NEURAL REGENERATION RESEARCH
Volume 8, Issue 35, December 2013

www.nrronline.org

doi:10.3969/j.issn.1673-5374.2013.35.006 [http://www.nrronline.org; http://www.sjzsyj.org]
Liu JM, Liu ZL, Chen T, Xu RX. Treatment of epilepsy in China: formal or informal? Neural Regen Res. 2013;8(35):3316-3324.

Treatment of epilepsy in China

Formal or informal?

Jianming Liu[1], Zhiliang Liu[1], Tao Chen[2], Ruxiang Xu[1]

1 *Bayi Brain Hospital, Affiliated to General Hospital of Beijing Military Area Command of Chinese PLA, Beijing 100700, China*
2 *Laser Institute of Engineering, Beijing University of Technology, Beijing 100080, China*

Research Highlights

(1) Previous studies addressing anti-epileptic drugs have focused on the therapeutic efficacy and safety of various drugs, and some papers have discussed the application of traditional Chinese medicine and acupuncture in the treatment of epilepsy. The drug-dependence of epileptic patients and influence of changes in treatment regimens on therapeutic effect have been widely investigated through surveys. There has been no systemic analysis of the reviews assaying the formal treatment of epilepsy.
(2) Informal treatment may cause intractable epilepsy. Therefore, this study was designed to observe the present drug treatments for epilepsy and found that informal treatment is very common in China.

Abstract

Antiepileptic drugs are the preferred treatment approach for epileptic patients. However, informal treatment is important for intractable epilepsy. In this study, 500 epileptic patients were recruited from the General Hospital of Beijing Military Area Command of Chinese PLA during the period of October 2009 to January 2012. These involved patients that had been medically treated for at least 1 year. Information on the initial treatment and changes to treatment regimens for each patient was collected through questionnaires. The survey results showed that 52.3% of the epileptic patients searched for treatment after the first seizure, and the mean numbers of seizures was 12.8; 59.8% of the epileptic patients were diagnosed at the first visit, and the mean onset time was 17 months after the first seizure. After diagnosis, patients were treated for an average of 20 days, and the median time was 1 day. Formal anti-epileptic drugs were selected as the first treatment regimen by 67.8% of patients, and 77.5% of these drugs were monotherapies. The mean and median numbers of seizure were respectively 36.9 and 3.0 times before the first regimen was changed. The regimen was changed within the first 6 months by 46.6% of patients, and after the first and second years of treatment, the proportions increased to 54.0% and 71.8%, respectively. In total, 78.5% of the regimens were changed to informal treatments. The informal treatment of epilepsy in China is common, being initiated by either patients or physicians. Enhancing epileptic treatment services in hospital, improving physicians' professional quality, and strengthening health propaganda may promote the normalization of drug treatment of epilepsy in China.

Key Words

neural regeneration; epilepsy; intractable epilepsy; drug treatment; survey; normalization; treatment regimen; nervous system diseases; cross-sectional survey; retrospective study; grants-supported paper; neuroregeneration

Jianming Liu, Master, Attending physician.

Corresponding author: Zhiliang Liu, M.D., Associate chief physician, Bayi Brain Hospital, Affiliated to General Hospital of Beijing Military Area Command of Chinese PLA, Beijing 100700, China, sxljm10282@163.com.

Received: 2013-06-01
Accepted: 2013-09-02
(N201202033)

Acknowledgments: We would like to thank all the staff from the Third Ward, Bayi Brain Hospital, Affiliated to General Hospital of Beijing Military Area Command of Chinese PLA, for collecting data.

Funding: This work was supported by Beijing Natural Science Foundation, No. 4132017.

Author contributions: Liu ZL designed the study. Liu JM performed the experiments and statistics and wrote the manuscript. Xu RX and Chen T participated in partial experiments. All authors approved the final version of the paper.

Conflicts of interest: None declared.

Author statements: The manuscript is original, has not been submitted to or is not under considera-tion by another publication, has not been previously published in any language or any form, including electronic, and contains no disclosure of confidential information or authorship/patent application/funding source disputations.

INTRODUCTION

Epilepsy is a common and widespread neurological disorder, affecting people of all ages and socioeconomic classes worldwide, with a worldwide prevalence estimated at 50 millions[1]. Approximately 85% of epileptic patients live in developing countries[2]. There are approximately 9 million people with epilepsy in China, among them 6 million with active epilepsy. There are 0.4 million new cases each year[3].

Antiepileptic drugs are the initial treatment modality for the vast majority of epileptic patients[4]. Epilepsy can be treated with more than 15 different antiepileptic drugs[4]. It has been estimated that approximately one-third of patients with epilepsy still have seizures despite the prescription of appropriate doses of antiepileptic drugs[5-8]. Uncontrolled epilepsy is associated with excess mortality[9], cognitive[10] and language dysfunction[11], psychosocial outcome[12], and social and educational disadvantage[13-15], for which society pays a high price[16].

