The influence of endophenotypic, disease-specific, and environmental variables on the expression of anxiety in pediatric epilepsy

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ABSTRACT

Children and adolescents with epilepsy often show higher rates of anxiety, which carries an increased risk for reduced health-related quality of life (HRQOL). The current study assessed the role of parental psychiatric history (i.e., anxiety, depression, and/or bipolar disorder) on the rate of anxiety features in youth seen in a tertiary epilepsy clinic. Data included parental ratings on the Behavior Assessment System for Children (BASC-2) and the Quality of Life in Childhood Epilepsy (QOLCE) questionnaire for 180 children and adolescents (mean age = 11.40, SD = 3.98). Our results identified clinically elevated anxiety ratings in nearly half the sample (47%) with previous psychiatric history endorsed by 48% of parents. The effect of parental psychiatric history on youth anxiety was found to be significant and associated with a threefold increase in the rate of youth anxiety features. This risk increased to fourfold in refractory epilepsy, and the impact of family psychiatric history is greater in adolescent females and in families that report higher levels of stress. In those families who reported no psychiatric history, anxiety was best predicted by epilepsy-specific factors above and beyond sociodemographic factors. Parental psychiatric history was also identified as a significant risk factor for diminished patient HRQOL, even after accounting for seizure control. These findings highlight the impact of family and epilepsy factors on psychological functioning and offer further support for the strong relationship between parental adjustment and child outcome in pediatric epilepsy.

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1. Introduction

Anxiety disorders are considered to be one of the most common psychiatric diagnoses in children and adolescents [1]. Population-based studies demonstrate that anxiety affects roughly 0.6–7% of typically developing children [2] and up to 15–20% of youth with epilepsy [3]. Of those children with epilepsy, the risk for anxiety doubles when seizures are medically intractable [4,5]. Most cases of anxiety appear to go unrecognized and untreated in children with epilepsy [5–11], and this unrecognized psychopathology has been associated with negative health-related quality of life (HRQOL) outcomes [7,12–14] and higher rates of epilepsy-related stigma [15,16].

In the general population, the study of endophenotypes of anxiety have become more common [17], and the results of more than a dozen controlled family studies of probands with anxiety demonstrated a three- to fivefold increase risk of anxiety disorders among first-degree relatives of affected probands compared to controls. The importance of the role of genetic factors in the familial clustering of anxiety has been demonstrated by numerous twin studies of anxiety symptoms and

disorders [18,19]. The high rates of anxiety disorders among offspring of parents with a psychiatric history suggests that there may be underlying psychological or biological vulnerability that may be exacerbated or fully realized by adverse environmental consequences (i.e., poor parenting, family stress, insecure attachment).

This diathesis-stress relationship can be amplified in the context of parenting a child with a chronic health condition, like epilepsy [20]. Findings from studies investigating both epilepsy and family variables as predictors of child behavior show that family variables often have a greater influence on youth anxiety features than seizure-related factors [21]. Families of a child with epilepsy have been found to experience significantly more stress, anxiety features, and restrictions in family life than other families [22,23] and especially in the context of refractory epilepsy [24]. It can be deduced that limited parental resources may contribute to parenting stress and, in turn, lead to ineffective parenting behaviors. Those parents with previous or ongoing mental health problems may be at even greater risk [25]. Unfortunately, parents of children with epilepsy are known to be a greater risk for depression and anxiety features, with rates ranging as high as 50% [26–28]. These parents are likely to have fewer coping resources to devote to their child and may be less capable of managing the complexities of their child's medical condition. The interaction between parental adjustment and patient disease severity may lend a partial explanation for past research

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indicating that children with higher seizure frequency [15,29–32], polytherapy [29], longer duration of epilepsy [29], and adolescent age [15,26,29,33] often experience greater anxiety features. To date, the contribution of parental adjustment to youth anxiety features has not been fully explored in the pediatric epilepsy literature.

Several reviews have evaluated family factors in childhood epilepsy, yet these reviews typically focus mainly on the consequences of epilepsy for the family, instead of the impact of family factors on child psychopathology [20,25]. While seizure control likely plays a large role in the presence of anxiety features, little attention has been given to the contribution of parental adjustment on the expression of anxiety features in children and adolescents with epilepsy. To address this gap in the literature, the current study explored the following research questions: [1] does parental history of psychopathology impact the rate of anxiety features in children with epilepsy? [2] How does seizure control affect the relationship between parental psychiatric history and anxiety features in children with epilepsy? [3] What factors predict anxiety features in children with epilepsy when parental psychiatric history is either present or absent? [4] How does parental psychiatric history impact quality of life in children and adolescents with epilepsy?

2. Methods

2.1. Participants

The study included 180 children and adolescents with epilepsy (61.7% male) aged 6–21 years (mean age = 11.40, SD = 3.98). Participants came from various ethnic backgrounds, with 56% Caucasian, 22% Hispanic, 13% African American, and about 9% identifying as Other. Children and adolescents were referred to pediatric neuropsychology services based upon clinical need as part of the comprehensive care protocol for the epilepsy program. Around 26% of the sample was referred as possible candidates for surgery to treat intractable seizures. The remainder of the sample was composed of children with chronic epilepsy who were experiencing cognitive difficulties that would warrant neuropsychological assessment. Children with caregivers who could not speak English were excluded from the study due to translation limitations for the measures that were used. The demographic and clinical characteristics of the sample are presented in Table 1.

