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Family study of epilepsy in first degree relatives: data from the Italian Episcreen Study

A. BIANCHI[†], S. VIAGGI[‡], E. CHIOSSI[§] & The LICE Episcreen Group[1]

[†]*Epilepsy Centre at the Department of Neurology, San Donato Hospital, Arezzo, Italy;* [‡]*QUBIsoft, Padova, Italy;* [§]*Link Italia, Modena, Italy*

Correspondence to: Dr Amedeo Bianchi, Centro Epilessia—U.O. Neurologia, Ospedale San Donato, Via Pietro Nenni 20, 52100 Arezzo, Italy. *E-mail*: bianchi.epigenet@tin.it

Objective: To evaluate the family history of epilepsy in first degree relatives of probands with epilepsy.
Methods: A sample of 10 787 patients with epilepsy with complete information about first degree relatives (parents, siblings and offspring) was selected from the database of the Episcreen Project, the largest Italian observational study on epilepsy. Family history was assessed by: (1) prevalence estimates of epilepsy among proband's relatives, (2) modified cumulative risks (MCR), adjusted using proband's age as censoring time in life tables, (3) standardised morbidity ratios (SMR), using a sub-group of symptomatic epilepsies as control group.
Results: Patients (9.1%) had a family history of epilepsy. The overall prevalence of epilepsy among first degree relatives was 2.6%. Idiopathic generalised epilepsies had the highest prevalence (5.3%). Cryptogenetic epilepsies had a lower prevalence (2.1%) than idiopathic epilepsies, but higher then symptomatic epilepsies (1.5%), both in generalised and focal forms (3.8% vs. 2.0% and 1.8% vs. 1.3%). A similar tendency was detected using MCR and SMR, with the higher values of risks/ratios for idiopathic and generalised epilepsies. Probands with idiopathic generalised epilepsies were highly concordant with respect to their relatives' type of epilepsy. Considering other strata factors, risks were higher in proband's epilepsies with an onset less then 14 years of age, while sex played no definite role in differentiating the family history.
Conclusions: The Episcreen model permits a variety of stratification factors to measure family risk, including age at onset, epilepsy localisation and aetiology with a large sample of more than 10 000 probands and 1065/40 544 relatives affected and classified.

Key words: epilepsy; family history; standardised morbidity ratio.

INTRODUCTION

The importance of genetics in the aetiology of epilepsy is well established[1,2]. Twin studies have shown higher concordance rates of epilepsy in monozygotic than

[1] The Episcreen Group consisted of the following: *Pilot Centres*: A. Montagnini, S. Berloffa, S. Cogo (B. Dalla Bernardina-VR); A. Vignoli, A. Saltarelli, E. Zambrelli (R. Canger-MI); E. Cusani Visconti (S. Franceschetti, F. Panzica, G. Avanzini-MI); P. Beffa Negrini, F. Cardinale (C. Munari, L. Tassi-MI); M. Viri, C. Croce (A. Romeo-MI); F. Fittipaldi, C. Di Bonaventura, F. Muzzi, F. Izzi (A.T. Giallonardo, M. Manfredi-RM); C. Pachatz, R. Cilio (F. Vigevano, L. Fusco-RM); D. Del Priore, A. Piacenti, P. Pulitano (M.R. De Feo, G. Ricci-RM); I. Sartori, L. Politini, N. Zanotta (A. Tartara-PV); M. Tripodi, C. Gattuso (A. Magaudda, R. Di Perri-ME); P. Riguzzi, F. Muzzi (C.A. Tassinari, R. Michelucci-BO); A. Cerullo, F. Bisulli (P. Tinuper, E. Lugaresi-BO); R. Meo (S. Striano-NA); G. Caravaglios (O. Daniele, F. Piccoli-PA); G. Buzzi, F. Magnani (A. Bianchi, P. Zolo-AR); *Other Centres*: M.T. Panozzo-P. Garofalo (VI), M. Mastrangelo-G. Pastorino (MI), C. Zucca/L. Radice-G. Spreafico (LC), A. Laneve/M.R. Mazzeo-L.M. Specchio (BA), A. Vetro-G. Amodeo (AG), S. Calzolari-P. De Marco (TN), P. Piccinelli-U. Balottin (VA), V. Romano-M. Paciello (PZ), L. Girelli (PG), M. Germano-M.I. Jussi (FG), A.T. Lazzaro-A. Bellini (LT), P. Moretti-F. Minicucci/G. Comi (MI), B. Cavaliere-P. Scarpa (FE), M. Gessaroli-F. Rasi (FO), B. Tripaldelli-N. Gigante/S. Internò (TA), D. Cocuzza-L. Pavone (CT), F. Vanadia/F. Consolo-V. D'Agostino (PA), P. Rasmini-D. Besana (AL), C. Paci/M.P. Buongarzone-M. Onofri (PE), G. De Maria/S. Parola-L. Antonini (LC), M. Vecchi-C. Boniver (PD), F. Pezzella (PG), G. Colicchio/M.L. Vaccario-S. Mazza (RM), M. Brinciotti-P. Benedetti (RM), C. Acquafondata-D. Battaglia-F. Guzzetta (RM), A. Panzetta-O. Bacchi (PG).

