Epilepsy Research (2008) **80**, 9—17

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

Familial epilepsy and developmental dysphasia: Description of an Italian pedigree with autosomal dominant inheritance and screening of candidate loci

Roberto Michelucci[a,*], Eva Scudellaro[b,d], Stefania Testoni[a], Daniela Passarelli[e], Patrizia Riguzzi[a], Erica Diani[d], Giovanni Vazza[b], Valeria Vianello[c], Aldo Scabar[f], Maria L. Mostacciuolo[b], Lilia Volpi[a], Guido Rubboli[a], Federica Pinardi[a], Maria Margherita Mancardi[g], Carlo Alberto Tassinari[a], Carlo Nobile[d]

[a] *Department of Neurosciences, Division of Neurology, Via Altura 3, Bellaria Hospital, 40139 Bologna, Italy*
[b] *Department of Biology, University of Padua, Padua, Italy*
[c] *Department of Neurosciences, University of Padua, Padua, Italy*
[d] *CNR-Institute of Neurosciences, Section of Padua, Padua, Italy*
[e] *Division of Neurology, Infermi Hospital, Faenza, Italy*
[f] *Division of Infantile Neuropsychiatry ''Burlo Institute'', Trieste, Italy*
[g] *Muscular and Neurodegenerative Disease Unit, Institute ''G. Gaslini'', University of Genova, Genova, Italy*

Received 2 February 2006; received in revised form 15 January 2008; accepted 5 March 2008

KEYWORDS
Familial epilepsy;
Developmental dysphasia;
Autosomal dominant trait;
Focal and generalized EEG paroxysms

Summary
Purpose: To describe a familial epileptic condition combining a peculiar electro-clinical pattern with developmental language dysfunction in a large Italian kindred.
Methods: We studied the clinical and neurophysiological features of a 4-generation family with 10 affected members (3 deceased). We also analysed in 7 affected and 7 healthy members microsatellite markers for 51 candidate loci for epilepsy, including 42 loci containing ion channel genes expressed in the brain, as well as the SPCH1 and SRPX2 loci.
Results: Five of the seven living affected members (aged 20—58 years) had the full phenotype (seizures, EEG epileptiform abnormalities and dysphasia). The language dysfunction was the first symptom, becoming evident since the period of language development and mainly consisting of phonemic and syntactic paraphasias, difficulty of expression and reduced verbal fluency. The seizures had their onset between 2 and 23 years and were reported as epileptic falls (4)

* Corresponding author. Tel.: +39 0516225734; fax: +39 0516225369.
E-mail address: roberto.michelucci@ausl.bo.it (R. Michelucci).

0920-1211/$ — see front matter
doi:10.1016/j.eplepsyres.2008.03.014

associated or not with myoclonic features, absences (3), tonic–clonic (1) and complex partial seizures (1). The seizures were easily controlled by antiepileptic treatment in all patients except one. In the five patients with a good response of seizures to treatment, the EEG tracings showed the coexistence of focal and generalized epileptiform abnormalities; in the refractory patient the interictal EEG demonstrated bilateral asynchronous fronto-temporal paroxysms with left predominance and ictal SEEG recording suggested a multifocal origin of the discharges. MRI of the brain was normal in all patients. Linkage analysis provided negative LOD scores for all the investigated loci.

Conclusion: We have described a novel familial pattern of epilepsy and developmental dysphasia which is not genetically linked to epilepsy or speech disorder loci, as documented by a candidate-gene linkage approach.

Introduction

The association between epilepsy/epileptiform abnormalities and ''interictal'' language disturbances has long been the subject of debate and includes a number of clinical scenarios. Landau-Kleffner syndrome (LKS) is a non-familial epileptic encephalopathy characterized by the development in previously normal children of ''acquired'' aphasia as the result of paroxysmal abnormalities over the temporal regions, markedly activated during non-REM sleep in the form of Continuous Spike and Waves during Sleep (CSWS) pattern (Tassinari et al., 2000). Similarly, a number of children with developmental dysphasias may show ''epileptiform'' EEG abnormalities, which have been causally related to the language disturbances (Echenne et al., 1992; Picard et al., 1998). Lastly a familial condition, called autosomal dominant rolandic epilepsy with speech dyspraxia, combines an epileptic focal motor disorder with interictal language problems in the form of speech dyspraxia (Scheffer et al., 1995). Now we describe a large Italian kindred exhibiting the association of epilepsy (with focal and generalized features) and developmental language dysfunction over four generations. We also report a family study of selected candidate loci, either associated to other epilepsy syndromes or harbouring ion channel genes.

