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New-onset Geriatric Epilepsy in a Latin American Country: A Multi-centric Study from Mexico

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ABSTRACT

Background: In Latin America, epilepsy in the elderly is a neglected issue that has never been studied. The epidemiological transition has significantly altered the demographics of epilepsy, and therefore, we would like to draw attention to this topic. **Objective:** We require local real-world evidence, as the literature often depicts a different scenario, including pharmacological management. **Methods:** From 2007 to 2018, we recruited all patients with new-onset geriatric epilepsy (first seizure after the age of 60) tracked from ten Mexican hospitals, adding them to patients with similar characteristics from a previously published study. The diagnosis was confirmed in all patients by a certified neurologist, and they were also studied using a conventional electroencephalogram and imaging workup. **Results:** A diagnosis of new-onset geriatric epilepsy (Elderly patients was established in 100 cases. No specific cause was found in 26% of patients, while 42% had a stroke and 10% had neurocysticercosis (NCC). Monotherapy was the choice in 83 patients, and phenytoin was the most used drug (50%), followed by carbamazepine (25%). **Conclusion:** NCC remains a frequent cause of new-onset geriatric epilepsy. This distribution is not seen in the literature, mainly representing patients from wealthy economies. In our setting, financial constraints influence the choice of the drug, and newer antiepileptic drugs should be made more affordable to this population with economic and physical frailty. (REV INVEST CLIN. 2023;75(4):203-11)

Keywords: Elderly patients. Late-onset epilepsy. Mexico. Neurocysticercosis. Structural epilepsy.

INTRODUCTION

The most frequent neurologic disorders in the elderly are stroke, dementia, and epilepsy[1,2]. Data on epilepsy prevalence in Latin America even in the latest publications are supported in studies dating several decades back and data on geriatric epilepsy are not mentioned at all[3]. Moreover, the Report on Epilepsy in Latin America and the Caribbean from the Pan American Health Organization does not display any statistics on the epilepsy in the elderly, and even less on new-onset geriatric epilepsy[4].

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As we have mentioned before[5], experiences from Latin America must be published as the social and economic characteristics of our population are different from those available in the literature. In Mexico, like in other countries in the region, the proportion of people aged 60 and older has jumped from 6.1% in 1990 to 11% in 2020 and is expected to be 14% by 2030[6]. As Chen has mentioned, characteristics of epilepsy in older people are different from other age groups and diagnosis may be difficult[7].

The objective of our study is to provide real-world evidence, as the clinical features and the pharmacological management of this particular group of patients greatly differ from what has been published in other settings. We should emphasize that no other series of new-onset geriatric epilepsy is available for Latin America and that our study might create awareness, as epidemiological studies simply do not exist in our region.

METHODS

New-onset geriatric epilepsy is defined as epilepsy that first occurs after 60 years of age.

Patient recruitment

From the first study published in 2009[8] (patients over 20 years old with late-onset epilepsy), we recruited those aged over 60 and having their first seizure after that age; additionally, from January 2007 to December 2018, we prospectively enrolled only patients with new-onset geriatric epilepsy at outpatient epilepsy departments in nine public and one private centers across the country. Six centers were located outside Mexico City and provided half of our patient population. Written consent was required from all patients before enrolment.

Inclusion criteria: patients with an established diagnosis of epilepsy and a first seizure after the age of 60. As a descriptive study, there is no control group, and no pre-determined hypothesis was defined.

Epilepsy is defined as at least two unprovoked (or reflex) seizures occurring > 24 h apart[9], and therefore, patients with an acute isolated symptomatic seizure are excluded (they are not epileptic)[2]. An acute symptomatic seizure is defined as a clinical seizure occurring at the time of or in close temporal association with a documented brain insult (inflammation, metabolic, toxic, structural, or infectious)[10]. Remote symptomatic seizures were not included, because the concept dates back to 2014 and the precise characteristics allowing us to classify some of our patients into that category is not retrievable from our database. An individual case record form was used to collect demographic data, center, neurological status, etiology, and antiepileptic drugs (AEDs).

