

FULL-LENGTH ORIGINAL RESEARCH

Impact of diagnostic delay on seizure outcome in newly diagnosed focal epilepsy

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Abstract

Objective: In the current study, we aimed to assess the diagnostic delay and the impact of diagnostic delay on seizure outcome in a cohort of newly diagnosed patients with focal epilepsy.

Methods: The study material was compiled from eight clinical antiseizure medication monotherapy trials conducted at Kuopio Epilepsy Center during 1995–2016. We analyzed the time from first seizure to diagnosis, the number of seizures before diagnosis, and the response to treatment at five years.

Results: Of the 176 patients (age range 15–75 years) in the cohort, 135 (77%) had had more than two seizures before treatment. The majority of these (79 patients, 45%) had had three to ten seizures. Median number of all seizures before diagnosis was 5 (range 2–2000). Focal aware seizures and focal impaired awareness seizures were more frequent than focal to bilateral tonic-clonic seizures; median number 45 (range 2–2000), 11 (range 2–220), and 3 (range 2–30), respectively ($P < .001$). Median delay was 12 months (range 0–362). Diagnostic delay alone did not correlate with the treatment response at five years. However, an increasing number of seizures before diagnosis indicated a worse seizure outcome ($P < .001$).

Significance: This study shows that patients with focal epilepsy experience significant delays in diagnosis even in developed countries, especially with seizure types other than tonic-clonic seizures. In these cases, a long delay in diagnosis alone might not affect the long-term outcome. However, when accompanied with recurrent seizures misinterpreted by the patient or healthcare providers, the effect of such delay on prognosis can be considerable.

KEYWORDS

diagnostic delay, epilepsy, prognosis, refractory epilepsy

1 | INTRODUCTION

In his review article in 1984, Shorvon¹ posed that chronic active epilepsy may lessen the possibility of attaining

remission. He raised the question of whether early effective treatment with antiseizure medication could affect the long-term outcome of epilepsy.¹ Only few studies have been since conducted on this subject.

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In earlier studies, 38%-55% of patients have reported previous undiagnosed seizures before the index seizure leading to seek medical advice.²⁻⁵ In a study by King et al,⁶ 17% of patients with tonic-clonic index seizure reported prior tonic-clonic seizures and 28% reported previous minor epileptic symptoms. Moreover, 60% of patients with only non-tonic-clonic seizures reported having other similar seizures before.⁶ Large number of seizures before treatment has been associated with poor prognosis.⁷⁻⁹

Only few studies have assessed the diagnostic delay itself. Firkin et al² found the time from first seizure to diagnosis to be longer than six months in 21% and longer than two years in 14% of participants. The same percentages in a study in Rochester¹⁰ were 50% and over 30%, respectively. In the CAROLE study,³ the median of diagnostic delay was seven months (range from 1 day to 52 years). In the majority of cases (59%), diagnosis was made within the first year, but for up to 15% of patients, the diagnostic delay was over five years.³ In a cohort of newly diagnosed patients with focal epilepsy, Gasparini et al¹¹ discovered a considerable mean delay of seven years (SD 11.3).

Diagnostic delay has been associated with nonconvulsive seizures and socioeconomic disadvantage.² Factors earlier identified to cause diagnostic delay have been (a) no access to medical care, (b) patients not seeking medical care owing to not recognizing the nature of the symptoms, and (c) symptoms brought to medical attention but not diagnosed as seizures.^{3,12}

In the current study, we aimed to assess the diagnostic delay—that is, the time from first seizure to diagnosis—in a cohort of newly diagnosed patients with focal epilepsy. We also studied the impact of diagnostic delay on long-term seizure outcome.