Patients and methods

Clinical data collection

We identified a relatively large four-generation non-consanguineous Italian family comprising 21 members (excluding spouses) of which 10 were affected (3 deceased). The family came to our attention through the index patient, IV:1, who was referred at our epilepsy unit for intractable focal epilepsy. The pedigree structure is presented in Fig. 1.

All the 16 living members, including the 7 affected, were directly examined by 3 of the authors (RM, DP, ST). A personal and family history was obtained from each member along with a physical and neurological examination. At the time of our evaluation only one patient had active epilepsy whereas all the affected members had a previous history of childhood benign epilepsy, whose seizure semiology could be ascertained by means of direct interview of the parents/relatives and available clinical records. EEGs from patients III:4, IV:4, IV:5, IV:8, IV:9 covering several years of the history were already available at the time of our evaluation and were thoroughly reviewed by 3 of the authors (RM, DP, PR). Sleep EEGs had been performed in patients IV:1, IV:4, IV:5 and IV:9. Serial neuropsychological examinations, including intelligence (WISC-III) and receptive or expressive language tests, were also available in five cases (IV:1, IV:4, IV:5, IV:8, IV:9). Routine and sleep EEGs were obtained in family members III:2 and IV:1. Each affected patient (except family members III:8 and III:4) had previously undergone a magnetic resonance imaging (MRI) with 1.5 T fixed-strength unit. The MRI was repeated twice in the index patient (with a 3 T machine).

Genotype determination

All individuals participating in the study gave their written informed consent. Ten-milliliter venous blood samples were collected from all 7 affected and 7 unaffected family members (III:2, III:3, III:4, III:6, III:8, IV:1, IV:2, IV:4, IV:5, IV:6, IV:7, IV:8, IV:9, IV:10), and genomic DNA was extracted using a standard method. Nine loci linked to other familial epilepsy syndromes with unknown gene (2q24, 6p11-12, 8q24, 10q24, 15q14, 15q24, 16p12-q12, 19q22, and 22q11.12) (5), 42 additional loci harbouring one or more ion channel genes expressed in the brain (see Table 1), the SPCH1 locus at 7q31, linked to familial severe speech disorder (Fisher et al., 1998), and the SRPX2 locus linked to rolandic seizures, speech dyspraxia and mental retardation on chromosome Xp11.21 (Roll et al., 2006) were screened by typing at least one informative microsatellite marker for each locus according to standard PCR conditions. At ion channel loci, markers were chosen based on their positions within or flanking ion channel genes using the Human Genome Browser Gateway (http://genome/ucsc/edu/cgi-bin/hgGateway). Fifty-five markers from the ABI PRISM linkage mapping set version 2.5 were utilized because they were within few Mb of a selected ion channel gene; if no marker from the linkage panel was sufficiently close to a given ion channel gene, other microsatellites were chosen. In the case of the KCNQ2 gene on chromosome 20q13, we developed a new intragenic microsatellite marker (KCNQ2A) with higher informativity than pre-existing markers in that region

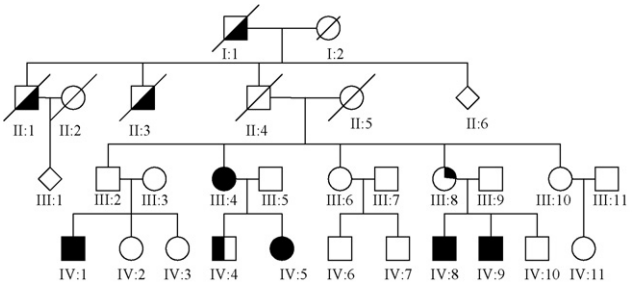

Figure 1 Pedigree of the family. (○) (●) women; (□) (■) men; (●) (■) full phenotype (epilepsy, EEG abnormalities and dysphasia); (◔) single tonic–clonic attack; (◧) EEG abnormalities and dysphasia; (◪) unclassified seizures.