Challenges in the first seizure clinic for adult patients with epilepsy

Anvesh Jackson [1], Louise Teo [1], Udaya Seneviratne [1,2]

[1] Department of Neuroscience, Monash Medical Centre, Clayton
[2] School of Clinical Sciences at Monash Health, Department of Medicine, Monash University, Melbourne, Victoria, Australia

ABSTRACT – *Aims.* (1) To delineate the challenges in seizure diagnosis in the first seizure clinic setting for adult patients of a teaching hospital, and (2) quantify the diagnostic accuracy of the referral source and the yield of routine investigations, including blood tests, EEGs, and neuroimaging.
Methods. We retrospectively reviewed medical records of patients referred by the emergency department to the adult first seizure clinic and seen by the same epilepsy specialist between June 2007 and June 2011. The diagnostic accuracy in the emergency department was calculated by comparing with the final diagnosis made by an epilepsy specialist.
Results. In total, 219 patients were referred to the first seizure clinic. Median age was 45 and 60% of patients were male. From the cohort, 38 (17%) patients presented with seizure mimickers; the most common were reflex syncope (74%) and psychogenic non-epileptic seizures (16%). From the remaining 181 patients presenting with seizures, only 110 (61%) of these patients were diagnosed with true first seizures, and 71 (39%) patients had evidence of previous seizures. Nineteen (17%) of true first-ever seizures were provoked. The most frequent cause of provoked seizures was alcohol and illicit drugs (65%). In the emergency department, sensitivity and specificity in seizure diagnosis were 0.74 and 0.32, respectively. In our true first seizure patients, the EEG demonstrated epileptiform discharges in 22 (21%) patients. In the same cohort, computed tomography and magnetic resonance neuroimaging conferred 16% and 20% probability of finding a potentially epileptogenic structural abnormality, respectively. The most common epileptogenic abnormality found on magnetic resonance neuroimaging was cortical infarct.
Conclusions. The diagnosis and management of first seizure remains challenging due to the variety of seizure mimickers and low yield of investigations. Our data highlight the potential pitfalls and practical challenges in this process, as well as the need for these patients to be assessed in dedicated first seizure clinics.

Key words: first seizure, seizure mimicker, psychogenic non-epileptic seizure, syncope, emergency referral epilepsy

Correspondence:
Udaya Seneviratne
Department of Neuroscience,
Monash Medical Centre,
Clayton, Melbourne VIC 3168, Australia
<udaya.seneviratne@monash.edu>

The first seizure is a common clinical problem encountered by general practitioners, emergency physicians, and neurologists. Approximately 6% of the population is likely to experience an afebrile seizure during their lifetime, and this value increases to 8% when febrile seizures are taken into account (Hauser and Kurland, 1975). Further, the median annual incidence of unprovoked seizures is 56 per 100,000 (Kotsopoulos *et al.*, 2002), with the incidence of single unprovoked seizures ranging from 23 to 61 per 100,000 person-years (Hauser and Beghi, 2008).

Seizure recognition holds great importance as the failure of diagnosis leads to inappropriate management. Furthermore, overlooking previous seizures amounts to a missed diagnosis of epilepsy, potentially resulting in under-treatment. The misdiagnosis places patients at significant medical risk, including the risk of burns, drowning, head injuries, and death. In addition to this medical risk is the often unappreciated social morbidity, including anxiety of seizure recurrence and negative effects on mood (Marsh and Rao, 2002). There are also considerable implications for employment and driving (Brown *et al.*, 2015).

The diagnosis of epilepsy is usually considered in patients with a history of two or more unprovoked seizures occurring at least 24 hours apart (Fisher *et al.*, 2014). This knowledge should prompt clinicians to ascertain whether first seizure presentations reflect a *true* first seizure or whether patients have a history of past seizures. Epilepsy may now be diagnosed in patients who have experienced a single unprovoked seizure with a recurrence probability of 60% or more in the following 10 years (Fisher *et al.*, 2014). This highlights the important role of first seizure clinics, not only to give a verdict amongst diagnostic dilemmas but also to guide appropriate and individualised management plans.

In our study, we sought to investigate practical challenges in the first seizure clinic due to difficulties in first seizure diagnosis, as well as the variable yield of investigations in the diagnostic work-up, including blood tests, EEG, and neuroimaging. We hypothesised that poor diagnostic sensitivity and specificity of the referral source, as well as low yields in investigations, pose challenges in the first seizure clinic setting.

Materials and methods

Study design

We retrospectively reviewed medical records of patients referred by the emergency department (ED) to the adult first seizure clinic and seen by the same epilepsy specialist (US) at Monash Medical Centre, Melbourne, Australia between June 2007 and June 2011. Patients were identified from the electronic database of clinic visits. This study was approved by the Human Research Ethics Committee of Monash Health.

