Clinical characteristics of patients with epilepsy attending primary health care

Carlos Arteaga-Rodríguez, Mariana Menine-Kubis, Carlos B. Teixeira-Arteaga, Otto J. Hernández-Fustes

Objective. This study aimed to fill the current knowledge gap in the literature by identifying the demographic and clinical characteristics of patients with epilepsy attending primary health care (PHC).

Patients and methods. This was a cross-sectional study involving adults (≥ 18 years of age) with epilepsy attending PHC from a developing country between 2015 and 2019. Demographic information and epilepsy-related data were collected.

Results. A total of 140 patients (51.4% male; mean [± SD] age 44.9 ± 17.8 years) were evaluated. The mean age at onset of seizures was 29.9 ± 22.9 years, with a mean evolution of 14.3±15.4 years. Focal seizures accounted for 88.57% of cases and evolved into bilateral tonic-clonic attack (45.16%). Of those that were generalized, motor seizures accounted for 81.82%, absence 9.09%, and motor + absence 9.09%. Among generalized onset motor seizures, tonic-clonic was predominant, accounting for 55.56%. Among types, focal epilepsy predominated (88.57%). The primary etiologies were unknown (62.14%), structural causes (27.85%) and infectious (9.28%). Patients undergoing monotherapy accounted for 66.1%, with epilepsy control in 92.4%. The most commonly used antiepileptic drugs were carbamazepine (33.1%), valproic acid (28.2%), and phenobarbital (10.4%).

Conclusions. Male sex, seizures, and focal epilepsy were prevalent. Magnetic resonance imaging was more useful than computed tomography. Most etiologies were unknown; however, mesial temporal sclerosis and neurocysticercosis were the most prevalent known causes. Most patients were controlled using a monotherapy regimen. The implementation of International League Against Epilepsy classifications and definitions was feasible and useful.

Key words. Antiepileptic drugs. Epilepsy. Mesial temporal lobe epilepsy. Neurocysticercosis. Primary health care. Seizures.

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Introduction

Epilepsy is characterized by recurrent seizures and is considered to be one of the most common neurological diseases, with significant social and economic impact, being the second most common neurological disorder in the world [1-3]. It is estimated that > 50 million individuals worldwide are affected, with 80% of the burden of epilepsy attributed to the developing world [4]. The prevalence of epilepsy ranges from 5 to 10 cases per 1,000 inhabitants, and its incidence peaks in the first and seventh decades of one's life. Furthermore, its cumulative annual incidence is estimated to be 67.77 per 100,000 persons [3,5-9].

There is a broad spectrum of demographic and clinical data regarding epilepsy; as such, it is interesting to investigate relevant parameters in different countries and the origin of epilepsy among patients. Epilepsy affects individuals of all ages and has social, behavioral, health, and economic consequences for patients, their families, and society. Studies from Brazil have reported a lifetime prevalence of epilepsy ranging from 11.9 to 21 per 1,000 inhabitants. The first study was a door-to-door epidemiological survey of epilepsy, treatment gaps, and the socioeconomic influence of epilepsy in the Brazilian population. The prevalence of epilepsy in Brazil is similar to that in other countries, although with fewer resources [10].

A greater number of epilepsy investigations have been performed in tertiary care centers versus primary health care; as such, little is known about the clinical characteristics of patients with epilepsy treated in these centers. The purpose of this study, therefore, was to fill this knowledge gap by supporting its importance and contributing to an appeal made in *The Lancet* [11] to 'make epilepsy a global health priority'. The objectives of this study were to identify the demographic and clinical characteristics of patients with epilepsy attending primary health care.

Patients and methods

A retrospective, descriptive, cross-sectional study of adults (≥ 18 years of age) with epilepsy from primary health care who attended the outpatient clinic of the Municipal Secretary of Health of Curitiba Municipality, Paraná, Brazil, between 2015 and 2019, was conducted. For a theoretical basis, a literature search of the PubMed and SciELO databases was performed using the key words: 'epilepsy', 'clinical characteristics', and 'primary health care'.

