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Risk factors for learning problems in youth with psychogenic non-epileptic seizures

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ABSTRACT

Objectives: This study examined the risk factors for learning problems (LP) in pediatric psychogenic non-epileptic seizures (PNES) and their specificity by comparing psychopathology, medical, cognitive/linguistic/achievement, bullying history, and parent education variables between subjects with PNES with and without LP and between subjects with PNES and siblings with LP.
Methods: 55 subjects with PNES and 35 siblings, aged 8–18 years, underwent cognitive, linguistic, and achievement testing, and completed somatization and anxiety sensitivity questionnaires. A semi-structured psychiatric interview about the child was administered to each subject and parent. Child self-report and/or parent report provided information on the presence/absence of LP. Parents also provided each subject's medical, psychiatric, family, and bullying history information.
Results: Sixty percent (33/55) of the PNES and 49% (17/35) of the sibling subjects had LP. A multivariable logistic regression demonstrated that bullying and impaired formulation of a sentence using a stimulus picture and stimulus word were significantly associated with increased likelihood of LP in the PNES youth. In terms of the specificity of the LP risk factors, a similar analysis comparing LP in the youth with PNES and sibling groups identified anxiety disorder diagnoses and bullying as the significant risk factors associated with LP in the PNES youth.
Conclusions: These findings emphasize the need to assess youth with PNES for LP, particularly if they have experienced bullying, have linguistic deficits, and meet criteria for anxiety disorder diagnoses.

1. Introduction

Psychogenic non-epileptic seizures (PNES) in youth is a form of conversion disorder with a complex risk factor profile and a long lag in diagnosis [1,2]. Learning problems (LP) are one of the more common risks for pediatric PNES [1,3]. Nevertheless, there have been no studies on the risk factor profile for LP in youth with PNES, and whether it differs from LP in the general youth population and in youth with other medically unexplained symptoms. Delineation of the risk factors and their specificity for PNES may both aid in earlier diagnosis of PNES and inform treatment approaches.

Risk factors for LP in the general population include below-average IQ scores [4], language difficulties [4], lower socioeconomic status [5], and comorbid psychopathology [6]. Attention deficit hyperactivity disorder is the most well studied psychiatric comorbidity of LP in the general population [6]. Learning problems are also associated with increased risk for anxiety and depression [7]. Although more than 50% of youth with medically unexplained symptoms were found to have undiagnosed LP in a recent study [7], no studies have examined the risk factors associated with their LP.

Studies of youth with medically unexplained symptoms have found comorbid psychopathology risk factors similar to those in PNES [1] including depression [8], generalized anxiety [9,10], social anxiety [11], performance anxiety [12], and anxiety sensitivity (the tendency to be fearful of physical sensations) [9,10]. Internalizing disorders (depression, anxiety) and anxiety sensitivity also distinguish youth

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with PNES from their siblings [1]. Thus, internalizing disorders, found in LP in the general population, in youth with medically unexplained symptoms, and in those with PNES, as well as anxiety sensitivity, evident in the two latter disorders [13], might play a role in the observation of perceived/reported LP of PNES youth.

Bullying and learning difficulties (variably determined through formal testing, language testing, non-standardized measures designed by the study team, parent report, and self-report) are bi-directionally related so that bullying appears to increases the likelihood of LP and vice versa [14,15]. Youth with LP who experience bullying are also at greater risk for the development of functional symptoms, especially medically unexplained pain [9,16]. Children who struggle with language-related learning difficulties might be at particular risk for bullying [14,15]. In a previous study we examined a range of childhood adversities and found that history of bullying played a role in differentiating youth with PNES from their siblings [1].

To examine risk factors for LP in PNES and their specificity on our previously studied youth with PNES and sibling subjects [1], we compared (a) youth with PNES with and without LP, and (b) youth with both PNES and LP and the siblings with LP. We explored if the following variables were risk factors for the LP in PNES: lower IQ, language, and achievement scores; parents with fewer years of education; ADHD, anxiety disorder, and depression diagnoses; higher somatization and anxiety sensitivity; and history of bullying. Since 29.1% of the youth with PNES had epilepsy, and 29.1% were on anti-seizure drugs, variables that might contribute to learning difficulties [17], we also examined the role of these variables in the LP of PNES. We then compared youth with PNES and sibling subjects with LP on all of the above variables to determine if youth with PNES and LP had specific risk factors compared to their siblings.