Study settings and population

Monash Health is a tertiary care health facility in Melbourne, Australia, with approximately 210,000 annual patient visits to the ED (Monash Health, 2015). The baseline investigations for first seizure presentations at the Monash Health ED include full blood examination and tests for blood glucose levels, liver function, urea and electrolytes, as well as calcium and magnesium. Drug and ethanol levels are performed on a case-by-case basis. Computed tomography (CT) neuroimaging is usually performed for all patients presenting with first seizures, unless there is a contraindication, such as pregnancy. Cerebrospinal fluid (CSF) examination is performed when meningitis or encephalitis is suspected. Patients who are clinically safe with stable vital signs are discharged from the ED with a referral to the outpatient first seizure clinic managed by four neurologists. The first seizure clinic was established with the primary aim of rapid assessment of patients presenting with a first seizure who have been discharged from the ED.

Data acquisition and analysis

The demographic information, clinical details, and investigations were collated from medical records. Investigations analysed included blood tests, EEG, CT, and magnetic resonance imaging (MRI) of the brain. We only included specific "epileptogenic" neuroimaging abnormalities in the analysis. We carefully examined the ED medical records in order to determine the diagnosis made by the doctor (ED diagnosis). In the discharge summary, the ED doctors documented the most likely diagnosis based on their assessment. The ED evaluation was based on the history, examination, CT brain scans, and blood tests. The MRI brain scans and EEGs were performed as outpatient tests after discharging from the ED and before attending the first seizure clinic. We then classified the ED diagnosis into two groups: seizures and seizure mimickers. Seizure mimickers included a plethora of conditions, such as psychogenic non-epileptic seizures (PNES), syncope, and migraine. We used a similar dichotomous classification for the "final diagnosis" made by the epilepsy specialist after evaluating history, examination, and investigations. We then calculated the specificity, sensitivity, and predictive values for the diagnosis of seizures by ED doctors based on "ED diagnosis" and "final diagnosis". For this calculation, we considered "final diagnosis" by the epilepsy specialist as the gold standard for comparison. The diagnostic yield of an investigation was defined as the percentage of positive
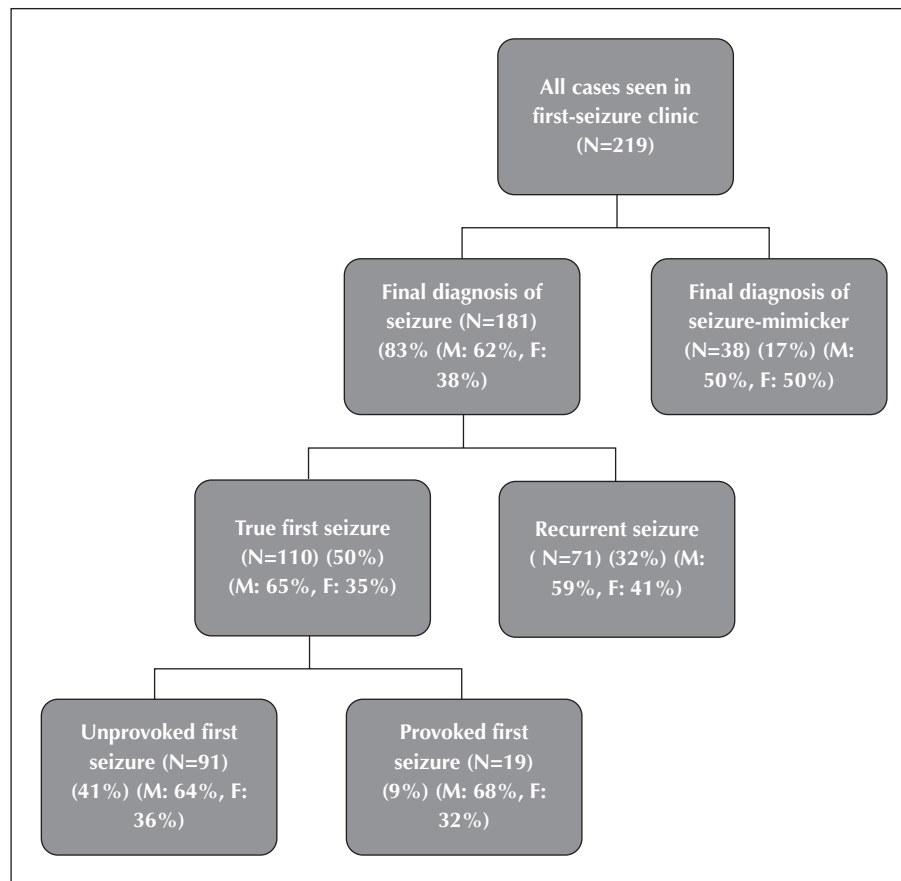
Figure 1. Flow-chart of patient stratification after first seizure clinic referral from the emergency department.

tests out of the total number of tests performed for patients with the final diagnosis of first-ever seizures. The diagnosis of epilepsy and epilepsy syndromes in the first-ever seizure cohort were established according to the current ILAE criteria (Fisher *et al*., 2014).