The drug treatment of epilepsy is more difficult than treatment of other chronic diseases, because many factors should be considered seriously in epilepsy, such as whether we should give drug treatment after the first seizure, how to choose the first antiepileptic drug, if sezures are still happening how long we should wait to change the regimen, whether we should change to a new antiepileptic drug or combine with a second antiepileptic drug, and whether there are any alternative treatments other than antiepileptic drug. All these related factors can influence the effect of epilepsy treatment.

Previous studies addressing the drug treatment of epilepsy have mentioned some factors such as medication adherence[17-18], traditional Chinese medicine[19], and frequency of antiepileptic drug regimen changes[20], however, no articles described the whole treatment process.

We conducted a cross-sectional retrospective study of present epilepsy treatment in China, in a broader attempt to analyze the related factors for informal treatment and normalize the drug treatment for epilepsy.

RESULTS

Quantitative analysis of involved subjects

A sample of 722 patients was selected from the Bayi Brain Hospital, Affiliated to General Hospital of Beijing Military Area Command of Chinese PLA, China. Among the involved patients, 667 patients were diagnosed as having epilepsy[21] and 101 of them were excluded according to inclusion and exclusion criteria. Finally, 566 patients were invited to participate in this study, 66 patients refused to participate and 500 patients agreed, yielding a response rate of 88.3%. Figure 1 shows the process of screening the patients.

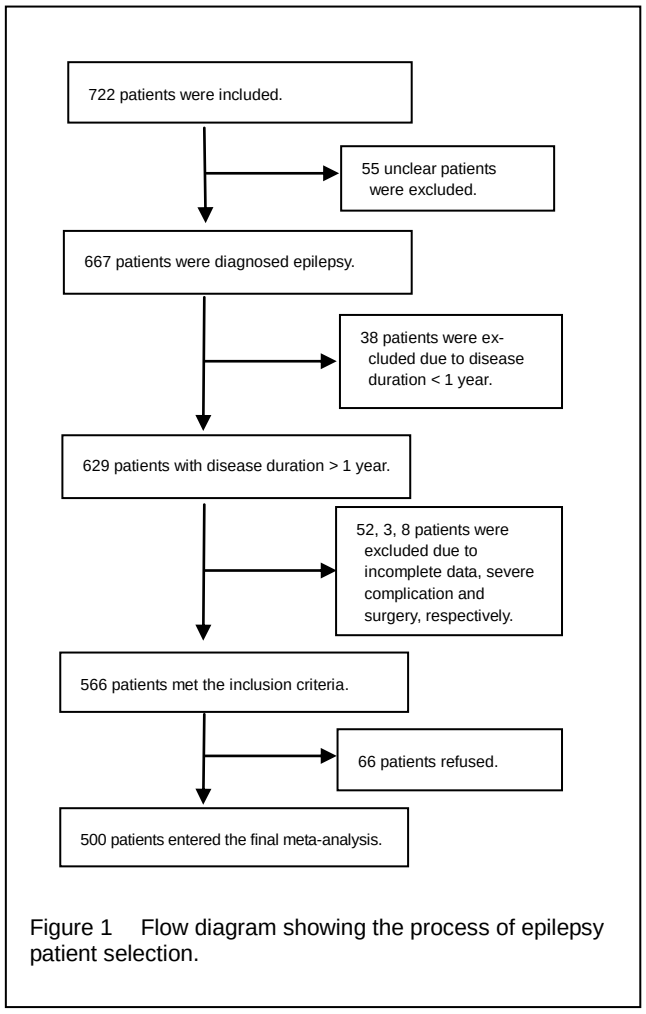

Figure 1 Flow diagram showing the process of epilepsy patient selection.

Types of epileptic patients

The seizure types in the involved patients were categorized into partial seizures (simple or complex partial; *n* = 231), original or secondary generalized tonicclonic seizures (*n* = 252), and other seizures (absence, myoclonic, tonic, atonic, clonic; *n* = 17). Detailed information on the seizure types in our patient set is shown in Figure 2.

Initial treatment of epileptic patients

Visit and diagnosis

The survey results revealed that 261 patients (52.3%) searched for treatment after the first seizure, and the mean numbers of seizures were 12.8, with a median of

1.0. A total of 299 patients (59.8%) were diagnosed with epilepsy at the first visit; for the correct diagnosis the mean number of visits required was 1.7 and the mean length of time to diagnosis was 17 months after the first seizure. Original or secondary generalized tonic-clonic seizures were most strongly associated with epilepsy being detected, and, among those showing original or secondary generalized tonicclonic seizures, the mean number of visits to achieve a correct diagnosis was 1.2. This seizure type was followed in terms of ease of epilepsy detection by partial seizures (1.8 visits) and other generalized seizures (2.2 visits).

