Epilepsy Research 154 (2019) 86–89

Contents lists available at ScienceDirect

Epilepsy Research

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

Epidemiology and familial clustering of pediatric epilepsy in the geographic isolate of Ischia

Vincenzo Buono[a,b], Giorgia Giussani[c], Elisa Bianchi[c], Vincenzo D'Ambrosio[d], Antonietta Coppola[d], Leonilda Bilo[e], Federico Zara[f], Pasquale Striano[a,b], Ettore Beghi[c,*]

[a] Pediatric Neurology and Muscular Diseases Unit, IRCCS "G. Gaslini" Institute, Genova, Italy
[b] Department of Neurosciences, Rehabilitation, Ophthalmology, Genetics, Maternal and Child Health, University of Genoa, Genova, Italy
[c] Istituto di Ricerche Farmacologiche Mario Negri IRCCS, Dip. Neuroscienze, Lab. Malattie Neurologiche, Milano, Italy
[d] ASL Napoli 2 Nord, Ischia, Napoli, Italy
[e] Department of Neuroscience, Reproductive and Odontostomatological Sciences, Federico II University, Napoli, Italy
[f] Laboratory of Neurogenetics, Department of Neurosciences, "G. Gaslini" Institute, Genova, Italy

ARTICLE INFO

Keywords:
Pediatric epilepsy
Prevalence
Incidence
Geographic isolate
Genetics

ABSTRACT

Background: Geographic isolates are the ideal setting to study the genetic background and the epidemiology of epilepsy. There are only few published reports on the epidemiology of pediatric epilepsy in geographic isolates.
Methods: This study was performed in the Ischia island, district of Napoli (Southern Italy). The local population includes 61,086 individuals, 8381 of them aged from 0 to 14 years. We included children with two or more unprovoked seizures or one unprovoked seizure associated to a high risk of relapse, observed from 2004 to 2017. Neonatal, febrile and acute symptomatic seizures were excluded. Eligible patients were identified through the local pediatricians' medical records. All probands and their parents underwent a face-to-face interview. Clinical charts were reviewed and electroclinical diagnoses were confirmed by two authors (AC, VB).
Results: Thirty-six children and adolescents were included. Overall, the prevalence of epilepsy in the Ischia island was 4.3 per 1,000 (95% CI 3.0–5.9). Incidence was 51.7 per 100,000 person-years (95% CI 36.2–71.6). Sixteen (44.4%) patients had a genetic (idiopathic) origin and 20 (55.6%) a symptomatic (structural/metabolic) etiology. Nine probands (25%) had at least one family member with epilepsy (including third-degree relatives). Their pedigrees were suggestive of dominant inheritance in six and of recessive inheritance in three families.
Conclusions: The epidemiological features of pediatric epilepsy in this geographic isolate are similar to the general population. A family history was reported in one fourth of the patients with a wide clinical heterogeneity, likely reflecting genetic heterogeneity in this population.

1. Introduction

Epilepsy is a chronic disease with a fairly complex etiology in which environmental and genetic factors act independently or in various combinations. A genetic component has been increasingly documented in the last decades, leading to the discovery, in addition to classic Mendelian disorders, of clinical entities with complex inheritance (Nolan and Fink (2018)). So far, genetic epilepsies account for up to 30% of all epilepsy syndromes (Orsini et al., 2018).

Children represent a population at high risk of epilepsy because the incidence of the disease peaks in this age group (Berg et al., 2003). Geographic isolates represent an ideal setting to calculate the frequency of a disease in the area of interest and, at the same time, to assess the role of genetic background because consanguineous marriages are favored. In this context, the collection of family trees is easier when probands are children because many of their relatives are still alive and able to recollect the history of diseases, including epilepsy, in the family.