2. Methods

2.1. Participants

This multi-site study included 55 youth with a confirmed video-EEG (vEEG) diagnosis of PNES and 35 of their siblings as a control group. The mean age of PNES onset was 14.3 years. We excluded participants from this study if they had known cognitive impairment (IQ < 70), history of epilepsy surgery, other types of non-epileptic events, and if they had non-English speaking parents. Youth with PNES were recruited from seven USA tertiary epilepsy centers. At each site, a pediatric epileptologist confirmed the PNES diagnosis, defined as paroxysmal events with semiology inconsistent with seizures due to epilepsy and without associated epileptiform discharges on v-EEG in concert with the ILAE diagnostic levels [18]. A child psychiatrist or psychologist conducted a semi-structured psychiatric interview to assess psychiatric diagnoses associated with the PNES symptoms. Youth were not excluded from the study if they had past psychiatric diagnoses, including autism.

We categorized a child as having LP if during the semi-structured psychiatric interview, described below, a child and/or parent reported poor grades, difficulty with specific or all subjects, boredom in subjects with poor grades, or not completing or handing in homework. Follow-up questions for youth who reported these problems determined if they reflected learning or social problems at school. School-related social difficulties were not categorized as LP. Of the 55 PNES probands, 33 had LP and 17 of the 35 siblings had LP.

Table 1 presents demographic, educational, and clinical characteristics of the study groups. The age range for the PNES group was 8.6–18.4 years. There were no statistically significant differences between the groups with regard to age, gender, ethnicity, mother's education, and special education. While probands with LP missed significantly more school days in the month prior to testing than those without LP, there were no significant differences in this variable in the siblings with and without LP. Table 1 does not include information on father's education since only a few fathers participated in the study. For a detailed report of the participant demographic, psychiatric, cognitive, academic, hassles, parenting, and coping profiles, see Plioplys et al. (2014).

Table 1
Demographic characteristics and outcome measures of PNES proband and sibling groups.

Variables[a]	PNES probands		Siblings	
	LD (N = 33)	No LD (N = 22)	LD (N = 17)	No LD (N = 18)
Age (years)	14.3 (2.8)	15.5 (2.3)	13.7 (2.6)	13.3 (2.2)
Gender				
Females (%)	22 (66.7)	17 (77.3)	7 (41.2)	11 (61.1)
Ethnicity				
Caucasian (%)	17 (51.5)	16 (72.7)	11 (68.8)	8 (47.1)
Mother education[b]				
College grad (%)	10 (30.3)	10 (50.0)	6 (37.5)	5 (29.4)
Number of school days missed (past month)[c]	4.9 (5.4)	10.4 (8.4)	1.4 (1.8)	1.9 (2.3)
Special education (%)[d]	8 (25.8)	3 (13.6)	2 (13.3)	2 (11.8)
Full scale IQ	98.0 (14.5)	105.0 (13.5)	103.3 (14.1)	109.4 (23.0)
WIAT achievement	98.2 (15.3)	102.2 (10.1)	103.8 (12.6)	103.1 (17.7)
CELF				
Formulated sentences	10.0 (3.4)	11.5 (2.1)	11.0 (2.8)	15.4 (12.0)
Word associations	8.9 (3.3)	10.8 (2.4)	10.1 (2.7)	10.3 (2.4)
Epilepsy-related				
Epilepsy present (%)	9 (27.3)	7 (31.8)	0 (0)	0 (0)
On anti-seizure drugs (%)	8 (24.2)	8 (36.4)	0 (0)	1 (5.6)
Experienced bullying (%)	18 (54.6)	5 (22.7)	2 (11.8)	4 (22.2)
Psychiatric diagnoses				
ADHD (%)	13 (39.4)	3 (13.6)	5 (29.4)	2 (11.1)
Anxiety (%)	27 (81.8)	19 (86.4)	6 (35.3)	6 (33.3)
Depression (%)	13 (39.4)	11 (50.0)	1 (5.9)	4 (22.2)
Somatization				
Total score	27.7 (19.4)	35.7 (19.2)	14.0 (14.4)	15.9 (19.4)
Anxiety sensitivity				
Total score	13.9 (7.3)	15.5 (6.9)	11.1 (5.4)	9.0 (5.7)

