLE can begin anytime from infancy to mid-adulthood; however, most begin in childhood. Approximately 35% to 60% of patients with frontal lobe epilepsy are characterized by nocturnal seizures that occur almost exclusively during sleep [9, 10]. These patients have been classified into a specific subgroup, known as nocturnal frontal lobe epilepsy (NFLE) [7, 11, 12]. In 1994, Scheffer *et al.* first described its familial form, ADNFLE, which is characterized by clusters of motor seizures during sleep [13]. Steinlein discovered the epilepsy-related gene mutation in 1995. ADNFLE was the first epilepsy syndrome for which monogenetic bases

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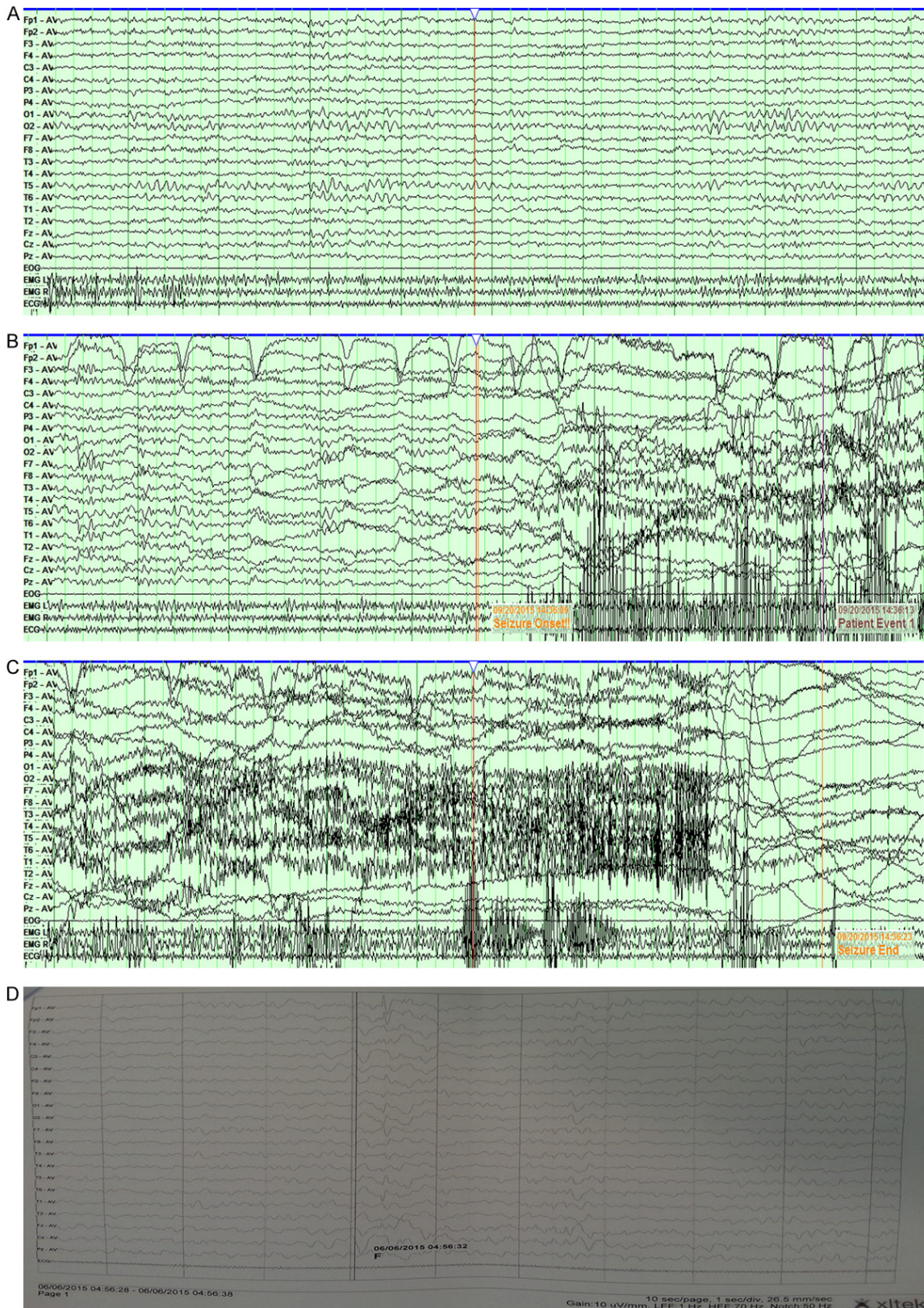


Figure 2. 24-hour EEG showed normal background activity (A). During seizure episodes, real-time EEG showed low-amplitude fast wave activity and several muscle artifacts (B). The electric amplitudes reduced significantly as the seizure resolved (C). During REM-sleep stage, slow waves were noted in the left frontal area (D).