Diagnosis

Epilepsy was diagnosed by a board-certified neurologist based on clinical information. This included a clinical history, basal neurological examination, and physical findings[9]. In all patients, ancillary studies such as scalp-recorded electroencephalogram (EEG), and neuroimaging workup (magnetic resonance imaging/computed tomography [CT]) would complete the etiological inquiry. Data were prospectively recorded in a database (demographical and clinical characteristics, results of diagnostic examinatons, and antiepileptic treatment). Seizures were classified according to the criteria of the ILAE[11].

Electroencephalogram

All the patients had a conventional EEG (international 10-20 system, digital), interpreted by a certified neurophysiologist.

– Normal EEG: Recordings within the normal range according to the patient's age, without epileptiform discharges or focal/diffuse slowing

– Abnormal EEG: Interictal epileptiform discharges or ictal patterns classified as focal or generalized. The focal abnormal slowing was also classified as a focal abnormality, and diffuse slowing as a generalized abnormality.

Neuroimaging

All studies were interpreted by a board-certified radiologist blinded to diagnosis. If the lesion visible on imaging could be correlated with the seizure, we considered it as causal, and the disorder was categorized as structural epilepsy[11].

The lesions were classified into four different aetiologies (Neurocysticercosis [NCC], stroke, tumor, and atrophy):

– NCC

  a. Active NCC: Single or multiple cystic lesions with or without contrast enhancement, and/or perilesional edema. Treatment consisted of albendazole 30 mg/kg/d for at least 15 days, plus steroids if needed. In a second imaging 3 months later, fewer lesions or even the absence of residual lesions, or a heterogeneous aspect of intralesional fluid on CT (vesicular phase) was considered a good response, and the diagnosis was positive. Patients with no changes after treatment were not considered as due to NCC

  b. Inactive NCC: One or more parenchymal calcifications with a diameter > 0.5 cm, without perilesional edema[12], and no previous history suggestive of tuberculosis, cytomegalovirus, or vascular malformations[13,14].

– Cerebrovascular disorder: Any lesion on imaging compatible with stroke (territory, shape, and mode of onset)

– Neoplasm: A mass compatible with an expanding intraparenchymal or dural process

– Atrophy: Brain parenchymal volume loss unexpected for the patient's age.

Antiepileptic medication

Antiepileptic medication (AED) was recorded (monotherapy, two or more drugs), with respective dosage. Drugs were considered as first (e.g., phenytoin and carbamazepine) or second generation (e.g., levetiracetam, lamotrigine) and should have been given for at least 3 months.

Statistics

We performed an exploratory study, and no inferential statistics were calculated. For the different variables (age, sex, seizure type, and drugs used), we recorded descriptive statistics (percentages, measurements of central tendency, and so on).

RESULTS

Patients

During the study period, we recruited 525 adult patients (aged over 20) with LOE, of which 19 % (100 elderly patients) had new-onset geriatric epilepsy. The average age of the geriatric patients was 69.2 years (SD ± 7.4), with a slight male predominance (53%). All patients with new-onset geriatric epilepsy experienced their first seizure after the age of 60; those who had a first seizure before that age were not included in the study.

The age distribution is summarized in table 1, showing a constant decrease, with 26% of the patients being over 75 years old, and approximately half of them being under 70 years old.

Clinical symptoms

In our sample, each seizure was identified as a focal onset seizure. The breakdown included 18 focal motor onset seizures, three focal sensory onset seizures, and ten focal onset impaired awareness seizures (formerly known as complex partial seizures). It is important to note that many seizures commonly classified as "generalized tonic-clonic" by most authors are focal to bilateral tonic-clonic seizures (focal-onset seizures with secondary generalization, comprising 69% of cases). The distribution of seizure types is shown in table 1.

Neurological examination

The neurological examination was unremarkable in 63 patients, while the remaining 37 patients exhibited at least one focal neurological sign.

Electroencephalography

Initial EEG showed generalized abnormalities (e.g., diffuse slowing) in 41% of the cases and focal paroxysmal abnormalities in 31%. It was rated as normal in 28% of the cases.