Additionally, we used Cohen's kappa statistics to measure the degree of agreement between ED diagnoses and the neurologists' diagnoses. Kappa values were interpreted as follows: <0 (poor agreement), 0.01-0.20 (slight agreement), 0.21-0.40 (fair agreement), 0.41-0.60 (moderate agreement), 0.61-0.80 (substantial agreement), and 0.81-0.99 (almost perfect agreement) (Landis and Koch, 1977). Data analyses were conducted with SPSS (version 21, IBM Corporation, New York, USA).

Results

Characteristics of patients presenting to the first seizure clinic

During the four-year study period, 219 patients were seen by the same epilepsy specialist (US) in the first seizure clinic. Of these, 87 (40%) were females and 132 (60%) were males. The median age was 45 years with an interquartile range of 28 to 62 years. From the total cohort of 219 patients, 38 patients presented with seizure mimickers based on the final diagnosis (*figure 1*, *table 1*).

Table 1. Presentation of seizure mimickers.

Variable	Number (total=38) (%)
Reflex syncope	28 (74%)
Psychogenic non-epileptic seizures	6 (16%)
Transient global amnesia	1 (3%)
Benign paroxysmal positional vertigo	1 (3%)
Parasomnia	1 (3%)
Asterixis due to renal encephalopathy	1 (3%)

Characteristics of patients presenting with seizures

In total, 181 (83%) patients who were referred to the first seizure clinic received a diagnosis of seizures; 71 (39%) of these patients were found to have evidence of previous seizures. Generalized tonic-clonic seizures (GTCS) were the most frequent in this group (26 patients; 37%), followed by focal dyscognitive seizures (17; 24%), simple focal seizures (10; 14%), myoclonic seizures (7; 10%), tonic seizures (1; 1%), and unclassified seizures (10; 14%). Notably, nine (13%) patients with recurrent seizures had evidence of previous nocturnal seizures during sleep.

In the same cohort, EEGs were performed in 176 (97%) patients, of which 103 (59%) and 36 (20%) were either normal or had non-epileptiform abnormalities such as slowing. Five patients failed to attend their appointments. CT and MRI neuroimaging were performed in 155 (86%) and 162 (90%) patients, respectively. Nineteen (10%) patients did not undergo MRI neuroimaging due to contraindications or patient refusal. From the 155 seizure patients who were investigated with CT neuroimaging, "epileptogenic" abnormalities were found in 33 (21%) patients. The CT abnormalities included cortical infarcts (nine patients; 47%), encephalomalacia (6; 32%), subdural haematoma (2; 11%), tumour (1; 5%), and cavernoma (1; 5%). Amongst the 162 patients who underwent brain MRI, 51 (31%) had "epileptogenic" abnormalities. Cortical infarct was the most frequent MRI abnormality (10 patients; 38%), followed by encephalomalacia (4; 15%), focal cortical dysplasia (4; 15%), hippocampal sclerosis (3; 12%), tumour (1; 4%), subdural haematoma (1; 4%), cavernoma (1; 4%), vasculitis (1; 4%), and nodular heterotopia (1; 4%). CT neuroimaging conferred a 12% probability in detecting a seizure focus compared with 16% for MRI.

Characteristics of patients presenting with true first seizures

In total, 110 (50%) of the 219 patients referred to the first seizure clinic had true first seizures, defined as presentation with a first-ever seizure to the ED with no evidence of previous seizures. From the 110 true first seizures, a total of 91 (83%) were unprovoked and 19 (17%) cases were provoked seizures. The most common cause of provoked seizures was alcohol and illicit drug use (65%). Based on seizure semiology, EEG, and neuroimaging findings, a total of 22 (20%) patients presenting with true first seizures were classified with focal epilepsy syndrome and six (5.5%) with genetic generalised epilepsy.

Diagnostic yield of EEG in the true first seizure cohort

In our true first seizure population, 107 (97%) patients had EEG recordings (routine EEG for 104 and sleep-deprived EEG for three). Three patients failed to attend their appointments for EEG. The presence of epileptiform discharges was the criterion for a diagnostic EEG. Eighty-five (79%) true first seizure patients had non-diagnostic EEGs. An EEG suggestive of focal or generalised epilepsy was identified in 16 (15%) and six (5.6%) patients, respectively. The overall diagnostic yield of EEG was 20.6%.