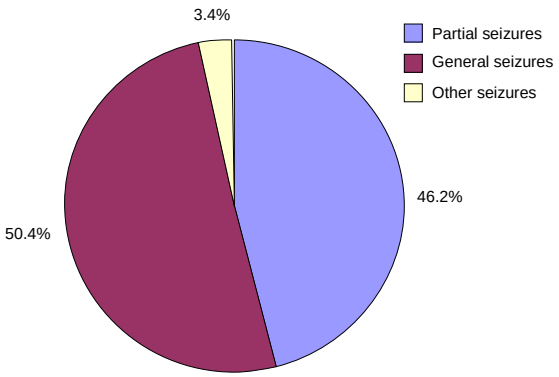

Figure 2 The distribution of epilepsy types.

There are 500 epileptic patients; other seizures included absence, myoclonic, tonic, atonic and clonic.

Drug treatment

Overall, 475 (95.1%) newly diagnosed epileptic patients received therapy on the day of diagnosis. The mean and median lengths of treatment were respectively 20 days and 1 day after the diagnosis. A total of 339 (67.8%) patients selected formal antiepileptic drugs as the first treatment regimen, and this was followed in popularity by traditional Chinese medicine, superstitions, other methods, and multiple methods. The initial treatment of all patients is shown in Figure 3. Sixty-three (12.6%) patients received antiepileptic drugs after the first seizure. When a formal antiepileptic drug treatment was given, 262 (77.3%) patients used monotherapy (19.2% of them could not remember the first antiepileptic drug; Figure 4 shows the details of the formal antiepileptic drugs used by the patients); 47 (13.9%) patients used two antiepileptic drugs as the initial regimen (valproic acid and phenytoin, carbamazepine and valproic acid, carbamazepine and phenytoin, carbamazepine and phenytoin); and 30 (8.8%) patients received three or more antiepileptic drugs as the first antiepileptic drug regimen.

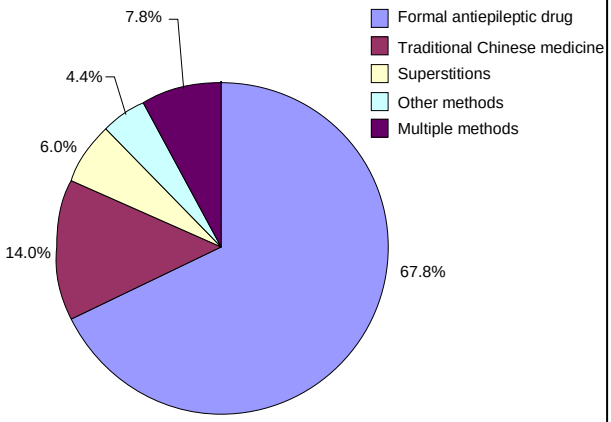

Figure 3 The initial treatments in the 500 epileptic patients.

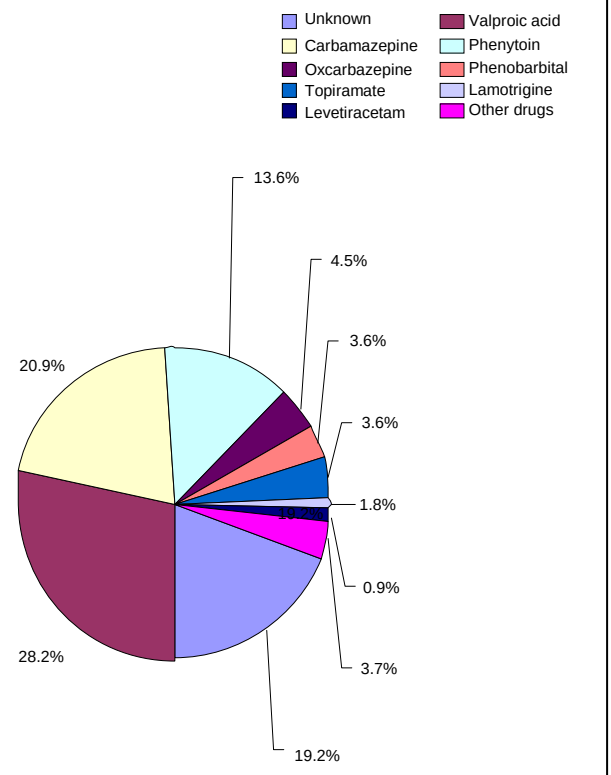

Figure 4 The initial formal antiepileptic drug treatments of patients.

The first regimen change in epileptic patients

Most patients could not continue on their initial antiepileptic regimen, and the mean and median numbers of seizures were 36.9 and 3.0 times, respectively until the first regimen change. Two-hundred and thirty-three (46.6%) patients changed the regimen within the first 6 months; after the first and second years of treatment, the proportions increased to 54.0% and 71.8%, respec-

tively. The changes could be explained by a lack of efficacy (72.6%); worry about side effects (12.3%); and other reasons (17.1%) such as idiosyncratic reactions, planning a pregnancy, a change of mind about drug treatment and the treatment cost.

