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Review

Epidemiology of early stages of epilepsy: Risk of seizure recurrence after a first seizure

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ABSTRACT

A single unprovoked seizure is a frequent phenomenon in the general population and the rate of seizure recurrence can vary widely. Individual risk prognostication is crucial in predicting patient outcomes and guiding treatment decisions. In this article, we review the most important risk factors associated with an increased likelihood of seizure recurrence after a single unprovoked seizure. In summary, the presence of focal seizure, nocturnal seizure, history of prior brain injury, family history of epilepsy, abnormal neurological exam, epileptiform discharges on electroencephalography and neuroimaging abnormalities, portend increased risk of seizure recurrence. Elucidation of these risk factors in patient assessment will augment clinical decision-making and may help determine the appropriateness of instituting anti-epilepsy treatment. We also discuss the Canadian model of single seizure clinics and the potential use to assess these patients.

1. Introduction

In this narrative review we focus on the evidence pertaining to risk of seizure recurrence after a first unprovoked seizure and appropriateness of initiating treatment. Seizures are common and it is suggested that at least 10% of the population will experience one [1]. The evaluation of a patient with a first unprovoked seizure merits close scrutiny, as the clinician must decide if the index event constitutes epilepsy and whether the patient is at heightened risk of seizure recurrence. The answers to these two questions will guide work-up, diagnostic considerations, and the need to initiate anti-epileptic drug (AED) treatment. Seizures carry significant morbidity, ranging from self-injury to death. Quality of life is also affected, with the effects of stigmatization and marginalization evident in employment challenges, driving restrictions, and prejudicial beliefs regarding seizure causation [2].

Initially, the clinician must verify if the index event was a seizure and systematically exclude a broad differential that includes syncope, psychogenic non-epileptic events, transient ischemic attacks, parasomnias, panic attacks, complicated migraines and movement disorders [3]. Owing to the predominance of seizures and seizure mimics, several epilepsy centers around the world have established single seizure clinics.

A first epileptic seizure is a life-changing event with physical and psychological consequences. There is an urgent need to properly assess and manage patients after a single unprovoked seizure. Although, prognosticating seizure recurrence risk may be imprecise, it behooves clinicians to not only review the current state of the evidence, but to strengthen it. In evaluating the patient who presents with a first seizure, the neurologist must decide whether predisposing factors to seizure recurrence exist, and based on those factors, stratify risk of future events.

2. Materials and methods

We performed a narrative review of the evidence on this topic. Our aim was to provide a summary of the evidence on risk of seizure recurrence after a single unprovoked seizure and predictors that may affect that risk. A literature search was performed including Medline, Embase, index medicus, Google Scholars, Current Contents and Cochrane databases for relevant articles published from 1980 to June 2016 using the following key words: first seizure; convulsion; unprovoked seizure; acute symptomatic seizure; epilepsy; children; adolescent; adult; epidemiology; risk; treatment; antiepileptics; medications; therapy; management; recurrence; relapse; prognosis. We searched

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bibliographies of pertinent reviews and original articles; book chapters; expert consultation and our personal archives. Reviews were screened to find additional cases. These searches produced 534 titles of journal articles. Titles and abstracts were reviewed for content regarding first unprovoked seizures and seizure recurrence in children and adults. We included original articles; clinical trials; narrative reviews; systematic reviews and meta-analysis with data on seizure recurrence after a first unprovoked seizure. Publications were chosen based on the quality of data and their relevance to the present review. Articles pertaining to neonatal seizures; febrile seizures; myoclonic seizures; absences; infantile spasms; epileptic encephalopathy; diagnosed epilepsy and status epilepticus were excluded. Full texts of all remaining articles were screened. Two authors independently screened and reviewed all the documents. We considered all outcomes in children and adults. Children were classified as those with age of less than 16 years.

3. Results

Five hundred and thirty-four articles were identified, and after titles and abstracts were reviewed, we excluded 452. Eighty-two full text articles were reviewed, including original articles, clinical trials, meta-analysis, systematic reviews and narrative reviews.