Diagnostic yield of neuroimaging in the true first seizure cohort

In the true first seizure cohort, 100 and 95 patients had CT and MRI brain scans, respectively. For those who had neuroimaging, CT conferred a 16% probability in detecting a potential seizure focus compared with 20% for MRI. From the same true first seizure cohort, CT brain scans of 84 (84%) patients did not demonstrate an epileptogenic focus; 75 of these patients proceeded to have brain MRI which resulted in six (8%) patients subsequently demonstrating a potentially epileptogenic structural abnormality. These revealed cortical infarcts (*n*=3), focal cortical dysplasia (*n*=2), and hippocampal sclerosis (*n*=1). In true first seizure patients, the most common cause of a potential seizure focus on MRI neuroimaging was a cortical infarct (nine patients; 9.5%). Non-specific, non-epileptogenic abnormalities, such as white matter changes, were seen on MRI scans of 28 patients (29.5%).

Diagnostic yield of blood tests of the true first seizure cohort

In the total study population, no electrolyte disturbances contributed to seizures. In some patients, mild to moderate changes in electrolytes were detected, but those changes did not fulfil criteria for acute symptomatic seizures (Beghi *et al.*, 2010). Alcohol and drug screens were inconsistently performed in the ED and returned positive in three patients. Two patients with diabetes presented with provoked seizures related to significant hypoglycaemia, defined as a blood glucose reading <2 mmol/l (Beghi *et al.*, 2010). Both readings were recorded by paramedics on the scene, but subsequent blood glucose measurements in the ED were >2 mmol/l.

Diagnostic accuracy of seizures in the emergency department

Pertaining to our population of 181 patients who presented with seizures to the ED, 133 were correctly diagnosed. Twenty-six of the 38 patients who presented with seizure mimickers were incorrectly diagnosed with seizures. Hence, the diagnostic sensitivity in identifying seizures within the ED was 0.74, and the specificity was 0.32. The positive and negative predictive values were 0.84 and 0.20, respectively. The kappa values indicated only slight agreement between ED and the neurologists' diagnoses (k=0.04; 95% CI=-0.09 to 0.17).

Discussion

Our study details the complexities in first seizure diagnosis. In particular, our study demonstrates the poor diagnostic yield of routine investigations in the first seizure population, underscoring the importance of clinical diagnosis based on a good history, including eye-witness accounts. Among the cohort of patients with seizures seen in the first seizure clinic, 71 (39%) patients in fact had experienced previous seizures. This finding highlights the importance of a detailed history to elicit evidence of previous seizures for patients presenting as "first seizure" patients. Among first-ever seizure patients, 17% had provoked seizures. These distinctions (first-ever seizure *vs* recurrent seizure; unprovoked first-ever seizure *vs* provoked first-ever seizure) are very important for further management. Our study also shows low diagnostic specificity (0.32) within the ED, highlighting the need for improved skills for seizure diagnosis among doctors. Overall, our study found four major challenges and areas that need attention in the management of patients presenting with a first seizure:

– Poor diagnostic accuracy of the referring doctors.
– Under-detection and under-reporting of previous seizures.
– The need to differentiate provoked from unprovoked seizures.
– Low yield of investigations.

Poor diagnostic accuracy of the referral source

Our study demonstrated a diagnostic sensitivity and specificity of 0.74 and 0.32, respectively, in identifying seizures in the ED. This suggests that ED doctors exhibit moderate skills in labelling epileptic seizures as such, however, they are less skilled in excluding a diagnosis of epileptic seizures in patients who present with seizure mimickers. This is reflected in the positive and

negative predictive values of 0.84 and 0.20, respectively, inferring that patients who receive an emergency diagnosis of seizure tend to receive the same diagnosis at the first seizure clinic, whereas there is poor predictive correlation in those patients who are labelled as not having seizures within the ED.

The kappa statistics indicate only slight agreement between the ED diagnoses and the neurologists' diagnoses. The MRI and EEG data were not available to the ED doctors as those tests were performed after patients were discharged from the ED. Hence, it may be argued that the two observers (the ED doctor and neurologist) are not directly comparable. However, the diagnosis of seizures remains predominantly a clinical decision, mostly based on a detailed history, including eye-witness accounts. Hence, we do not believe that the lack of MRI and EEG data available to the ED doctor had an impact on diagnostic accuracy.