Medical records included demographic data, age at epileptic seizure onset, epilepsy evolution time, type of seizure(s) and epilepsy, results of cranial computed tomography, magnetic resonance imaging, and electroencephalogram was performed in sleep/wake, and activation with hyperventilation and photostimulation, etiology, type of antiepileptic drugs (AEDs), use of monotherapy or polytherapy, and degree of control. Data recorded in the clinical history and diagnoses were reviewed and confirmed by the primary author.

The type of seizure(s), epilepsy, and etiology were defined according to criteria from the International League Against Epilepsy (ILAE) classification [12,13]. Epileptic seizure was defined and diagnosed as a transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain [14]. Epilepsy was defined and diagnosed based on criteria from the ILAE: 'At least two unprovoked (or reflex) seizures occurring >24 h apart; one unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next 10 years' [14]. Drug-resistant epilepsy was defined as the occurrence of epileptic seizures despite the use of at least two, correctly chosen AEDs (whether as monotherapy or in combination) and used in an appropriate period [15].

Data was transcribed to an electronic form in a flat file format according to the following variables: categorical (sex, type of seizure/s and epilepsy, complementary examinations, etiology, and AEDs); and continuous (age, age at onset, and duration of epilepsy). Data analysis was performed using R software version 3.6.3 (R Core Team, 2019). Descriptive evaluation was performed by verifying the quantities and percentages of categorical variables and descriptive measures (minimum, maximum, quartiles, mean, and standard deviation) of continuous variables. The χ^2 test and Fisher's exact test were used to compare demographic data, clinical features of seizures, type of epilepsy, results of complementary tests, etiology, and AEDs. Differences with $p < 0.05$ were considered to be statistically significant.

The present research was approved by the Brazil Platform and Ethics Committee (Certificate of Presentation for Ethical Appreciation - CAAE no. 09049719.1.0000.8040).

Results

A total of 140 adults with epilepsy (72 males; 51.4%) were studied. The mean (± standard deviation) age of the study cohort was 44.9 ± 17.8 years (range, 15 to 82 years); 10.7% were between 15 and 20, and 89.3% were > 20 years of age. The mean age of the females was 44.8 ± 20.9 years and 45.2 ± 16.1 years for males. The age at onset of epileptic seizures was distributed as follows: <10 years of age, *n* = 30 (21.4%); 11 to 20 years, *n* = 36 (25.7%); and >20 years, *n* = 74 (52.9%). The mean age at onset of epileptic seizures was 30.8 ± 25.3 years for females and 29.6 ± 21.9 years for males. The mean age at onset of epileptic seizures in both sexes was 29.9 ± 22.9 years, with a minimum onset before 1 year and a maximum of 82 years of age. Epilepsy evolution according to the number of patients was as follows: 0-10 years, *n* = 80 (57.1%); 11-20 years, *n* = 22 (15.7%); and >20 years, *n* = 38 (27.1%). The mean evolution was 14.3 ± 15.4 years. Among females, the mean evolution was 12.8 ±16.2 years and 15.2 ± 15 years among males. The types of epileptic seizures and epilepsies are summarized in table I.

Cranial computed tomography was performed in 73 (52.1%) patients, revealing abnormalities in 48.6%, distributed as follows: 31.4% exhibited calcifications of the central nervous system; 8.6% exhibited post-traumatic encephalomalacia; and 8.6% exhibited cerebral infarction. Cranial magnetic resonance imaging was performed in 86 (61.4%) patients, revealing abnormalities in 67 (77.9%), distributed as follows: mesial temporal sclerosis, *n* = 28 (47.8%); hippocampal asymmetry, *n* = 12 (18%); generalized cerebral atrophy, *n* = 11 (16.4%); cerebral infarction, *n* = 6 (9%); brain tumor, *n* = 5 (7.5%); calcifications of the central nervous system, *n* = 2 (3%); and post-traumatic encephalomalacia, intracranial vascular malformations, and encephalitis sequelae, *n* = 1 (1.5%). Etiologies are summarized in table II.