3.1. First seizure classification

Etiologically, seizures are subdivided into the following categories:

1) Provoked immediate (caused by toxin, medication, or metabolic factors);
2) Acute symptomatic (a seizure occurring at the time of a systemic insult or in close temporal association with a documented brain insult, such as stroke, traumatic brain injury, active infection for central nervous system infection. Suggestions are made to define acute symptomatic seizures as those events occurring within 1 week, however it may often exceed the first seven days) [4];
3) Remote symptomatic (seizure caused by preexisting brain injury);
4) Seizure associated with epileptic syndrome (e.g., juvenile myoclonic epilepsy);
5) Unidentified [5].

Based on ILAE criteria, a seizure provoked by transient factors acting on an otherwise normal brain to temporarily lower the seizure threshold does not count toward a diagnosis of epilepsy. In the literature, the term “provoked seizure” appears synonymous with “situation-related seizure”, “reactive seizure” and “symptomatic seizure” [6].

3.1.1. Provoked immediate seizures

Provoked immediate seizures typically result from severe metabolic derangement documented within 24 h of onset [4]. Common causes are alcohol or benzodiazepine intoxication or withdrawal, hyponatremia, hypocalcaemia, hypomagnesemia, hypoglycemia, hyperglycemia, exposure to epileptogenic drugs such as antibiotics, antipsychotics, antidepressants, pain medications, amphetamines, sympathomimetic agents, hallucinogens, and other drugs of abuse, (e.g. clozapine, tramadol, imipenem, theophylline, bupropion, cocaine, amphetamines, normeperidine, meperidine, methaqualone, glutarimide, inhalants and phencyclidine). The etiology is usually toxic-metabolic and the risk of recurrence is low in the absence of the provoking factor [5]. Regardless of their multiplicity, symptomatic seizures do not confer a diagnosis of epilepsy. It merits consideration, however, that external stresses may unmask underlying epilepsy in susceptible individuals. It its important to bear in mind that in an individual with an enduring predisposition to have seizures, a borderline provocation might trigger a seizure, whereas in a non-predisposed individual, it might not [6]. Moreover, people with epilepsy can also experience immediate provoked seizures [4].

3.1.2. Acute symptomatic seizures

Acute symptomatic seizures are an emergent manifestation of the insult and may not recur when the underlying cause has been removed or the acute phase has elapsed. It represents 40–50% of all cases of seizures [7]. The risk of acute symptomatic seizures is higher in males than females. This sex difference has been attributed to the disparate incidence of predisposing risk factors such as head trauma [8].

Causes of acute symptomatic seizures in developed countries may differ from the causes in developing countries. A study in India demonstrated that a single CT enhancing lesion was the provoking factor in 50% of patients and meningitis in 28% [9]. Similarly, a recent study in Nigeria found 94 cases of acute symptomatic seizures accounting for 5.2% (95% CI: 4.17–6.23) of 1802 medical admissions. The etiological risk factors were infections in 36% of cases, stroke in 30%, metabolic in 13%, and toxic in 11%. Neuroinfection was predominant in patients below 50 years of age while stroke was more in those aged 50 and above. HIV infection was the etiological risk factor for 12% of cases [10].

The risk of presenting an acute symptomatic seizure changes with the age and the particular risk factor. In a cohort of 270 children with meningitis in Brazil, 24% suffered at least one in-hospital seizure. The factors described in the group with seizures were impaired mental status (OR 3.47 CI 95% 1.66–7.26 $p = 0.001$), and streptococcus pneumoniae etiology (OR 4.55 CI 95% 1.88–11.0 $p = 0.001$) [11]. Other acute symptomatic seizures are seen in association with arterio-venous malformations, multiple sclerosis relapse, autoimmune diseases relapse and anoxic encephalopathy, among others and the etiology is highly variable in studies [4].

Acute symptomatic seizures may not necessarily confer a diagnosis of epilepsy. Although initial mortality in the first month is higher, the overall risk for seizure recurrence is relatively lower. Over a 10-year period, individuals with a first acute symptomatic seizure were 80% less likely to experience a second unprovoked seizure compared to individuals with a first unprovoked seizure due to a remote symptomatic cause [12].

3.1.3. Unprovoked seizures

Unprovoked seizures include remote symptomatic seizures (directly related to prior brain injuries or lesions such as stroke), seizure associated with epileptic syndrome (underlying genetic basis) and unidentified seizures. As the term implies, unprovoked seizures, by contrast, occur in the notable absence of an inciting stimulus [5]. The unprovoked seizure, therefore, raises concerns of an underlying predisposition towards generating epileptic seizures. A single unprovoked seizure carries a twofold increase in risk of death, which is in keeping with standardized mortality ratios of 1.6–4.1 in epilepsy [13].

