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Original Article

The Timing, Nature, and Range of Neurobehavioral Comorbidities in Juvenile Myoclonic Epilepsy

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ABSTRACT

Background: Accumulating evidence suggests that considerable cognitive and psychiatric comorbidity is associated with juvenile myoclonic epilepsy, for which the etiology remains controversial. Our goal was to *comprehensively* characterize the status of multiple neurobehavioral comorbidities in youth with new- or recent-onset juvenile myoclonic epilepsy, before effects of chronic seizures and medications.
Methods: A total of 111 children aged eight to 18 years (41 new- or recent-onset juvenile myoclonic epilepsy and 70 first-degree cousin controls) underwent neuropsychological assessment (attention, executive, verbal, perceptual, speed), structured review of need for supportive academic services, parent reports of behavior and executive function (Child Behavior Checklist and Behavior Rating Inventory of Executive Function), and formal structured psychiatric interview and diagnosis (Kiddie Schedule for Affective Disorders and Schizophrenia—Present and Lifetime Version).
Results: Children with juvenile myoclonic epilepsy performed worse than controls across all tested cognitive domains ($F(1,105) = 3.85$, $P < 0.01$), utilized more academic services (47% versus 19%, $P = 0.002$), had more parent-reported behavioral problems and dysexecutive function with lower competence ($P < 0.001$), and had a higher prevalence of current Axis I diagnoses (attention-deficit/hyperactivity disorder, depression, and anxiety; 54% versus 23%, $P = 0.001$). Academic and psychiatric problems occurred antecedent to epilepsy onset compared with comparable timeline in controls.
Conclusion: Comprehensive assessment of cognitive, academic, behavioral, and psychiatric comorbidities in youth with new- or recent-onset juvenile myoclonic epilepsy reveals a pattern of significantly increased neurobehavioral comorbidities across a broad spectrum of areas. These early evident comorbidities are of clear clinical importance with worrisome implications for future cognitive, behavioral, and social function. It is important for health care providers to avoid delays in intervention by assessing potential comorbidities early in the course of the disorder to optimize their patients' social, academic and behavioral progress.

Introduction

Juvenile myoclonic epilepsy (JME) is a common idiopathic epilepsy that represents 10% of all epilepsies.[1] JME is characterized as a generalized genetic epilepsy syndrome[2] with a peak age of onset between 12 and 18 years.[3,4] Originally thought to have a benign course throughout the lifespan due to normal intellect and positive response to antiepileptic medication,[5] approximately two-thirds of individuals with JME will be seizure free while on antiepileptic

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medications or have extensive periods of seizure freedom.[6] However, recent studies indicate that cognitive dysfunction and psychiatric comorbidities are a major component of the JME phenotype.[2,22]

Studies show evidence of various cognitive deficits associated with JME compared with controls[8] in areas such as executive and social function, memory, mental speed, attention, and language.[9-16] On the one hand, some evidence suggests that the most consistent deficit occurs in executive function (EF),[12,13,15,17,19,20] as observed on EF tests including structured verbal fluency (e.g., phonemic fluency), speeded mental flexibility (Trails-B), and response inhibition (Stroop Interference). Up to 60% to 64% of patients with JME show difficulty in concept formation and mental flexibility, 47% to 53% have difficulty with cognitive speed, and 33% exhibit difficulty in planning and other aspects of EF.[17] On the other hand, a recent review/meta-analysis indicated that cognitive deficits in JME are more widespread in nature and without predominance of dysexecutive function.[40] Both visual and nonverbal memory, as well as attention, are also adversely affected.[19] Intelligence quotient is also lower than average when compared with controls, but overall preserved in JME in contrast to other types of epilepsies.[11,12,18]

In addition to cognitive abnormalities, psychiatric and behavioral comorbidities have also been reported in JME. Approximately one-third of patients with JME experience a comorbid psychiatric disorder,[29] with the highest prevalence in individuals with early onset.[30] Depression, anxiety, low self-esteem, and attention-deficit/hyperactivity disorder (ADHD) are frequently reported in the current JME literature as well.[23-27] Ertem et al. reported that among a cohort of patients with JME, 37% exhibited a comorbid psychiatric disorder.[7] Of the 37%, 17% had anxiety, 13% had a mood disorder, and 7% had a psychotic disorder, rates that are significantly higher than controls. Other studies have corroborated these findings. Fihlo et al. noted 49% psychiatric comorbidity among patients with JME (23% anxiety, 19% mood disorders, 8% psychotic disorders).[28]

The reasons underlying these cognitive and psychiatric comorbidities in JME are yet to be defined; however, it is clear that several clinical factors may play a role. Seizure course has been a factor of major interest as a potential contributor to cognitive and psychiatric deficits in JME. Cross-sectional research suggests that cognitive dysfunction may worsen with longer duration of epilepsy.[12,20,21] Specifically, worsening performance in immediate memory, attention, and visual working memory have been reported to be associated with longer duration of epilepsy.[20] Seizures that are refractory to treatment can also contribute to this cognitive and psychiatric dysfunction, as those with refractory JME exhibit poorer cognitive performance and higher rates of impulsive traits.[22] These cognitive and psychiatric comorbidities can lead to social and academic consequences,[31] poor functional outcomes,[41] and impaired quality of life[41]; however, this link remains to be clearly defined.[32]