When analyzing EEG results in relation to the cause of epilepsy, we found that all NCC patients had abnormal recordings, probably because any active form of NCC causes an important inflammatory response

Table 1. Demographic characteristics along with etiology, type of seizures and medication

Clinical characteristics	Age of patient (years)						All groups Total 100
	60-64 (n = 30)	65-69 (n = 28)	70-74 (n = 16)	75-79 (n = 15)	80-85 (n = 9)	≥86 (n = 2)	
Etiology							
No structural cause	10	11	3	2	0	0	26
Cysticercosis	4	3	2	0	1	0	10
Stroke	11	10	8	8	4	1	42
Atrophy	3	2	3	3	3	0	14
Neoplasms	1	1	0	2	0	1	5
Other	1	1	0	0	1	0	3
Type of seizure							
F-imp aw*	3	3	2	2	0	0	10
F-sens**	2	0	0	1	0	0	3
F-mot***	2	5	3	4	4	0	18
F-bil TC****	23	20	11	8	5	2	69
Anti-epileptic drugs							
1st generation	22	18	10	9	5	2	66
2nd generation	4	5	3	3	2	0	17
Polytherapy	4	5	3	3	2	0	17

*Focal with impaired awareness.
**Focal sensory.
***Focal motor onset.
****Focal to bilateral tonic-clonic.

reflected by EEG changes. Patients with stroke, mostly ischemic, also showed abnormal recording, with only 18% having a normal EEG.

Neuroimaging and etiology

Imaging revealed normal results in 26% of the patients. Among those with a structural finding, stroke constituted the largest group at 42%, while brain neoplasms accounted for 5%. In 10% of cases, the responsible lesion was infectious (NCC, as shown in Table 1). Of this group, only three patients had active vesicular NCC, while the remaining seven exhibited calcification.

Treatment

Most patients were on monotherapy (83%), with 66 receiving first-generation AEDs such as phenytoin (n = 42), carbamazepine (n = 21), and valproic acid (n = 3). Second-generation AEDs were prescribed for 17 patients, including levetiracetam (n = 8), lamotrigine (n = 2), oxcarbazepine (n = 3), and topiramate (n = 4). Polytherapy was required for 17 patients, with 11 on two drugs and six on three drugs. The data is summarized in table 1. Valproate was the most frequently used drug during polytherapy.

DISCUSSION

Only a few epidemiological data are available on renew-onset geriatric epilepsy in the elderly (aged over 60). A bimodal distribution of incidence and prevalence of epilepsy is a well-known fact: one peak in the early years of life and the other one after 60 years[15-17]. After dementia and stroke, epilepsy is the third most common neurological disorder in older individuals[1].

Our study examined the clinical profile of a sample of 100 older individuals, selected from an initial population of 525 patients who experienced their first seizure after the age of 20. It is important to note that all 100 patients in our sample had their first seizure after the age of 60.

The true prevalence of epilepsy in Mexico remains unknown; however, based on the incidence reported in similar countries, it is estimated that at least two million Mexicans have epilepsy. As the prevalence of epilepsy is bimodal, understanding the condition in older individuals is almost as crucial as it is in children. Additionally, the most recent epidemiological study available dates back 40 years[18], research examines a representative sample, including ten centers across the country[8]. We have previously published a similar study on late-onset epilepsy in Mexico, although it encompassed all age groups without separately analyzing older patients[8].

Diagnosing epilepsy in older individuals can be challenging due to its atypical presentation[19,20] including shorter seizure duration, less overt symptoms, or symptoms masked by cognitive disorders or other neurological diseases[2,21,22]. Focal seizures with non-motor onset are often unspecific or atypical (like dizziness). This differs as compared to younger individuals, where typical auras are frequent, and they may start with fear, ascending epigastric sensation, and déjà-vu[23].

In our study, all cases exhibited a focal onset. Even among patients initially suspected to have generalized onset seizures, a more detailed and thorough interview revealed atypical auras, leading to their reclassification as focal onset seizures. This supports the findings of other researchers who also identified a strong predominance of focal onset seizures in similar studies[7,24-26]. The progression of focal onset seizures to generalized seizures occurred frequently, with two-third of the cases in our sample experiencing this evolution, like other populations[27].

