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A pediatric epilepsy diagnostic tool for use in resource-limited settings: A pilot study

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ABSTRACT

Objective: It is estimated that nearly 80% of the 50 million people affected with epilepsy globally live in regions where specialist care and diagnostic tests are scarce and care is often delivered through a primary health provider with limited training. To improve diagnostic accuracy of the history and physical examination, we developed and piloted a questionnaire to discriminate between focal versus generalized epilepsy, with the future goal to guide medication choices.

Methods: Through literature review and retrospective chart review of 75 children with epilepsy at Boston Children's Hospital, a 15-item questionnaire was developed. Simple motor seizures were excluded for the purposes of this questionnaire. The questionnaire was then translated in local dialects and prospectively validated at Muhimbili National Hospital in Dar Es Salaam, Tanzania, and University Teaching Hospital in Lusaka, Zambia. Children 6 months–18 years of age with suspected or active epilepsy were identified, and a non-physician administered the questionnaire to the patient's caregiver. Next, each patient was evaluated by a pediatric neurologist blinded to the questionnaire results, and together with locally obtained but remotely interpreted EEG, an electroclinical diagnosis was made. The questionnaire data were compared with this clinical gold standard.

Results: A total of 59 children participated: 28 from Tanzania and 31 from Zambia. Sixteen patients were excluded: 5 were excluded because of incomplete data, and 11 did not meet criteria for epilepsy based on initial screening questions. Of the remaining 43 patients, 28 had focal or multifocal epilepsy (65%), and 15 (35%) had generalized epilepsy. The questionnaire had a sensitivity of 78% and positive predictive value of 81.5%. Data were analyzed using a Rasch model, testing the questionnaire's internal consistency, reliability, and its discriminative validity in classifying focal versus generalized epilepsy against an electroclinical diagnosis. The mean epilepsy score for focal epilepsy was 0.084 logits compared with −1.147 logits for generalized epilepsy, demonstrating a large effect size [$F(1, 41) = 13.490$, $p < 0.001$].

Conclusions: Our questionnaire provides a straightforward method to improve diagnostic accuracy, and could assist in bridging the diagnostic gap in pediatric epilepsy in resource-limited settings. This tool was specifically designed to be easily implemented by any healthcare provider. This pilot study prompts broader prospective validation in additional settings for further refinement, and for performance assessment of impact on provider's practice, ability to guide medication choices, and ultimately improve treatment outcomes in resource-limited regions.

1. Introduction

Epilepsy is a disorder affecting over 50 million people worldwide [1]. A disproportionate portion of people with epilepsy, estimated as high as 80–85%, reside in low and middle-income countries (LMIC) where there is limited access to specialist care, appropriate diagnostic tests, and medication supply [2,3]. Together with a high prevalence in these regions, this gap has led to a high morbidity and mortality of up to twice that of the population without epilepsy [4].

The access to pediatric neurological care is an even larger problem. As per the World Health Organization, the median number of pediatric

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neurologists per 100,000 population varies from zero in Southeast Asia to 0.14 in Europe, with many countries in Africa without even a single specialist [1]. The diagnosis of epilepsy is most often made by medical officers in rural areas and psychiatric nurses in urban regions [5]. While epilepsy can be successfully treated in up to 70%, the lack of providers leads to substantial undertreatment of epilepsy in LMIC, contributing significantly to the global burden of neurologic disorders [1,6,7].

The majority of epilepsy care in LMIC is delivered by primary health providers, including clinical health workers, nurses, clinical health officers, and general practitioners. With little training and high patient load, there is limited opportunity to accurately differentiate focal from generalized seizures. This distinction is a key determinant in the choice of appropriate antiepileptic drug (AED) therapy as narrow spectrum medications, appropriate for focal seizures, when used in generalized epilepsy syndromes, can be ineffective and cause seizure aggravation [8,9].

In LMIC, treatment choices may not be patient-specific because of time and training restraints. To reduce this diagnostic gap, we developed a questionnaire to discriminate focal from generalized seizures, and acquired pilot data in 2 LMIC.

2. Methods

2.1. Generation and retrospective validation of questionnaire

Literature review identified 45 key semiology characteristics distinguishing between focal and generalized seizures in children. The 15 most discriminating features were identified through qualitative comparison to existing literature, and extracted by a retrospective chart review of 100 children at Boston Children's Hospital (BCH). These items were formatted into yes/no questions for ease of use.

Next, the questions were further refined based upon individual item predictive value to formulate the initial draft 15-item questionnaire. Three initial screening questions from existing validated questionnaires were also included to confirm that the child had met criteria for epilepsy (confirming impairment of consciousness, recurrent events, and events without fever; simple motor seizures were excluded) [10–14].