In contrast, a recent emerging theme in the investigation of neurobehavioral comorbidities is that children with different epilepsy syndromes, including JME, may exhibit cognitive, academic, behavioral, and psychiatric abnormalities at or near the time of diagnosis, with evidence that many of these issues may even antedate the onset and diagnosis of the epilepsy[38,39,51-53] and persist even with successful treatment of seizures.[44] The origin and underlying mechanisms of these difficulties remain to be clarified, but there appears to be a clear neurodevelopmental contribution. Furthermore, this cognitive and psychiatric pathology may not be entirely attributable to the presence of epilepsy as early reports suggest that unaffected siblings of these patients exhibit similar deficits, suggesting a potential familial or genetic contribution.[16,42,43]

The goal of this study is to characterize cognitive, academic, behavioral, psychiatric, and social status of youth with JME at or near the time of their diagnosis and treatment in order to contribute to the understanding of the neurodevelopmental origins of the neurobehavioral comorbidities of JME. Prior studies on children with new-onset JME[8,19,45,46] have tended to focus on specific issues such as cognition only or behavior only. Our broader approach presented here provides more detailed insight into the origins of multiple known or potential comorbidities of JME, before the effects of chronic seizures and medication obscure the underlying baseline dysfunction, as well as informing the social and academic costs that may even exist before diagnosis of the disorder.

Methods

Participants

Research participants consisted of 111 children aged eight to 18 years, including youth with recent-onset JME (n = 41) and first-degree cousin controls (n = 70). All participants attended regular schools at the time of the study assessment visit. Children with epilepsy were recruited from pediatric neurology clinics at three Midwestern medical centers (University of Wisconsin-Madison, Marshfield Clinic, Dean Clinic) and met the following inclusion criteria: (1) diagnosis of epilepsy within the past 12 months, (2) no other developmental disabilities (e.g., intellectual impairment, autism), (3) no other neurological disorder, and (4) a brain magnetic resonance imaging obtained as part of routine clinical care that was interpreted as normal. All children entered the study with active epilepsy as diagnosed by their treating pediatric neurologists, and confirmed by medical record review by the research study pediatric neurologist. We did not exclude children on the basis of psychiatric comorbidities (including ADHD) or learning disabilities. We did, however, exclude children with intellectual disability or autism. In general, we tried to stay true to the concept of "epilepsy only" as defined broadly in the literature by normal neurological examinations, intelligence, and attendance at regular schools.

Each child's epilepsy syndrome was defined in a research consensus meeting by the research pediatric neurologist who reviewed all available clinical data (e.g., seizure description and phenomenology, electroencephalography, clinical imaging, neurodevelopmental history) while being unaware of all research cognitive, behavioral, and neuroimaging data. Two levels of epilepsy syndrome classification were undertaken by the research study pediatric neurologist. Children with epilepsy were first classified into broad syndrome groups including idiopathic generalized epilepsies and localization-related epilepsies, followed by classification specifying JME.

First-degree cousins were used as controls, and exclusion criteria were as follows: (1) history of any initial precipitating insult (e.g., simple or complex febrile seizures, cerebral infections, perinatal stroke), (2) any seizure or seizure-like episode, (3) diagnosed neurological disease, (4) loss of consciousness for greater than 5 minutes, and (5) other family history of a first-degree relative with epilepsy or febrile convulsions.

This study was approved by the Institutional Review Board of each institution. On the day of study participation, families and children gave informed consent and assent, respectively, and all procedures were consistent with the Declaration of Helsinki.[33]

Procedures

Cognition

All participants were administered a comprehensive test battery that included measures of intelligence, academic achievement,

language, immediate and delayed verbal memory, EF, and speeded fine motor dexterity. Tests were selected for relevance to the cognitive domains of interest and their applicability across the study's age range (eight to 18 years), ensuring identical test items or task demands, thereby providing a uniform test protocol. The test battery was reduced via confirmatory factor analysis into five core cognitive domains (details provided below).

Academic services

Parents were questioned through a structured interview about their child's school progress and, in particular, any specific educational services provided to address academic problems. These services included the traditional individualized educational plan (IEP) process, and also included early childhood interventions, including speech therapy, physical therapy, occupational therapy, mandatory summer school, grade retention, special tutoring services (e.g., reading, mathematics), and other specific educational services (inventory available from the authors). This interview was conducted blind to cognitive and behavioral results. Parents were also specifically queried regarding whether these issues were present before the onset of seizures and their diagnosis and treatment.

Parent-reported behavioral (CBCL) and executive function (BRIEF)

Parents completed the Child Behavior Checklist for Ages 6-18 years (CBCL/6-18) from the Achenbach System of Empirically Based Assessment.[36] The CBCL instrument is designed to assess behavioral problems with lower scores on the Total Competence scale indicating greater impairment, and higher scores on the Internalizing and Externalizing Problems scale indicating greater impairment. Parents completed the Behavior Rating Inventory of Executive Function (BRIEF).[37] Variables of interest were Meta Cognition Index (MIT) (Monitor, Working Memory, Plan/Organize, Organization of Materials, and Task Completion) and Behavior Regulation Index (BRI) (Inhibit, Shift, and Emotion) scales. The BRIEF instrument is designed to assess EF with higher scores indicating greater impairment.