3.2. Incidence of unprovoked seizures

The incidence of unprovoked seizures varies from 50 to 70 per 100,000, and of epilepsy from 30 to 50 per 100,000 [14–18]. A review of the Stockholm Incidence Registry of Epilepsy reported the crude incidence rate of all unprovoked seizures as 33.9 per 100,000 person years. The incidence rates were highest among males >85 years of age (96.9/100,000 person years) and among the very young (77.1 per 100,000 person years under 1 year of age) [19].

Diagnostic uncertainty remains a challenge, for instance, in a pediatric single seizure clinic 25% of children were incorrectly diagnosed as having an unprovoked seizure, while the diagnosis of epilepsy was missed in over 30% [20]. Up to 50% of patients assessed for suspected new-onset seizures report previous undiagnosed events [21]. Up to 30% of patients with generalized seizures have previously unreported myoclonus or absences [1]. Unless specifically ascertained by the clinician, focal seizures and auras, may not be volunteered by the patient. Hamiwka et al. [20] reported in their pediatric single seizure clinic study that 38% (36/94) of cases had suffered at least one previous episode. In some cases the event was unrecognized by the family or caregiver, the event was misdiagnosed for the attending physician, or the family did not seek medical attention. Over half had partial complex seizures [20]. Delay appears particularly likely when events are nonconvulsive or low-impact (simple partial seizures), suggesting that these seizure types may be underrepresented in studies of new-onset epilepsy [21].

3.3. Epilepsy definition

There is conflicting data regarding the suggestion that a cluster of seizures occurring within a 24-h time span confers the same overall recurrence risk as a single seizure. In 2006 Kho and colleagues [22] compared 72 patients with multiple seizures in a 24-h period as their first seizure presentation to 425 patients presenting with a single seizure. The group of multiples seizures had a recurrence rate of 40% (29/72), and the single seizure group had a rate of 38% (162/425). There was no significant difference in seizure recurrence between the multiple and single seizure groups at the first year; irrespective of etiology or treatment. The risk of recurrence seems to be similar in children. A pediatric study established that even when the initial seizure presentation is status epilepticus (mean time of 42.5 min), recurrence of epilepsy in children younger than 16 years of age occurs only in 21.5% [23].

However, a population-based study of a pediatric cohort with 490 children determined that ≥2 seizures occurring within 24 h carry a similar risk of recurrence (42%) to a child with two seizures occurring on different days (44%). Therefore, the authors stated that if two or more unprovoked seizures occur on the same day, the child has epilepsy and will have a clinical course identical to that of the child with a longer time interval between the first two seizures [24]. According to the ILAE, epilepsy is defined as the occurrence of least two unprovoked seizures occurring more than 24 h apart; one unprovoked seizure and a probability of further seizures recurrence risk of 60% or more over the subsequent 10 years; or the diagnosis of an epileptic syndrome [6]. This new definition emphasizes the importance of treating some patients after a single seizure.

3.4. Risk factors for seizure recurrence (see Table 1)

3.4.1. Etiology

The overall risk of recurrence after a first generalized tonic–clonic seizure is approximately 30% at 5 years, assuming that subtle prior seizures or known ongoing risk factors are absent [50]. If the seizure is idiopathic, only 17% had a recurrence at 20 months. If the seizure was idiopathic and the patient had a sibling with seizures, the risk of seizure recurrence increased to 29%, and if the seizure was idiopathic with spike-wave discharges on electroencephalogram (EEG), the risk of seizure recurrence increased to 50% [50]. The recurrence rate is higher in individuals who have a symptomatic etiology compared to those with an idiopathic or cryptogenic etiology. For children with first seizures that are

Table 1
Identified risk factors for seizure recurrence after first unprovoked seizure.