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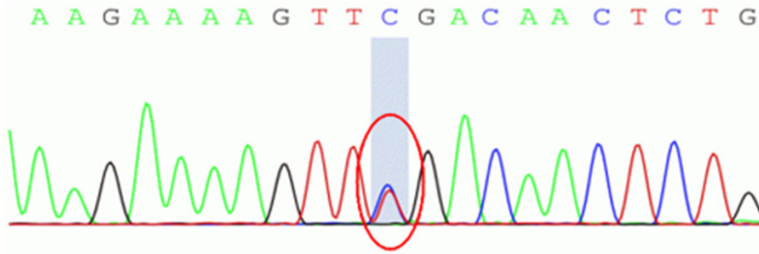


Figure 3. DNA sequencing revealed a novel heterozygous nonsense mutation (c.766C>T) in the SNAP29 gene (chr22:21242113).

were identified [14]. Recently, several gene variations related to ADFLE have been reported, including *CHRNA4*, *CHRNA2*, and *CHRNA2*; these genes code for different parts (subunits) of a larger molecule called a neuronal nicotinic acetylcholine receptor, and this receptor plays an important role in inter-neuronal chemical signaling brain [15, 16].

ADNFLE usually appears within the first two decades of life and may spontaneously resolve in adulthood. The reported ages at onset of ADFLE range from 2 months to 52 years; 53% of these cases presented within the first decade of life, while 35% developed ADFLE within the second decade. All reported cases of ADFLE manifested nocturnal seizures; 58% of seizures occurred soon after the patients fell asleep, 48% occurred in the early morning, and 9% occurred during the whole night. Interestingly, 30% of the patients with ADFLE experienced seizures during the daytime sleep as well [17].

Most patients with ADFLE have normal intellectual development; there is no loss of consciousness or brain dysfunctions during the seizure episodes. Patients may be aware of the seizures, whereas they are usually unable to respond to external stimulation or recall the seizure experience. However, some patients with ADFLE may have psychiatric disorders, behavioral problems, or intellectual disability. It is unclear whether these additional features are directly related to epilepsy in these individuals. The differential diagnoses should include sleep disorders, such as REM sleep behavior disorder (RBD), sleep rhythm abnormal movements, panic attacks at night, and psychogenic non-epileptic seizure [18]. Most seizure episodes in patients with nocturnal frontal lobe epilepsy occur during non-REM phase of sleep; 70% of these occur during the Phase I or Phase II sleep. Thus a detailed history taking can help

in the differential diagnosis [19-21]. In the current case, though the middle-aged onset is atypical, the high frequency of seizures, concurrent loss of consciousness, and abnormal EEG helped us identify nocturnal frontal lobe epilepsy.

In the present case, all seizure episodes occurred in sleep, and the duration of interictal phase was fixed (3

months) and the ictal phase reached up to 1 month. Such long-duration interictal and ictal phases have never been reported in patients with frontal lobe epilepsy. The therapeutic course and relevant outcome indicate that carbamazepine can be an effective approach for the treatment of nocturnal frontal lobe epilepsy.

Genetic analysis revealed a heterozygous nonsense mutation (c.766C>T) in the *SNAP29* gene, causing a premature termination codon and thus generating a truncated protein. This mutation has not been reported in the HGMDpro database. There has been no relevant study indicating the *SNAP29* gene plays a definitive role in ADFLE. *SNAP29* gene, also known as synaptosomal-associated protein 29 gene, located at 22q11.21. This gene belongs to the *SNAP25* gene family, consisting of 5 coding exons. *SNAP29* gene codes for the SNARE protein, which participates in the cell membrane transport and vesicle fusion. Recently, mutations in *SNAP29* gene has been found to cause CEDNIK syndrome, a neurocutaneous syndrome characterized by cerebral dysgenesis, neuropathy, ichthyosis, and keratoderma [22]. This syndrome clinically manifests as microcephaly, psychomotor retardation, facial deformity, palmoplantar keratoderma, and late-onset ichthyosis. The patients usually show signs of developmental retardation of brain on MRI, such as agenesis of corpus callosum and cortex dysplasia. However, in the current study, the brain MRI abnormality and cutaneous presentations were absent, thus a diagnosis of CEDNIK syndrome could be excluded [23]. The specific association between this mutation in *SNAP29* gene and ADFLE still need further research.

In conclusion, nocturnal frontal lobe epilepsy with long interictal and ictal phases is extremely rare. We identified a novel mutation (c.766-

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C>T) in *SNAP29* gene (chr22:21242113 loci). This case report will add to the understanding as well as the genetic profiles of nocturnal frontal lobe epilepsy.

Disclosure of conflict of interest

None.