dizygotic twins and family studies have disclosed a higher incidence of epilepsy in the proband's relatives as compared to the general population[3–6]. Genetic factors play a major aetiologic role in idiopathic epilepsy and a less important role in cryptogenetic and symptomatic epilepsy[7–9]. Within idiopathic epilepsy, some rare forms are characterised by Mendelian inheritance while the commonest forms show more complex patterns of inheritance and family aggregation. A genetic mutation has been identified for rare idiopathic epilepsies such as benign familial neonatal convulsions[10,11], nocturnal frontal lobe epilepsy[12] and generalised epilepsy with febrile seizures plus[13], whereas no mutation has been identified as yet for the more common generalised and partial epileptic syndromes, although some genetic loci have been considered as possible candidates for harbouring this mutation[14].

Not surprisingly, a smaller number of genetic and family studies are available for cryptogenetic and symptomatic epilepsy, in which genetics play, by definition, a minor role. It should nonetheless be pointed out that mutated genes along with their altered products have been identified for some rare symptomatic epilepsies such as myoclonic progressive epilepsy[15,16].

Family studies of epilepsy have hitherto been of three types: (1) studies aimed at quantifying the risk of epilepsy in the proband's offspring and siblings[17–22], (2) studies of family history and genetic risk in the relatives of probands with different epileptic syndromes[23–29] and (3) studies of phenotypic and syndromic variability in families with many epileptic subjects[30–32]. The family studies available in the literature are difficult to compare on methodological grounds because they employ different diagnostic criteria and differ in the evaluation of febrile convulsions, isolated convulsions and convulsions secondary to acute events. In many of these studies, family data are obtained by history taking, making it difficult to interpret events occurred during infancy. Another limitation of these studies is that they exclude possible epileptic cases when they occur at an age that is deemed incompatible with the suspected syndrome. Population studies may enrol a large number of subjects but they are less reliable and are often limited to single geographic areas. Besides, their inability to enrol a large number of subjects, family studies may introduce families with a spuriously high number of epileptic subjects thus inflating the estimated risk. We assessed the family history of epilepsy in a large sample of first degree relatives of epileptic probands followed by the Italian League Against Epilepsy (LICE). Owing to the large number of subjects enroled throughout all Italy, we were able to assess family history also in the least common forms of epilepsy.

METHODS

The Episcreen Project

The Episcreen Project[33,34] is a multicentre longitudinal observational study of epilepsy started in 1994 by the LICE. The Episcreen Project started in 15 Italian epilepsy clinics for protocol standardisation and after 2 years extended to 41 centres throughout Italy. LICE selected the study centres because of the nature of reference clinics for the diagnosis and treatment of epilepsy in Italy, taking care that their geographical distribution was as wide as possible. All consecutive patients with convulsive disorders seen at the study centres were enroled in the Episcreen Project.

Classification criteria

The International Classification of Seizures (ICES) and Epilepsies (ICE) were used for classification purposes[35]. Moreover, standardised criteria were developed for the collection and interpretation of clinical, EEG and neuroradiological data. The following definitions were adopted for the initial general classification of idiopathic, symptomatic and cryptogenetic syndromes.