Seizure recurrence factors, studies = 26		
Factor	Studies	Author/year
Age (<2 yo)	1	Hirtz et al. [25]
(<16 yo)	1	FIR.S.T. [26]
(>50 yo)	1	Hopkins et al. [27]
Sex (women)	1	Gilad et al. [28]
Duration of seizure	1	Das et al. [29]
Type of seizure (partial)	9	Hirtz et al. [25], Annegers et al. [30], Shinnar et al. [31], Bora et al. [32], Stroink et al. [33], Ramos-Lizana et al. [34], Daoud et al. [35], Kim et al. [36], Pereira et al. [37], Mizorogi et al. [38].
Multiples seizures (≥2 seizures)	2	Hauser et al. [39], Kim et al. [36]
Nocturnal seizure (sleep state)	6	Hopkins et al. [27], Shinnar et al. [40], Bora et al. [32], Shinnar et al. [41], Martinovic et al. [42], Ramos-Lizana et al. [34].
Etiology (remote symptomatic)	4	Annegers et al. [30], Shinnar et al. [31], Shinnar et al. [40], Shinnar et al. [41].
EEG epileptic abnormality	14	Annegers et al. [30], Shinnar et al. [31], Donselaar et al. [43], FIR.S.T. [26], Shinnar et al.* [40], Shinnar et al. [44], Martinovic et al. [42], Stroink et al. [33], Das et al. [29], Winckler et al. [45], Kim et al. [36], Pereira et al. [37], Kanemura et al. [46], Mizorogi et al.** [38], Paliwal et al. [49].
Epilepsy family history (first degree relatives)	4	Hauser et al. [47], Shinnar et al. [31], Das et al. [29], Daoud et al. [35].
Neurological exam (abnormal)	3	Annegers et al. [30], Hauser et al. [39], Kim et al. [36].
Neuroimaging (abnormality on MRI)	2	Arthur et al. [48], Paliwal et al. [49].

*In this study an abnormal EEG was defined as any EEG abnormality, whether epileptiform or not. ** EEG abnormality as a risk factor was statistically significant ($p < 0.001$) when there was focal epileptiform activity.

idiopathic/cryptogenic, the recurrence risk is 40% by 2 years, while for symptomatic seizures the estimate of recurrence risk is above 50% [51] .

Patients with head trauma have a high recurrence risk (46% at 20 months). Overall, a history of a previous neurologic injury is associated with a 2.5-fold increased risk of recurrence [5]. Prolonged seizures, status epilepticus, prior acute symptomatic seizures, and a Todd paralysis also increase the risk of recurrence in patients with remote symptomatic seizures [50]. A population-based study in Italy reported that among ischemic strokes, seizure recurrence risk factors were younger age ($p = 0.004$) and cortical location of stroke ($p = 0.004$). Within intracerebral hemorrhages, the only risk factor for seizure recurrence was the presence of a previous early seizure ($p = 0.017$) [52].

3.4.2. Electroencephalogram

In children, the 5-year recurrence risk after a first seizure hovers around 42% [41]. Shinnar et al. [53] observed that the risk of seizure recurrence in a child with a first seizure in the presence of epileptiform abnormalities on EEG is comparable to the recurrence risk after a second seizure (>50% likelihood of seizure recurrence). In their quantitative review of 1930 patients, Berg and Shinnar [1] determined that an abnormal neurological exam or EEG, and partial epilepsy emerged as the strongest predictors of a second seizure. The lowest seizure recurrence risk was in the idiopathic group with normal EEGs (24%, 95% CI = 19%, 29%) and the highest risk was carried by the group with remote symptomatic seizures and abnormal EEGs (65%, 95% CI = 55%, 76%).

Recently a meta-analysis examining patients who underwent routine EEG after a first unprovoked seizure and were followed for seizure recurrence for at least 12 months, was published. They reported differences between adults and children. An adult with epileptiform discharges on routine EEG after a first unprovoked seizure has a 77% probability of having a second seizure, whilst a child with similar findings has a 66% probability [54]. Another study evaluated the yield of 24-h video-EEG in assessing recurrence risk after a first unprovoked seizure. Chen and colleagues reported a risk of recurrence of 73.2% in the epileptiform discharges abnormality group. Overall, epileptiform abnormalities were associated with an increased risk of seizure recurrence (RR 2.84, 95% CI 1.67–4.82, $p < 0.001$) [55]. Finally there is a study by Dash et al. [56] assessed the yield of portable EEG in adult population. In this study the portable EEG was used in a subgroup of patients with clear single unprovoked seizures. Epileptiform activity was identified in all of them. These patients were started on medication. This study suggests that the identification of epileptiform activity in patients with single unprovoked seizures using prolonged recording could help to avoid seizure recurrence.