Under-detection and under-reporting of previous seizures

GTCS are often the first seizure type that causes patients to seek medical attention, and patients with GTCS comprise the vast majority at the first seizure clinic (King *et al.*, 1998). In fact, 39% of patients in our seizure cohort referred to the first seizure clinic had evidence of preceding seizures elicited by detailed history. McFadyen (2004) describes a relatively comparable rate (34%) of recurrent seizure presentations in their Scottish first seizure clinic (*table 2*). Awareness of this pitfall is important. Though it is relatively easy to elicit a history of previous GTCS, clinical acumen is required to determine other seizures types which are often not recognised and/or considered trivial by patients. These include brief absences, focal dyscognitive seizures, myoclonic jerks, and nocturnal tongue biting due to unwitnessed seizures during sleep. In our study, a history suggestive of nocturnal seizures was elicited in 13% of the patients presenting with recurrent seizures. This is of particular importance as nocturnal seizures are associated with a high risk of recurrence and sudden unexpected death in epilepsy (Lamberts *et al.*, 2012; Krumholz *et al.*, 2015). On the whole, the determination of previous seizures is an important step in the diagnosis of epilepsy given that together with other investigations, it allows an accurate assessment of a patient's risk of seizure recurrence, and thus the provision of AEDs (Seneviratne, 2009). In fact, without being privy to any investigations, the risk of seizure recurrence rises from 33% to 73% after a second seizure compared with the first-ever seizure (Hauser *et al.*, 1998).

Table 2. Comparison of publications on first-seizure cohorts.

	Current study	McFadyen, 2004	Breen *et al.*, 2005	Lawn *et al.*, 2015	Pathan *et al.*, 2014	King *et al.*, 1998
Total number of subjects	219	200	190	798	439	300
Sex	M: 87 (40%); F: 132 (60%)	M: 116 (58%); F: 84 (42%)	M: 123 (53%); F: 109 (47%)	M: 525 (66%); F: 273 (34%)	M: 369 (84%); F: 70 (16%)	M: 170 (57%); F: 130 (43%)
Design	Retrospective	Prospective	Prospective	Prospective	Retrospective	Prospective
Setting	Australia (first seizure clinic)	Scotland (first seizure clinic)	Scotland (first seizure clinic)	Australia (first seizure clinic)	Qatar (emergency department)	Australia (tertiary hospital epilepsy clinic)
Referral sources	Emergency department	General practitioner, Specialists, Emergency department	Emergency department, General Practitioner, Hospital inpatient	Emergency department, General Practitioners, Hospital inpatient, Specialists	N/A	Emergency department, General Practitioners, Specialists, Neurology clinics
True first seizures in whole cohort	110 (50%)	48 (24%)	98 (52%)	798	N/A	300
Recurrent seizures in whole cohort	71 (32%)	68 (34%)	N/A	N/A	N/A	N/A
Provoked seizures	20 (9%) in first seizure patients	24 (12%) in whole cohort	69 (36%) in first seizure patients	N/A	N/A	N/A
Main cause of provoked seizure	Alcohol	Alcohol	Alcohol	N/A	N/A	N/A
Seizure mimickers	38 (17%)	82 (41%)	92 (48%)	N/A	N/A	N/A
Types of seizure mimickers	Syncope (74%), PNES (16%)	Uncertain (13.5%), syncope (12.5%), PNES (1.5%)	Syncope (28%), PNES (0%)	N/A	N/A	N/A

Table 2. (*Continued*)

	Current study	McFadyen, 2004	Breen et al., 2005	Lawn et al., 2015	Pathan et al., 2014	King et al., 1998
Yield of blood tests	0	0	0	N/A	N/A	N/A
Epileptiform EEG abnormalities	21% in true first seizure cohort	29% in whole cohort	24% in first seizure clinic patients	17%	N/A	43%
Potentially epileptogenic structural abnormality on CT	16% in first seizure cohort	29% in whole cohort	19% in first seizure clinic patients	N/A	Normal CT in 65% of patients	N/A
Potentially epileptogenic structural abnormality on MRI	20% in first seizure cohort	N/A	31% in first seizure clinic patients	N/A	N/A	N/A
Potentially epileptogenic structural abnormality on MRI & CT	20% in first seizure cohort	N/A	N/A	28%	N/A	14%
Most common structural abnormality on MRI neuroimaging	Stroke	N/A	carcinoma, arachnoid cyst, vasculitis, stroke, AVM	Stroke	Neurocysticercosis	Tumour
Diagnostic accuracy of the referral source	Sensitivity:0.74; Specificity: 0.32	N/A	N/A	N/A	N/A	N/A