A total of 118 patients were using AEDs, of whom 78 received monotherapy (66.1%). Therapeutic control was achieved in 92.4% of patients. AEDs included carbamazepine (33.1%), valproic

acid (28.2%), phenobarbital (10.4%), lamotrigine (6.1%), clobazam (6.1%), gabapentin (3.7%), topiramate (5.5%), phenytoin (4.9%), and oxcarbazepine (1.2%).

Discussion

The mean age of the entire cohort was 44.9 ± 17.8 years, and was similar for both sexes: 44.8 ± 20.9 years for females and 45.2 ± 16.1 years for males. This data is consistent with other studies that reported an age range of 41 to 44 years [16,17]. We found a predominance of males (51.4%); however, as in most studies, this difference can be attributed to the greater exposure of males to head trauma and the fact that females tend to conceal their diagnosis of epilepsy [8,18-20].

The age at onset of seizures is variable, even for patients with the same epileptic syndrome [21]. In our patients, the mean age at onset of seizures for both sexes was 29.9 ± 22.9 years, the majority of which (52.9%) were >20 years of age. We did not find significant differences between the age at onset of crises and sex: among females, they started at 30.8 ± 25.3 years and 29.6 ± 21.9 years in males. The mean duration of epilepsy was 14.3 ± 15.4 years, with slightly longer durations among males (15.4 years) than in females (12.8 years). Fernández-Suárez et al [3] reported an age of onset of seizures of 31.6 years (range, 27.81-35.38 years) and a mean duration of 16 years (range, 13.76-18.5 years), both of these results were similar to ours.

Regarding the types of seizures (Table I), we found a predominance of focal onset epileptic seizures (88.57%), of which 19.36% were disperceptive and 45.16% presented evolution to bilateral tonic-clonic seizures. Among crises with a generalized onset (7.86%), motor crises were predominant.

In a review, Banerjee et al [22] reported focal onset seizures between 20% and 66%, drawing attention to the fact that generalized onset seizures are more frequent in developing countries, particularly in Africa. According to these authors, such differences could be explained by a lower degree of diagnostic sophistication and ambiguities in the use of the classification [22]. In support, we verified the diversity of interpretation and use of the classifications of seizures/epilepsies proposed by the ILAE [12,13].

Garcia-Martin et al [23] reported a predominance of epileptic seizures with focal onset (75.5%) versus generalized seizures (17.5%). In a study involving adults (mean age, 31.5 years) with epilepsy,

Table I. Frequency distribution according to the type of epileptic seizure and epilepsy syndrome.

Seizure types	Number of cases (%)
Focal onset	124 (88.57)
Focal onset + generalized onset	5 (3.57)
Generalized onset	11 (7.86)
Total	140 (100)
Focal onset	**Number of cases (%)**
Impaired awareness	24 (19.36)
Impaired awareness to bilateral tonic-clonic	17 (13.71)
Aware	13 (10.48)
Aware + impaired awareness	4 (3.23)
Aware to bilateral tonic-clonic	10 (8.06)
Focal to bilateral tonic-clonic	56 (45.16)
Total	124 (100)
Generalized onset	**Number of cases (%)**
Motor	9 (81.82)
No motor (absence)	1 (9.09)
Motor + no motor (absence)	1 (9.09)
Total	11 (100)
Generalized onset – motor	**Number of cases (%)**
Mioclonic	1 (11.11)
Mioclonic+ tonic-clonic	3 (33.33)
Tonic-clonic	5 (55.56)
Total	9 (100)
Epilepsy types	**Number of cases (%)**
Unknown	5 (3.57)
Focal	124 (88.57)
Generalized	11 (7.86)
Total	140 (100)