3.4.3. Epidemiological factors

Epidemiological studies indicate that most patients with a single unprovoked seizures range between 16-60 years of age, with an average age of 40 [27,57]. Putatively, elderly and patients younger than 12 years could have a higher risk of recurrent seizures.

A positive family history, history of febrile seizures, partial seizures and a Todd paralysis increase the risk for epilepsy later in life [47]. Finally, children whose first seizure occurred during sleep demonstrated a 75% chance for recurrence by 2 years, compared to 49% for those who did not [34]. However, no one factor reliably portends a high recurrence risk, and a clinician must take into account the totality of clinical evidence in order to formulate a specific patient's recurrence risk.

3.5. Treatment after a single unprovoked seizure

A self-propagating mechanism of kindling – seizures promoting the occurrence of more seizures, causing intractable epilepsy – has been cited as a reason to start early AED treatment after a first seizure. However, despite evidence of kindling and secondary epileptogenesis in animal models, there is no firm evidence of this phenomenon occurring in humans [58]. The decision to initiate AED treatment is relatively straightforward in patients who experience two or more unprovoked seizures, and hence have a diagnosis of epilepsy. The decision to treat a patient in the wake of a solitary unprovoked seizure is more complex and requires a thorough consideration of various demographic and personal risk factors such as socioeconomic impact, stigma, sick role, medical comorbidities, patient age, employment, need to drive, insurance concerns, personal preference, and AED side-effect profile and teratogenicity. The adverse effects range from mild symptoms to life threatening reactions and up to 30% of patients discontinue their first prescribed AED due to adverse effects [50,60]. In the National General Practice Study of Epilepsy, only 15% of patients received AED treatment after a first seizure [61]. AED treatment was justified when there was a high risk of seizure recurrence or potential for serious injury.

3.5.1. Evidence from clinical trials (See Table 2)

Data from six clinical trials [26,28,29,62–64] confirm that a robust effect of commencing AED treatment after a first unprovoked seizure is a significant reduction in seizure recurrence risk. Nonetheless, owing to limitations with respect to study design, methodology, patient selection, and follow-up duration, the results of these trials cannot be generalized to all patients. Only one study [63] used a double blind design including participants, providers and outcome assessors. All the other studies were open randomized trials. Two trials assessed only generalized seizures [26,28]. Another [64] randomized patients with single or multiple seizures. One study [62] included only children. A single trial included also subjects older than 1 month of age [29]. Additionally, selection bias cannot be entirely excluded because the random sequence generation was described in only three studies [26,62,64] .

A meta-analysis of these six trials [65] concluded that the overall absolute risk reduction was 34% (CI 95% 15%–52%). Of note, the two studies with the lowest effect size, 21% [26] and 8% [64] were also the largest trials. The authors determined the presence of EEG epileptiform abnormalities, family history of epilepsy, imaging lesions, and remote symptomatic seizures increased the risk of recurrence. However, the results of these investigations confirmed that the prognosis for the development of epilepsy does not appear to be altered by early intervention. The explanation of this statement, however, is nuanced, as patients enrolled in the RCTs did not remain in their assigned treatment groups over the long-term. For instance, by three years of follow-up, many patients had crossed over from their initial trial assignments.

A Cochrane systematic review [66] of the same six randomized and quasi-randomized controlled trials reported as high quality evidence that patients randomized to immediate AED treatment had a lower probability of recurrence at one year (RR 0.49, 95% CI 0.42–0.58, $p < 0.00001$), at five years (RR 0.78; 95% CI 0.68–0.89; $p = 0.00028$) and a higher probability of an immediate five-year remission (RR 1.25; 95% CI 1.02–1.54, $p = 0.033$). However there was no difference between immediate treatment and control in terms of five-year remission at any time (RR 1.02, 95% CI 0.87–1.21, $p = 0.95$) [66]. Their findings overlap with the results of the previous meta-analysis [65]. It is important to emphasize that despite their high incidence of first seizures, elderly and children populations are under represented in these trials.

Table 2
Heterogeneity and biases of the published clinical trials.