F: female; M: male; N/A: not available; PNES: psychogenic non-epileptic seizures

The need to differentiate provoked from unprovoked seizures

The incidence of acute symptomatic seizures approximates 39 per 100,000 person-years with common precipitants including traumatic brain injury, acute stroke, and drug withdrawal (Annegers *et al.*, 1995). Their recognition holds importance given the two-year mortality rate of 30% and recurrence rate of 32% (Leung *et al.*, 2010). In our sample of first seizure patients, 17% of our true first seizure cohort represented provoked seizures. This finding was comparable with the 12% of provoked seizure patients in a Scottish first seizure clinic (McFadyen, 2004). The most common cause of provoked seizures in our cohort was alcohol and illicit drug use. Alcohol excess was also reported to be the most common seizure precipitant by Breen *et al.* (2005). A study by Fields *et al.* (2013) showed that amongst hospitalised patients with new-onset provoked seizures, metabolic derangements were the most common cause. Overall, when presented with a first seizure, provoking factors for seizures must be elicited, and this should be pursued, as is the case for the specific population group addressed at the first seizure clinic. The importance of this lies in the fact that these seizures would not typically be treated with AEDs unless there are outstanding medical or social circumstances.

Low yield of investigations

Routine blood tests, such as those for blood glucose and electrolytes, as well as full blood counts, are usually performed in the ED. A study by Breen *et al.* (2005) concluded that in their first seizure cohort, no single blood test was associated with a final diagnosis of first seizure. This is comparable to our study. Although there is insufficient evidence to recommend or refute routine full blood examinations or urea, electrolyte and blood glucose measurements in patients presenting with seizures (Krumholz *et al.*, 2007), these are relatively cheap, readily available, and alter management if abnormalities are found. Toxicology screens should be considered on a case-by-case basis (Krumholz *et al.*, 2007).

EEG is a key investigation to facilitate predictions of seizure recurrence and determine specific epilepsy syndromes. In our study, the diagnostic yield of a routine EEG was poor, providing evidence of focal or generalised epileptiform abnormalities in only 15% and 6% of patients, respectively. This is in keeping with a recent study reporting an EEG diagnostic yield of 18% (Lawn *et al.*, 2015). There have been reports of improved yields, as high as 61%, following sleep-deprived EEG (King *et al.*, 1998). Our study reaffirms that the diagnostic yield of routine EEG is low in the

first seizure population and more detailed evaluation, such as prolonged EEG, may be considered in selected patients.

The finding of CT abnormalities in first seizure patients averages approximately 10%, but varies widely with a reported incidence of up to 40% (Henneman *et al.*, 1994; Krumholz *et al.*, 2007). As may be expected, the detected abnormalities depend on the population studied. For example, Pathan *et al.* (2014) reported that the most common abnormality seen in their Qatar population was neurocysticercosis, with an incidence of 9%. In our cohort, cortical infarct was the most common structural abnormality; a finding comparable with another study describing an Australian cohort (Lawn *et al.*, 2015).

MRI neuroimaging is considered the gold standard in the determination of structural brain abnormalities in patients with epilepsy. In our true first seizure cohort, MRI neuroimaging conferred a 20% detection rate for potentially epileptogenic foci; slightly lower than the approximate 30% reported by Lawn *et al.* (2015). Different sample sizes may explain this discrepancy.

As MRI is more sensitive than CT in detecting subtle lesions, it is not surprising that the number of pathological findings increases when MRI modalities are utilised. Several studies report an additional yield of 12-17% with MRI neuroimaging in patients with normal brain CT (Ho *et al.*, 2013; Kapina *et al.*, 2013).

The EEG and neuroimaging abnormalities are useful in establishing the diagnosis of epilepsy syndromes and stratifying the risk of seizure recurrence. According to the MRC Multicentre trial for Early Epilepsy and Single Seizures (MESS) study, those patients with first seizures and either an abnormal EEG or abnormal neurological status were considered to be at medium risk of seizure recurrence (Kim *et al.*, 2006). These patients may derive benefit from early AED treatment. There are many factors associated with an increased yield of EEG, including the age of the patient, provocation techniques used, and timing of an EEG in relation to the index seizure, with the latter suggesting a yield of up to 70% in the first 48 hours (Pohlmann-Eden and Newton, 2008). Allocating patients with EEG appointments close to their index seizure should therefore be considered. Alongside EEG abnormalities, epileptogenic foci on neuroimaging are considered the strongest predictors of seizure recurrence risk (Berg and Shinnar, 1991). Many guidelines suggest performing immediate CT neuroimaging only in patients who demonstrate focal neurological deficits, persistent altered mental status, and in those who are at risk of bleeding or who are immunocompromised (Krumholz *et al.*, 2007; NICE, 2016). The MESS study, which included a population of patients with either a first seizure or early epilepsy, also suggested that patients with both abnormal EEG and MRI are at greatest risk of seizure recurrence,

highlighting the importance of these two investigations in first seizure patients in aiding risk stratification (Kim *et al.*, 2006).