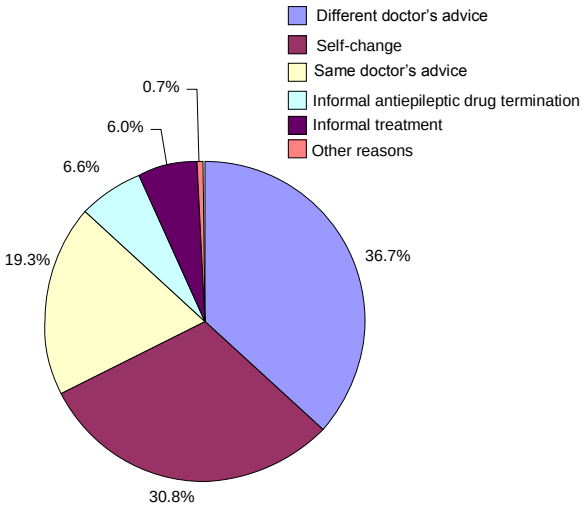

Figure 5 The reasons stated for treatment regimen changes.

When the patients wanted to change the treatment, 67.9% of them selected a new doctor, 7.5% returned back to the initial doctor, and 24.6% selected other methods such as following another patient's advice, visiting an informal doctor, and changing the regimen themselves or other ways. The most common change was switching to a new antiepileptic drug (63.2%), followed by adding a new antiepileptic drug (19.3%), adjusting the antiepileptic drug dosage (8.8%), and changing to a new treatment method (8.7%).

Subsequent regimen changes in epileptic patients

If the result of the first regimen change was not successful or not satisfactory, the patients would consider more doctors or more treatment methods. In our study, each patient looked for 0.5 different doctor per year, and 16.6% of the doctors were not in the formal clinic. The number of different types of antiepileptic drugs the patients received ranged 1 to 8 (mean = 3).

All of the 500 epileptic patients had received formal drugs. The majority of the patients bought their antiepileptic drugs from hospitals (73.5%), other pharmacies (21.5%), mail order (3%) and other ways (2%). More than half of the patients (63.6%) had two antiepileptic drugs, 181 (36.3%) patients had three antiepileptic drugs, and 87 (17.5%) patients had four or more antiepileptic drugs. Besides formal antiepileptic drugs, 324 (64.8%) of the 500 patients had received traditional Chinese medicine treatment, including Chinese patent medicines (the mean number of different types was 1.5) and herbal medicine (the mean number of different types was 1.2); 227 (45.4%) patients had received other treatments (mean number = 1.6) such as acupuncture, folk prescription, catgut implantation at acupoints, superstition and so on, and many of the patients had received these treatments more than once.

The mean number of regimen changes per person per year was 0.64, and 78.5% of regimens were changed to informal ones. Figure 5 shows the reasons for the regimen changes, including a different doctor's advice, self-change, the same doctor's advice, informal antiepileptic drug termination, informal treatment and other reasons.

DISCUSSION

This study is the first to investigate the present situation regarding the treatment of epilepsy in China. In this study, the samples came from all the provinces of the China Mainland. We will assess the present situation from the aspect of both patients and doctors.

The aspect of patients

A large number of seizures before treatment was a poor prognostic indicator[22]. In this study, half of patients searched for treatment after the first seizure. Nearly all of the patients received treatment on the day of diagnosis. Patients tried many treatment methods and changed the regimen frequently: the mean number of regimen changes per person per year was 0.64. All of these factors indicate that the patients have an urgent desire to treat the disease. However, the frequent regimen changes increased the risk of pharmacoresistant epilepsy[5]. Many regimen changes are decided by patients themselves. We summarize the reasons as follows:

In China nearly half of patients changed the initial regimen within the first 6 months, and only 7.5% of patients returned back to their initial doctor. The patients looked for 0.5 different doctor per year, and 16.6% of the doctors consulted are not in formal clinics. Informal antiepileptic drug termination was reported by 6.6% of patients. All these findings indicate that, when seizures recur, many patients begin to suspect the doctor's prescription, and they do not understand the regular dose-adjustment process. They do not trust the doctors.

In China, 6.0% and 4.4% of patients selected superstitions and other methods as the initial treatment. In the process of treatment 45.4% had received other treatments such as acupuncture, folk prescription, catgut implantation at acupoints, superstition. Many methods have no scientific basis such as magnetic iron implantation under the scalp. In China 12.3% of patients changed the initial regimen because they worried about adverse events, yet most of them had no side effects or only mild side effects. Many people selected traditional Chinese medicine and other methods also because they worried about adverse events. Patients with epilepsy often reported inadequate provision of information and advice, so we think that the low level education background and lack of medical knowledge leads to use of these informal treatments.

The aspect of doctors

The diagnosis of epilepsy has important physical, psychosocial and economic implications for patients. The diagnosis should be made by a neurologist or other epilepsy specialist. In fact epilepsy may be difficult to diagnose in the early stages, especially in the absence of a witnessed account. Physicians have differing knowledge of the differentiation of epileptic seizures and stereotyped behavioral phenomena. It is important for the neurologist to accurately diagnose the type of seizures in order to select the most appropriate therapy[23]. It has been shown that a significant proportion of epilepsy diagnoses made by non-specialists is incorrect[24]. In China, many patients could not get a correct diagnosis at the first visit; they often visited the nearest clinic in China, and most of these clinics are primary clinics in which there are few epilepsy specialists. Because it has the most obvious symptoms, the generalized tonic-clonic seizure is the easiest type from which to diagnose epilepsy.