Randomized and quasi-randomized clinical trials N = 6											
Author/ year	Randomized	Blinded	Selection bias	Attrition bias	Reporting bias	Intervention/ control	Total	Population	Seizure recurrence intervention group (%)	Seizure recurrence control group (%)	Outcome time (months)
Camfield et al. [62]	Yes	No	No	No	No	14/17	31	Children	14.3	52.9	12
Chandra et al. [63]	Yes	Yes***	Yes	Yes	Yes	115/113	228	Adults	4.3	55.7	12
FIR.S.T* [26]	Yes	No	No	No	No	204/193	397	Adults	18	39	12, 24, 60
Gilad et al. [28]	No**	No	Yes	No	No	46/45	91	Adults	22	71	12, 24, 36
Das et al. [29]	Yes	No	Yes	Yes	Yes	40/36	76	Adults	11.1	45	3, 6, 9, 12, 18, 24
Marson et al.*^ [64]	Yes	No	No	No	No	722/721	1443	Neonates, children, adults	18	26	12, 24, 36, 60
Total						1141/1125	2266				

*FIRST and MESS were the only two multicenter randomized clinical trials, as well as the largest population studies. ^This study included patients with documented history of one or multiple clinically definite unprovoked seizures. **Gilad 1996 was a quasi-randomized study. ***Chandra 1992 is the only blinded study. They used placebo in the control group.

The MESS trial [64] was a large, pragmatic, multicenter; unmasked trial in which 722 patients were assigned to immediate AED treatment while 721 were assigned deferred treatment. This trial included patients with history of one or multiple unprovoked seizures. An absolute recurrence risk reduction of 8% at 6 months and 6% at 8 years was observed with immediate treatment. Furthermore, immediate treatment resulted in significantly increased time to the next seizure and reduced time to achieve 2-year remission. However, 76% of patients in the immediate treatment group and 77% of those in the deferred treatment group were seizure free between 3 and 5 years after randomization. The issue of potential selection bias is pertinent, as enrollees were recruited if both the clinician and the patient were uncertain as to whether to commence AED treatment, thus participants may not be representative of the general population of people presenting with a first seizure. It is conceivable that patients with remote symptomatic first seizures who were likely to have a poor outcome if left untreated were excluded. It bears emphasis that a comparison was made between immediate versus deferred treatment as opposed to no treatment. The convergence of outcomes between the two groups may reflect some patients achieving AED withdrawal due to remission in the treated group and untreated subjects receiving later treatment secondary to seizure recurrence.

Further analysis of the MESS trials results in the form of a prognostic model where number of seizures, presence of a neurological disorder, and an abnormal EEG were significant factors in indicating future seizures. Individuals with two or three seizures, a neurological disorder, or an abnormal EEG were identified as the medium-risk group, those with two of these features or more than three seizures as the high-risk group, and those with a single seizure only as the low-risk group. The model suggested that there is little benefit to immediate treatment in patients at low risk of seizure recurrence, but potentially worthwhile benefits are seen in those at medium and high risk [36].

FIRST [26] was a multicenter, randomized, open trial, of patients with a first tonic-clonic seizure of 419 patients who were randomized to immediate treatment or to treatment only after another seizure. The probability of achieving a 2-year remission was 72 versus 57% at 3 months, 84 –79% at 3 years, and 85 to 86% at 10 years (not statistically significant). The probability of entering 5-year remission was 47–40, 58–58, and 64–64% (not statistically significant). Early treatment did not affect the long-term prognosis of epilepsy. Age (younger than 16) and EEG abnormalities were found to be significant predictors of seizure relapse [68]. Notably, patients treated after the first seizure and those treated after seizure relapse had the same probability of achieving seizure-free remission at 1 and 2 years. Recent follow-up data indicated that starting AED treatment immediately or only after seizure recurrence did not affect survival over the following 20 years [68].

Gilad et al. [28] found that treated men (<40% treated vs. 90% untreated $p < 0.001$) were less likely to have recurrent seizures than were treated women (45% treated vs. 70% untreated $p = 0.03$). The authors also noted that in a 3-year study, the highest rate of recurrence was in the first year, when untreated patients had 3 times as many seizures as treated patients. Chandra et al. [63] conducted a double blind and placebo-controlled trial of 228 patients with one single seizure 2 weeks before presentation to the investigator. One group received sodium valproate, while the control group received placebo over 12 months. The results of this trial revealed a significant difference in seizure recurrence in those treated with valproic acid (4.3%) versus placebo (55.7%). Time of follow-up was variable and remission and risk recurrence factors were not assessed.

