Seizure 21 (2012) 118–123

Contents lists available at SciVerse ScienceDirect

Seizure

journal homepage: www.elsevier.com/locate/yseiz

Mutations in familial nocturnal frontal lobe epilepsy might be associated with distinct neurological phenotypes

Ortrud K. Steinlein [a,*], Jean-Charles Hoda [b], Sonia Bertrand [b], Daniel Bertrand [b]

[a] Institute of Human Genetics, University Hospital, Ludwig-Maximilians-University, Goethestr. 29, D-80336 Munich, Germany
[b] Department of Neuroscience, Medical Faculty, Centre Médical Universitaire, CH-1211 Geneva, Switzerland

ARTICLE INFO

Article history:
Received 17 August 2011
Received in revised form 12 October 2011
Accepted 12 October 2011

Keywords:
Epilepsy
ADNFLE
Cognition
Mental retardation
Acetylcholine receptor
Electrophysiology

ABSTRACT

Autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE) is a rare familial seizure disorder caused by mutations in at least two different subunit genes of the neuronal nicotinic acetylcholine receptor (nAChR), *CHRNA4* and *CHRNB2*. ADNFLE was initially described as a "pure" seizure disorder with a mostly benign course. We have analysed the clinical features of 19 ADNFLE families from 12 countries with a total of 150 patients and grouped them with respect to their nAChR mutations. These data suggest that certain nAChR mutations might be associated with an increased risk for major neurological symptoms such as mental retardation, schizophrenia-like symptoms or marked cognitive deficits, but the risk for these disorders seems to be low for most other ADNFLE mutations. The functional data confirm that the mutations differ from each other with respect to the size of their gain-of function effects and other biopharmacological characteristics although these functional changes are not predictive for the severity of the clinical phenotype.

1. Introduction

Epilepsies affect about 1% of the population, rendering it one of the most common neurological disorders. Most non-lesional epilepsies arise on an oligogenic or polygenic background, but several seizure disorders are known to segregate in a Mendelian fashion. These rare monogenic epilepsies are valuable models for scientific approaches and have already helped to uncover parts of the various pathomechanisms underlying epileptogenesis. Autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE) has a special role within this group of monogenic epilepsies because it was the first epilepsy in humans for which specific mutations were identified. So far, mutations in at least two genes, *CHRNA4* and *CHRNB2* encoding the α4 and β2 subunits of the neuronal nicotinic acetylcholine receptor (nAChR), are known to give rise to ADNFLE.[1,2] These mutations cause a clinical phenotype that was initially described as a "pure" epilepsy characterized by nocturnal seizures that arise mostly from non-REM sleep. In the original family 27 individuals were affected and, except for the seizures, no neurological symptoms, psychiatric disturbances or mental deficiencies were reported.[3] Subsequent studies indicated that borderline intelligence or mild deficits in executive tasks are not uncommon in ADNFLE patients.[4] However, major neurological features such as schizophrenia-like symptoms, mental retardation or cognitive deficits have been described only in a few families.[5–10] So far it is unknown if these additional features occur by chance, or if they are indeed causally related to specific nAChR mutations. The systematic analysis of the clinical variability presented here suggests that the risk for additional major neurological and psychiatric features might be increased for ADNFLE patients with certain nAChR mutations but rare for the carriers of most other mutations. The functional studies show that ADNFLE mutations differ from each other with respect to their biopharmacological characteristics but that no obvious correlation can be detected between the severity of the clinical phenotypes and the respective changes in receptor function.

2. Methods

2.1. Subjects

Clinical data from 20 ADNFLE families with known nAChR mutations were either taken from the histories of families diagnosed in our lab (Munich) or collected by reviewing the relevant literature (for references see Table 1). The study protocol was approved by the institutional review board and informed consent was given from the participants.

2.2. Mutation construct

CHRNA4 and *CHRNB2* mutations were introduced by PCR-based site-directed mutagenesis (QuikChange II site-directed mutagene-

* Corresponding author. Tel.: +49 89 5160 4468; fax: +49 89 5160 4470.
E-mail address: Ortrud.Steinlein@med.uni-muenchen.de (O.K. Steinlein).

1059-1311/$ – see front matter © 2011 British Epilepsy Association. Published by Elsevier Ltd. All rights reserved.
doi:10.1016/j.seizure.2011.10.003

Table 1
Summary of clinical data for ADNFLE families.