It is widely agreed that, after two or more seizures, patients should be given antiepileptic treatment, but there are still some controversies around the treatment after a first unprovoked seizure. After an initial first seizure the risk of recurrence was 36% by 1 year, 48% by 3 years, and 56% by 5 years[25]. Some patients may have only one seizure in their life. There is a consensus that immediate or delayed treatment after a first seizure does not impact the long-term outcome of the seizure disorder[26-27]. In addition, in a study of children with epilepsy, the initiation of treatment after 10 or fewer seizures did not influence the remission rate[28]. In China, 12.6% of patients received antiepileptic drugs after the first seizure. We think there is no need to prescribe antiepileptic drugs after the first seizure. Whether to treat after a single seizure should be largely decided on the basis of the risk of further seizures, and only those patients with a high possibility of relapse need early treatment. The variables that increase the risk of seizure have been summarized previously[29].

Because many patients with newly diagnosed epilepsy will be controlled on a modest dose of the first drug, it is important to choose the first antiepileptic drug. The most suitable antiepileptic drug should maximize the chance of remission without producing side effects[30]. The financial implications are also a factor that doctors should consider[31].

Until the early 1980's, polytherapy was widely practiced as the first-line treatment with the hope of achieving synergistic effects or less severe drug toxicity[32]. Subsequent trials have led to a change toward the use of monotherapy as a first-line treatment[33-36]. In developed countries, 89% of newly diagnosed patients are prescribed monotherapy as their first antiepileptic drug regimen[37]. Comparative, randomized, double-blind trials in patients with newly-diagnosed partial and generalized tonicclonic seizures suggest similar efficacies for phenytoin, carbamazepine, sodium valproate, lamotrigine and oxcarbazepine[38-41]. We still do not really know if new antiepileptic drugs have better efficacy than the traditional drugs[37], but the newer antiepileptic drugs such as lamotrigine and oxcarbazepine seem to be better tolerated and may produce fewer long-term side effects and adverse interactions[42-43]. For this point, we think it is better to use new antiepileptic drugs. According to our statistics, the most common initial antiepileptic drugs were valproic acid and carbamazepine in China, and new antiepileptic drugs were less frequently used. We think there are some reasons for this: financial complication, fewer sales channels and a poor understanding of the new antiepileptic drugs by doctors.

Response to initial antiepileptic drug therapy appears to be an important prognostic factor with evidence that failure of the first two antiepileptic drug monotherapies is significantly associated with a diagnosis of pharmacoresistant epilepsy[44]. Kwan and Brodie[5] found only 11% of patients who fail on the first antiepileptic drug subsequently become seizure-free; they thought the failure of treatment was strongly associated with the first drug. So the regular use of the first antiepileptic drug is very important. In China, within the first 6 months, 75.4% of patients visit formal doctors and want to change the regi-

men; only 8.8% of them adjust the antiepileptic drug dosage, while 63.2% switch to a new antiepileptic drug. This suggests that the doctors are not aware of the importance of the initial antiepileptic drug.

In total, 30–40% of patients remain uncontrolled on a single antiepileptic drug[5]. For these patients, polytherapy is not only acceptable, but is standard practice[45]. No differences in adverse effects as reported spontaneously or through questionnaires were found between monotherapy and polytherapy[46-47]. The vast majority of patients reaching seizure freedom do so with two antiepileptic drugs[48]. The important question is whether three or more antiepileptic drugs can ever be rational. In fact only a few patients will become seizure-free on three antiepileptic drugs[49], But four or more antiepileptic drugs are not likely to be any more successful[48]. In China, 63.6% of patients had been on two antiepileptic drugs, 36.3% had been on three antiepileptic drugs, 17.5% had been on more than three antiepileptic drugs. Approximately two-thirds of patients in our study were on polytherapy. This is higher than the proportion reported in studies from developed countries. In the United States, 56% of patients were on polytherapy[50], while in a European study 53% of patients were found to be on poly-therapy[51]. Therefore, we think two antiepileptic drugs are rational and sometimes necessary; if a regimen of two antiepileptic drugs cannot control the seizures, we can attempt to add a third antiepileptic drug, but four or more antiepileptic drug should be avoided.

Seizures are poorly controlled in many patients despite adequate current antiepileptic treatments. There is increasing interest in alternative traditional Chinese medicine therapies. Dr. Schachter introduced the concept that herbs and botanicals may represent an economical and effective resource for modern epilepsy treatment. These therapies are important sources in China. However, until now, the evidence is insufficient to support the use of traditional Chinese medicine[52], acupuncture, and other methods[53] as a treatment for epilepsy. In this study 64.8% of patients received traditional Chinese treatment. We do not advise using these as monotherapy; however, in terms of finance and potential effectiveness, these methods may become an assistance treatment to antiepileptic drugs. Much larger, high-quality randomized clinical trials are needed to evaluate the effectiveness and safety of traditional Chinese medicine for treating epilepsy. If seizures are not fully controlled, work-up for epilepsy surgery should be considered[54].