Two smaller trials [29,62] showed a significant reduction in seizure recurrence in treated patients in the short-term. Das et al. [29] obtained a follow-up duration of up to 2 years and found 11.1% seizure recurrence in treated versus 45% in untreated patients ($p < 0.002$). Analyses revealed that patients of a single unprovoked idiopathic seizure with a normal CT scan are less likely to have a recurrence if the duration of seizure at presentation is short, EEG is normal, more than 3 months have passed since the first seizure and if treatment has been started. Camfield et al. [61] followed children for a year and found 14.3% seizure recurrence in treated versus 52.9% in untreated patients ($p = 0.0295$). After 15 years of follow-up the Nova Scotia group reassessed the relapse [69] in the 31 patients randomized in 1989 [62]. They were able to contact 26 (84%) of the original patients. Over the next 15 years the overall recurrence rate after a first seizure in this cohort was 58%. Seizure freedom during more than 2 years was achieved by 80% of the treated group and 88% of controls (RR, 0.73; 0.24–2.2). According to it for children

treated with AED after a first seizure, the subsequent clinical course and remission rates are not improved in comparison with a no-treatment strategy [69]

3.5.2. The model of single seizure clinics

As part of the integrative evaluation of patients with presumed seizure episodes we have created a model for medical attention called Single Seizure Clinic (SSC) [70]. Patients with a single seizure are referred with an epileptologist, who performs detailed clinical history taking and a neurological examination. Based on their assessment, the epileptologist may decide if further investigations (e.g. neuroimaging, video EEG telemetry, EKG, or Holter monitoring) are required. If the patient's spells are deemed to be non-epileptic, the epileptologist may suggest that the referring physician redirect care as appropriate.

In our initial experience, 200 patients were evaluated prospectively over two years (2011–2013). Ethics approval was obtained from the University of Saskatchewan Research Ethics Board (Saskatoon, Saskatchewan, Canada). Mean patient age was 42.1 years. The largest referral sources were emergency department physicians (52.5%) and general practitioners (36.5%). A diagnosis was established at first contact in 80.5% of cases while 16.0% of patients required a second visit. Only 1.5% of patients required three consultations. No conclusive diagnosis could be made in 2.0% of cases. Eighty-two patients (41%) were diagnosed with epilepsy. For the diagnosis of epilepsy, the 2005 criteria established by the ILAE were utilized [71]. The epilepsy syndrome could not be classified in 7.5% of cases. As patient evaluation revealed that syncope was diagnosed in 20%, single unprovoked seizure in 14%, psychogenic non-epileptiform spells in 11%, convulsive syncope in 4%, and alcohol withdrawal seizures in 4.5%. The study emphasized the importance of an informative historical account as historical risk factors for an epilepsy diagnosis were: being amnestic to event (OR = 2.45, 95% CI 1.22–4.9, p = 0.010), limb stiffening (OR = 2.03, 95% CI 1.03–3.98) p = 0.038, tongue trauma (OR = 5.80, 95% CI 2.86–11.8, $p < 0.001$), and incontinence (OR = 4.15, 95% CI 1.63–10.5, $p < 0.001$). Moreover, light-headedness before the seizure (OR = 0.18, 95% CI 0.06–0.54, $p < 0.001$) reduced the likelihood of a patient being classified as having epilepsy [70].

An abnormal MRI was found in 18% of the epilepsy cases (OR = 2.7, 95% CI 1.1–6.5, p = 0.02). On the other hand, a normal EEG was found in 76.3% of patients without epilepsy in comparison to 36% of patients with epilepsy (OR = 0.18 95% CI 0.09–0.33) $p < 0.01$. Generalized epileptic discharge was found in 41% of patients with epilepsy and focal spikes were found only in 11% of this group of patients. A total of 63 patients were started on AED and the most common used AED was lamotrigine. In 43 (21.5%) cases, the referring physician notified the local motor vehicle licensing authority of the need for driving restrictions. In 36 (18%) cases, the SSC epileptologist had to make this referral. In total 39.5% of patients were restricted to drive. The SSC appeared to expedite patient assessment. Our study compared the waiting times with a previous study using the usual care [72]. The mean wait-time for first assessment by an epileptologist was 23.6 days (2–134 days) at the SSC, versus 80.1 days (0–550 days) with usual care, representing a reduction of mean wait-times by 70.5% ($p < 0.0001$). The mean wait time for an EEG was 4.0 days (0–150) versus 37.1 days (0–255 days) with usual care, a mean wait-time reduction of 89.2% ($p < 0.0001$). Mean wait-time to perform an MRI was 44.9 days versus 81.3 days with usual care, representing a reduction of 44.7% ($p < 0.0001$) [71]. The SSC model reduces wait-times, streamlines assessments, and impacts clinical care decisions.