2 | METHODS

The study group was compiled from eight clinical antiseizure medication monotherapy trials conducted at Kuopio Epilepsy Center during 1995-2016. The list of the eight clinical trials is provided as Supporting Information. Patients were diagnosed at the Epilepsy Center by an experienced epileptologist (RK or LJ). All the studies had nearly comparable main inclusion and exclusion criteria: age range of 15-75 years, diagnosis after at least two epileptic seizures within the last 12 months, MRI and EEG performed, and no progressive etiology or active concomitant somatic, psychiatric, or cognitive disease. At our Epilepsy Center, we included in the clinical trials every consecutive patient fulfilling the inclusion criteria and giving their informed consent. In the current study, we included only patients with focal epilepsy. Because our patient records served as the data source for the clinical

Key Points

- Patients with focal epilepsy experience considerable diagnostic delays
- Long diagnostic delay alone might not affect the long-term seizure outcome
- Increasing number of seizures before diagnosis is associated with poorer outcome
- Increasing public and healthcare worker awareness of the diversity of symptoms of epilepsy is important
- Increasing public and healthcare worker knowledge of the morbidity and mortality related to untreated epilepsy is important

trials, they are exceptionally detailed and structured regarding the seizure history. We also followed these patients after the drug trials to obtain long-term follow-up data.

The time of the seizure onset, the number of seizures before diagnosis, and the time of the diagnosis were determined from the patient records. Focal seizure type was divided into three subcategories according to the ILAE 2017 classification¹³: focal aware seizures, focal seizures with impaired awareness, and focal to bilateral tonic-clonic seizures.

Seizure freedom with either first or other medication options was entered on a yearly basis. Response to treatment during the five-year follow-up was divided into three categories:

1. Patient is completely seizure-free during follow-up.
2. Seizure freedom is achieved either by increasing the dosage of or by changing the medication, or patient has had occasional provoked seizures.
3. Epilepsy is refractory—that is, patient has seizures despite medication.

For statistical analyses, the Kruskal-Wallis test and Mann-Whitney U test were used.

All clinical antiseizure medication monotherapy trials were approved either by the Ethics Committee of the Kuopio University Hospital or the Research Ethics Committee of the Northern Savo Hospital District. The patients gave their informed consent before participating in the trial. For the purpose of this retrospective study, no additional informed consent was required, as this is a single-center registry-based study of the follow-up data.

3 | RESULTS

The demographic characteristics of the patients are shown in Table 1. Of 176 patients, 135 (77%) had had more than two seizures before diagnosis and treatment. The majority of these (79 patients, 45%) had had three to ten seizures. The number of seizures before diagnosis is presented in Figure 1. Median number of seizures before diagnosis was 5 (range 2-2000), and the mean was 38 (standard deviation (SD) 190). The median values for focal aware and focal impaired awareness seizures were higher than for focal to bilateral tonic-clonic seizures, 45 (range 2-2000, mean $461 \pm \text{SD } 808$), 11 (range 2-220, mean $26 \pm \text{SD } 47$), and 3 (range 2-30, mean $4 \pm \text{SD } 5$), respectively ($P < .001$). For multiple seizure types, the median was 14 (range 3-351, mean $34 \pm \text{SD } 55$).

Diagnostic delay varied between 0 and 362 months (median 12 months, mean $50 \pm \text{SD } 77$). The longest delay was hereby over 30 years. For 27 patients (15%), diagnostic delay was over 10 years. Diagnostic delay is presented in Figure 2. The diagnostic delay was significantly shorter (median 6 months, mean $35 \pm \text{SD } 72$), if the patient had only focal to bilateral tonic-clonic seizures.

TABLE 1 Demographic data of the cohort

Patient characteristics	n (%)
Gender	
Male	90 (51)
Female	86 (49)
Seizure type	
Focal aware seizures	8 (5)
Focal impaired awareness seizures	25 (14)
Focal to bilateral tonic-clonic seizures	83 (47)
Multiple seizure types	60 (34)
Age (median, range)	39, 15-75 years

In total, 71 patients (40%) remained seizure-free throughout the five-year follow-up. In another 71 patients (40%), seizure freedom was achieved by either increasing the dosage of or changing the medication. Moreover, 24 patients (14%) continued to have seizures despite medication. Outcome could not be determined for 10 patients. Five of these (3%) had a follow-up period of less than five years. Five patients (3%) dropped out of the study owing to noncompliance.