Focal onset with impaired awareness seizures is reported in up to 47% of cases in the literature[28]. However, they represent only 10% in the present series, while focal aware seizures (motor or sensory) are reported in 21% of cases. In the literature from older patients, generalized-onset seizures and simple partial seizures accounted for only 7.1% and 5.7%, respectively[22,29]. Our low observed percentage might be because several patients presenting focal seizures with impaired awareness became bilateral tonic-clonic (69%).

All patients had at least one EEG; however, the recording was unremarkable in one-third of cases. Unspecific abnormalities were observed in 41%, with barely 31% having some form of epileptiform activity. In elderly patients with epilepsy, the EEG can be unremarkable in up to one-third of cases (15-32%), with slowing or non-epileptiform abnormalities in 25-45% and interictal epileptiform activity in 21-28%[24,30].

Therefore, routine EEG might be helpful for establishing the diagnosis of epilepsy in patients aged over 60 years[31]. When analyzing EEG results in relation to the cause of epilepsy, we found that all NCC patients had abnormal recordings, probably because any active form of NCC causes an important inflammatory response reflected by EEG changes. Patients with stroke, mostly ischemic, also showed abnormal recording, with only 18% having a normal EEG. Older patients represent several challenges beyond diagnosis: they are at increased risk of epilepsy, and their numerous morbidities and polypharmacy render their management highly difficult[17,32-34].

New-onset geriatric epilepsy has well-known risk factors like stroke, which can account for 5-50% of identified causes of epilepsy. Dementias are the next disorder that can explain 10-20% of new-onset geriatric epilepsy and trauma between 1% and 13%. Some authors have found that up to 50% have no identified cause. In our series, a determined cause could be shown in 60% of cases, in line with the literature[2,26,28,35-40]. Epilepsy after a stroke in the elderly has an odds ratio of 8.4-10.6 in comparison with patients without a cerebrovascular disorder[41]. In our series, stroke accounts for 42% of all causes of epilepsy, and it has been reported in the literature to explain between 44% and 70% of cases[35,42-44]. The proportion of stroke in our series is somewhat different due to two factors: infectious causes (NCC) are not frequent in other series, and their population is often older than ours.

In developing countries, another important cause of epilepsy in all age groups is NCC (an infectious

cause)[45-48]. The current prevalence of NCC in our country is unknown, but it remains an endemic disease in Mexico, where up to 2% of autopsy cases of adults have some form of NCC[12,46,48,49]. In LOE (patients aged over 20) in our country, we have identified NCC as the first cause in a previous series[8]. In the present series, NCC was the second known cause of epilepsy, with 10% of our patients having the parasite. However, this is a rather high number compared to other studies that are mainly conducted in developed countries where the disorder is uncommon. Epilepsy secondary to NCC is a common manifestation of this parasitic disease and may be caused by the active or the inactive form of cysticercus[48,50]. In developed economies, brain tumors are a frequent cause of epilepsy in the elderly (10-30%), second only to stroke[2,51]. Older patients with brain tumors will have seizures at any stage of the disease in 45% of cases, and 20-40% of them will have them as their inaugural manifestation[42,44,52,53]. Alternatively, in our series, only 5% of patients presented with a brain tumor, thus being the third identified cause after stroke and NCC.

Alzheimer's disease and other neurodegenerative diseases are at risk of developing epilepsy[38,52,54-56]. In different series, epilepsy has been observed in 10-22% of patients[57,58] However, in our series, no cases of new-onset geriatric epilepsy caused by dementia were found. This might be due to a recruitment bias in our country. The diagnosis of dementia is usually made by a neurologist, but their long-term medical care is provided by internists, psychiatrists, or geriatricians. Therefore, neurologists participating in our study did not have patients with late-stage dementias where seizures usually occur. In our series, we did not have a single patient with posttraumatic seizures (epilepsy). The structure of care for these patients in our country also causes a recruitment bias. Those patients are usually seen by traumatologists and are rarely referred to neurologists.

