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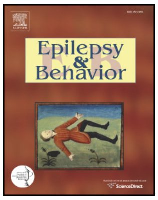

Developing the Pediatric Refractory Epilepsy Questionnaire: A pilot study

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ABSTRACT

Purpose: Up to 14% of children with epilepsy continue to experience seizures despite having appropriate medical therapy and develop medically refractory epilepsy (MRE) [8,9]. Assessing clinical outcomes and therapeutic efficacy in children with MRE undergoing palliative epilepsy surgery has been challenging because of the lack of a quantitative instrument capable of estimating the clinical status of these patients. The ideal instrument would at once consider seizure control, neurodevelopment, caregiver burden, and quality of life. The purpose of this study was to develop and pilot the Pediatric Refractory Epilepsy Questionnaire (PREQ), a quantitative instrument to assess the severity and individual burden of epilepsy in children with MRE undergoing palliative epilepsy treatments.

Methods: The caregivers of 25 patients with MRE completed the PREQ and the Quality of Life in Childhood Epilepsy (QOLCE) measure and participated in a semistructured interview. Medical records of the patients were reviewed, an Early Childhood Epilepsy Severity Scale (E-CHESS) score was calculated, and a Global Assessment of Severity of Epilepsy (GASE) score was obtained for each patient.

Key findings: The initial PREQ was modified based on the analysis of responses, association with previously validated scales, comments from caregivers, and expertise of the PREQ panelists. Pediatric Refractory Epilepsy Questionnaire subscale scores were calculated based on clinical paradigm and compared with independent measures of seizure severity and quality of life. Significant correlations were observed between the seizure severity subscale and the GASE score ($r = 0.55$) and between the mood subscale and the well-being score ($r = 0.61$) on the QOLCE. Significant correlations were also observed between the caregiver rating of seizure severity and the GASE score ($r = 0.53$), the social activity score ($r = 0.57$), and the behavior score ($r = 0.43$) on the QOLCE. Correlations between the caregiver rating of quality of life and the quality of life score ($r = 0.58$) and the number of AEDs used ($r = 0.45$) were also significant.

Significance: This pilot study is an initial, critical step in the development of the PREQ. The significant correlations between the PREQ subscales and the external epilepsy severity and quality of life measures lend preliminary support to our hypothesis that the PREQ is assessing the severity of epilepsy along with other important domains, such as mood, neurodevelopment, and quality of life. A larger prospective study of this modified PREQ is currently underway to further develop the PREQ.

1. Introduction

Epilepsy is a common neurological disorder in children [1], resulting in considerable morbidity, including cognitive, behavioral, and developmental impairment [2,3]. Furthermore, pediatric epilepsy is associated with increased mortality [4,5], substantial medicoeconomic burden [6,7], and incalculable human suffering. While pharmacotherapy is effective in many children with epilepsy, 6–14% of these children will continue to experience seizures despite having medical treatment [8,9]. Termed medically refractory epilepsy (MRE), this condition is characterized by failure to achieve seizure control after therapy with at least two appropriately chosen and appropriately dosed first-line antiepileptic drugs [10]. Children with MRE frequently have diffuse, poorly localized, or multifocal seizure onset, and treatment goals are often recalibrated to seizure palliation [11].

Assessing clinical outcomes and therapeutic efficacy in children with MRE is particularly challenging, as most traditional measures of

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outcomes in patients with epilepsy focus on seizure frequency and severity [12–20]. In palliative epilepsy treatments, important considerations in assessing clinical status also include mood, behavior, schooling, neurodevelopment, medication side effects, and quality of life [21–26]. Several scales have been proposed to address these aspects but possess similar shortcomings as the traditional seizure severity scales [18,21,26–29]. Thus, there is a pressing need for a quantitative instrument capable of estimating the clinical status of patients with MRE undergoing palliative epilepsy treatments that at once considers seizure control, neurodevelopment, quality of life, and other issues.

The purpose of this study was to develop and pilot the Pediatric Refractory Epilepsy Questionnaire (PREQ), a 22-question instrument completed by the child's caregiver. It is intended to assess the severity of epilepsy in children with MRE under consideration for palliative epilepsy treatments. The questionnaire focused on seizure severity, mood, behavior, development, schooling, and quality of life. The 22 items were initially developed using a literature review of current scales and input from clinicians and researchers relevant in the field of epilepsy and questionnaire development. The scale was then piloted with caregivers of 25 patients with MRE. Here, we present the results of the pilot phase of this study.

2. Methods

2.1. Questionnaire development

Because of age- or disease-specific cognitive limitations in patients with MRE, the questionnaire was designed to be completed by caregivers of children with MRE. Health professionals with experience in dealing with MRE, including pediatric neurosurgeons, pediatric epileptologists, and pediatric neuropsychologists, were involved in identifying important parameters affecting the overall health status of a child with epilepsy. The following domains were identified as being important in assessing the status of a child with epilepsy: seizure severity, mood, behavior, development, medication requirements and side effects, impact on daily activities, schooling, caregiver burden, and quality of life.