[a] Mean (SD) are presented for continuous variables and n(%) are presented for categorical variables.
[b] Mother education data are missing for 2 proband and 2 sibling families.
[c] Data on number of school days missed are unavailable for 8 proband and 5 sibling families.
[d] Special education data are missing for 2 proband and 3 sibling families.

2.2. Procedures

The parents completed a questionnaire about their children's demographic information, illnesses, epilepsy, medications, adversities, family composition, as well as parents' years of education and marital status. Institutional review board approval was obtained for all co-authors at each site.

2.2.1. Psychopathology

2.2.1.1. Schedule for Affective Disorders and Schizophrenia for School Age Children-Present and Lifetime Version (K-SADS-PL) [19]. This semi-structured instrument assesses current and past psychiatric diagnoses according to the DSM-IV-TR criteria. The study's child psychiatrists/psychologists, trained to administer the K-SADS-PL, interviewed each subject and parent, separately, about the child. A study co-investigator (RC), blinded to the subjects' group assignment, reviewed all the video-recorded interviews. The interviewer and reviewer reached a consensus diagnosis on cases for which there was diagnostic disagreement. The interview yielded summary diagnoses based on both the child and parent interviews. As described above, self-report by the study subjects and/or by the parents during the interview provided information on the presence/absence of LP.

2.2.1.2. Childhood Anxiety Sensitivity Index (CASI) [20]. This 18-item self-report scale measures the tendency to view anxiety-related bodily sensations as dangerous. Items are scored on a 3-point scale (none, some, a lot); total scores are calculated by summing all items. The

instrument has high internal consistency (alpha = 0.87) and adequate test-retest reliability (range = 0.62–0.78). Its scores correlate well with trait anxiety measures (r = 0.55–0.69).

2.2.1.3. Children's Somatization Inventory (CSI) [21,22]. This self-report measure assesses the severity of somatic symptoms. Respondents rate the extent to which they have experienced each of the 35 symptoms using a 5-point scale. Total scores range from 0 to 140. Adequate reliability and validity have been established on clinical, school, and well children samples. The 1-year test–retest Pearson reliability was 0.61 for well children and 0.34 for pediatric sample; coefficients were 0.91 and 0.90 for the well and clinical samples, respectively.

2.2.2. Cognitive and academic functioning

2.2.2.1. Wechsler Abbreviated Scale of Intelligence (WASI) [23]. The WASI provides a valid estimate of intellectual functioning and generates a Full Scale IQ (FSIQ) index based on four subtests; Vocabulary, Similarities, Block Design, and Matrix Reasoning. Scores on the Vocabulary and Similarities subtests yield a Verbal Intelligence Quotient (VIQ). The Performance Intelligence Quotient (PIQ) is comprised of the Block Design and Matrix Reasoning subtests.

2.2.2.2. Wide Range Achievement Test-4 [24]. The WRAT-4 is a valid and commonly used screener for academic achievement, and consists of four subtests: Word Reading, Sentence Comprehension, Spelling, and Math Computation.

2.2.2.3. Clinical Evaluation of Language Fundamentals-Fourth Edition (CELF-4) [25]. The 13 subtests of the CELF-4, a measure of general language ability, estimate expressive and receptive language. We used the Word (subjects provides a word corresponding to a picture), Concepts & Following Directions (subject points to colored shapes in the order presented), and Formulated Sentences (subjects construct a sentence based on a stimulus picture and using the stimulus word) subtests. Test-rest reliability was studied on a healthy sample of students. Stability coefficients ranged from 0.71 to 0.86 for subtests and from 0.88 to 0.92 for composite scores based on the standardization population.