Table II. Etiology of epilepsy

	Number of cases (%)
Unknown	87 (62.14)
Structural	39 (27.85)
Mesial temporal sclerosis	17 (12.14)
Cerebral infarction	11 (7.85)
Cerebral tumor	4 (2.86)
Post-traumatic encephalomalacia	4 (2.86)
Cerebral vascular malformations	3 (2.14)
Metabolic	1 (0.71)
Infectious	13 (9.28)
Encephalitis sequels	2 (1.43)
Neurocysticercosis sequels	11 (7.85)
Genetic	0 (0)
Total	140 (100)

Rezaeian et al [24] reported a predominance of generalized crises (78%) versus focal crises (22%). Among the generalized crises, tonic-clonic seizures were prevalent, similar to our data. In an investigation of a primary health care population, Fernández-Suárez et al [3] reported a slightly higher proportion of focal onset seizures (58.2%).

Our study found a high proportion of focal epilepsies (88.57%), followed by generalized epilepsy (7.86%), and unknown epilepsy (3.57%). However, other studies have reported contrasting results. Fernández-Suárez et al [3] reported a considerable number of unknown epilepsy cases (31.1%), followed by focal epilepsy (50%) and generalized epilepsy (18.9%). Torres-Ferrús et al [25] reported a predominance of focal epilepsies (73%), followed by generalized (19.5%) and indeterminate (5%) epilepsies. We believe that these different results depend on the origin of the sample and whether the patients are followed-up by the investigator or investigators.

The recording of epileptiform activity is important for the diagnosis, classification, and choice of optimal treatment [26]. Electroencephalogram results in our study revealed epileptiform activity in 47.9% of cases, a result similar to that reported in other investigations [24].

All the patients underwent at least one brain imaging examination. Positive results between computed tomography and magnetic resonance imaging of the skull were 48.6% and 77.9%, respectively. This result, however, is consistent with the literature, in which the superiority of magnetic resonance imaging has been confirmed and is recommended as the imaging modality of choice in epilepsy [27,28].

The most frequent findings on skull computed tomography were calcifications of the central nervous system (31.4%), post-traumatic encephalomalacia (8.6%), and cerebral infarction (8.6%). In a series of adult patients with epilepsy, Guberman [29] detected abnormalities in 16% using computed tomography, which was lower than in our series (48.6%). Such differences may be explained by technological advances in computed tomography and the high number of patients with calcifications in our study.

Magnetic resonance imaging reveals signs of epileptogenic lesions in approximately 20% of patients with newly diagnosed epilepsy and more than one-half of those with drug-resistant focal epilepsy.[9] In our cohort, the most frequent findings on magnetic resonance imaging included: mesial temporal sclerosis (MTS), 47.8%; hippocampal asymmetry, 18%; brain atrophy, 16.4%; cerebral infarction, 9%; and brain tumor, 7.5%. These results were similar to those reported in other studies [25,30-34].

Regarding secondary causes, a variation between 34% and 51% has been reported across different studies [3,23,30-32], with a predominance of cerebral infarction, post-traumatic, and MTS [3,23,30]. Kim et al [20] found secondary causes in 65% of their patients, the most common of which were trauma (10%), cerebrovascular accidents (9.6%), central nervous system infections (5.7), and MTS (4.9%). Using the same etiological terminology used in our research, a study from northern Spain by Quintana et al [34] reported causes as follows: 40.9% unknown, 45.5% structural, 6.6% metabolic, 6.6% infectious, and 0.9% autoimmune. The authors reported the following specific causes of epilepsy and the proportion affected: vascular, 43.1%; tumor, 21.5%; post-traumatic, 12.3%; cavernoma/arteriovenous malformation, 10.8%; malformation of cortical development, 4.6%; and MTS, 1.5%.

In our patients unknown causes predominated (62.14%), similar to other investigations [22]. We found that 27.85% of structural causes were distributed as MTS (12.14%), cerebral infarction (7.85%),

brain tumor (2.8%), and post-traumatic (2.8%). Infectious causes accounted for 9.28% in our study, with the majority due to neurocysticercosis (Table I).