We were able to diagnose an epilepsy syndrome in only 25.5% of the cohort, compared with 55% in the study by Lawn *et al.* (2015). We believe this discrepancy is due to methodological reasons. We used stringent criteria to establish the diagnosis of epilepsy according to the current ILAE criteria (Fisher *et al.*, 2014). An unprovoked seizure, epileptiform EEG abnormality, and/or epileptiform neuroimaging abnormality were mandatory requirements in our study to establish an epilepsy diagnosis. Both studies had comparable yields of EEG (21% and 17%) and neuroimaging (20% and 28%), yet the percentage diagnosed with epilepsy was markedly different (25.5% *vs* 55%). This is most probably due to different diagnostic criteria used. Furthermore, our true first seizure cohort included patients with unprovoked seizures, as well as provoked seizures, whereas Lawn *et al.* (2015) investigated only patients with unprovoked seizures. The small sample size in our study (110 *vs* 798) is another potential cause for this discrepancy.

Study limitations

We acknowledge some limitations in our study. First, this was a retrospective analysis, hence, study conditions were not uniform. In order to make the conditions as uniform as possible, we included only those patients referred by the same emergency medicine department and seen by the same epilepsy specialist. However, this process may have introduced some selection bias in the meantime. Diagnostic yield of the EEG appears to depend on the time gap between the seizure and the test, the length of recording, and the induction techniques such as sleep deprivation (King *et al.*, 1998). These factors were not uniform in our cohort as the study was retrospective.

Second, our sample was biased due to several reasons. Some patients with a first seizure of mild severity might not have presented to the ED and patients with more severe seizures were likely to be over-represented in the sample. Hence, our cohort cannot be considered representative of a true community sample (tertiary centre bias). It is also possible that some patients referred by the ED did not attend the clinic. Only those patients who were stable enough to be discharged from the ED were referred to the first seizure clinic. Others were admitted as inpatients and subsequently followed in different clinics. Hence, severe aetiologies of the first seizure, such as CNS infections and intracerebral haemorrhages, were not represented in the cohort. Finally, the most frequent seizure mimickers in the cohort were reflex syncope (74%), followed by PNES (16%), in keeping with previous studies (Chowdhury *et al.*, 2008). However, we believe PNES is under-represented in the sample due to failure of patients with PNES attending the clinic following ED referral. In our experience, patients with PNES tend to visit multiple hospitals and clinics without regular follow-up. A state-wide study with data captured from multiple hospitals would likely yield more robust results demonstrating the true magnitude of this problem.

Conclusions

Our study highlights the practical challenges in the management of patients presenting with a first seizure. Syncope remains the main differential diagnosis in patients presenting with "first seizures". Alcohol and illicit drug use is the main aetiology for provoked first seizure presentations. Previous cortical stroke is the most frequent aetiology for first remote symptomatic seizures. A fair proportion of patients presenting to the first seizure clinic show evidence of previous seizures, hence, careful history-taking facilitates a diagnosis of epilepsy. The diagnostic accuracy of seizures within the ED is low. Routine investigations including blood tests, EEGs, and neuroimaging have a low yield, and the diagnosis of seizures and epilepsy remains a clinical one. Given the difficulties in the diagnosis, the low yield of investigations, and the long-term consequences of misdiagnosis, we emphasise the need for these patients to be assessed in dedicated first seizure clinics by neurologists with expertise in seizure management. □

References

Annegers JF, Hauser WA, Lee JR, *et al.* Incidence of acute symptomatic seizures in Rochester, Minnesota, 1935-1984. *Epilepsia* 1995; 36: 327-33.

Beghi E, Carpio A, Forsgren L, *et al.* Recommendation for a definition of acute symptomatic seizure. *Epilepsia* 2010; 51: 671-5.

Berg AT, Shinnar S. The risk of seizure recurrence following a first unprovoked seizure: a quantitative review. *Neurology* 1991; 41: 965-72.

Breen DP, Dunn MJ, Davenport RJ, *et al.* Epidemiology, clinical characteristics, and management of adults referred to a teaching hospital first seizure clinic. *Postgrad Med J* 2005; 81: 715-8.

Brown JW, Lawn ND, Lee J, *et al*. When is it safe to return to driving following first-ever seizure? *J Neurol Neurosurg Psychiatry* 2015; 86: 60-4.

Chowdhury FA, Nashef L, Elwes RD. Misdiagnosis in epilepsy: a review and recognition of diagnostic uncertainty. *Eur J Neurol* 2008; 15: 1034-42.

Fields MC, Labovitz DL, French JA. Hospital-onset seizures: an inpatient study. *JAMA Neurol* 2013; 70: 360-4.