2.2.3. Bullying

A history of bullying was abstracted from the information on adversities taken from the K-SADS-PL Post Traumatic Stress Disorder module of the youth and parent interviews. Study subjects or their parents endorsed historical experiences of bullying if the child experienced physical, verbal, or mental aggression by a peer.

2.3. Statistical analysis

Study data were entered at each site and managed using REDCap electronic data capture tools hosted at the UCLA site [26]. Prior to statistical analyses, all data were inspected for outliers, skewness, and homogeneity of variance to ensure their appropriateness for parametric statistical tests. From among a set of variables postulated to predict LP, we explored if they differentiated between youth with PNES with and without LP and between PNES probands and their siblings who have LP. The postulated variables were lower IQ, language, and achievement scores; parents with fewer years of education; ADHD, anxiety disorder, and depression diagnoses; higher somatization and anxiety sensitivity; and history of bullying; and epilepsy and anti-seizure drugs.

The risk factors for LP in PNES were determined as follows: first we compared probands with and without LP using univariate analyses (*t*-tests for continuous and chi-square or exact tests for categorical measures) on all the variables of interest (IQ, language, and achievement scores; parents' years of education; bullying, and epilepsy; number of anti-seizure drugs; CSI and CASI scores; and ADHD, anxiety, and depression diagnoses). Following the univariate analyses, those variables that were significant at a significance level of 0.1 were used in a multivariable logistic regression model, with presence of LP as the dependent variable; this model was then trimmed using Akaike Information criterion to select the final model. The results (both parameter estimates and statistics) from this final model are reported.

To test the second hypothesis, probands and siblings with LP were compared on all the variables of interest using a mixed model with family as a random effect, in order to take into account the correlation between probands and siblings in the modeling of the covariance structure. A mixed model also allows for the use of all proband and sibling data, even though only 64% of the probands had siblings in the present study. For continuous measures, a linear mixed model, as implemented in PROC MIXED, and for categorical measures, a generalized linear mixed model, as implemented in PROC GLIMMIX, were used to compare probands and siblings (SAS 9.4 Software, SAS Institute, Cary, NC). Following these preliminary analyses, as was done for Hypothesis 1, a final model (with group, proband vs. sibling, as the dependent variable) was estimated that explained the data optimally. For both hypotheses, effect size estimates (odds ratios) are presented to give an idea of the magnitude of the strength of the associations between the risk factors and the outcome measure. We also report the area under the receiver operating characteristic curve (AUC) for these final models; AUC measures discrimination, that is, the ability of the variables to correctly classify those with and without the condition (LP in PNES youth for model 1 or PNES in those with LP for model 2). The substantive findings of the paper are based on the two final logistic regression models, one for each hypothesis, and a probability level of 0.05 was considered as significant.

3. Results

Sixty percent of youth with PNES (N = 33) reported LP, while only a small proportion, 21% (N = 7), of their parents recognized this concern. Among the siblings, nearly 49% (N = 17) reported LP, and this was recognized by only 12% (N = 2) of their parents.

3.1. Risk factors for LP in PNES probands

The preliminary univariate analyses indicated that Full Scale IQ (LP: 98.0 (14.5) vs. no LP: 105.0 (13.5), t(53) = 1.8, p = .08), bullying (LP: 54.6% vs. no LP: 22.7%, Fisher's exact p = 0.02), ADHD diagnosis (LP: 39.4% vs. no LP: 13.6%, Fisher's exact p = 0.07), CELF Formulated Sentences score (LP: 10.0 (3.4) vs. no LP: 11.5 (2.1), t (50) = 1.7, p = 0.09), and CELF Word Associations score (LP 8.9 (3.3) vs. no LP: 10.8 (2.4), t (49) = 2.3, p = 0.03) should be considered further.

The final model yielded only bullying (OR = 8.1 (95% CI 1.9–35.7), p = 0.005) and the CELF Formulated Sentences score (OR for 5-unit change in score = 4.8 (95% CI 1.1–20.6), p = 0.03) as the significant risk factors for LP in this sample of subjects with PNES. The area under the receiver operating characteristic curve was 0.81 for this model.