A list of items for the questionnaire was developed using two sources. Primarily, a review of the literature was performed to generate an inventory of items used in previous epilepsy severity and quality of life instruments. A team including clinicians, clinical researchers, and a questionnaire development expert was assembled to construct the individual questions and response options.

2.2. Pilot study

2.2.1. Study design and research subjects

Following approval by the Human Research Protection Office of Washington University/St. Louis Children's Hospital (SLCH) (IRB # 201303059), data were collected from 25 subjects deemed to have MRE by an attending epileptologist. Patients with MRE and their families were approached in the outpatient neurology and neurosurgery clinics and on the video-EEG monitoring floor at SLCH. Participating caregivers began by completing the PREQ, and the time it required for completion was recorded. When more than one caregiver was present, both caregivers independently completed the PREQ. After completing the PREQ, caregivers participated in a semistructured interview to give feedback on the questionnaire. Caregivers were asked to comment on the clarity of the current questionnaire and identify question stems and answer choices that seemed confusing. Moreover, caregivers were also asked to determine whether the PREQ adequately addressed all aspects of their child's health and to identify additional aspects of their child's health that they thought should be included in the measure. A summary of their responses was recorded in writing. Following the interview, the caregivers filled out the Quality of Life in Childhood Epilepsy (QOLCE) measure [29]. Each subject's epileptologist then rated the severity of the subject's epilepsy on the Global Assessment of Severity of Epilepsy (GASE) scale [21]. Finally, the medical records of each subject were reviewed, and data on demographics/clinical profile, seizure characteristics, use of medical care, pharmacotherapy, surgical treatment, and results of diagnostic studies (EEG and radiographic imaging) were collected. Review of medical records was limited to six months before patient enrollment, except to obtain data on surgical procedures and diagnostic studies. These data were then used to assign an Early Childhood Epilepsy Seizure Severity (E-CHESS) score for each subject [20].

2.2.2. Statistical analysis

Descriptive statistics were used to characterize demographic variables and interview responses. Data are presented as mean ± standard deviation for continuous variables and number of patients (% of group) for categorical variables. Descriptive statistics were also used to evaluate the responses to each item on the PREQ. To assess accuracy of caregiver recall, responses to select questions on the PREQ (seizure frequency and use of care) were correlated with corresponding data points obtained from medical records. Interrater reliability analysis was conducted using Pearson correlations (Fisher transformation). Interrater correlations were evaluated by comparing the lower bound of the 95% confidence interval to one.

Questionnaire items were combined based on clinical context and a correlation matrix to create subscale scores for seizure severity, mood, impact on daily life, development, caregiver rating of seizure severity, and caregiver rating of quality of life. Cronbach's alpha was calculated to assess internal consistency and reliability of items on each subscale. These subscales were then evaluated for their association with age at onset of seizures, number of antiepileptic drugs (AEDs), MRI and EEG findings, GASE scores, E-CHESS scores, and QOLCE subscores. Pearson correlations (2-tailed *t*-test) were used to assess associations between subscales and continuous variables. Between-group comparisons of subscales were performed using analysis of variance (ANOVA). A p-value ≤ 0.05 was considered statistically significant. The data analysis was generated using SAS software (version 9.3) and SPSS software (version 19).

3. Results

3.1. Patient and seizure characteristics and interview responses

Patient demographics and seizure characteristics are summarized in Table 1. Interview responses are summarized in Table 2.

Table 1
Patient demographic and seizure characteristics.

Total number of patients			25
Female gender			13 (52%)
Age at seizure onset (in months)			19.6 ± 8.0
Age at time of survey (in months)			110.4 ± 13.5
Delay between seizure onset and time of survey (in months)			88.6 ± 13.2
Seizure type(s)	GTC		5 (20%)
	Tonic		11 (44%)
	Clonic		2 (8.0%)
	Atypical absence		4 (16%)
	Atonic		1 (4.0%)
	Myoclonic		3 (12%)
	Simple partial seizures		3 (12%)
	Complex partial seizures		9 (36%)
	Infantile spasms		2 (8.0%)
Seizure frequency	More than 10×/day		5 (20%)
	Daily		7 (28%)
	Weekly		8 (32%)
	Monthly		3 (12%)
	A few times in the past 6 months		1 (4.0%)
Epilepsy surgery	VNS		4 (16%)
	CC		3 (12%)
		Partial	1 (4.0%)
		Complete — 1 stage	1 (4.0%)
		Complete — 2 stage	1 (4.0%)

Abbreviations: GTC, Generalized Tonic Clonic; VNS, Vagus Nerve Stimulation, CC, Corpus Callostomy.