Our study has a few limitations. The relatively small sample size makes the detection of significant results less likely. Data from hospital-based centers are subject to referral bias, as more cases with refractory epilepsy are expected than from primary care physicians.

In summary, the informal treatment of epilepsy in China is common, which is one possible reason for treatment failure. The reasons relate to both patients and their doctors. There remains considerable scope for the development of better epilepsy services in both primary and secondary care.

SUBJECTS AND METHODS

Design

A cross-sectional survey and retrospective case study.

Time and setting

This study was performed in the General Hospital of Beijing Military Area Command of Chinese PLA, China from October 2009 to January 2012.

Subjects

Patients with epilepsy were recruited from General Hospital of Beijing Military Area Command of Chinese PLA, China from October 2009 to January 2012.

Inclusion criteria

At least two unprovoked seizures were required for the diagnosis of epilepsy[21]. There was no age limit for the inclusion of participants, and all patients gave informed consent. To be included in analyses, patients also had at least 1 year of minimal duration of treatment. This was to allow time for treatment regimen change.

Exclusion criteria

Patients with the following could be excluded: (1) when the diagnosis of epilepsy could not be determined without doubt, or with a single seizure; (2) information from patients could not be identified; (3) combined with the other serious diseases leading to treatment interruption for epilepsy; (4) after epilepsy surgery.

A total of 500 epileptic patients were studied, including 295 (59%) males and 205 (41%) females. Patients' mean age was 35.3 ± 11.7 years (range 2–75 years). The onset of epilepsy ranged from the first month of life to 70 years (mean 15.1 ± 10.7 years). A total of 57% of the patients were residing in rural locations. The mean duration of epilepsy was 8.8 ± 7.3 years.

Methods

Assessment and measures

Key clinical and treatment information on each patient were gathered using questionnaires designed for this study. The content of assessment in this study consisted of three parts as follows:

Part 1: This part included sections on demographics such as age, sex, city where the patient come from, the lived place (rural of urban); epilepsy characteristics such as age at epilepsy diagnosis, duration of epilepsy, and types of the seizures.

Part 2: This part was about the initiation of treatment, including when patients go to see the doctor; when they were correctly diagnosed (we recorded the numbers and times according to different types of seizure); when they received treatment after diagnosis; what was the first treatment regimen; and which was the first formal antiepileptic drug. In this section, the polytherapy was defined as two or more antiepileptic drugs prescribed within 14 days.

Part 3: This part was about the process of the treatment, including: when and how the patients began the first change of the regimen and the related reasons; after the first regimen change this study specifically described the frequency and type of change in treatment regimen and factors associated with the regimen change. Descriptive analyses calculated the mean numbers of treatment regimen changes per person per complete year of follow-up.

In our questionnaire we listed the reasons for regimen change as different doctor's advice, self-change, the same doctor's advice, informal antiepileptic drug termination, and interference with informal treatment; if there was any other reason they could write it under "other reasons".

The following items were considered as treatment regimens: (1) augmenting or reducing the number of antiepileptic drugs; (2) adjusting antiepileptic drug dosages (increase or decrease); (3) switching antiepileptic drug type; (4) switching or adding a new treatment; (4) terminating one treatment.

Definition of formal and informal treatment regimen

The formal way to change to a different antiepileptic drug is to start taking a new antiepileptic drug as well as your previous antiepileptic drug. Once you are taking the right dose of the new antiepileptic drug, the previous antiepileptic drug is gradually reduced. This method of changing antiepileptic drugs is used to make sure that there is always enough medicine in a patient's body to control seizures. If patients have been seizure free for a few years, they can stop antiepileptic drugs following a specialist's advice, but they should stop taking them very gradually, and this may take a few months. Other ways to change or stop the antiepileptic drug were defined as informal regimen changed; in our study we defined these as traditional Chinese drugs (Chinese patent medicines, herbal medicine), other treatments such as acupuncture, folk prescriptions, catgut implantation at acupoint, and superstition as informal treatment regimen too.

Statistical analysis

All analyses were conducted using SAS 16.0 software (SAS, Raleigh, North Carolina, USA). Continuous variables are expressed as means and median.