Fisher RS, Acevedo C, Arzimanoglou A, *et al*. ILAE official report: a practical clinical definition of epilepsy. *Epilepsia* 2014; 55: 475-82.

Hauser WA, Kurland LT. The epidemiology of epilepsy in Rochester, Minnesota, 1935 through 1967. *Epilepsia* 1975; 16: 1-66.

Hauser WA, Beghi E. First seizure definitions and worldwide incidence and mortality. *Epilepsia* 2008; 49(1): 8-12.

Hauser WA, Rich SS, Lee JR, *et al*. Risk of recurrent seizures after two unprovoked seizures. *N Engl J Med* 1998; 338: 429-34.

Henneman PL, DeRoos F, Lewis RJ. Determining the need for admission in patients with new-onset seizures. *Ann Emerg Med* 1994; 24: 1108-14.

Ho K, Lawn N, Bynevelt M, Lee J, Dunne J. Neuroimaging of first-ever seizure: contribution of MRI if CT is normal. *Neurol Clin Pract* 2013; 3: 398-403.

Kapina V, Heydrich L, Haller S, *et al*. "First seizure clinic": the impact on patient care and adherence - a prospective study. *J Neurol Sci* 2013; 333: e49.

King MA, Newton MR, Jackson GD, *et al*. Epileptology of the first-seizure presentation: a clinical, electroencephalographic, and magnetic resonance imaging study of 300 consecutive patients. *Lancet* 1998; 352: 1007-11.

Kim LG, Johnson TL, Marson AG, Chadwick DW. Prediction of risk of seizure recurrence after a single seizure and early epilepsy: further results from the MESS trial. *Lancet Neurol* 2006; 5: 317-22.

Kotsopoulos IA, van Merode T, Kessels FG, *et al*. Systematic review and meta-analysis of incidence studies of epilepsy and unprovoked seizures. *Epilepsia* 2002; 43: 1402-9.

Krumholz A, Wiebe S, Gronseth G, *et al*. Practice parameter: evaluating an apparent unprovoked first seizure in adults (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology and the American Epilepsy Society. *Neurology* 2007; 69: 1996-2007.

Krumholz A, Wiebe S, Gronseth GS, *et al*. Evidence-based guideline: management of an unprovoked first seizure in adults: Report of the Guideline Development Subcommittee of the American Academy of Neurology and the American Epilepsy Society. *Neurology* 2015; 84: 1705-13.

Lamberts RJ, Thijs RD, Laffan A, *et al*. Sudden unexpected death in epilepsy: people with nocturnal seizures may be at highest risk. *Epilepsia* 2012; 53: 253-7.

Landis JR, Koch GC. The measurement of observer agreement for categorical data. *Biometrics* 1977; 33: 133-58.

Lawn N, Chan J, Lee J, *et al*. Is the first seizure epilepsy- and when? *Epilepsia* 2015; 56: 1425-31.

Leung H, Man CB, Hui AC, *et al*. Prognosticating acute symptomatic seizures using two different seizure outcomes. *Epilepsia* 2010; 51: 1570-9.

Marsh L, Rao V. Psychiatric complications in patients with epilepsy: a review. *Epilepsy Res* 2002; 49: 11-33.

McFadyen MB. First seizures, the epilepsies and other paroxysmal disorders prospective audit of a first seizure clinic. *Scott Med J* 2004; 49: 126-30.

Monash Health. *Delivering exceptional care, outstanding outcomes*. Monash Health Corporate Office, Clayton, Australia. Annual Report 2014-15.

NICE. Epilepsies: diagnosis and management. *National Institute for Health and Care Excellence Guidelines 2016*. https://www.nice.org.uk/guidance/cg137 (accessed on 07/04/2016).

Pathan SA, Abosalah S, Nadeem S, *et al*. Computed tomography abnormalities and epidemiology of adult patients presenting with first seizure to the emergency department in Qatar. *Acad Emerg Med* 2014; 21: 1264-8.

Pohlmann-Eden B, Newton M. First seizure: EEG and neuroimaging following an epileptic seizure. *Epilepsia* 2008; 49(1): 19-25.

Seneviratne U. Management of the first seizure: an evidence based approach. *Postgrad Med J* 2009; 85: 667-73.

TEST YOURSELF

(1) Provoked and unprovoked seizures carry the same prognosis and thus have comparable management strategies. True or false?

(2) It is possible to diagnose epilepsy in a patient who has suffered a single unprovoked seizure. True or false?

Note: Reading the manuscript provides an answer to all questions. Correct answers may be accessed on the website, www.epilepticdisorders.com, under the section "The EpiCentre".