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Multivariate trajectories across multiple domains of health-related quality of life in children with new-onset epilepsy

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ABSTRACT

The diagnosis of epilepsy in children is known to impact the trajectory of their health-related quality of life (HRQOL) over time. However, there is limited knowledge about variations in longitudinal trajectories across multiple domains of HRQOL. This study aims to characterize the heterogeneity in HRQOL trajectories across multiple HRQOL domains and to evaluate predictors of differences among the identified trajectory groups in children with new-onset epilepsy. Data were obtained from the Health Related Quality of Life in Children with Epilepsy Study (HERQULES), a prospective multi-center study of 373 children newly diagnosed with new-onset epilepsy who were followed up over 2 years. Child HRQOL and family factors were reported by parents, and clinical characteristics were reported by neurologists. Group-based multi-trajectory modeling was adopted to characterize longitudinal trajectories of HRQOL as measured by the individual domains of cognitive, emotional, physical, and social functioning in the 55-item Quality of Life in Childhood Epilepsy Questionnaire (QOLCE-55). Multinomial logistic regression was used to assess potential factors that explain differences among the identified latent trajectory groups. Three distinct HRQOL trajectory subgroups were identified in children with new-onset epilepsy based on HRQOL scores: "*High*" (44.7%), "*Intermediate*" (37.0%), and "*Low*" (18.3%). While most trajectory groups exhibited increasing scores over time on physical and social domains, both flat and declining trajectories were noted on emotional and cognitive domains. Less severe epilepsy, an absence of cognitive and behavioral problems, lower parental depression scores, better family functioning, and fewer family demands were associated with a "Higher" or "Intermediate" HRQOL trajectory. The course of HRQOL over time in children with new-onset epilepsy appears to follow one of three different trajectories. Addressing the clinical and psychosocial determinants identified for each pattern can help clinicians provide more targeted care to these children and their families.

1. Introduction

Health-related quality of life (HRQOL) is an important consideration in the diagnosis and management of chronic conditions such as epilepsy [1]. A new diagnosis of epilepsy in children is known to affect their emotional, behavioral, social, academic, and family functioning [2,3]. Prospective, longitudinal assessment of HRQOL in these children is important to understand variations in the course of HRQOL over time, and factors associated with different outcomes. In turn, this knowledge can inform clinical decision-making about disease management according to different prognostic factors.

In recent years, there has been increased interest in identifying children with epilepsy who are less likely to have favorable health outcomes based on longitudinal trajectories of HRQOL [4–6]. For example, Ferro et al. [4] characterized variations in longitudinal trajectories of HRQOL in children with new-onset epilepsy and found five distinct trajectory subgroups where number of antiepileptic drugs (AEDs) prescribed, presence of comorbid behavioral or cognitive problems, parental depression, and family functioning and demands predicted differences among the various trajectories. In another study that used

Abbreviations: AEDs, antiepileptic drugs; CES-D, Center for Epidemiological Studies Depression; FIRM, Family Inventory of Resources and Management; FILE, Family Inventory on Life Event and Changes; GASE, Global Assessment of Severity of Epilepsy; HERQULES, HEalth-Related QUality of Life in children with Epilepsy Study; HRQOL, health-related quality of life; MCIC, minimum clinically important change; QOLCE-55, 55-item Quality of Life in Epilepsy in Childhood Epilepsy Questionnaire; OR, odds ratio; SD, standard deviation; 95%CI, 95% confidence interval.

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the same measure [Quality of Life in Childhood Epilepsy Questionnaire (QOLCE)], Ramsey et al. [6], investigated longitudinal trajectories of HRQOL in 94 children with epilepsy and identified at least one trajectory subgroup of children experiencing poor long-term HRQOL. However, both studies characterized variations in longitudinal HRQOL trajectories based on a global or domain-specific HRQOL, which might not provide a comprehensive picture about patients' longitudinal trajectories across the multiple aspects of the HRQOL. Trajectory analysis based on global score or a single domain might not provide information on particular domains of HRQOL for which an intervention might be of benefit.

Previous research has demonstrated that clinical interventions in children with epilepsy often result in different degrees of impact on various dimensions of their HRQOL [7,8]. Therefore, understanding variations in longitudinal trajectories across HRQOL dimensions might shed more light on the impact of epilepsy interventions in children with new-onset epilepsy. To date, there are limited investigations of multivariate longitudinal trajectories of HRQOL across multiple domains of QOLCE in children with new-onset epilepsy. This study aims to characterize variations in longitudinal trajectories across multiple domains of HRQOL and to evaluate predictors of differences across the identified trajectory groups in children with new-onset epilepsy.