Among 118 patients (84.29%) who used AEDs, therapeutic control was achieved in 92.4%, the majority of whom received monotherapy (66.1%). The most commonly used drugs were carbamazepine, valproic acid, phenobarbital, and lamotrigine. In Spain, several authors have reported control of epileptic seizures in approximately 72-77.3% of patients [3,16,30]. More recent studies have reported similar figures for difficult-to-control epilepsy, between 20% and 30% [35]. The use of new AEDs did not modify the degree of control of epileptic seizures [36,37]; as such, we believe that different data among studies do not hinder comparison of the degree of therapeutic control.

We believe that the high percentage of therapeutic control in our series (92.4%) was due to the fact that the patients attended primary health care. This high rate explains why most of our patients were undergoing monotherapy (66.1%). Monotherapy varies between 48.6% and 60% [3,23,25,30], which is lower than our results. The AEDs used in our study were similar to those used in other studies [3,23,25].

Conclusion

In the present study, a greater number of males had epilepsy, without significant differences between sex and age at seizure onset. Focal seizures were the predominant seizure type. Magnetic resonance imaging was more useful than computed tomography for detecting brain lesions. The group with unknown etiology predominated. MTS and neurocysticercosis were the most frequent known causes of epilepsy. Most cases were controlled using a monotherapy regimen. Carbamazepine, valproic acid, and phenobarbital were the most widely used AEDs. The implementation of ILAE classifications and definitions was feasible and useful.

We recommend that investigators use the new definitions and classifications for seizures/epilepsy proposed by the ILAE and, moreover, seek a common language that will make it possible to objectively compare results across studies.

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Características clínicas de pacientes con epilepsia atendidos en la atención primaria

Objetivo. Este estudio tuvo como objetivo llenar el vacío de conocimiento actual en la bibliografía mediante la identificación de las características demográficas y clínicas de los pacientes con epilepsia que asisten a la atención primaria de salud.

Pacientes y métodos. Éste fue un estudio transversal que involucró a adultos (18 años o mayores) con epilepsia que asistieron a atención primaria de salud de un país en desarrollo entre 2015 y 2019. Se recopilaron información demográfica y datos relacionados con la epilepsia.

Resultados. Se evaluó a un total de 140 pacientes –51,4%, varones; edad media (± desviación estándar), 44,9 ± 17,8 años–. La edad media de inicio de las crisis fue de 29,9 ± 22,9 años, con una evolución media de 14,3 ± 15,4 años. Las crisis focales supusieron el 88,57% de los casos y evolucionaron a crisis tonicoclónicas bilaterales (45,16%). De las generalizadas, las crisis motoras supusieron el 81,82%; las ausencias, el 9,09%; y las motoras + ausencias, el 9,09%. Entre las crisis motoras de inicio generalizado, predominó la tonicoclónica, con un 55,56%. Entre los tipos, predominó la epilepsia focal (88,57%). Las etiologías primarias fueron desconocidas (62,14%), causas estructurales (27,85%) e infecciosas (9,28%). Los pacientes en monoterapia representaron el 66,1%, con control de la epilepsia en el 92,4%. Los fármacos antiepilépticos más utilizados fueron la carbamacepina (33,1%), el ácido valproico (28,2%) y el fenobarbital (10,4%).

Conclusiones. Predominaron el sexo masculino, las convulsiones y la epilepsia focal. La resonancia magnética fue más útil que la tomografía computarizada. La mayoría de las etiologías se desconocían; sin embargo, la esclerosis temporal mesial y la neurocisticercosis fueron las causas conocidas más prevalentes. La mayoría de los pacientes se controlaron con un régimen de monoterapia. La implementación de las clasificaciones y definiciones de la Liga Internacional contra la Epilepsia fue factible y útil.

Palabras clave. Convulsiones. Epilepsia. Epilepsia del lóbulo temporal mesial. Fármacos antiepilépticos. Neurocisticercosis. Primeros auxilios.