An Epilepsy Type Algorithm Developed in India is Accurate in Sudan: a prospective validation study

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Abstract

Purpose

The effects of epilepsy are worse in lower-middle-income countries (LMICs) where most people with epilepsy live, and where most are untreated. Correct treatment depends on determining whether focal or generalised epilepsy is present. EEG and MRI are usually not available to help so an entirely clinical method is required. We applied an eight-variable algorithm, which had been derived from 503 patients from India using naïve-Bayesian methods, to an adult Sudanese cohort with epilepsy.

Methods

There were 150 consecutive adult patients with known epilepsy type as defined by two neurologists who had access to clinical information, EEG and neuroimaging ("the gold standard"). We used seven of the eight variables, together with their likelihood ratios, to calculate the probability of focal as opposed to generalised epilepsy in each patient and compared that to the "gold standard". Sensitivity, specificity, accuracy, and Cohen's kappa statistic were calculated.

Results

Mean age was 28 years (range 17-49) and 53% were female. The accuracy of an algorithm comprising seven of the eight variables was 92 %, with sensitivity of 99% and specificity of 72% for focal epilepsy. Cohen's kappa was 0.773, indicating substantial agreement. Ninety-four percent of patients had probability scores either less than 0.1 (generalised) or greater than 0.9 (focal).

Conclusion

The results confirm the high accuracy of this algorithm in determining epilepsy type in Sudan. They suggest that, in a clinical condition like epilepsy, where a history is crucial, results in one continent can be applied to another. This is especially important as untreated epilepsy and the epilepsy treatment gap are so widespread. The algorithm can be applied to patients giving an individual probability score which can help determine the appropriate anti-seizure medication. It should give epilepsy-inexperienced doctors confidence in managing patients with epilepsy.

Introduction

Epilepsy affects about 70 million individuals globally, the majority of whom reside in developing countries. The estimated prevalence of epilepsy in Africa is as high as 15 per 1000[1], a figure that is about three times higher than the prevalence of epilepsy in the industrialized world[2]. Epilepsy, if not treated, is associated with excess deaths and significant morbidity in the form of burns, injuries and stigma[3]. In Sudan, epilepsy causes an increase in both death and disability-adjusted life years[4].

In many cases, patients with epilepsy can maintain a normal and undisturbed life because anti-seizure medicines (ASMs) can provide satisfactory control or total relief of seizures[5]. In one trial, nearly half of newly diagnosed patients were seizure-free on the first-ever ASM, with more than 90% of them becoming so at moderate or even low doses[6]. Despite this, over 90% of people in sub-Saharan Africa with epilepsy do not receive treatment[7]. Lack of medical infrastructure, resources, and personnel is a driving force behind the treatment gap in sub-Saharan Africa[8].

Classification of epilepsy into focal and generalised types is a key clinical tool that can guide the selection of ASMs[5]. Narrow spectrum ASMs such as carbamazepine (CBZ) are effective in focal epilepsies but sometimes exacerbate generalized seizure types such as myoclonus and absence seizures. Newer, broad-spectrum ASMs are useful in both focal and generalized epilepsy, but they are much more expensive. Their efficacy too may not be as good as CBZ[9].

Hence, classification of epilepsy in resource-limited settings, based exclusively on clinical semiology without recourse to often-unavailable EEG or neuroimaging, is required. A companion study[10] from an Indian population[11] describes eight clinical variables which distinguish focal from generalised epilepsy (Box 1).

Consistent asymmetry or unilateral posturing
Myoclonic jerks
Behavioural arrest
Attacks mostly on awakening
Aura before seizure
Head version
Automatism
Onset age<5 years

Box 1. Clinical variables which constitute the algorithm to separate focal from generalised epilepsy.

It is important however that the algorithm should be validated in different populations. In this study, we applied this algorithm to consecutive adult Sudanese patients with epilepsy and report our results below.

Methods

Location

This single centre, prospective, cross-sectional study was conducted within the neurology outpatient clinic at Soba University Hospital in Khartoum, Sudan. This hospital is a tertiary centre, and a central referral hospital for all of Sudan. It provides services in all branches of medicine and surgery. The clinic is staffed on average by five neurology fellows, three neurology specialists and one consultant neurologist. In Sudan, there are 35 neurologists, 30 of them are within the capital, Khartoum. In other states, patients with epilepsy are seen by medical officers/general practitioners and are referred to Khartoum when needed. Access to EEG and MRI is similarly limited.