In a third step, the initial draft questionnaire then underwent retrospective validation via chart review of 75 other, randomly selected children aged 1–18 years with a diagnosis of epilepsy at BCH, with focal or generalized semiology confirmed by EEG and clinical evaluation seen from January 2006–January 2011. The questionnaire's predictive ability to diagnose focal epilepsy based on retrospective chart review ($n = 75$) was 0.85 ($p < 0.05$) with sensitivity of 81.2%. The 15-item questionnaire was then translated into local dialects for prospective validation, followed by reverse translation to ensure optimal performance. The full questionnaire can be found in Appendix A.

2.2. Pilot validation

First, the questionnaire was translated into Kiswahili and prospectively validated at Muhimbili National Hospital in Dar Es Salaam, Tanzania in August 2013. Twenty-eight children aged 6 months to 18 years with suspected or active epilepsy were identified by presenting complaint to the general pediatrics clinic over a three-week period. A local medical student administered the questionnaire to the parent. A visiting pediatric neurologist (AAP, as no specialist was available at MNH at time of study) then performed the clinical evaluation, and routine EEG was performed locally but interpreted remotely at BCH by a board-certified neurophysiologist blinded to clinical data.

Next, the questionnaire was translated into Bemba and Nyanja and prospectively validated in Lusaka, Zambia. All 15 items remained the same for translation; however, question order was revised for ease of translation. Thirty-one children aged 6 months to 18 years were identified by referral to the local child neurologist (OC) at the Paediatric Centre of Excellence of University Teaching Hospital over a 2-month period, from March to May 2015. The questionnaire was administered to the patient's caregiver by a nonmedical staff member of the clinic. The child then underwent specialist evaluation and routine EEG, which was also remotely read.

All cases from Tanzania and Zambia were given a diagnosis of focal or generalized epilepsy by questionnaire alone, and by combined electroclinical diagnosis (clinical evaluation and EEG). In cases of discrepancy between EEG interpretations, a consensus diagnosis was reached between 2 board-certified pediatric neurologists with additional certification in clinical neurophysiology (JMP and CH).

2.3. Statistical analysis

Construct validity of the questionnaire was assessed using the confirmatory factor analysis (CFA) model in which the proposed unidimensional structure was tested. Evidence favoring the one-factor model would be manifested with Root Mean Square Error of Approximation (RMSEA) values <0.08 and descriptive fit index values greater than 0.900 [15]. However, in order not to severely penalize the measure for the modest sample size, we employed Bartlett's correction for evaluating model fit. This approach involves estimating a corrective factor and multiplying it with the Likelihood Ratio test estimated by the model. The correction involves the number of latent variables k, the number of observed variables p, and the sample size N as shown below:

$$B = 1 - \frac{4k + 2p + 5}{6n} \tag{1}$$

Discriminant validation was tested using the electroclinical diagnosis regressed on the unidimensional structure via the Rasch model [16]. The Rasch model estimates the probability p of endorsing an item i as a function of: person ability B and item difficulty D_i. Based on the formula below, when the ability of the person matches the difficulty of the item, the probability of success is 50% (the theoretical postulate of the Rasch model):

$$\text{Probability}_{ni}(x_{ni} = 1/B_n,\ D_i) = \frac{e^{(B_n - D_i)}}{1 + e^{(B_n - D_i)}} \tag{2}$$

with P_{ni} ($x_{ni} = 1/B_n, D_i$) being the probability of person n getting item i correct given a person's level of ability B, and an item's difficulty level D. The term $e = 2.71828$ is the mathematical exponential constant rounded to the 5th decimal digit. All analyses were performed using Mplus and Rumm software.

For a more detailed description of the analysis, including the uncorrected and corrected estimates of fit of the CFA model, and the verification process of the unidimensionality of the epilepsy measure, please refer to Appendix B. This also details the R function developed to address the small sample size in the CFA model.

2.4. Ethical approval

Ethical approval was obtained at all research sites: Boston Children's Hospital in Boston, MA, USA, Muhimbili University of Health and Allied Sciences in Dar Es Salaam, Tanzania, and University Teaching Hospital in Lusaka, Zambia. All caretakers gave informed consent in their native language.

3. Results

3.1. Demographics

A total of 59 children participated: 28 from Tanzania and 31 from Zambia. Five patients from Zambia were excluded from analysis because of incomplete data collection; either the questionnaire was not completed in full or the evaluation with the pediatric neurologist and/or