Appendix

Consensus Conference methodology and event

Planning and execution of the project was carried out in four phases: (1) assignment, (2) scoping, (3) assessment, and (4) the consensus conference itself. In the assignment phase, the entities and their roles were defined and participants were nominated and invited. In the scoping phase, the scope and protocol for the conference were defined. The Scientific Committee identified the topics, formulated the questions to be addressed, and defined the three corresponding workgroups (clinical history, electro-clinical features, etiologic and pathogenic background). In the assessment phase, the Scientific and Technical Committees carried out a systematic review with evidence mapping, to assess the state-of-knowledge on the syndrome.[e1] They then sent to each Workgroup participant a detailed summary of the systematic review with evidence mapping, the questions, and the abstracts of the most prominent studies, classified by topic and study design. Each workgroup, led by either one or two participants, produced draft answers to be discussed during the Consensus Conference.

The Consensus Conference was held over two days. On the first day, the Consensus Development Panel established the rules for the open discussion meetings, appraised the state-of-knowledge on the syndrome and the preliminary answers provided by the workgroups, and proposed future strategies for publication of the consensus statement. During contemporaneous closed meetings, the three workgroups independently discussed and reached final answers to the questions assigned to them. Finally, an open discussion was held in which each Workgroup presented its findings and all participants debated openly to reach consensus regarding each topic and the need for further research.

On the second day, the Consensus Development Panel drafted a summary of the findings in a closed session. The chairperson then reported the findings in an open session that included the consensus conference participants as well as other members of the scientific community and officials from the organizing institution. Finally, two experts from the Workgroups gave a presentation on needs for future research.

Search strategies

Pubmed search strategy

Nocturnal Paroxysmal DystoniaMeSH	OR
"Epilepsy, Frontal Lobe"[Mesh] AND (NOCTURN*[TITLE/ABSTRACT] OR HYPNOGENIC*[TITLE/ABSTRACT] OR SLEEP*[TITLE/ABSTRACT])	OR
Somnambulism[mesh] and epilepsy[all fields]	OR
(Nocturnal OR Hypnogenic OR Sleep*) AND (paroxysmal AND Dystonia*)	OR
("paroxysmal arousal" OR "paroxysmal arousals")	OR
(Nocturnal OR Hypnogenic OR Sleep*) AND (“frontal lobe” OR hyperkinetic OR hypermotor) AND (epilepsy OR seizure*)	OR
NFLE	OR
ADNFLE	OR
CHRNA2 OR CHRNB2 OR CHRNA4 AND humans	OR
KCNT1	OR

EMBASE search strategy

nocturnal wandering	OR
"Frontal Lobe Epilepsy”[EMTREE] AND (NOCTURN* OR HYPNOGEN* OR SLEEP* OR NIGHT)	OR
Somnambulism[mesh] and epilepsy	OR
(Nocturn* OR Hypnogen* OR Sleep OR Night) AND (paroxysmal AND Dyston*)	OR
"paroxysmal arousal" OR "paroxysmal arousals"	OR
NFLE	OR
ADNFLE	OR
CHRNA2 OR CHRNB2 OR CHRNA4 OR KCNT1	

Categories used for classification of studies by topic

1. Proof of concept, i.e., studies referring to the early development of the concept of NFLE and ADNFLE;
2. Etiology of NFLE and ADNFLE (including genetic studies)
3. Epidemiology
4. Clinical features
5. Electroclinical features
6. Diagnosis (including only true diagnostic studies: i.e., reliability studies, diagnostic accuracy studies)
7. Prognosis (including only studies with a proper design: i.e., case-control studies, cohort studies)
8. Therapy
9. Boundary topic: studies dealing with conditions strictly related to NFLE or manifesting as NFL seizures.

Data extraction and analysis plan

The following data were extracted from each included study independently by two of the three reviewers, and then descriptively analysed. Disagreements were resolved by discussion.

1. Nationality of the study
2. Year of publication
3. Study design
4. Number of included patients
5. Age of patients (children / adults)
6. Category of patients (ADNLFE; NFLE)
7. Topic
8. Definition of NFLE

Categories used for classification of study design

1. Case report / family report
2. Case series / family series
3. Cross-sectional study
4. Case-control study
5. Cohort study (either prospective or retrospective)
6. Clinical (non-randomized) controlled trial
7. Randomized controlled trial

Studies on NFLE-related topics have been published since the early 1970s with an increasing trend and more than 100 studies in the last decade (See Figure e-1). Seventy per cent of studies have involved European research groups, the majority of them from Italy (See Table e-1).

Figure e-1: Secular trend of publication of studies on NFLE-related topics since 1970

