Epilepsy & Behavior 55 (2016) 30–37

Contents lists available at ScienceDirect

Epilepsy & Behavior

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

A population-based study of active and drug-resistant epilepsies in Northern Italy

Giorgia Giussani [a], Valentina Canelli [a], Elisa Bianchi [a], Carlotta Franchi [a], Alessandro Nobili [a], Giuseppe Erba [b], Ettore Beghi [a,*], the EPIRES Group [1]

[a] IRCCS-Istituto di Ricerche Farmacologiche "Mario Negri", Milan, Italy
[b] Department of Neurology, SEC, University of Rochester, Rochester, NY, USA

ARTICLE INFO

Article history:
Received 6 October 2015
Revised 19 November 2015
Accepted 21 November 2015
Available online 28 December 2015

Keywords:
Prevalence
Epilepsy
Drug resistance
Medical practitioners

ABSTRACT

Drug-resistant epilepsy (DRE) is defined by the International League Against Epilepsy as a failure of adequate trials of two tolerated, appropriately chosen, and used antiepileptic drugs to achieve sustained seizure freedom. Our aim was to calculate the following: (1) the prevalence of active epilepsy and DRE in a well-defined population of Northern Italy and (2) the proportion of incident cases developing DRE.

The study population (146,506; year 2008) resided in the province of Lecco, Northern Italy. The medical records of 123 general practitioners were reviewed to identify patients with epilepsy, diagnosed by a neurologist during the period 2000–2008. The point prevalence of active epilepsy and DRE was calculated on December 31, 2008. A total of 747 prevalent patients with epilepsy, 684 patients with active epilepsy, and 342 incident cases were identified. The frequency of DRE was 15.6% (107/684) of all active epilepsies and 10.5% (36/342) of incident cases. The point prevalence was 0.73 per 1000. The standardized prevalence of DRE was 0.7 per 1000 (Italian population) and 0.8 per 1000 (world population).

Our data indicate that 1/6 patients with active epilepsy in the general population has DRE, and 1/10 patients with newly diagnosed epilepsy will develop DRE within nine years from the diagnosis.

1. Introduction

Drug-resistant epilepsy (DRE) has been variously defined in published reports. Strict definitions have been used like the one proposed by Berg [1]: (1) uncontrolled seizures with an average frequency of 1+/month for 2+ years, (2) usage of at least 3 different antiepileptic drugs (AEDs) (singly or in combination), and (3) treatment failure measured by lack of control of seizures or discontinuation for adverse reactions. Loose definitions have also been used, like the one proposed by Arts et al. [2]: at 6 months after diagnosis, failure to be ≥3-month seizure-free. As a consequence, the prevalence of DRE has been reported to vary from 9 to 24% of cases [3].

In 2010, the International League Against Epilepsy (ILAE) issued a new definition of DRE, which was defined as the failure of adequate

* Corresponding author at: Laboratory of Neurological Disorders, Via Giuseppe La Masa 19, 20156 Milan, Italy. Tel.: +39 02 39014542; fax: +39 02 39001916.
E-mail address: ettore.beghi@marionegri.it (E. Beghi).