3.2. Comparing probands and siblings with LP

The preliminary univariate analyses indicated that anxiety diagnosis (probands: 81.8% vs. siblings: 35.3%, F(1,12) = 9.7, p = 0.01), depression diagnosis (probands: 39.4% vs. siblings: 5.9%, F(1,12) = 4.6, p = 0.05), epilepsy (probands: 27.3% vs. siblings: 0%, p = 0.02), use of anti-seizure drugs (probands: 24.2% vs. siblings: 0%, p = 0.03), CSI somatization score (probands: 27.7 (19.4) vs. siblings: 14.0 (14.4), F [1,12] = 12.3, p = 0.004), and bullying (probands: 54.6% vs. siblings: 11.8%, F(1,12) = 7.0, p = 0.02) should be further investigated.

The final model yielded only anxiety diagnosis (OR = 9.3 (95% CI 2.0–43.1), p = 0.004) and bullying (OR = 10.3 (95% CI 1.7–63.4), p = .01) as the significant risk factors associated with PNES in this sample of probands and siblings with LP. The area under the receiver operating characteristic curve was 0.83 for this model.

4. Discussion

Although LP are a risk factor for pediatric PNES in >50% of patients [1,2], this is the first study to examine the risk factor profile (demographic, family, medical, psychopathology, and bullying variables) associated with LP in youth with PNES and its specificity. We found that bullying and poor use of a stimulus picture and word to formulate a sentence were significantly associated with increased likelihood of LP in subjects with PNES. Anxiety disorder diagnoses and history of bullying were specific risk factors for LP in the subjects with PNES compared to the sibling subjects. Our findings in youth with PNES and LP corroborate the studies of adults with PNES who were found to have a lifetime history of LD [26–28].

By utilizing siblings as a control group, this is also the first study, to our knowledge, to control for family effect on the LP of pediatric PNES. Though LP was frequent in the subjects with PNES (60%) and their siblings (49%), only a fraction of the parents recognized this concern in the subjects with PNES (21%) and in their siblings (12%). Evidence for unrecognized and untreated LP [9], as well as low average IQ [12], in other medically unexplained conditions underscores the subtle nature of the learning challenges children with these disorders experience. Despite the cross-sectional design of our study and of studies on LP in youth with medically unexplained symptoms [9], our findings raise the question about the role of LP in the development of medically unexplained symptoms, such as PNES. They also emphasize the importance of comprehensively assessing LP and obtaining information about LP from children and adolescents with PNES rather than relying on parental report about their school functioning.

4.1. PNES subjects with and without LP

This is also the first study, to our knowledge, that has examined the role of bullying in the LP of youth with PNES. Similar to youth with PNES with LP, patients with medically unexplained symptoms and their parents describe bullying and LP as common stressors [9]. Replication of our risk factor findings in future large-scale studies will confirm the need for earlier identification of bullying and its association with LP in children and adolescents with PNES [1].

Language-related learning challenges have not been studied in PNES and in children and adolescents with medically unexplained symptoms. Poor formulation of sentences played a significant independent role in distinguishing the youth with PNES with LP from those without LP. This subtest evaluates the ability to use language to express thoughts. This skill is essential for school performance given its role in writing and composition. The ability to formulate and express ideas through language also plays an important role in social problem solving and functioning. This is particularly relevant in problem social circumstances, such as teasing and bullying [14]. Our finding suggests that, like bullying, language testing, should also be included early in the diagnostic process. Evidence for linguistic deficits using comprehensive language testing in large samples of youth with PNES will confirm different risk factor profiles in patients with and without LP. These findings would also have important treatment implications.

Children and adolescents with epilepsy with intelligence in the average range also have high rates of LP [29], impaired language [17,29], and experience bullying [30]. Just over 29% of our subjects with PNES had epilepsy, yet the univariate analysis did not find an association between the presence of epilepsy and LP. This negative finding might be due to the relatively small sample of PNES subjects with epilepsy. Although 29.1% of the subjects with PNES were taking anti-seizure drugs, this variable was unrelated to an increased risk for LP. This finding, even though cross-sectional, suggests that the LP in these youth with PNES already existed, and that possible adverse cognitive effects of the anti-seizure drugs [17] did not appear to have an additive effect.

