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Do neurologists around the world agree when diagnosing epilepsy? – Results of an international EpiNet study

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ABSTRACT

Objective: Previous studies have shown moderate agreement between physicians when diagnosing epilepsy, but have included small numbers. The EpiNet study group was established to undertake multicentre clinical trials in epilepsy. Before commencing trials, we wanted to determine levels of agreement between physicians from different countries and different health systems when diagnosing epilepsy, specific seizure types and etiologies.
Methods: 30 Case scenarios describing six children and 24 adults with paroxysmal events (21 epileptic seizures, nine non-epileptic attacks) were presented to physicians with an interest in epilepsy. Physicians were asked how likely was a diagnosis of epilepsy; if seizures were generalised or focal; and the likely etiology. For 23 cases, clinical information was presented in Step 1, and investigations in Step 2.
Results: 189 Participants from 36 countries completed the 30 cases. Levels of agreement were determined for 154 participants who provided details regarding their clinical experience. There was substantial agreement for diagnosis of epilepsy (kappa = 0.61); agreement was fair to moderate for seizure type(s) (kappa = 0.40) and etiology (kappa = 0.41). For 23 cases with two steps, agreement increased from step 1 to step 2 for diagnosis of epilepsy (kappa 0.56–0.70), seizure type(s) (kappa 0.38–0.52), and etiology (kappa 0.38–0.47). Agreement was better for 53 epileptologists (diagnosis of epilepsy, kappa = 0.66) than 56 neurologists with a special interest in epilepsy (kappa = 0.58). Levels of agreement differed slightly between physicians practicing in different parts of the world, between child and adult neurologists, and according to one's experience with epilepsy.
Conclusion: Although there is substantial agreement when epileptologists diagnose epilepsy, there is less agreement for diagnoses of seizure types and etiology. Further education of physicians regarding semiology of different seizure types is required. Differences in approach to diagnosis, both between physicians and between countries, could impact negatively on clinical trials of anti-epileptic drugs.

1. Introduction

There have been few studies to determine how consistently or accurately doctors diagnose epilepsy. Agreement when two to six physicians have independently determined if patients have epilepsy has been fair to moderate (Hoefnagels et al., 1992; Rinaldi et al., 2000; Stroink et al., 2004; van Donselaar et al., 1989). Agreement regarding type of seizure (Bodensteiner et al., 1988; van Campen et al., 2013; van Donselaar et al., 1990) and epilepsy syndrome (Ottman et al., 1990; Rinaldi et al., 2000) has generally been poorer with occasional exceptions (Berg et al., 1999; Kellinghaus et al., 2004). No studies have compared diagnostic agreement between neurologists from multiple countries.

Most clinical trials in epilepsy have presumed investigators can make an accurate diagnosis, and distinguish generalised from focal

Abreviations: AEDs, Anti epileptic drug; AVM, arterio-venous malformation; CAE, Childhood absence epilepsy; EEG, Electroencephalogram; ILAE, International league against epilepsy; JAE, Juvenile absence epilepsy; JME, Juvenile myoclonic epilepsy; NOS, not otherwise specified; REM, Rapid eye movement; TC , Tonic clonic

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seizures. This is not necessarily the case. Trials including large numbers of centres from multiple countries tend to have lower effect sizes than trials conducted in fewer centres or a single country (Friedman and French, 2012). Some trials may have obtained negative results because patients have been included who do not have epilepsy, or the seizure type under investigation (Friedman and French, 2012).

The EpiNet study group was established to undertake investigator-led clinical research in epilepsy. Initially formed by members of the New Zealand League against Epilepsy, it now comprises neurologists and epileptologists from many countries (www.epinet.co.nz) (Bergin et al., 2007; Bergin et al., 2012). The EpiNet study group has recently commenced trials in newly diagnosed patients with epilepsy (Bergin et al., 2015). The EpiNet steering committee undertook a Validation study to determine the diagnostic accuracy and consistency of investigators prior to undertaking these trials.

It was decided to invite any epileptologist, neurologist or paediatrician with an interest in epilepsy to participate in this study.

The EpiNet Validation study had two aims:

1) to accredit investigators for the EpiNet-First trials.
2) to determine how much variability there is between neurologists and epileptologists in diagnoses.

A separate paper looking at the process to accredit investigators for the EpiNet-First trials is in press (Bergin et al., 2017).

This paper addresses the second of these aims – assessing the levels of agreement between neurologists and epileptologists from different countries around the world.

2. Methods

The processes undertaken for the EpiNet Validation study have been described elsewhere (Bergin et al., 2017). In summary, the EpiNet steering committee prepared 30 case scenarios describing patients with various paroxysmal attacks. Case histories described real patients, nearly all of whom had been seen by members of the steering committee; all identifying details were removed. Not all patients had epileptic seizures; nine patients had attacks often confused with epilepsy (e.g. syncope, psychogenic non-epileptic episodes). The 30 cases were chosen by consensus by the EpiNet steering committee from an initial pool of 40 cases that had been prepared by PB. Most of the cases represented patients with new-onset epilepsy or patients who were seen in first-seizure clinics, since the study was also being undertaken to accredit investigators for the EpiNet-First trials (Bergin et al., 2017). Many patients had typical histories, but cases where the diagnosis was less clear were also included. Some scenarios described attacks in detail, but others contained limited information, as it is recognised that physicians are sometimes required to make decisions regarding treatment when information is incomplete.