- *Idiopathic*: normal clinical and neuroradiological picture with EEG features consistent with a genetic origin pattern.
- *Symptomatic*: evidence of a neurological and/or intellectual impairment, and/or neuroradiological evidence of an organic pathology of known or unknown origin.
- *Cryptogenetic*: normal clinical and neuroradiological picture, without EEG features consistent with a genetic origin pattern of idiopathic forms.

A complementary sub-classification of epileptic syndromes was developed with the aim of describing forms not taken into account by the ICE. A particular distinction between unclassifiable and unclassified epilepsies was made and used in the present paper. We defined 'unclassifiable' an epilepsy not classifiable despite the availability of a full clinical picture and 'unclassified' an epilepsy for which insufficient data was available to make a classification.

Data collection

A specific case report form was designed to collect information from every consecutive patient referring to the centres, for a new entry visit or a control visit in the Episcreen data bank. Each centre was also provided with a computerised system for the storage and

retrieval of observed data into the local database and for scheduled data set transmission to the main national data bank. A Scientific Board was appointed by LICE as a permanent expert committee. More than 250 descriptive variables were collected to acquire precise data on patient characteristics and clinical evolution. Variables included demographic and family history data, medical history, clinical and diagnostic examinations, therapeutic data and activities of daily living.

Study population and family history data

The sub-set of patients from the Episcreen Project analysed in this study was selected according to the following criteria: diagnosed with epilepsy, complete information about family composition and documented family history. Family history was ascertained from the medical interview of the proband. Information about family history were recalled and confirmed during follow-up visits. A specific interview was conducted in order to ascertain the presence of relatives affected by epilepsy, febrile convulsions or both. When an affected relative was recognised, every effort was made—according to the proband's consent—in order to achieve complete medical history, clinical and diagnostic documentation of his/her disease. If it was not possible to directly interview the proband's relative, or complete information about his/her epilepsy could not be determined, the relative was classified as of unknown aetiology. All analyses of family history of epilepsy were performed considering only first degree relationships (parents, siblings and offspring). According to this selection process, 10 787 patients with epilepsy were selected from the Episcreen database.

Measures of family history

Three measures were used to quantify the family history of epilepsy in proband's relatives: (1) prevalence

Table 1: Proband's characteristics and family history of epilepsy and febrile convulsions.

Characteristics		*N*	Percent	(a) Family history for epilepsy (%)	(b) Family history for febrile convulsions (%)	(c) Family history for epilepsy and febrile convulsions (%)
Sex	Female	5249	48.7	9.2	3.5	0.7
	Male	5538	51.3	7.8	3.1	0.5
Age at onset	0–4	3180	29.5	8.7	4.0	0.5
	4–13	4070	37.7	9.4	4.0	0.8
	14–19	1191	11.0	9.6	2.6	0.5
	20–64	2023	18.8	6.7	1.7	0.4
	≥65	323	3.0	3.1	0.3	
Age	0–10	2696	25.0	8.2	4.9	0.7
	10–20	2803	26.0	10.0	4.2	0.7
	20–30	1896	17.6	8.6	2.8	0.5
	30–40	1276	11.7	7.8	1.4	0.2
	40–50	697	6.5	10.0	2.6	0.4
	50–60	557	5.2	6.1	1.8	0.4
	≥60	862	8.0	5.7	0.6	0.6
Localisation	Focal	6365	59.0	6.2	2.8	0.5
	Generalised	3399	31.5	12.6	4.0	0.8
	Undetermined	321	3.0	9.7	3.7	0.6
	Unclassifiable	308	2.9	7.1	3.2	0.3
	Unclassified	394	3.7	11.7	5.1	0.8
Aetiology	Idiopathic	3138	29.1	13.4	5.2	1.1
	Symptomatic	4311	40.0	5.4	1.6	0.3
	Cryptogenetic	2796	25.9	7.4	3.4	0.5
	Unknown	542	5.0	10.5	5.5	0.7
Total		10787	100.0	8.5	3.3	0.6
Epileptic syndromes						
Idiopathic	Focal	941	8.7	9.4	5.0	1.0
	Generalised	2159	20.0	15.3	5.3	1.1
Symptomatic	Focal	3142	29.1	4.9	1.8	0.3
	Generalised	913	8.5	6.2	1.1	0.2
Cryptogenetic	Focal	2282	21.2	6.5	3.2	0.5
	Generalised	327	3.0	12.2	3.7	0.6

Total family history for epilepsy is given by (a) + (c).

of family history (PFH), (2) modified cumulative risk (MCR) and (3) standardised morbidity ratio (SMR).