There are only few studies on pediatric epilepsy in geographic isolates. In these areas, there is indication of a higher than expected frequency of the disease. In the Avalon region of Newfounland, Canada, the incidence of epilepsy in children was threefold greater than that reported in high-income countries (Mahoney et al., 2012). Family history of epilepsy (including second-degree relatives) was reported in 64% of local families. In Italy, the prevalence and characteristics of all epilepsies were assessed in the Eolian islands (Gallitto et al., 2005). In

* Corresponding author at: Laboratory of Neurological Disorders, Istituto di Ricerche Farmacologiche Mario Negri IRCCS, Via Giuseppe La Masa 19, 20156, Milan, Italy.
E-mail address: ettore.beghi@marionegri.it (E. Beghi).

https://doi.org/10.1016/j.eplepsyres.2019.05.004
Received 31 January 2019; Received in revised form 2 May 2019; Accepted 3 May 2019
Available online 04 May 2019
0920-1211/

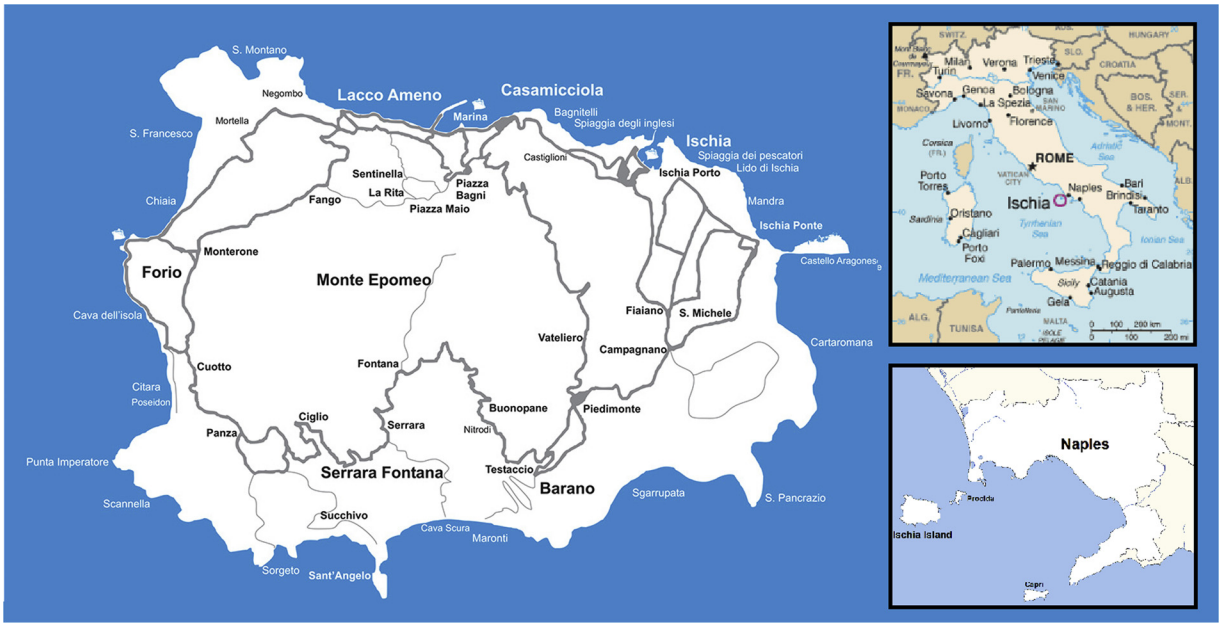

Fig. 1. Map of the Ischia island.

that study, the point prevalence of active epilepsy was 3.13 per 1000 in the entire population and 5.05 in children aged 5–14 years. Family history of epilepsy was present in 17% of cases (including second-degree relatives). However, in that study there was no detailed investigation of the patients' pedigrees. Therefore, we investigated the frequency and characteristics of pediatric epilepsy in a typical geographic isolate, with a twofold purpose: 1) to calculate the incidence and prevalence of the disease; 2) to investigate the genetic component through family history, concordance of epilepsy type and drawings of the family pedigrees.

2. Patients and methods

2.1. Study population

The island of Ischia is located in the northern part of the gulf of Naples, in Southern Italy (Fig. 1). The surface area is 46.3km^2. The total population is 61,086 (2011 ISTAT census; http://demo.istat.it/), including 8381 children and adolescents aged 0–14 years. The island includes six municipalities. The pediatric population is assisted by seven family pediatricians (FPs), who participated in the study identifying the eligible patients in their medical records between 2004 and 2017. Only children and adolescents aged from 0 to 14 years in 2017 were eligible for investigation.