[1] EPIRES Group = neurologists and child neurologists: Elio Agostoni, Larissa Airoldi, Francesco Basso, Marialuisa Carpanelli, Mariolina Di Stefano, Andrea Magnoni, Ottaviano Martinelli, Andrea Rigamonti, Andrea Salmaggi, Lorenzo Stanzani, Cristina Volpe, Nicoletta Zanotta, and Claudio Zucca. General practitioners: Marco Agudio, Flavio Arienti, Graziano Rocco Arrigoni, Giancarlo Balestra, Piercarla Ballabio, Stefano Marco Balossi, Maria Rita Baratti, Fabrizia Enrica Barteselli, Fausto Bellani, Mauro Bellani, Gianpiero Bellini, Pier Aldo Beretta, Roberto Beretta, Massimo Bergamini, Annalisa Bertella, Francesco Bertolini, Rolando Bevilacqua, Marcellino Arturo Bianchi, Patrizia Bigiolli, Giuseppe Binda, Gigliola Biondelli, Libero Bodega, Edoardo Giovanni Bolis, Marco Vincenzo Carlo Bolla, Carlo Ambrogio Bonacina, Marco Bonfanti, Fausta Borghetti, Roberto Brambilla, Wilma Brancaleone, Francesco Brusadelli, Sabine Bub, Giovanna Caccia, Myriam Caglio, Carlo Calvi Rossi, Daniela Capra, Davide Carone, Giuseppe Carì, Silvio Carrera, Rosalia Cavenago, Maria Luisa Cecchetti, Bice Antonella Centonze, Fabio Cereghini, Ciro Cerrone, Maria Pia Ciappetta, Bruno Cogliati, Ombretta Colombano, Alberto Colombo, Daniela Colombo, Maria Lia Corti, Nicla Cremonini, Marco Crippa, Rolando Antonio Crippa, Mario Crotta, Salvatore Curto, Patrizia Daielli, Domenico De Gilio, Giuseppe Pasquale De Pascalis, Elena Decet, Luigi Della Morte, Felice Duvia, Antonia Favorito, Roberto Ferrario, Luigi Fezzi, Angela Laura Finzi, Bruno Ugo Fiorentino, Agnese Fornaciari, Silvana Franceschetti, Fabio Fulconis, Giovanni Fumagalli, Maurizio Fumagalli, Giuseppe Galbiati, Carlo Andrea Galimberti, Donatella Gecchele, Barbara Ghiazza, Paolo Ghislanzoni, Laura Gioffredi, Taraneh Hassibi, Simone Julita, Giuseppe Leone, Claudio Levi, Giovanni Locatelli, Anna Alessandra Locati, Enrico Giovanni Longhi, Ingrid Lukacova, Mauro Giovanni Manfroi, Paola Manzoni, Claudio Marcolini, Fabio Minicucci, Mohammed Safwan Martini, Rita Masperi, Sussele Mayan, Valeria Mazzoleni, Antonio Menga, Fiorella Merlini, Enrico Messina, Marta Micheli, Rocco Micò, Andrea Millul, Barbara Montini, Alberto Palazzuolo, Silvano Primo Panzeri, Giovanni Passoni, Laura Pensotti, Maria Marcella Petrone, Roberto Pezzuto, Elisabetta Pigazzini, Nicoletta Pirovano, Margherita Pontiggia, Roberto Pozzi, Carlo Quadrelli, Filomena Rampello, Marco Realini, Giovanni Righetti, Cesare Ripa, Sonia Rivetta, Antonino Romeo, Carlo Rota, Tiziana Rusconi, Andrea Santarpia, Ivana Santi, Luigi Sciani, Gianni Scoccimarro, Eugenio Scopinaro, Angelo Giuseppe Semerano, Daniela Sferco, Anna Ersilia Sirtori, Angela Spandri, Bruno Spinelli, Fausto Stefanoni, Raffaele Taiana, Libero Tamagnini, Laura Tassi, Giorgio Tentori, Augusto Teodoro, Katerina Tinterova, Ampelio Tocchetti, Michela Todeschini, Lorenzo Trezza, Valter Valsecchi, Roberto Vanini, Claudio Felice Vercelloni, Anna Villella, Maria Viola, Pietro Vismara, and Daniele Mario Zoboli. Research assistants: Mariagrazia Montesano and Silvia Romi.

http://dx.doi.org/10.1016/j.yebeh.2015.11.021
1525-5050/

trials of two tolerated and appropriately chosen AEDs (monotherapy or in combination) to achieve sustained seizure freedom [4]. To our knowledge, only two studies have used this definition to assess the prevalence of DRE in retrospective patient cohorts. Ramos-Lizana and co-workers [5] studied 508 children younger than 14 years seen in a Spanish hospital and followed them for more than two years. Eighty-seven (19%) patients met the criteria for DRE. Kong et al. [6] investigated 557 adults attending a neurology clinic of a tertiary referral hospital in Singapore. Patients with DRE accounted for 21.5% of the entire cohort. However, 5% of children and 37.5% of adults could not be classified for various reasons. No studies have as yet been done to assess the frequency of DRE in well-defined populations conforming to the ILAE definition.

The primary objectives of this study were as follows: (1) to calculate the prevalence of active epilepsy and DRE in a population sample from a well-defined geographic area, using as reference the ILAE definition and (2) to calculate the proportion of incident cases developing DRE.

2. Materials and methods

The study was a retrospective, cross-sectional, noninterventional investigation extending over a nine-year period (January 1, 2000–December 31, 2008). Patients with epilepsy residing in the province of Lecco, a well-defined geographic area of Northern Italy, were the study population. The local population is almost entirely of Caucasian origin (96%) and is fairly stable, with a migration rate of 3.3% for the year 2008 (emigration 1.2%; immigration 2.1%) according to the Italian Statistics Institute (ISTAT: http://demo.istat.it).