PFH is the ratio between the number of relatives with epilepsy and the total number of first degree relatives. PFH was calculated for all relatives and for parents, siblings and offspring separately. MCR allows taking into account the problem of time exposure to the risk of epilepsy. Because information about the age at onset of epilepsy was not always available for proband's relatives, MCR was calculated using proband's age as a likely correlated variable. Risks were then calculated for age classes using a life-table approach.

SMR was calculated by standardising PFH on a control group and summarising the ratio between expected and observed relatives with epilepsy. Among study patients with symptomatic epilepsy, 1818 patients with traumatic, infective, inflammatory, expanding lesion or post-anoxic causes of epilepsy were considered as the control group for PFH calculation[8,9]. Stratification for age was made using the following classes: 0–10, 10–20, 20–30, 30–40, 40–50, 50–60 and >60 years. A further stratification was made for age at onset using the following classes: 0–4, 5–13, 14–19, 20–64 and >64 years.

All measures of family history were calculated for detailed sub-groups of age, sex, localisation and aetiology, and for the overall sample as well.

RESULTS

Ten thousand seven hundred eighty-seven patients were available for analysis; the total number of first degree relatives amounts to over 40 000 subjects (40 544). Table 1 gives the main characteristics of the study population and the frequency of epilepsy according to sex, age at onset, localisation and aetiology. Focal forms of epilepsy (59.0%) were more frequent than generalised forms and the most frequent aetiology was symptomatic (40.0%). An overall family history of epilepsy could be ascertained in 9.1% of probands; considering also febrile convulsions, the values goes up to 12.4%. A higher frequency of family history was seen in generalised than partial syndromes and, as expected, in idiopathic than symptomatic forms. These results do not take into account the proband's family composition and thus give only types limited picture of the family history of epilepsy.

PFH

A more detailed analysis is given in Table 2, reporting PFH values for the different proband's epileptic forms. Idiopathic (4.7%) and generalised (4.2%) epilepsies had the higher values of PFH while the lowest ones

Table 2: Prevalence of family history (PFH) among first degree relatives.

		Total number of first degree relatives (*N*)	First degree relatives with epilepsy (%)	Parents with epilepsy (%)	Siblings with epilepsy (%)	Offspring with epilepsy (%)
Sex	Female	20312	2.8	2.3	3.8	1.8
	Male	20232	2.4	2.0	3.2	1.9
Age at onset	0–4	9505	3.2	2.4	5.0	4.3
	5–13	13785	3.3	2.4	4.5	4.5
	14–19	4667	3.0	2.1	4.3	1.7
	20–64	10341	1.5	1.6	1.5	1.4
	≥65	2246	0.5	0.2	0.5	0.8
Localisation	Focal	24890	1.8	1.5	2.3	1.1
	Generalised	12059	4.2	3.1	6.0	4.2
	Undetermined	1217	2.9	2.5	3.4	2.8
	Unclassifiable	1023	2.4	1.8	3.8	1.6
	Unclassified	1355	3.9	3.4	5.0	2.2
Aetiology	Idiopathic	10685	4.7	3.3	6.7	6.3
	Symptomatic	16805	1.5	1.3	2.1	0.8
	Cryptogenetic	11214	2.1	1.9	2.5	1.6
	Unknown	1840	3.6	3.0	4.8	2.6
Total		40544	2.6	2.1	3.5	1.9
Epileptic syndromes						
Idiopathic	Focal		3.4	2.3	5.5	0.0
	Generalised		5.3	3.8	7.2	6.9
Symptomatic	Focal		1.3	1.2	1.6	0.8
	Generalised		2.0	1.5	3.4	0.3
Cryptogenetic	Focal		1.8	1.7	2.2	1.5
	Generalised		3.8	3.2	4.9	2.5

Table 3a: Epilepsy localisation in affected first degree relatives (% row).