No statistically significant association was observed between diagnostic delay and treatment response ($P = .35$, Figure 3). However, the large number of seizures before diagnosis was associated with poor response to treatment ($P < .001$, Figure 4). Difference in distributions of number of seizures before diagnosis was found between completely seizure-free and other treatment response groups (between groups one and two, $P < .001$; between groups one and three, $P = .001$) but not between groups two and three ($P = .21$).

4 | DISCUSSION

This study shows that patients with focal epilepsy experience significant delays in diagnosis even in developed countries. One third of even those patients who met the strict criteria of clinical trials had had tens or hundreds of seizures before diagnosis. Diagnostic delay might not alone indicate poor prognosis, as also pondered in other reports.¹² This might be attributable to the natural course of epilepsy. In this cohort, some patients had had one presumably unprovoked seizure years before the second seizure. In these cases, a long delay in diagnosis might not affect the long-term seizure outcome. However, when accompanied with recurrent seizures and symptoms misdiagnosed by the patient or healthcare providers, the negative effect of diagnostic delay on prognosis can be considerable.

Numerous factors may pose obstacles to the timely diagnosis of epilepsy and may represent opportunities for

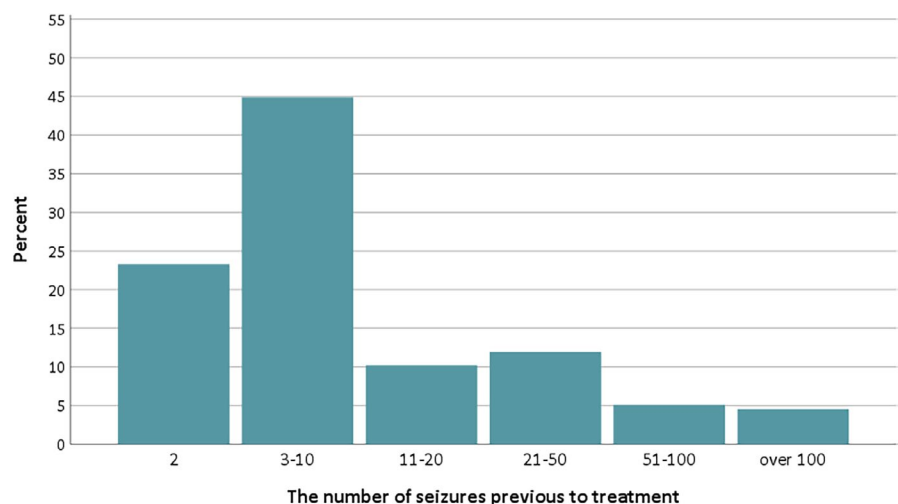


FIGURE 1 The distribution of seizures before diagnosis

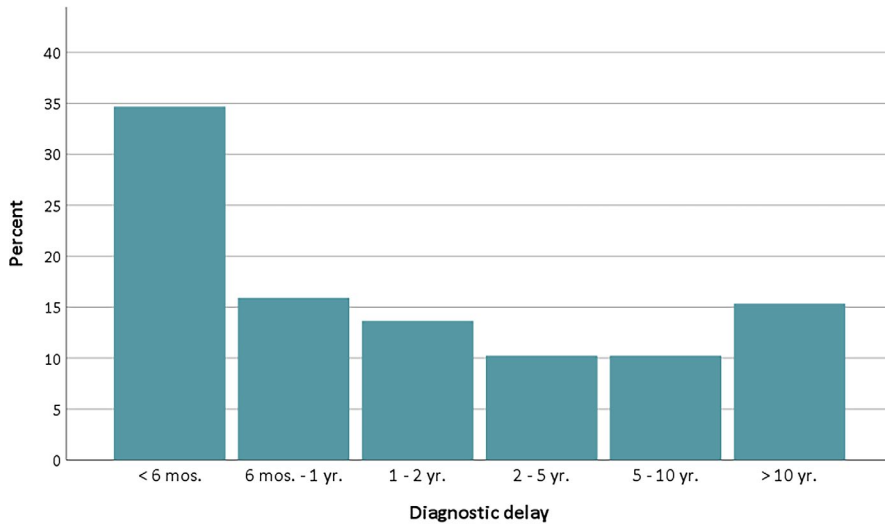


FIGURE 2 The distribution of diagnostic delay

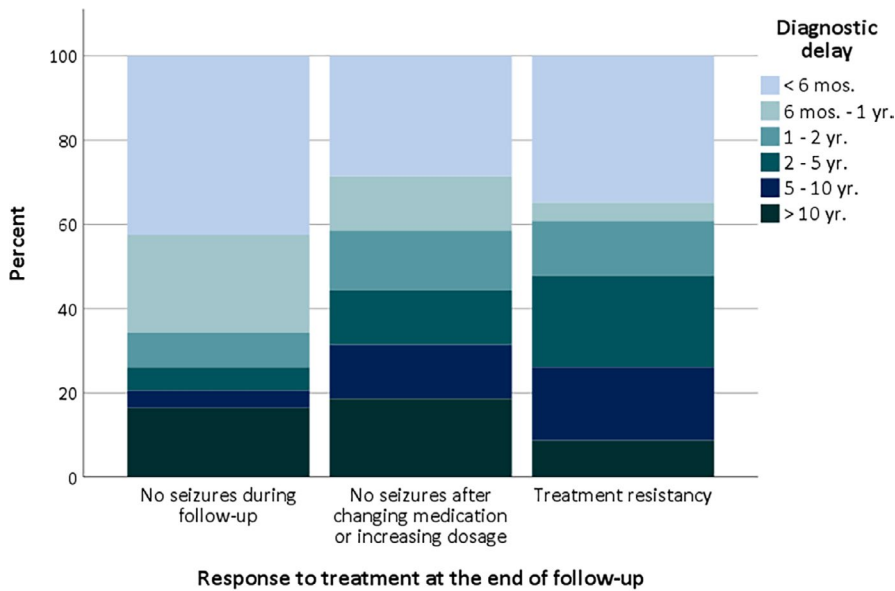


FIGURE 3 Diagnostic delay compared with treatment response

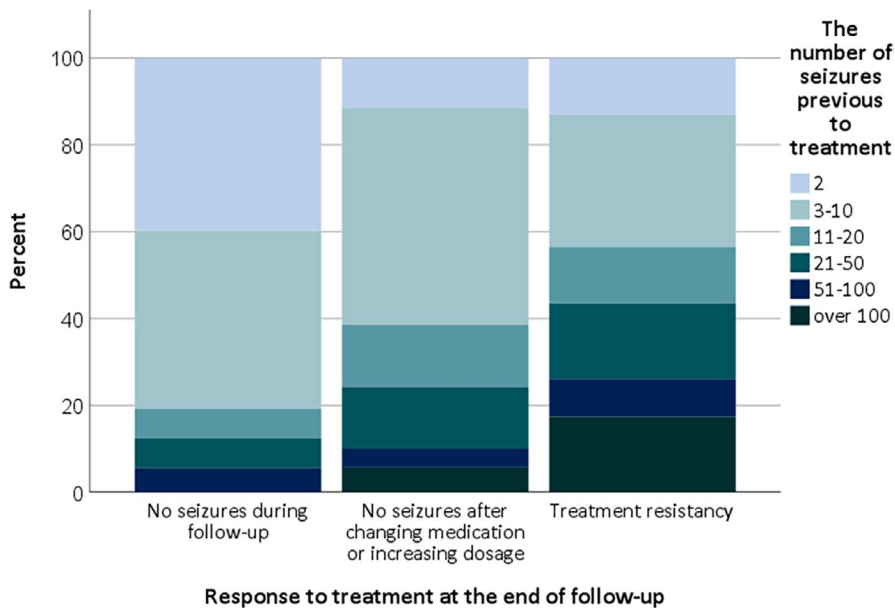


FIGURE 4 The number of seizures before diagnosis compared with treatment response