Study Population. One hundred and sixty patients with known epilepsy over 16 years of age, presenting between January 2020 and December 2020, were included. Patients with non-epileptic seizures, single epileptic seizures, or acute symptomatic seizures were excluded. Sample size was not pre-determined, but is over twice the "rule of thumb" recommendation of 10 patients per variable.

Questionnaire.

One of the authors, SE, gathered clinical data from all patients/legal guardians (for disabled patients) through administering a questionnaire. This included seven of the eight questions which made up the algorithm in the companion paper; one variable on the algorithm, *age at onset less than 5 years*, was inadvertently not included. Questions were all yes/no, and were framed in simple and culturally-contextualised language to elicit the history of the common seizure types. The instrument was translated from English to Arabic and back-translated to English before the study was undertaken. The Arabic instrument was pretested in 20 adults to look for difficulties in administering/understanding the questions and time needed to complete assessment.

Classification of epilepsy type.

This was made by two neurologists, SME and IM, taking into account clinical findings together with EEG and brain imaging, when available. This classification was considered the gold standard. Patients who remained unclassified were excluded.
For each patient, seizures were classified according to the most recent classification of seizures. The diagnosis of epilepsy was made according to the 2017 classification of epilepsies[5,12]. There is no firm epidemiological evidence about difference in the

prevalence of focal and generalised epilepsy in India, where the algorithm was derived, and Sudan.

Testing the algorithm.

The algorithm from the companion paper was tested on the questionnaire data. We calculated the sensitivity, specificity and accuracy in diagnosing focal and generalised epilepsy, as well as Cohen's kappa for the agreement between the algorithm and the "gold standard" classification by the two neurologists.

Ethical and governance considerations.

Ethical approval was obtained from the research and ethics panel at the Faculty of Medicine, University of Khartoum, Sudan. Written consent was taken from the patient/legal guardian (for disabled patients) after explaining the aim of the study in simple language. All patients/legal guardians provided consent for the publication of their clinical details. The study is presented according to the TRIPOD guidelines for validation studies.

Results

Study Population

A hundred and sixty consecutive new referrals were included. In 10 the diagnosis of epilepsy was uncertain, leaving a final sample of 150. The mean age was 28 years, median age 27 years, and range 17 to 49 years. Eighty (53.3%) were female. A hundred and eleven (74%) had focal epilepsy and 39 (26%) had generalized epilepsy.

Application of the algorithm

Pre-test odds of having focal epilepsy are 111/39 or 2.85 to 1. The algorithm was applied to each patient's results individually, and a probability score of 0.5 or less was taken as indicating generalised epilepsy, and one of greater than 0.5 taken as indicating focal epilepsy. The accuracy was 92 %, with sensitivity of 99% and specificity of 72% for focal epilepsy.

The frequency of probability scores is shown in Figure 1, with 94% of patients having scores of less than 0.1, or greater than 0.9, with only 6% in the intermediate range. Cohen's kappa was 0.773 (95% confidence intervals 0.650, 0.896), indicating substantial agreement.

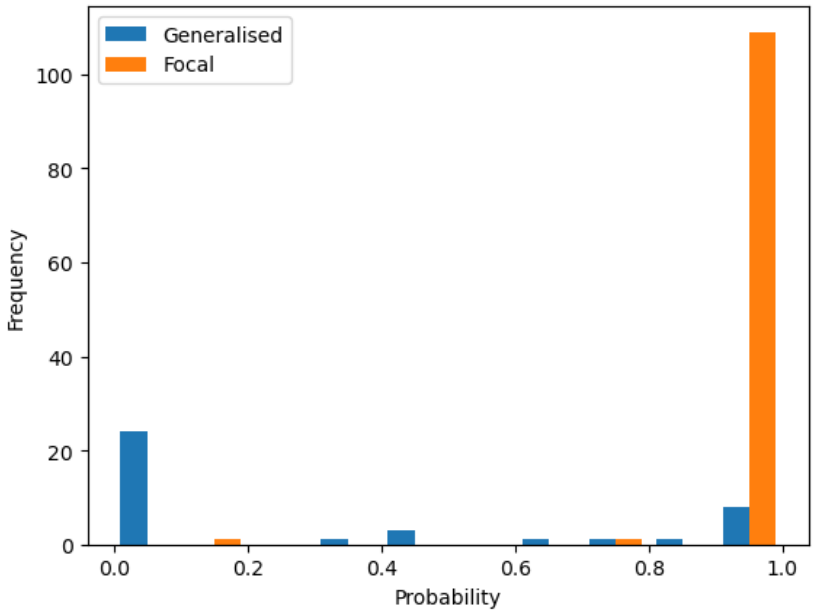

Figure 1. Frequency distribution of probability scores for focal (n= 111) and generalised (n=39) epilepsy.