4.2. Comparing LP in PNES and siblings

History of bullying and anxiety independently differentiated between the LP of subjects with PNES and their siblings. As previously mentioned, ADHD [6], anxiety [14], and bullying [15] are associated with LP in youth in the general population [7]. While ADHD is a common co-morbidity in the general population [6], in our study it only approached significance in the preliminary comparisons of youth with PNES with LP versus no LP. There were also no significant differences between Youth with PNES with LP and siblings with LP with regard to ADHD. Similarly, while presence of depression was a preliminary indicator of LP in PNES compared to the siblings, depression was no longer significant in the final model. This may reflect the small number (13/33) of youth with PNES and of siblings (1/17) who had depression and LP (Table 1), and needs to be replicated.

Despite increased LP [29], language difficulties [17], depression [30,31], anxiety [17,32], and bullying [1,32] in pediatric epilepsy, the subjects with PNES and comorbid epilepsy did not account for our findings comparing the subjects with PNES and siblings with LP. This underscores that anxiety disorder diagnoses and history of bullying are specific to the LP risk factor profile of PNES.

The study's within-group and between-group findings highlight the importance of expressive difficulties involving formulation of sentences, as well as history of bullying and anxiety disorder diagnoses as risk factors for the LP of youth with PNES. Given the cross-sectional nature of our study and the relatively small sample size of the study's subgroups, future large-scale studies are indicated to determine which of these variables mediate or moderate LP in youth with PNES.

4.3. Clinical implications

The LP of a large percentage of youth in this sample was undiagnosed and untreated, and the subjects' parents did not recognize or report about their children's problems with learning. Youth typically avoid self-reporting about learning difficulties, bullying, and anxiety to their parents and physicians [32]. However, parents and physicians do not have the expertise to identify subtle linguistic or learning problems. In children with a confirmed PNES diagnosis, our findings highlight the need to rule out LP and associated bullying, linguistic deficits, and anxiety disorder.

Learning problems [29], anxiety [30,32], bullying [30], and language impairment [17] co-occur in pediatric epilepsy and, as evident from our study, in youth with PNES. Therefore, in children and adolescents who present with seizure-like episodes, clinicians should assess for these risk factors, and when found include PNES in addition to epilepsy in the differential diagnosis.

4.4. Limitations

Although the study's sample size was relatively small, this is the largest controlled study of LP in youth with PNES. While a number of preliminary univariate analyses were conducted to identify an initial set of variables to be studied further, all inferences are based on only two final logistic regression models, one comparing PNES with and without LP and another comparing PNES with LP and siblings with LP. Further, this was the first hypothesis-based study examining PNES youth with LP and their siblings, and our findings provide a starting point for better understanding the complexity of the risk factor profile of LP in pediatric PNES. Given the small number of PNES subjects with depression, the negative depression findings need to be confirmed on a larger sample of PNES subjects and their siblings.

Similar to prior studies in PNES and in other functional disorders [9,13], the diagnosis of LP was based on youth and/or parent report of learning difficulties during the semi-structured interview, not on formal educational testing. The WASI and achievement measures were not sensitive to the subtle LP of this group. Due to limited funding, we included only two language subscales of the CELF. Although this was the first

study that examined the role of cognition, achievement, and language, replication of our findings is needed using a comprehensive LP battery that includes a full intelligence test and detailed language assessment. The small number of siblings with ADHD in this sample does not rule out that ADHD could be associated with LD in siblings of youth with PNES, as is true in the general population.

Due to the small sample size of subjects with PNES with epilepsy and lack of an epilepsy-only control group, we cannot rule out a possible role of epilepsy in the study's findings. Replication of these findings is needed comparing youth with PNES and LP, epilepsy and LP, and LP without PNES or epilepsy.

5. Conclusion

Youth with PNES should be assessed both clinically and with comprehensive formal psychoeducational testing for LP, particularly if they have experienced bullying, have subtle linguistic deficits, and meet criteria for anxiety disorder diagnoses.

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