3.6. Clinical recommendations

3.6.1. Recommendations in adults

One out of 1500 adults in the U.S. will experience unprovoked first seizure, with the profound physical, emotional and social consequences [73]. In 2015, the American Academy of Neurology published an evidence-based guideline on the management of an unprovoked first seizure in adults [74]. As less than 50% of patients who have a first unprovoked seizure will have a second episode, the evaluation must focus on determining the patient's risk of seizure recurrence [4]. The guidelines state that risk of recurrence is greatest in the first 2 years (21–45%) [73]. The AAN described four clinical factors with the highest risk of recurrence: EEG with epileptiform abnormalities, a prior brain insult such as stroke or head trauma (remote symptomatic etiology), a significant de novo brain-imaging abnormality and a nocturnal seizure [75]. Although the new ILAE definition states a patient can be diagnosed with a first seizure and a risk of 60% to have another seizure, no formula can be applied for additive risks since there is no evidence about the risks combination, and the final risk have to be decided by individualized considerations [6].

In evaluating the adult with a "first" seizure, the physician must ensure that this truly is the "first" seizure occurrence. It is common for patients to seek medical care after the first generalized tonic-clonic seizure, but they may not report myoclonic jerks, nocturnal tongue biting, or subtle dyscognitive features [4]. Early AED therapy is likely to reduce the risk of a second seizure over the next 2 years, but the delay in initiating therapy until after a second unprovoked seizure do not influence the chance of long-term remission (i.e. >3 years) [73]. The risk of side effects with AEDs is 7–31% and they are often mild and reversible, however it is important to consider that the studies concluding it used first-generation AEDs, although the second- or third-generation of AEDs could be better-tolerated by patients.

After a patient suffers the second seizure the risk for a subsequent seizure is almost 60% by the first year and 70% by four years. With this high risk, the rationale to initiate AED treatment is fairly convincing [75]. An EEG and high-resolution MRI are the methods of choice for an accurate diagnosis after a first seizure presentation. Together with a careful history and examination, they will allow definition of the epilepsy syndrome in two-thirds of patients and help assess the individual risk for seizure recurrence [76]. The duration of the EEG study (20 min study vs. an extended 24–48 h), and how soon EEG is initiated after the index event need to be addressed.

3.6.2. Recommendations in children

Before any treatment decisions are approached, it is critical to determine whether the event is truly a seizure and whether it is in fact the first seizure event. The decision as to whether or not to treat children and adolescents who have experienced a first unprovoked seizure must be based on a risk-benefit assessment that weighs the risk of having another seizure against the risk of chronic therapy. As in adults, early treatment with AED reduces the risk of early seizure recurrence, but does not prevent the development of epilepsy. Additionally, AED therapy in children has potential side effects such as somnolence, headache, anorexia, nausea or abdominal pain, increased irritability, rash, hirsutism, weight gain (7–58%), and significant cognitive, behavioral and psychosocial side effects, particularly affecting brain development during infancy [51].

Clinicians must involve the patient and caregivers in the shared decision making process. In general, clinicians should advise patients with an unprovoked non-febrile first seizure that the risk of recurrence is highest in the two years following the seizure. Family should also be informed of factors that place a child increase

risk, as well as initiation detailed discussion of the side-effect profiles of relevant AED agents. Ultimately, the decision to withhold or initiate AED treatment is based on assessment of individualized risk and benefit as determined by the clinician [6].

4. Conclusions

The available literature demonstrates that although early AED treatment robustly reduces seizure recurrence risk in the short-term, the prognosis for the development of epilepsy is unchanged. The indication for early AED treatment depends on the presence of key risk factors such as epileptiform abnormalities on EEG, a remote symptomatic etiology, a significant abnormality on neuroimaging, abnormal neurological exam, and a nocturnal seizure among others. A decision on whether to initiate AED treatment following a first seizure must therefore be tailored to an individual's patient's clinical, demographic, and socioeconomic profile. We propose the creation of single seizure clinics around the world to improve the referral of patients.

Conflict of interest

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