2.2. Epilepsy definition and diagnosis

Epilepsy was diagnosed according to the definition recently issued by the International League Against Epilepsy (ILAE) that includes two or more unprovoked seizures 24+ hours apart, one unprovoked seizure associated to a high risk of relapse, or a well-defined electroclinical syndrome (Fisher et al., 2014). Patients with neonatal seizures at the time of the study were excluded as well as subjects with febrile seizures and acute symptomatic seizures (Beghi et al. (2010)). Epilepsy diagnosis was confirmed by two authors (VB, PS) through consultation of the FPs' records and, for children judged to have idiopathic epilepsy, through direct interview with the patient and the family. The response rate was 100%.

2.3. Data collection

From the FPs' medical records and direct interviews, the following data were obtained: date of probands' birth, gender, date of onset of seizures, seizure types, date of diagnosis, epilepsy syndrome, interictal EEG findings, brain imaging (CT, MRI) findings, comorbidities, psychomotor development, history of perinatal complications and other diseases with epileptogenic potential (i.e. traumatic brain injury, infections, metabolic disorders, immune disorders), current treatments. All probands and their parents were invited for an interview aimed to building a detailed pedigree (up to the third degree) and obtaining blood samples for future genetic studies. The diagnosis evidence of the family members who reported having epilepsy was supported by review of available clinical data, including seizure descriptions, EEG/neuroimaging examinations, and additional medical history.

An informed consent approved by the IRB of University of Genova was signed by participants.

2.4. Statistical analysis

Data collected were anonymized and uploaded in a password-protected web-database and used to tabulate the general characteristics of the sample and calculate prevalence and incidence of epilepsy and correlate each pedigree to the clinical, laboratory and instrumental findings of the proband. Life-time prevalence and cumulative incidence in the cohort of subjects born between 2003 and 2017, were calculated during the period 2004–2017, with 95% confidence intervals (CI) according to the binomial and Poisson distribution respectively. Crude ratios and rates were calculated on the entire sample and by sex.

3. Results

3.1. Epidemiology

A total of 36 children and adolescents (17 girls, 19 boys) were affected by epilepsy, sixteen with a presumed genetic etiology and 20 with symptomatic origin. Their main features are summarized in Table 1. Age at epilepsy onset ranged from 3 months to 13 years (median 1; interquartile range 0–6). The etiology was symptomatic in 20 and idiopathic in 16 patients. Eleven patients out of the seventeen (61.1%), whose we obtained information, showed mild to severe

Table 1
General features of the study cohort.

Feature(s)	Genetic/idiopathic etiology N (%)	Symptomatic/metabolic etiology N (%)
Gender		
F	7 (43.8)	10 (50)
M	9 (56.3)	10 (50)
Age at onset		
0-6months	–	7 (35)
7-12 months	3 (18.7)	6 (30)
1-4 years	8 (50)	2 (10)
5-9 years	5 (31.3)	4 (20)
10 + years	–	1 (5)
Family history of epilepsy		
Yes	10 (62.5)	1 (5)
No	1 (6.3)	5 (25)
NA	5 (31.3)	13 (65)
Epilepsy type		
Generalized	10 (62.5)	15 (75)
Focal	6 (37.5)	5 (25)
Number of AEDs		
No treatment	2 (12.5)	–
1	12 (75)	16 (80)
2 +	2 (12.5)	4 (20)
Drug treatment		
Valproate	11 (68.7)	15 (75)
Ethosuximide	2 (12.5)	–
Phenobarbital	–	2 (105)
Carbamazepine	–	2 (10)
Levetiracetam	2 (12.5)	4 (20)
Other drug(s)	1 (6.3)	2 (10)
N. indigenous grandparents		
4 of 4	2 (12.5)	2 (10)
3 of 4	3 (18.7)	1 (5)
2 of 4	4 (25)	–
1 of 4	–	1 (5)
0 of 4	–	1 (5)
ND	7 (43.8)	15 (75)

intellectual disability. Nine out of the 16 patients with idiopathic epilepsy and 6 out of the 20 patients with symptomatic epilepsy participated with their family members to the direct interview. None of the patients diagnosed with epilepsy died during the study. The prevalence was 4.3 per 1,000 (95% CI 3.0–5.9). Prevalence in girls and boys was, respectively, 4.2 (95% CI 2.5–6.8) and 4.4 (95% 2.6–6.8). The incidence, calculated during the 14-year period, was 51.7 per 100,000 person-years (95% CI 36.2–71.6). Incidence in girls and boys were, respectively, 50.2 (95% CI 29.2–80.3) and 53.2(95% CI 32.0–83.1) per 100,000 person-years. Given the small sample size, age-specific incidence and prevalence were not calculated.