Discussion

Principal findings

This Indian-derived algorithm is very accurate (92%) at distinguishing between focal and generalised epilepsy in a Sudanese population, even when it was supplied with only seven of its eight variables. This is an important finding as it provides clear evidence that an algorithm derived in one population or continent can be usefully applied to another, despite concerns being raised that this might not be the case[13]. The reasons for this are most probably that the features associated with epileptic seizures are the same everywhere, and the individual features of these seizures, as determined by a series of yes/no questions, are also the same everywhere. So, the “cultural contextualisation”, which the previous reference rightly highlights as important, is achieved by the accurate local translation of the yes/no questions into the local language, as was done in the present study. Our observation is therefore important because it suggests that it is not necessary to develop and validate algorithms in every single community in which they are to be deployed, enabling people with untreated epilepsy in one place to receive the benefits of an algorithm developed in another. A previous algorithm for episode diagnosis also shows that “globalisation” is possible; it was derived in Nepal[14], validated in India[15], and applied successfully in Bolivia[16].

Additionally, the spread of values is such that the great majority of the patients studied had either very high probability scores for focal epilepsy, or very low ones, indicating generalised epilepsy. Applying this algorithm to individual patients can therefore give personalised indication of probable epilepsy type, and therefore appropriate ASM therapy.

Strengths and Weaknesses

The use of eight explanatory factors minimizes overreliance on single symptoms, none of which is invariably correct in making or rejecting an epileptic seizure diagnosis. The algorithms were evaluated at a specialized centre, rather than a community setting, because the assessment required availability of a diagnostic gold standard. We could have only carried out this study at Soba University Hospital in Khartoum as this is the only clinic in Sudan that has the necessary number of patients needed to validate the tool. The mean age of patients (28 years) was similar to the population from which the algorithm was derived (25 years)[11].

Another apparent weakness of this study however could be the "gold standard" of diagnosis of focal and generalised by two neurologists with EEG and MRI imaging rather than electro-clinical confirmation with simultaneous video and EEG recording of an event. The latter however is impossible to obtain for most epilepsy patients in the world, and we felt that the assessment we performed was the best possible given our circumstances.

That one of the eight variables was missing from the test set might seem to be a problem, but the use of naïve-Bayes in the assessment overcomes that, as missing values do not seem to be problematic[17].

Comparison to other studies

There is little information on inter-observer agreement on epilepsy type. In one study of clinical scenarios, with all information available, 53 epileptologists achieved a modified kappa score of 0.424 for seizure type, indicating only moderate agreement[18]. This contrasts with a kappa score of 0.773 for epilepsy type in the present study. A recent study[19] reported on the development of an algorithm which optimized the choice of ASM by clinical evaluation of seizure types, rather than epilepsy type. Ultimately this is probably the same thing, since generalized epilepsy and focal epilepsy are often associated with pathognomonic seizure types. They used a modified Delphi method, which does not involve actual data from individual patients. In their study the diagnostic accuracy of ASM choice (a surrogate for epilepsy type) was 87.2 % when neuroimaging information was included, but it fell to 74.4% with just the clinical variables, compared to the 92% of the present study.

Conclusion

This tool we developed is likely to be beneficial in other LMICs where adult epilepsy problems are comparable to those in Sudan. This tool can be provided as a smartphone application similar to the one which was developed in Sudan for epilepsy diagnosis in children[20] or as a spreadsheet on a computer. It is simply a tool that less experienced doctors or non-physician health workers can use to enhance epilepsy diagnosis in

people, close the gap in epilepsy treatment, and avert disability, stigma, and mortality. It fits in well with the aims of the World Health Organisation's IGAP report[21].
Although further validation in a variety of patients and nations, and by other health workers as well as doctors, would be useful, this algorithm is a viable option now for the many adults suffering from epilepsy, especially considering the scarcity of neurologists in LMICs.

Declaration of interest
VP is the co-developer of smartphone applications for epilepsy diagnosis and management.
The other authors have no interests to declare.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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