2. Methods

2.1. Data source

Data were obtained from the Health Related Quality of Life in Children with Epilepsy Study (HERQULES), a prospective multicenter study of 373 children with new-onset epilepsy followed up for 2 years. Details of HERQULES have been described elsewhere [9]. Children were recruited from pediatric neurology outpatient clinics, and the inclusion criteria were the following: (1) age: 4–12 years; (2) new diagnosis of epilepsy (≥2 unprovoked seizures); (3) no significant comorbid neurologic or nonneurologic conditions known to affect HRQOL, such as progressive degenerative disorders, asthma requiring daily medication, and renal failure; and (4) parents had sufficient English language skills and were primarily responsible for the child's care for at least 6 months. Parents completed four mailed questionnaires (postdiagnosis and 6, 12, and 24 months later) and consented for their child's neurologist to provide clinical information at the same time points. Of the 456 eligible children, 373 (82%) parents returned completed postdiagnosis questionnaires, and 283 (62%) completed all four questionnaires.

Data on children's sociodemographic and clinical characteristics included sex, age, type and frequency of seizures, number of antiepileptic drugs (AEDs) prescribed, age of onset, and the presence of behavioral and cognitive problems. Neurologists reported on seizure type (categorized here as generalized, partial, or undetermined) and frequency (seven-point scale ranging from "not at all frequent" to "extremely frequent"), side effects (same seven-point scale). Seizure frequency was based on an overall assessment by the neurologist regarding the period since the last clinic visit. Children who were rated as "not at all frequent" may include children in remission. Cognitive and behavioral comorbidities were assessed by neurologists at each visit and were rated using a single-item measure as having severe, moderate, or mild problems if present and then were categorically coded as absent or present based on the distribution of scoring. It should be noted that this assessment by neurologists was not based on any formal diagnostic measures, unless they had access to additional information from the parent or teacher or neuropsychological reports from a school or hospital. Data were also collected on parents' and family characteristics including parents' sociodemographic information (age, sex, marital status, employment status, education level, and annual household income). Data on the child's HRQOL and severity of epilepsy, as well as parental depression, family functioning, demands on family, and family resources were obtained using the following measures:

2.1.1. 55-Item Quality of Life in Childhood Epilepsy Questionnaire (QOLCE-55)

Health-related quality of life was assessed using the recently developed 55-item version of Quality of Life in Childhood Epilepsy Questionnaire (QOLCE-55), a parent-reported disease-specific measure [10]. The QOLCE-55 is a modified version of the original 76-item QOLCE [11,12] and provides an overall assessment of parent-reported HRQOL of children with epilepsy across four domains of HRQOL: cognitive, emotional, social, and physical functioning. The items are rated using a five-point Likert scale and transformed to a score ranging from 0 to 100, with higher scores indicating better functioning. The QOLCE-55 has strong psychometric properties and the internal consistency of each domain is excellent (Cronbach's alpha): cognitive ($\alpha = 0.97$), emotional ($\alpha = 0.88$), physical ($\alpha = 0.82$), and social functioning ($\alpha = 0.89$) [10,13,14].

2.1.2. Global Assessment of Severity of Epilepsy (GASE)

The severity of children's epilepsy was assessed by neurologists using the GASE scale [13]. This is a single-item, seven-point Likert scale that asks neurologists to rate the overall severity of ad child's epilepsy at the time of clinical assessment with possible responses ranging from 1 ("*Not at all severe*") to 7 ("*Extremely severe*"). The GASE is known to have adequate psychometric properties including high reliability and validity [15,16]. Neurologists also documented the following seven core clinical aspects (selected by an expert clinical panel) of each patient's epilepsy: frequency of seizures, intensity of seizures, falls or injuries during seizures, severity of the postictal period, amount of AEDs, side effects of AEDs, and interference of epilepsy or drugs with daily activities. These aspects were rated on a seven-point Likert scale with 1 = "*None or never*" and 7 = "*Extremely frequent, severe or high*". As additional indicators of severity, neurologists also recorded the occurrence of convulsive status epilepticus, whether seizures were exclusively nocturnal, and the total number of AEDs. The severity of epilepsy for each child was documented at each visit. GASE scale captured important clinical aspects in assessing overall severity of epilepsy including seizure frequency, intensity of seizures, side effects of AEDs, falls or injuries during the seizures, severity of the postictal period, and the amount of AEDs [15,16].

2.1.3. Center for Epidemiological Studies Depression (CES-D) scale

Parents were asked to report on their own symptoms of depression using the CES-D. The CES-D is a reliable and valid 20-item instrument used to screen for depression in primary care settings by assessing depressive symptoms experienced in the past 2 weeks [17]. Total scores range from 0 to 60, and higher scores indicate more symptoms of depression. In HERQULES, the internal consistency reliability, as measured by Cronbach's alpha, ranged from 0.75 to 0.80 across the four time points.

2.2. Family relationships and functioning

2.2.1. The family adaptability, partnership, growth, affection, and resolve (family APGAR)

Parents completed the family APGAR, a generic measure of satisfaction with family relationships and functioning [18]. It is a five-item instrument that uses a five-point Likert scale, with higher scores (range: 0–20) indicating greater satisfaction with family functioning. In HERQULES, the internal consistency reliability for APGAR as measured by Cronbach's alpha ranged from 0.86 to 0.89 across the four time points.

2.2.2. Family Inventory of Resources and Management (FIRM)

Parents also completed the FIRM, a 98-item valid and reliable measure designed to identify a family's coping resources [19]. It consists of four subscales that assess esteem and communication, mastery and