Proband	Relatives with epilepsy (*N*)	Focal (%)	Generalised (%)	Undetermined (%)	Unknown (%)
Focal	431	33.6	26.0	10.4	29.9
Generalised	501	10.8	64.3	8.8	16.2
Undetermined	35	22.9	22.9	28.6	25.7
Unclassifiable	25	12.0	48.0	8.0	32.0
Unclassified	52	19.2	15.4	19.2	46.2
Total	1044	21.1	44.3	10.6	24.0

Table 3b: Epilepsy aetiology in affected first degree relatives (% row).

Proband	Relatives with epilepsy (*N*)	Idiopathic (%)	Symptomatic (%)	Cryptogenetic (%)	Unknown (%)
Idiopathic	493	61.7	5.5	5.7	27.2
Symptomatic	255	12.5	36.5	6.3	44.7
Cryptogenetic	230	22.2	11.3	12.2	54.3
Unknown	66	16.7	16.7	12.1	54.5
Total	1044	38.1	15.0	7.7	39.2

Table 3c: Summary of concordance.

Proband's localisation	Proband's aetiology		
	Idiopathic %[a] (% cell[b])	Symptomatic %[a] (% cell[b])	Cryptogenetic %[a] (% cell[b])
Focal	51.0 (38.8)	33.9 (18.2)	23.2 (8.3)
Generalised	65.4 (56.2)	54.6 (39.4)	69.1 (16.7)
Undetermined	0.0 (0.0)	23.1 (0.0)	35.0 (10.0)

[a] Concordance between epilepsy in probands and relatives in at least localisation. [b] Full concordance of epilepsy syndromes (both localisation and aetiology) between probands and relatives.

Table 4: Modified cumulative risks (MCRs).

		MCR in relatives	MCR in parents	MCR in siblings	MCR in offspring
Sex	Female	6.87	5.95	8.46	4.19
	Male	6.89	7.11	6.94	5.30
Age at onset	0–4	25.76	5.61	34.77	16.59
	5–13	27.06	15.11	35.27	36.24
	14–19	8.70	9.39	10.54	3.42
	20–64	5.05	7.66	4.56	3.11
	≥65	0.92	0.16	0.85	1.79
Localisation	Focal	4.80	5.02	5.16	3.28
	Generalised	11.89	9.67	14.01	9.03
	Undetermined	11.17	8.83	9.41	12.50
	Unclassifiable	6.35	5.12	7.90	3.03
	Unclassified	9.04	9.30	9.60	3.76
Aetiology	Idiopathic	34.31	17.48	40.57	24.65
	Symptomatic	3.46	3.21	4.19	1.92
	Cryptogenetic	7.44	7.59	7.17	6.92
	Unknown	9.60	9.18	9.88	6.65
Total		6.87	6.47	7.72	4.78
Epileptic syndromes					
Idiopathic	Focal	13.69	17.19	15.66	0.00
	Generalised	34.61	17.40	40.69	25.82
Symptomatic	Focal	3.34	3.21	3.83	2.21
	Generalised	3.79	3.14	5.65	0.60
Cryptogenetic	Focal	6.60	7.30	5.84	6.50
	Generalised	10.39	7.29	14.71	3.50

Table 5: Standardised morbidity ratios (SMRs).

		SMR in relatives	SMR in parents	SMR in siblings	SMR in offspring
Sex	Female	3.51	3.57	3.11	11.27
	Male	2.49	1.88	3.91	1.52
Age at onset	0–4	2.58	2.29	3.10	1.90
	5–13	2.56	2.03	3.07	4.51
	14–19	9.18	n.c.	5.53	n.c.
	20–64	2.18	1.98	3.17	1.46
	≥65	2.01	n.c.	0.53	n.c.
Localisation	Focal	1.96	1.69	2.37	1.51
	Generalised	4.74	6.65	3.80	4.15
	Undetermined	1.41	0.67	n.c.	n.c.
Aetiology	Idiopathic	3.36	2.77	3.59	7.77
	Symptomatic[a]	1.79	1.48	2.20	0.95
	Cryptogenetic	1.87	1.88	1.84	1.61
	Unknown	2.79	2.64	2.88	2.55
Total		2.92	2.44	3.51	2.76
Epileptic syndromes					
Idiopathic	Focal	2.03	1.65	2.35	n.c.
	Generalised	4.63	6.65	3.24	10.29
Symptomatic	Focal	1.46	1.29	1.69	0.97
	Generalised	2.67	3.29	2.87	n.c.
Cryptogenetic	Focal	1.62	1.56	1.66	1.45
	Generalised	3.73	5.29	2.60	2.67

n.c.: not computable.
[a] Not in control group.