REFERENCES

[1] Neligan A, Hauser WA, Sander JW. The epidemiology of the epilepsies. Handb Clin Neurol. 2012;107:113-133.
[2] Campos MG. Epilepsy surgery in developing countries. Handb Clin Neurol. 2012;108:943-953.
[3] Pi X, Cui L, Liu A, et al. Investigation of prevalence, clinical characteristics and management of epilepsy in Yueyang city of China by a door-to-door survey. Epilepsy Res. 2012;101(1-2):129-134.
[4] Bazil CW, Pedley TA. Clinical pharmacology of antiepileptic drugs. Clin Neuropharmacol. 2003;26(1):38-52.
[5] Kwan P, Brodie MJ. Early identification of refractory epilepsy. N Engl J Med. 2000;342(5):314-319.
[6] Sander JW. Some aspects of prognosis in the epilepsies: a review. Epilepsia. 1993;34(6):1007-1016.
[7] Hui AC, Wong A, Wong HC, et al. Refractory epilepsy in a Chinese population. Clin Neurol Neurosurg. 2007;109(8):672-675.
[8] Eatock J, Baker GA. Managing patient adherence and quality of life in epilepsy. Neuropsychiatr Dis Treat. 2007;3(1):117-131.
[9] Nevalainen O, Auvinen A, Ansakorpi H, et al. Mortality by clinical characteristics in a tertiary care cohort of adult patients with chronic epilepsy. Epilepsia. 2012;53(12):e212-214.
[10] Loring DW, Meador KJ. Epilepsy: maximizing cognitive outcomes in epilepsy. Nat Rev Neurol. 2012;8(8):416-417.
[11] Buchhalter JR. The relationship between nocturnal discharges and language dysfunction in rolandic epilepsy: treat the child, not the adage. Epilepsy Curr. 2012;12(5):192-193.

[12] Quintas R, Raggi A, Giovannetti AM, et al. Psychosocial difficulties in people with epilepsy: A systematic review of literature from 2005 until 2010. Epilepsy Behav. 2012; 25(1):60-67.
[13] Mitchell WG. Social outcome of childhood epilepsy: associations and mechanisms. Semin Pediatr Neurol. 1994; 1(2):136-143.
[14] Sillanpaa M, Jalava M, Kaleva O, et al. Long-term prognosis of seizures with onset in childhood. N Engl J Med. 1998;338(24):1715-1722.
[15] Thorbecke R, Pfafflin M. Social aspects of epilepsy and rehabilitation. Handb Clin Neurol. 2012;108:983-999.
[16] Begley CE, Famulari M, Annegers JF, et al. The cost of epilepsy in the United States: an estimate from population-based clinical and survey data. Epilepsia. 2000;41(3):342-351.
[17] Manjunath R, Davis KL, Candrilli SD, et al. Association of antiepileptic drug nonadherence with risk of seizures in adults with epilepsy. Epilepsy Behav. 2009;14(2): 372-378.
[18] Hovinga CA, Asato MR, Manjunath R, et al. Association of non-adherence to antiepileptic drugs and seizures, quality of life, and productivity: survey of patients with epilepsy and physicians. Epilepsy Behav. 2008;13(2):316-322.
[19] Hijikata Y, Yasuhara A, Yoshida Y, et al. Traditional Chinese medicine treatment of epilepsy. J Altern Complement Med. 2006;12(7):673-677.
[20] Cunnington MC, Webb DJ, Irizarry MC, et al. Risk factors for antiepileptic drug regimen change in patients with newly diagnosed epilepsy. Epilepsy Behav. 2011;21(2): 168-172.
[21] Blume WT, Luders HO, Mizrahi E, et al. Glossary of descriptive terminology for ictal semiology: report of the ILAE task force on classification and terminology. Epilepsia. 2001;42(9):1212-1218.
[22] Sillanpaa M. Remission of seizures and predictors of intractability in long-term follow-up. Epilepsia. 1993;34(5): 930-936.
[23] Smith D, Defalla BA, Chadwick DW. The misdiagnosis of epilepsy and the management of refractory epilepsy in a specialist clinic. QJM. 1999;92(1):15-23.
[24] Schachter SC. Antiepileptic drug therapy: general treatment principles and application for special patient populations. Epilepsia. 1999;40 Suppl 9:S20-25.
[25] Annegers JF, Hauser WA, Shirts SB, et al. Factors prognostic of unprovoked seizures after febrile convulsions. N Engl J Med. 1987;316(9):493-498.
[26] Leone MA, Solari A, Beghi E. Treatment of the first tonic-clonic seizure does not affect long-term remission of epilepsy. Neurology. 2006;67(12):2227-2229.
[27] Musicco M, Beghi E, Solari A, et al. Treatment of first tonic-clonic seizure does not improve the prognosis of epilepsy. First Seizure Trial Group (FIRST Group). Neurology. 1997;49(4):991-998.
[28] Camfield C, Camfield P, Gordon K, et al. Does the number of seizures before treatment influence ease of control or remission of childhood epilepsy? Not if the number is 10 or less. Neurology. 1996;46(1):41-44.
[29] Saito M, Munana KR, Sharp NJ, et al. Risk factors for development of status epilepticus in dogs with idiopathic epilepsy and effects of status epilepticus on outcome and survival time: 32 cases (1990-1996). J Am Vet Med Assoc. 2001;219(5):618-623.
[30] Brodie MJ, French JA. Management of epilepsy in adolescents and adults. Lancet. 2000;356(9226):323-329.
[31] Heaney DC, Beran RG, Halpern MT. Economics in epilepsy treatment choices: our certain fate? Epilepsia. 2002;43Suppl 4:32-38.
[32] Reynolds EH, Shorvon SD. Monotherapy or polytherapy for epilepsy? Epilepsia. 1981;22(1):1-10.
[33] Callaghan N, Kenny RA, O'Neill B, et al. A prospective study between carbamazepine, phenytoin and sodium valproate as monotherapy in previously untreated and recently diagnosed patients with epilepsy. J Neurol Neurosurg Psychiatry. 1985;48(7):639-644.
[34] Ishikawa A, Sakuma N, Nagashima T, et al. Clonazepam monotherapy for epilepsy in childhood. Brain Dev. 1985; 7(6):610-613.
[35] Brodie MJ, Yuen AW. Lamotrigine substitution study: evidence for synergism with sodium valproate? 105 Study Group. Epilepsy Res. 1997;26(3):423-432.
[36] Shorvon SD, Chadwick D, Galbraith AW, et al. One drug for epilepsy. Br Med J. 1978;1(6111):474-476.
[37] Glauser T, Ben-Menachem E, Bourgeois B, et al. ILAE treatment guidelines: evidence-based analysis of antiepileptic drug efficacy and effectiveness as initial monotherapy for epileptic seizures and syndromes. Epilepsia. 2006;47(7):1094-1120.
[38] Bill PA, Vigonius U, Pohlmann H, et al. A double-blind controlled clinical trial of oxcarbazepine versus phenytoin in adults with previously untreated epilepsy. Epilepsy Res. 1997;27(3):195-204.
[39] Brodie MJ, Richens A, Yuen AW. Double-blind comparison of lamotrigine and carbamazepine in newly diagnosed epilepsy. UK Lamotrigine/Carbamazepine Monotherapy Trial Group. Lancet. 1995;345(8948):476-479.
[40] Mattson RH, Cramer JA, Collins JF. A comparison of valproate with carbamazepine for the treatment of complex partial seizures and secondarily generalized tonic-clonic seizures in adults. The Department of Veterans Affairs Epilepsy Cooperative Study No. 264 Group. N Engl J Med. 1992;327(11):765-771.
[41] Dam M, Ekberg R, Loyning Y, et al. A double-blind study comparing oxcarbazepine and carbamazepine in patients with newly diagnosed, previously untreated epilepsy. Epilepsy Res. 1989;3(1):70-76.
[42] Brodie MJ, Kwan P. The star systems: overview and use in determining antiepileptic drug choice. CNS Drugs. 2001;15(1):1-12.