2.2. Measures

Patient behavior was assessed with the Behavior Assessment System for Children–Second Edition: Parent Rating Scale (BASC-2: PRS), which is a comprehensive measure of caregiver's perceptions of their youth's emotional and behavioral functioning [34]. Caregivers complete the four-choice response format on either the child (ages 6–11 years) or adolescent (ages 12–21 years) version. The BASC-2 provides validity scales that assess the reporter's pattern of item responding. Raw scores are converted to T-scores, making scales comparable across the developmental range of 6–21 years. T-scores of 60–69 are considered "At Risk" and indicate behaviors that may warrant clinical attention; while, T-scores ≥70 are "Clinically Significant" and represent a high level of maladjustment warranting clinical attention. The BASC-2 has been deemed a "well-established" assessment tool in pediatric populations [35] and has demonstrated reliability and validity in pediatric epilepsy populations [14]. The present work examined clinical subscales across both developmental versions of the BASC-2, with specific focus on the Anxiety subscale.

Children's HRQOL was assessed using the Quality of Life in Childhood Epilepsy Questionnaire (QOLCE), a 91-item parent-rated measure designed to assess the HRQOL of children with epilepsy [36]. It was developed to assess the HRQOL of children aged 6–18 years. Caregiver ratings are measured on a five-point Likert scale range from "very often" or "all of the time" to "never" or "none of the time." Some questions ranged from "yes, limited a lot" or "very often" or "excellent" to "no, not

limited" or "N/A" or "poor" depending on the item content. The present study followed scoring procedures recommended by the authors, which included a linear transformation of raw scores to a 0–100-point scale [36,37]. Higher scores indicate a higher level of HRQOL. The advantage of this instrument over other epilepsy-specific instruments is that it offers assessment of HRQOL in a broad age group of children and has a representative number of functional life domains including: Physical Function, Emotional Well-Being, Cognitive Function, Social Function, and Behavior. An overall QOLCE score was calculated as the sum of the scores from all domains [36,37]. In the validation study by Sabaz et al. [36], the overall QOLCE score demonstrated high internal consistency (Cronbach's a = 0.93), and the individual subscales had similarly robust internal consistency (Cronbach's a = 0.72–.093). Convergent validity with theoretically similar constructs was adequate (r = 0.54–0.75) [36].

Sociodemographic and seizure-related variables were taken directly from a combination of prior medical records, parent interview, and a standardized family information questionnaire completed by a parent on the day of the evaluation. In-depth clinical interviews with the parents were conducted by licensed psychologists during the course of the patients' neuropsychological assessments. Parents were asked whether they had a history of depression, anxiety, and/or bipolar disorder(s). To control for underreporting, parent histories were subsequently verified through additional review of medical records. Parental psychiatric history was subsequently coded as 1 (positive identification) or 0 (no history identified). Additional sociodemographic data included the following: patient age, gender, ethnicity, and degree of family stress over the past year (coded: 1 = very little stress, 2 = lower than typical, 3 = typical stress, 4 = higher than typical, and 5 = very high stress). Seizure-related variables included the following: age at seizure onset, number of epilepsy-related medications (antiepileptic drugs [AEDs]), number of failed AEDs, seizure frequency (coded: 0 = never, 1 = yearly, 2 = quarterly, 3 = monthly, 4 = weekly, and 5 = daily), duration of epilepsy (i.e., time since the first seizure), and intractability status (i.e., failure to obtain seizure freedom after adequate trails of two seizure medications that were well-tolerated and chosen appropriately).

Table 1
Demographic characteristics (N = 180).

Mean age in years (SD)	11.40 (3.98)
Gender, male	111 (61.7%)
Full-scale IQ (mean/SD)	87.99 (17.50)
Racial ethnicity	
Caucasian/white	102 (56.7%)
Hispanic/Latina/Latino	39 (21.7%)
African-American/black	23 (12.8%)
Other	16 (8.9%)
Parental psychiatric history, positive	87 (48.3%)
Family stress	
Very little	12 (6.7%)
Lower than typical	22 (12.2%)
Typical	70 (38.9%)
Higher than typical	58 (32.2%)
Very high	16 (8.9%)
Age at seizure onset (years) (SD)	5.95 (4.16)
Duration of epilepsy (years) (SD)	5.58 (4.46)
Number of AEDs	1.67 (0.85)
Number of failed AEDs	2.35 (1.43)
Seizure frequency (at time of testing)	
Yearly	31 (17.3%)
Quarterly	33 (18.3%)
Monthly	42 (23.3%)
Weekly	39 (21.7%)
Daily	35 (19.4%)
Seizure control, refractory	103 (57.2%)
Reason for referral	
Nonsurgical	85 (64.4%)
Surgical candidate/phase 1	47 (35.6%)
Anxiety, BASC-2 (mean/SD)	54.11 (15.01)
At-risk range	59 (32.8%)
Clinically significant range	27 (15.0%)
Quality of life, QOLCE (mean/SD)	57.04 (15.06)