We found no correlation of the clinical neurological examination with the cause. While neuroimaging was normal in 26% of the cases, 63% had no focal sign. This might be explained by symptomatic lesions in a non-eloquent area (frontal meningioma) or small lesions causing only epilepsy without focalization (parenchymal NCC for example).

Only a few authors have focused on the study of the specific characteristics and management of epilepsy in this age range[2,21,59]. In the past decades before the introduction of new AED, classic AEDs such as phenytoin, carbamazepine, and valproic acid were considered first-line treatment in the elderly[60,61]. In the past, up to 79% of elderly patients were treated with these classic AEDs, like in our series[62]. The armamentarium has since been enriched with newer drugs on the market, but those are more expensive and might not be an affordable choice in our settings[2,59-61,63]. Whenever possible, monotherapy should be preferred to avoid collateral effects that may arise during polypharmacy[64]. However, it is important to note that polypharmacy often involves multiple drugs in addition to AEDs. Given that older people frequently take many medications for other common conditions, they are at higher risk for interactions with AEDs, as many AEDs can induce enzymes, as referenced by sources[23,65-67].

Phenytoin and carbamazepine were the most commonly used drugs for monotherapy in our series, accounting for 75% of cases. These drugs, along with valproic acid, mainly bind to serum albumin, resulting in lower plasma levels in older patients with poor nutritional status[68-70]. Treating epilepsy in older patients can be further complicated by age-related changes in pharmacokinetics, polypharmacy, and increased susceptibility to drug adverse effects. Moreover, AEDs may reduce the effectiveness of other drugs such as anticoagulants, steroids, and chemotherapeutic agents, all of which are commonly used in elderly patients[71,72].

Age is a well-known risk factor for osteoporosis. Older AEDs, such as carbamazepine, phenytoin, and phenobarbital, as well as newer ones[73,74] induce cytochrome P450 enzymes, which can alter the process of osseous mineralization and increase the risk of fractures[75-77]. To minimize side effects, a gradual escalation of drug dosage is recommended, starting at lower doses below the efficacy range, and increasing by small increments until a therapeutic and tolerable dose is reached[78,79]. The collateral effects of AEDs can negatively impact the quality of life in older patients[80] Newer generation AEDs (lamotrigine and levetiracetam) are better tolerated than the so-called classic AEDs[81]. Newer AEDs, such as lamotrigine and levetiracetam, are generally better tolerated than classic AEDs, but medication adherence is still a

challenge, with poor adherence rates ranging from 42% to 63%, possibly due to low health literacy[82].

In our series, 83% of patients were on monotherapy, which is comparable to other series[7]. Half of our patients were managed with phenytoin, mainly because they were treated in public hospitals with limited budgets where phenytoin is widely available and less expensive than newer generation AEDs, which can cost up to 10 times more[83]. However, this practice should be changed to increase access to second-generation AEDs in Latin America, as in China where levetiracetam, which has fewer side effects, is widely used in the elderly[7]. In contrast to our findings, the literature shows that only around 13% of patients use phenytoin, and almost 45% of them have access to newer generation AEDs[24], which represents only about 20% of our series.

Our demographic transition has experienced a rapid increase in the elderly population leading to a higher prevalence of epilepsy and epileptic seizures in older patients[7]. As our study shows, there is an urgent need for cooperative studies in our region to compare how healthcare systems deal with this growing public health problem. While our study's findings cannot be extrapolated to the entire country or region, they provide a real-world description of what is happening in this understudied group of epileptic patients. In developing countries, epilepsy is the third or fourth most common neurological disorder[84,85]. Although statistical data are scarce, we believe that these numbers may be similar in our country. Identifying the causes of epilepsy in the elderly can lead to better management and prevention of epilepsy in this age group and ultimately reduce its prevalence.

Our study is the first step in raising awareness of the need for more accurate and recent epidemiological data. We found that the latest studies in our region date back four decades[86,87].

In conclusion, NCC is still a common contributor to new-onset geriatric epilepsy. This distribution, which primarily represents patients from wealthy economies, is not mentioned in the literature. The choice of medication in our setting is influenced by financial considerations, therefore newer antiepileptic medications should be made more accessible to this population's financial and physical vulnerability.

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