characterised focal (1.8%) and symptomatic epilepsies (1.5%). A greater prevalence of epilepsy was observed in relatives of probands with an onset of epilepsy in the first 13 years of life; the prevalence of epilepsy then decreases for increasing values of age at onset. Considering the total number of relatives, PFH was slightly higher in female then male probands, but the reverse was seen for offspring. Table 3a and b gives a classification of epileptic types in proband's relatives: differently from the proband, generalised types were the most frequent (44.3%). Because of the lack of information, 39.2% of epilepsies of relatives were classified as of unknown aetiology. This makes it difficult to contrast the aetiology of relatives with that of probands. However, a comparison of the localisation in relatives versus probands is still possible. The comparison is given in Table 3c. Probands with idiopathic generalised epilepsy showed the highest concordance ratio, with 56.2% of relatives affected by the same form of epilepsy (both in localisation and aetiology).

MCR

MCR is an index of family history adjusted taking into account the age of probands. The rationale underlying its use is that the higher the age of relatives, the lower their probability of developing epilepsy. Because of the absence of information about the age at onset in relatives, we used the age of probands as a likely correlated variable. Consequently, MCR produces higher estimates than PFH, because it incorporates the time of exposure to the risk of epilepsy. MCR are given in Table 4, showing the highest estimates for relatives of probands with generalised idiopathic epilepsy (34.6%).

SMR

Table 5 gives SMR for the different proband's epileptic types. Generalised idiopathic epilepsy showed the highest value (4.6%) independently from the aetiology.

DISCUSSION

We performed a 'multi-way' analysis of family history in a very large sample of well-classified epileptic subjects, producing some relevant information based on a high number of relatives. The fact that the study centres were widely distributed throughout Italy, allowed us to recruit a sample of epileptic subjects which is comparable in distribution and clinical characteristics to samples obtained from population studies[36]. Our data confirm the higher frequency of a family history in idiopathic generalised epilepsy. In the present study, the risk of a positive family history was 4.6% higher in subjects with idiopathic generalised epilepsy than

controls and this was especially evident in parents whose risk was 6.6%. The reason why generalised epilepsy is associated with a high value of a family history may be due to the high frequency of idiopathic types (>63%) but this may not be the only reason. Generalised epilepsies had higher values of PFH and SMR than focal epilepsies and this was evident not only for idiopathic types but also for cryptogenetic and symptomatic ones, suggesting an independent contribution to epilepsy localisation.

This study offers some information about epileptic types that are not considered in detail by other studies. In cryptogenetic epilepsies, a prevalence of a family history was detected in 2.1% of relatives and the SMR was 1.87. Thus, according to our data, cryptogenetic epilepsies would stay halfway between idiopathic and symptomatic epilepsies, suggesting the possibility that epilepsies with high genetic influence may converge into this group together with purely secondary forms. It is also of interest that a high frequency of a family history was evident for the undetermined epileptic types with focal and generalised seizures. This may be partly explained by the presence in this group of severe myoclonic epilepsy whose familial component is well known. Another interesting result derives from the observation of a non-significant higher family history in female probands. SMR values (3.51% in females and 2.49% in males) suggest just this, but MCR values suggest that this difference may be influenced by the age of proband's relatives (in our study, estimated by means of proband's age). MCR also enabled us to show high values of a family risk in epilepsies with a younger age at onset whilst this was not so evident from prevalence rates alone. The high number of enroled patients allowed us to compare the epileptic types of probands with those of relatives. Probands with generalised epilepsy were more likely to have relatives while the same epileptic type. Further analyses could show other aspects of family history in epileptic types with low prevalence in population studies.

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