[43] Guerreiro MM, Vigonius U, Pohlmann H, et al. A double-blind controlled clinical trial of oxcarbazepine versus phenytoin in children and adolescents with epilepsy. Epilepsy Res. 1997;27(3):205-213.
[44] Kwan P, Arzimanoglou A, Berg AT, et al. Definition of drug resistant epilepsy: consensus proposal by the ad hoc Task Force of the ILAE Commission on Therapeutic Strategies. Epilepsia. 2009;51(6):1069-1077.
[45] Kwan P, Brodie MJ. Combination therapy in epilepsy: when and what to use. Drugs. 2006;66(14):1817-1829.
[46] Carpay JA, Aldenkamp AP, van Donselaar CA. Complaints associated with the use of antiepileptic drugs: results from a community-based study. Seizure. 2005;14(3):198-206.
[47] Canevini MP, De Sarro G, Galimberti CA, et al. Relationship between adverse effects of antiepileptic drugs, number of coprescribed drugs, and drug load in a large cohort of consecutive patients with drug-refractory epilepsy. Epilepsia. 2010;51(5):797-804.
[48] Stephen LJ, Brodie MJ. Seizure freedom with more than one antiepileptic drug. Seizure. 2002;11(6):349-351.
[49] Schiller Y, Najjar Y. Quantifying the response to antiepileptic drugs: effect of past treatment history. Neurology. 2008;70(1):54-65.
[50] Yeager KA, Diiorio C, Shafer PO, et al. The complexity of treatments for persons with epilepsy. Epilepsy Behav. 2005;7(4):679-686.
[51] Baker GA, Jacoby A, Buck D, et al. Quality of life of people with epilepsy: a European study. Epilepsia. 1997;38(3):353-362.
[52] Li Q, Chen X, He L, et al. Traditional Chinese medicine for epilepsy. Cochrane Database Syst Rev. 2009(3):CD006454.
[53] Cheuk DK, Wong V. Acupuncture for epilepsy. Cochrane Database Syst Rev. 2008(4):CD005062.
[54] de Tisi J, Bell GS, Peacock JL, et al. The long-term out-come of adult epilepsy surgery, patterns of seizure remission, and relapse: a cohort study. Lancet. 2011;378(9800):1388-1395.

(Reviewed by McGowan D, Raye W, Huang G, Jiang B)
(Edited by Wang LM, Yang Y, Li CH, Song LP, Liu WJ, Zhao M)