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References

- [1] Bancaud J, Talairach J. Clinical semiology of frontal lobe seizures. *Adv Neurol* 1992; 57: 3-58.
- [2] Rasmussen T. Characteristics of a pure culture of frontal lobe epilepsy. *Epilepsia* 1983; 24: 482-93.
- [3] Proposal for revised classification of epilepsies and epileptic syndromes. Commission on classification and terminology of the international league against epilepsy. *Epilepsia* 1989; 30: 389-99.
- [4] Kotagal P, Arunkumar G, Hammel J, Mascha E. Complex partial seizures of frontal lobe onset: statistical analysis of ictal semiology. *Seizure* 2003; 12: 268-81.
- [5] Williamson PD, Spencer DD, Spencer SS, Novelly RA, Mattson RH. Complex partial seizures of frontal lobe origin. *Ann Neurol* 1985; 18: 497-504.
- [6] Broglin D, Delgado-Escueta AV, Walsh GO, Bancaud J, Chauvel P. Clinical approach to the patient with seizures and epilepsies of frontal origin. *Adv Neurol* 1992; 57: 59-88.
- [7] Williamson PD, Jobst BC. Frontal lobe epilepsy. *Adv Neurol* 2000; 84: 215-42.
- [8] Williamson PD. Frontal lobe seizures. Problems of diagnosis and classification. *Adv Neurol* 1992; 57: 289-309.
- [9] Wieser HG, Swartz BE, Delgado-Escueta AV, Bancaud J, Walsh GO, Maldonado H, Saint-Hilaire JM. Differentiating frontal lobe seizures from temporal lobe seizures. *Adv Neurol* 1992; 57: 267-85.
- [10] Crespel A, Coubes P, Baldy-Moulinier M. Sleep influence on seizures and epilepsy effects on sleep in partial frontal and temporal lobe epilepsies. *Clin Neurophysiol* 2000; 111 Suppl 2: S54-9.
- [11] 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: 1017-31.
- [12] Meierkord H, Fish DR, Smith SJ, Scott CA, Shorvon SD, Marsden CD. Is nocturnal paroxysmal dystonia a form of frontal lobe epilepsy? *Mov Disord* 1992; 7: 38-42.
- [13] Scheffer IE. Autosomal dominant nocturnal frontal lobe epilepsy. *Epilepsia* 2000; 41: 1059-60.
- [14] Scheffer IE, Berkovic SF, Bhatia KP, Fish DR, Marsden CD, Lopes-Cendes I, Andermann F, Andermann E, Desbiens R, Cendes F, Manson JI. Autosomal dominant frontal epilepsy misdiagnosed as sleep disorder. *Lancet* 1994; 343: 515-7.
- [15] Bertrand D, Elmslie F, Hughes E, Trounced J, Sandere T, Bertranda S, Steinleinf OK. The *CHRNA2* mutation I312M is associated with epilepsy and distinct memory deficits. *Neurobiol Dis* 2005; 20: 799-804.
- [16] Aridon P, Marini C, Resta CD, Brillid E, Fusco MD, Politib F, Parrinic E, Manfredia I, Pisanoe T, Prunae D, Curiab G, Cianchettie C, Pasqualetti M, Becchettib A, Guerrinic R, Casaria G. 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: 342-50.
- [17] Scheffer IE, Bhatia KP, Lopes-Cendes I, Fish DR, Marsden CD, Andermann E, Andermann F, Desbiens R, Keene D, Cendes F, Manson JI, Constantinou JE, McIntosh A, Samuel F, Berkovic SF. Autosomal dominant nocturnal frontal lobe epilepsy. A distinctive clinical disorder. *Brain* 1995; 118: 61-73.
- [18] Derry CP, Duncan JS, Berkovic SF. Paroxysmal motor disorders of sleep: the clinical spectrum and differentiation from epilepsy. *Epilepsia* 2006; 47: 1775-91.
- [19] Derry CP, Davey M, Johns M, Kron K, Glencross D, Marini C, Scheffer IE, Berkovic SF. Distinguishing sleep disorders from seizures: diagnosing bumps in the night. *Arch Neurol* 2006; 63: 705-9.
- [20] Manni R, Terzaghi M, Repetto A. The FLEP scale in diagnosing nocturnal frontal lobe epilepsy, NREM and REM parasomnias: data from a tertiary sleep and epilepsy unit. *Epilepsia* 2008; 49: 1581-5.
- [21] Derry CP. The sleep manifestations of frontal lobe epilepsy. *Curr Neurol Neurosci Rep* 2011; 11: 218-26.
- [22] Schiller SA, Seebode C, Wieser GL, Goebbels S, Möbius W, Horowitz M, Sarig O, Sprecher E, Emmert S. Establishment of two mouse models for CEDNIK syndrome reveals the pivotal role of *SNAP29* in epidermal differentiation. *J Invest Dermatol* 2016; 136: 672-9.
- [23] Sprecher E, Ishida-Yamamoto A, Mizrahi-Koren M, Rapaport D, Goldsher D, Indelman M, Topaz O, Chefetz I, Keren H, O'Brien TJ, Bercovich D, Shalev S, Geiger D, Bergman R, Horowitz M, Mandel H. A mutation in *SNAP29*, coding for a

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SNARE protein involved in intracellular trafficking, causes a novel neurocutaneous syndrome characterized by cerebral dysgenesis, neurop-

athy, ichthyosis, and palmoplantar keratoderma. *Am J Hum Genet* 2005; 77: 242-51.