interventions.^{3,12} Impaired peri-ictal consciousness and memory may play an important role in affecting patients' ability to accurately recognize both the occurrence and nature of their seizures. In formal studies, only about 50% of seizures are reported by patients and underreporting is more frequent for focal seizures with impaired consciousness or seizures occurring during the night compared with generalized seizures or daytime seizures.¹⁴ Lack of awareness that a seizure has occurred appears to be the primary cause for underreporting. Patients might also not recognize subtle events as being of concern.¹⁵ They might have sought help for these symptoms, but physicians may have discounted their seizures as normal or nothing to worry about. Increasing both public health awareness and physician knowledge, particularly among non-neurologists, about the range of seizure types and impact of epilepsy are clearly areas for interventions.

Diagnosis of epilepsy is usually possible following a detailed history and a good eyewitness account. However, situations exist wherein absent or poor eyewitness descriptions or unusual clinical presentations make reaching a definite diagnosis challenging or impossible, at least in the short term. In these situations, diagnostic tests (EEG and MRI) may not be helpful or may even be potentially misleading. Epilepsy specialists are usually more capable of recognizing the limitations in the clinical information and are more likely to admit diagnostic uncertainty than nonspecialists.¹⁶ Risk of misdiagnosis (both positive and negative) in epilepsy is inherent, and clinicians should always be mindful that diagnoses may be wrong and adopt a practice where diagnoses are routinely reviewed.

4.1 | Limitations

This was a retrospective study; therefore, information was gathered from patient records. Patients often struggle to remember the exact number of seizures or the date of the first seizure they experienced. In this study, we minimized this factor by choosing patients from previous clinical trials conducted at Kuopio Epilepsy Center. Thus, for clinical trial purposes the seizure history had been systematically collected from several sources (both from the patient and from the eyewitness/eyewitnesses and family members) to verify history as carefully as possible. The medical records served as the source data for the clinical trials and had been monitored for consistency regarding the seizure history.

In this sample, only 14% of patients had refractory epilepsy. In general, 20%–30% of epilepsy is estimated to be refractory.¹⁷ The low amount of refractory epilepsy might be affected by the long follow-up duration, thus increasing the amount of people achieving seizure freedom. In addition, patients with only one focal seizure and high risk of recurrent seizures were excluded from the antiseizure medication monotherapy trials, as these

patients did not fulfill the inclusion criteria. However, patients with only one focal seizure and structural abnormality of the brain (eg, focal cortical dysplasia or long-term epilepsy related tumor) were most likely diagnosed with epilepsy right after the first seizure due to high risk of recurrence and potential for developing drug-resistant epilepsy. Moreover, the exclusion criteria of clinical trials excluded many comorbidities (active psychiatric or somatic disease or progressive neurological disease or intellectual deficits), leaving this cohort somewhat biased toward better prognosis. Patients were randomized to eight different antiseizure medications and our patients formed only subpopulation of each randomized trial, so the sample size of the study is not large enough to evaluate efficacy of the individual medications.

5 | CLINICAL RELEVANCE OR FUTURE DIRECTIONS

This study illuminates the consequences of delayed diagnosis of epilepsy, which can support further studies in investigating the potential interventions aimed at reducing delayed diagnosis and the potentially preventable harm created by this delay. It is particularly important to increase public health awareness and physician knowledge of all the different seizure types beyond generalized tonic-clonic seizures and the morbidity and mortality related to untreated epilepsy.

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CONFLICT OF INTEREST

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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