3.2. Familial clustering

The pedigrees of probands interviewed with presumed genetic etiology are shown in Supplementary Figures 1-9. Nine patients (60% of the interviewed individuals) had at least one family member with epilepsy. The disease was present in a first-degree relative in 4/15 probands (26.6%). No consanguinity was reported from parents families of the probands whose pedigrees were built. Five of out 9 probands interviewed (55.6%) with at least one family member with epilepsy showed a clinical concordance, defined as the presence of the same epilepsy type (generalized or focal) among family members.

4. Discussion

This study investigated the frequency of epilepsy in a geographic isolate, including details on the genetic components in patients in whom a genetic basis could be identified. The prevalence of the disease was 4.3 per 1000 and the incidence was 51.7 per 100,000 person-years.

Unlike other reports from geographic isolates, our findings do not confirm a higher than expected incidence and prevalence of epilepsy. The prevalence of active epilepsy in children in our study was even lower than in the Eolian islands that included in the diagnosis only patients with two or more unprovoked seizures (Gallitto et al., 2005). The difference could be explained by the use, in our study, of only one source of cases, ie the FPs' records. However, the event that children with epilepsy were followed by doctors other than the local FPs is unlikely. Another possibility is that some patients escaped notice because they did not receive treatment. Some epilepsy syndromes, like idiopathic focal epilepsy with centrotemporal spikes, can be left untreated. However, the number of missing cases, if present, should be negligible.

Analysis of familial risk according to proband and relative phenotypes can be helpful to identify the clinical features with the greatest genetic influences, and clarify the shared versus distinct genetic influences on different clinical features or syndromes (Peljto et al., 2014). In our cohort, 60% of children whose family trees were investigated reported at least one member (including third-degree relatives) affected by epilepsy, 46.7% had an affected first or second degree relative. Our findings are in keeping with the Canadian report (Mahoney et al., 2012). The proportion of probands with first-degree relatives reported to have epilepsy was 26.6%. This proportion is even higher than in other reports (Lennox, 1951; Harvald, 1951; Tsuboi and Endo, 1977; Ottman et al., 1996; Bianchi et al., 2003; Hemminki et al., 2006) in which it ranged from 2.2%–9.1%. The differences can be explained in part by the source of the study cohorts (population-based, clinic-based), the age of the probands (children, all ages), the type of epilepsy (overall, idiopathic), and the type of family members (parents, siblings, offspring). Our findings confirm a higher than expected frequency of the disease among family members of patients from a geographic isolate.

Our study has some strengths and several limitations. The main strength is the population base. This is one of the few studies on the epidemiology and genetics of epilepsy in a well-defined population. Another strength of the study is the accuracy of the diagnosis and the genetic epidemiology approach. The first limitation is the small sample size, which makes our frequency estimates inaccurate. An additional limitation lies in the reliance to the FPs' records as the only source of cases. Epilepsy is still a stigmatizing disease and we cannot exclude that some children with epilepsy were assisted by other physicians outside the study area to conceal the disease. Moreover, the information obtained by family members who reported having epilepsy could be affected by recall bias and lack of details on seizure types and number (isolated unprovoked, febrile, and other acute symptomatic seizures) (Ottman et al., 2011). Then, we cannot say if the prevalence of relatives with epilepsy in our sample is higher than expected in the general population. At present, we do not have the resources to investigate the percentage of first/second degree relatives with epilepsy in a representative sample of people without epilepsy from the study area. Finally, the inclusion of patients treated with antiepileptic drugs could have led to the exclusion of children in remission who withdrew treatment. Nevertheless, our study aimed to focus on children with active epilepsy. Further work on this cohort, including results of genetic mapping and next-generation studies, will provide additional data on the genetics of epilepsy in this geographic isolate.

5. Conclusions

The epidemiological features of pediatric epilepsy in this geographic isolate are similar to the general population. A family history was documented in one fourth of patients with a wide clinical heterogeneity, reflecting genetic heterogeneity. A large genetic study is warranted in this population.

Disclosures

PS has served on a scientific advisory board or received honoraria from Zogenix, GW pharma, Kolfarma s.r.l., and Eisai pharma. EBe reports grants from UCB-Pharma, grants from Italian Ministry of Health, outside the submitted work. VB, AC, LB, VDA, EBi and GG do not declare conflicts of interest.