3. Health-care provision in the study area

In Italy, primary care is administered free of charge by general practitioners (GPs) to all residents. Each GP follows up to 1500 individuals. Essential medical information on each person is collected by the GP in electronic records that are made available to the new GP in the infrequent case that an individual with an established chronic condition joins his/her practice. Further details on the medical history (including treatments) are collected in electronic or paper records. Children and adolescents (i.e., persons less than 18 years of age) and adults are generally assigned to two distinct GP categories with different education and background according to the patient's needs. Except for age, the populations assigned to each GP are comparable in their demographic and socioeconomic characteristics. As for other chronic diseases, persons with epilepsy are entitled to receive free of charge all medical consultations, diagnostic tests, and treatments for the detection and management of the disease. The exemption certificate is always released by a neurologist who has personally interviewed and examined the patient, requested the appropriate diagnostic tests, and confirmed the diagnosis. Through the exemption certificate, the GP can have access to the diagnosis and all related diagnostic tests.

4. Sources of case ascertainment

A total of 263 GPs were active in the area during the study period. All were contacted, and 123 (47%) of them volunteered to participate in the study. The GPs were requested to identify the medical records of all patients with seizures followed in their practice. These patients could be traced through diagnostic codes, EEG records, antiepileptic drug prescriptions, and disease-specific exemption codes. In addition, to ensure an accurate data collection, all participating GPs received a de-identified list of patients under their care with presumed diagnosis of epilepsy based on information contained in the database of the claims of health-care services for the province of Lecco. This list was generated by applying a validated algorithm that included requests of EEGs and the prescriptions of drugs [7,8]. All medical records of patients with epilepsy available in the GPs' office were reviewed by two trained junior investigators (GG and VC) who interacted with the GPs to confirm the diagnosis and exclude individuals not fulfilling the study's inclusion criteria (see below). They also reviewed the records of patients assigned to the GPs but currently followed in other inpatient and outpatient facilities of the province (hospitals, nursing homes, and ambulatory clinics).

When necessary, the same investigators personally called the neurologists (including those outside the study area) following the enlisted patients to confirm the diagnosis or to complete the data needed to identify epilepsy syndrome and drug response.

5. Inclusion criteria and study definitions

Children, adolescents, and adults fulfilling the diagnosis of epilepsy (i.e., two or more unprovoked seizures 24+ h apart), followed by the participating GPs, and residing in the area for at least one year during the study period were included. Patients with acute symptomatic seizures, neonatal seizures, single unprovoked seizures, and paroxysmal events other than epilepsy were excluded. In all cases, the diagnosis had been established through a neurological consultation on the basis of clinical assessment, interictal EEG findings, and, in some cases, brain neuroimaging (CT and MRI).

In keeping with the ILAE guidelines for epidemiologic studies in epilepsy [9], having active epilepsy was defined as either being currently treated or having had at least one seizure in the previous five years. Drug-resistant epilepsy was defined as the failure of adequate trials of two tolerated, appropriately chosen and used antiepileptic drugs (AEDs), monotherapy or in combination, to achieve sustained seizure freedom [4]. In conformity with this definition, patients with DRE were identified as those in whom at least two AEDs had been discontinued for lack of efficacy or those in whom a third AED, either in combination or in substitution of the previous treatment, had been prescribed. Adequacy of treatment was verified by two of us (EBe and GE) by reviewing all data available for each patient (see below). Drug plasma levels were not used to verify the appropriateness of treatment schedules.

Seizures and epilepsy syndromes were classified using the ongoing ILAE recommendations [10,11]. The new classification of the epilepsies [12], not available during the study period, was not applied. As detailed information was not available in all cases, seizures and syndromes were classified using broad categories. Seizures were classified as focal, generalized, or unclassifiable. Syndromes were classified as partial (idiopathic, symptomatic, or cryptogenic), generalized (idiopathic or symptomatic/cryptogenic), undetermined, and special.

6. Data collection

For each eligible case, the information was collected retrospectively until December 31, 2008, out-migration or death, whichever came first. The following data were collected anonymously in a semistructured format: (1) main demographics; (2) seizure type(s), disease duration (from the first seizure to the diagnosis), epilepsy syndrome, duration of follow-up (from the diagnosis); and (3) number and type of drugs including drug daily doses and changes and timing of administration. The reasons for discontinuation of each drug were also collected; these included lack of efficacy, adverse events and poor tolerability, seizure freedom, or others (pregnancy, death, etc.). In rare instances, where the medical records were not sufficiently detailed on the duration of treatments, the history of treatments and health-care utilization was collected from the administrative records that include details on when each drug was started and discontinued. Using these sources, we traced all putative epilepsy cases, we collected relevant data on epilepsy, and we identified patients with active epilepsy and DRE.

7. Statistical analysis

The prevalence of active epilepsy was calculated on December 31, 2008. The population at risk was calculated as the total number of patients assigned to the participating GPs at the prevalence date. Incident