The 30 case reports comprised six children (6–15 years) and 24 adults (18–90 years); 21 had epilepsy, and nine had an alternative diagnosis (Table 1). Examples of cases have been published elsewhere (Bergin et al., 2017).

1) how likely was it that the patient had experienced epileptic seizures;
2) the type of seizure, using the ILAE 2010 classification schema (Berg et al., 2010);
3) the etiology of the epilepsy, in broad categories, using the ILAE 2010 classification schema.

For the analysis performed here, there were three broad categories for diagnosis of epilepsy: Epilepsy; Possible Epilepsy; and Not Epilepsy.

Five broad categories were presented for classification of the attacks: Generalised seizures; Focal seizures; Epileptic seizures, but uncertain if focal or generalised; Turns/Attacks, possibly epileptic; Attacks not epileptic.

Etiology was classified according to the three major categories proposed in the ILAE 2010 report (genetic (presumed); structural/metabolic; unknown) (Berg et al., 2010) and Not Epilepsy.

In 23 cases, information was presented in two steps, with responses required after each step. Step 1 consisted of clinical information. Step 2 consisted of results of investigations (neuroimaging studies, EEGs and occasionally video monitoring). Investigators had the option of changing their responses from step 1 to step 2.

Inter-rater agreement was determined using the Kappa statistic to adjust for chance agreement. For the diagnosis of epilepsy (level of confidence that a patient had epilepsy) the overall agreement was calculated using the mean of all pairwise weighted kappa values. Pairwise weighted kappa values were obtained using Fleiss-Cohen weights (Fleiss and Cohen, 1973), giving the following values to the level of confidence that a patient had epilepsy: epilepsy = 2, possible epilepsy = 1, not epilepsy = 0. For seizure types and etiology, inter-rater agreement was calculated using Fleiss' kappa (Fleiss, 1971). Only the broad categories for seizure type and etiology were considered. Kappa values with 95% confidence intervals (CI) were calculated separately (and for each step separately) in the entire sample and in subgroups from differing geographic areas (Europe, North America, Latin America, Asia, and Oceania (Australia and New Zealand)), epileptologists vs. neurologists with a special interest in epilepsy, adult vs. child neurologists, subgroups with different levels of experience (< 15 vs. ≥ 15 years of experience) and investigators from countries where English was listed as an official language vs. those from other countries. Results for the steering committee were excluded. Kappa values were classified as poor (less than chance – kappa below 0), slight (0.01–0.20), fair (0.21–0.40), moderate (0.41–0.60), substantial (0.61–0.80), almost perfect (0.81–1.00) (Landis and Koch, 1977). No formal statistical tests were performed. Differences between subgroups of investigators should be considered as statistically significant if 95% CI do not overlap.

The study commenced in December 2013, and continued until the end of 2014. Epileptologists, neurologists and paediatricians with an interest in epilepsy were invited to participate. The study was advertised at international meetings, via the ILAE website and through the ILAE chapters.

The Northern B New Zealand Ethics committee approved this study.

Participants from outside New Zealand who completed the set of 30 cases before the end of March 2014 entered a draw to win a holiday in New Zealand.

3. Results

189 participants from 36 countries completed all 30 cases. 159 of those who completed the study (83%) provided information about their professional role and experience with epilepsy (See Table 2). One medical student, one neurosurgeon, one primary-care physician and two physicians (not otherwise specified) completed the study, but their results have been removed from this analysis. The results from the remaining 154 participants comprise the data set for the analysis reported here. Fifty-three of the 154 participants described themselves as epileptologists and 56 as neurologists with a special interest in epilepsy. Other roles are shown in Table 2.

Kappa values for the sample of 154 investigators and for subgroups of investigators are shown in Table 3. The overall kappa value for the 154 investigators for a diagnosis of epilepsy at step 1 was 0.61 (*95% CI 0.609–0.613*); seizure type was 0.40 (*0.399–0.403*); and etiology was 0.41 *(0.406–0.410)*.

For the 23 cases with two steps, kappa values increased between steps from 0.56 *(0.559–0.563)* to 0.70 *(0.692–0.700)* for diagnosis of epilepsy; from 0.38 *(0.379–0.383)* to 0.52 *(0.514–0.518)* for seizure type; and from 0.38 *(0.380–0.384)* to 0.47 *(0.464–0.468)* for etiology.

Agreement was better for epileptologists kappa for diagnosis of epilepsy = 0.66, *(0.647-0.663)* than neurologists with a special interest