Study funding

No targeted funding reported.

Author contributions

VB:Drafting/revising the manuscript
FZ, AC, PS:Revising/approving the manuscript
AC, VB, LB, VDA: Clinical and neurological evaluation
EBe:Drafting/revising the manuscript
GG:Performing literature search and revising the manuscript
EBi:Performing statistical analyses

Acknowledgments

We thank Drs. Salvatore Romano, Giuseppe Trofa, Salvatore Colella, Giacinto Calise, Nicola Impagliazzo, Raffaele D'Ambra for their support to contact the families. We also thank Drs. Salvatore Buono, Bernardo De Martino, Rosa Ambrosino, Giuseppe Parisi, Pietro Buono and Raffaela Di Scala for their support.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.eplepsyres.2019.05.004.

References

Beghi, E., Carpio, A., Forsgren, L., Hesdorffer, D.C., Malmgren, K., Sander, J.W., Tomson, T., Hauser, W.A., 2010. Recommendation for a definition of acute symptomatic seizure. Epilepsia 51 (4), 671–675.
Berg, A.T., Jallon, P., Preux, P.M., 2003. The epidemiology of seizure disorders in infancy and childhood: definitions and classifications. Handb. Clin. Neurol. 111, 391–398.
Bianchi, A., Viaggi, S., Chiossi, E., LICE Episcreen Group, 2003. Family study of epilepsy in first degree relatives: data from the Italian Episcreen Study. Seizure 12 (4), 203–210.
Fisher, R.S., Acevedo, C., Arzimanoglou, A., Bogacz, A., Cross, J.H., Elger, C.E., Engel Jr, J., Forsgren, L., French, J.A., Glynn, M., Hesdorffer, D.C., Lee, B.I., Mathern, G.W., Moshé, S.L., Perucca, E., Scheffer, I.E., Tomson, T., Watanabe, M., Wiebe, S., 2014. ILAE official report: a practical clinical definition of epilepsy. Epilepsia 55 (4), 475–482.
Gallitto, G., Serra, S., La Spina, P., Postorino, P., Laganà, A., Tripodi, F., Gangemi, S., Calabrò, S., Savica, R., Di Perri, R., Beghi, E., Musolino, R., 2005. Prevalence and characteristics of epilepsy in the Aeolian islands. Epilepsia 46 (11), 1828–1835.
Harvald, B., 1951. On the genetic prognosis of epilepsy. Acta Psychiatr. Neurol. Scand. 26 (3-4), 339–352.
Hemminki, K., Li, X., Johansson, S.E., Sundquist, K., Sundquist, J., 2006. Familial risks for epilepsy among siblings based on hospitalizations in Sweden. Neuroepidemiology 27 (2), 67–73.
Lennox, W.G., 1951. The heredity of epilepsy as told by relatives and twins. J. Am. Med. Assoc. 146 (6), 529–536.
Mahoney, K., Buckley, D., Alam, M., Penney, S., Young, T.L., Parfrey, P., Moore, S.J., 2012. High incidence of pediatric idiopathic epilepsy is associated with familial and autosomal dominant disease in Eastern Newfoundland. Epilepsy Res. 98 (2-3), 140–147.
Nolan, D., Fink, J., 2018. Genetics of epilepsy. Handb. Clin. Neurol. 148, 467–491.
Orsini, A., Zara, F., Striano, P., 2018. Recent advances in epilepsy genetics. Neurosci. Lett. 667, 4–9.
Ottman, R., Annegers, J.F., Risch, N., Hauser, W.A., Susser, M., 1996. Relations of genetic and environmental factors in the etiology of epilepsy. Ann. Neurol. 39 (4), 442–449.
Ottman, R., Barker-Cummings, C., Leibson, C.L., Vasoli, V.M., Hauser, W.A., Buchhalter, J.R., 2011. Accuracy of family history information on epilepsy and other seizure disorders. Neurology 76 (4), 390–396.
Peljto, A.L., Barker-Cummings, C., Vasoli, V.M., Leibson, C.L., Hauser, W.A., Buchhalter, J.R., Ottman, R., 2014. Familial risk of epilepsy: a population-based study. Brain 137, 795–805 2014.
Tsuboi, T., Endo, S., 1977. Incidence of seizures and EEG abnormalities among offspring of epileptic patients. Hum. Genet. 36 (2), 173–189.