Gene	Mutation	Ethnic origin	Number of clinically affected individuals (f/m)	Neurological/psychiatric features other than NFLE (*n*/*t*)	Antiepileptic drug treatment (*n*)/seizure severity (*n*)/drug efficiency (*n*)	References
CHRNA4	S248F (S280F)	British-Australian	27 (18/9)		CBZ average 690 mg (NA), MD (11)/controlled in most patients (NA)	1,16–18
		Spanish	11 (7/4)		CBZ 600–1000 mg (4), VPA 700 mg (1), NT (2), NA (4)/controlled (6), poorly controlled (2)	
		Norwegian	22 (10/12)	Mild mental retardation (1/22) Psychiatric disorder, unclassified (1/22)	NA/controlled (10), uncontrolled (1), SRI (6), NA (5)	
		Scottish	7 (4/3)	Psychological problems (NA)	NA (1), NT (6)/SRI (6), severe (1)	
	S252L (S284L)	Japanese	5 (2/3)	Mild mental retardation (3/5) Early childhood onset of epilepsy (3/5)	CBZ NA (1), MD (2), NT (1), NA (1)/controlled (1), SRI (1), poorly controlled (2), NA (1)	6–8,23,25
		Lebanese	2 (1/1)	Low average intellect (1/2) Early childhood onset of epilepsy (2/2)	NA/poorly controlled (1), NA (1)	
		Korean	9 (7/2)	Mild to moderate mental retardation (7 out of 9 available for testing)	CBZ (1), MD (5), NT (1), NA (2)/SRI (1), improvement (3), poorly controlled (3)	
		Polish	3(1/2)	Early childhood onset of epilepsy (2/3)	MD (2), NT (1)/poorly controlled (3)	
	776ins3 (865-873insGCT)	Norwegian	11 (5/6)	Schizophrenia (1/11) Negative symptoms of schizophrenia (1/11) Recurrent psychosis (1/11) Psychiatric disorder, unspecified (3/11) (5 family members were not available for testing)	NA	5,9
	T265I (T293I)	German	2 (0/2)		CBZ 2400 mg (1), CBZ NA (1)/improvement (1), poorly controlled (1)	19
	R308H (R336H)	Chinese	1 (0/1)	NA	MD (1)/poorly controlled (1)	13
CHRNB2	V287L	Italian	8 (2/6)		CBZ 400–800 mg (6), NT (2)/controlled (6), SRI (1), mild (1)	2,22
	V287M	Scottish	10 (6/4)	Psychological problems mentioned, numbers not specified	CBZ NA (4), MD (3), NT (3)/SRI (NA), poorly controlled (1)	18,20,21
		Spanish	6 (3/3)		CBZ NA (2), PB 150 mg (1), NT (3), NA (1)/SRI (1), improved (1), controlled (2), poorly controlled (1), NA (1)	
	L301V	Turkish Cypriot	3 (2/1)		CBZ NA (1), NT (2)/SRI (1), mild (1) poorly controlled (1)	15
	V308A	Scottish	5 (4/1)		LTG NA (1)/controlled (1)	15
		German	4 (2/2)		CBZ NA (2)/controlled (2)	
	I312M	English	2 (2/0)	Low average intellect with significant memory deficits (verbal) (2/2)	MD (2)/controlled (2)	10,24
		Korean	2 (2/0)	Psychiatric episode with delusional ideas (1/2) Normal intelligence with moderate memory deficits (verbal) (1/2) Normal intelligence with significant memory deficits (verbal/visual) (1/2)	NA	
CHRNA2	I279N	Italian	10 (8/2)	NA	NA/controlled (2), poorly controlled (8)	14

ADNFLE mutations frequently associated with additional major neurological or psychiatric symptoms are given in bold. Mutations are named as in the original references, for *CHRNA4* numberings according to reference sequences (NP_000735.1, NP_000739.1) are given in brackets; NA, data not available; NT, not currently treated; *n*, number of patients; f/m, female/male; *n*/*t*, number of total; MD, patients with more than one drug; SRI, spontaneous remission or improvement. Antiepileptic drugs (number of patients given in brackets): CBZ, carbamazepin; PB, phenobarbital; PHT, phenytoin; LTG, lamotrigine.