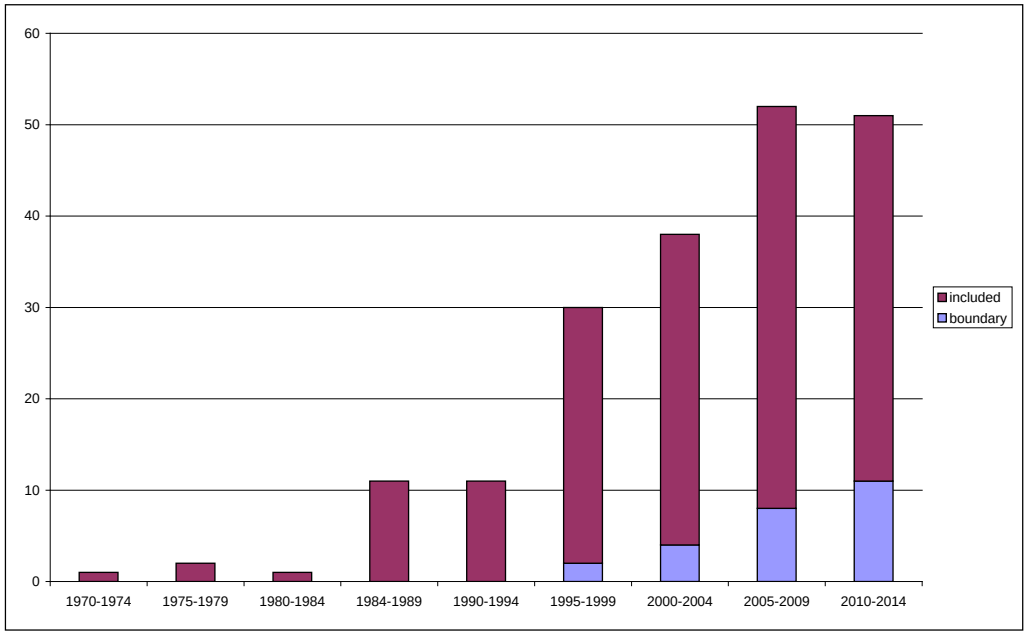

Table e-1: National origin of published studies on NFLE-related topics

Origin of the study	N	%
Total	197	100
Italy	83	42
Other Europe	56	28
Asia	18	9
Australia	16	8
USA	15	8
America other	9	5

Table e-2: Studies that form the basis of the statements with their level of evidence.

First Author / year	ref	Design	N. patients / N. families	Diagnostic criteria	Level of Evidence
Clinical Features					
Scheffer 1994	5	family series	39/6	no	IV
Bisulli 2012	7	case-control study	42 cases and 59 controls	yes	III
Nobili 2007	13	cohort	21	yes	III
Derry 2006	14	case-control study	31 cases and 31 controls	yes	III
Manni 2008	15	case-control study	14 cases and 57 controls	no	III
Derry 2009	16	case-control study	21 cases and 23 controls	yes	III
Provini 1999	17	case series	100	yes	IV
Scheffer 1995	18	family series	47/5	no	IV
Oldani 1998	19	family series	40/28	yes	IV
Electroclinical Features					
Scheffer 1994	5	family series	39/6	no	IV
Nobili 2007	13	cohort	21	yes	III
Derry 2009	16	case-control study	44	yes	III
Provini 1999	17	case series	100	yes	IV
Oldani 1998	19	family series	40/28	yes	IV
Nobili 2003	22	case report	1	no	IV
Rheims 2008	32	case series	11 (3 SHE)	yes	IV
Proserpio 2011	33	case series	8	yes	IV
Ryvlin 2006	34	case series	3	no	IV
Nobili 2004	35	case series	3	no	IV
Montavont 2013	36	case series	4 (1 SHE)	no	IV
Diagnostic certainty					
Nobili 2007	13	cohort	21	yes	III
Derry 2009	16	case-control study	21 cases and 23 controls	yes	III
Vignatelli 2007	38	cross-sectional study	66	no	III
Etiology / Genetics					
Scheffer 1994	5	family series with healthy family members as controls	39/6 (number of healthy family members not reported)	no	III
Steinlein 1995	6	case-control study	21/1 and 333 controls	no	II*
Provini 1999	17	case series	100	yes	IV
Scheffer 1995	18	family series with healthy family members as controls	47/5 (number of healthy family members not reported)	no	III
Oldani 1998	19	family series	40/28	yes	IV
Heron 2012	30	case-control study	110/3 and 111 controls	no	II*
Tassi 2012	31	cohort study	100 (53 SHE)	yes	III
Nobili 2009	40	cohort study	303 (39 SHE)	no	III
De Fusco 2000	41	case-control study	8/1 and 300 controls	no	I*
Aridon 2006	42	case-control study	10/1 and 340 controls	no	I*
Picard 2014	43	family series with healthy family members as controls	9/4 and 4 healthy family members	no	II*
Phillips 2000	44	case series	2/1	no	III*
Ishida 2013	45	case series	2/1	no	III*

*Clinical Genetics Society system of classification.

Legend: Quality-of-evidence

Each study was classified according to various descriptors, including topic domain, sample size, design, presence of diagnostic criteria of the syndrome and quality-of-evidence according to the Classification of Evidence Schemes of the Clinical Practice Guideline Process Manual of the American Academy of Neurology (2011).[e4]Each study is graded according to its risk of bias from class I to class IV (with I highest quality and IV lowest quality). Risk of bias is judged by assessing specific quality elements (i.e. study design, patient spectrum, data collection, masking, etc.) for each clinical topic (causation, diagnostic accuracy, prognostic accuracy, therapeutic). As this classification does not consider molecular genetic studies, they were assessed using the checklist proposed for molecular studies from the Clinical Genetics Society[e5] which also provides a four-level classification scheme with decreasing quality from 1 to 4) by assessing specific quality elements (e.g., study design, evidence of altered function of a gene product, evidence of genomic structure conserved across species).

e-References

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e7 Picard F, Bruel D, Servent D, et al. Alteration of the in vivo nicotinic receptor density in ADNFLE patients: a PET study. Brain 2006;129:2047-2060.
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