Psychiatric status (K-SADS)

Participating child and parent were interviewed separately and the Kiddie Schedule for Affective Disorders and Schizophrenia—Present and Lifetime Version (K-SADS),[34] was completed by the parent. A research assistant or psychologist administered the K-SADS interviews. Interviewers were not unaware of the seizure diagnosis because child and parent often talked about the child's seizures during the interview. A consensus regarding Axis I diagnosis was reached in cases wherein the parent and child were interviewed by two different interviewers. A randomly selected subset of child interview videos was also reviewed by a collaborating clinician and a consensus diagnosis was reached based on the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*.[35] Parents were also specifically queried regarding whether these issues were present before the onset of seizures and their diagnosis and treatment.

Statistical analyses

All analyses were conducted using IBM SPSS Statistics Software 21.0. An independent sample *t* test was conducted to assess potential group (controls versus JME) difference in participants' age. Chi-square and multivariate analysis of variance were employed as will be overviewed in the Results section. Sample demographics, rates of academic services, and Axis I diagnoses are presented in Table 1.

TABLE 1.
Sample Demographics, Academic Services, and Axis I Diagnosis

Measures	JME (N = 41)	Control (N = 70)
Gender		
Male	16 (39%)	35 (50%)
Female	25 (61%)	35 (50%)
Age in Years (M, S.D.)	15.0 (2.7)	14.1 (2.3)
JME Diagnosis Age (M, S.D.)	14.3 (2.7)	–
Number of AEDs (0/1/2)	1/38/2	–
Academic services	19 (47%)	13 (19%)*
Any current Axis I diagnosis	22 (54%)	16 (23%)*

Abbreviations:
AED = Antiepileptic drugs
JME = Juvenile myoclonic epilepsy
* $P < 0.01$.

Cognitive factor score computation

The relationship of the 17 neuropsychological measurements to five hypothesized underlying cognitive constructs (Verbal, Perceptual, Attention, Speed, and Executive) was tested in the control group by Confirmatory Factor Analysis. Fifteen of the 17 measurements were age-adjusted norm-referenced scores provided by the instruments and two were raw scores (Grooved Pegboard-dominant hand, and WISC-III Digit Symbol Coding [some participants exceeded the age range for norms so raw scores were used]). The two raw scores were regressed on age, and the residuals were used in place of the raw scores. *z* scores were calculated using the control mean and standard deviation for all 17 measurements.

The final model was derived using data from the control participants, and the same underlying structural equation model was then simultaneously fitted to both the control and epilepsy groups. In the control group, the five latent factors were set to have mean 0 and variance 1; these parameters were estimated freely in the epilepsy group. This specification reflects the assumption that both groups share a common measurement model, i.e., that the path coefficients and residual variances for the manifest variables are invariant across groups. Any differences between the two groups arise due to different means, variances, and correlations among the latent factors. This analysis was implemented in SAS (version 9.4, Cary, NC, USA) PROC CALIS with the GROUP statement for Multiple-Group Model and the FIML option to accommodate missing values. Using the 17 observed *z* scored measurements and the group-specific factor loadings, SAS PROC SCORES were used to estimate (extract) the five latent factor scores for each individual (details in Hermann et al[47]).

Analysis of cognitive factor scores, academic services, and CBCL and BRIEF scales

Pearson's chi-square analyses were used to assess group (controls versus JME) differences in rates of academic services, any current Axis I disorder, ADHD, depression, and anxiety. Three multivariate analysis of variance were computed to assess group (controls versus JME) differences for CBCL summary scales, BRIEF summary scales, and cognitive factor scores. The dependent variables of interest included the overall CBCL/6-18 summary scales for Total Competence, Internalizing Problems, and Externalizing Problems; the BRIEF summary scales for MIT and BRI; and the cognitive factor scores (Attention, Executive, Perceptual, Speed, and Verbal).

Results

Neuropsychological performance

Factor scores yielded a significant overall main effect, $F(1,105) = 3.85$, $P < 0.01$, partial $\eta^2 = 0.16$. Significant group

differences were found for Attention, F(1,105) = 6.45, $P < 0.05$; Executive, F(1,105) = 11.35, $P = 0.001$; Perceptual, F(1,105) = 13.06, $P < 0.001$; Speed, F(1,105) = 4.76, $P < 0.05$; and Verbal, F(1,105) = 5.62, $P < 0.05$, such that JME youth had lower factor scores compared with controls. Factor score means are summarized in Table 2 and Figure 1. It is important to note that of the 41 children with JME, 15 (36%) had at least one test result that fell below 1.5 standard deviations below average (z score < -1.5).

Academic services

Academic service rates before and at the time of diagnosis were significantly higher for children with JME compared with controls (47% versus 19%; see Table 1), [χ^2 (1, N = 111) = 9.73, $P = 0.002$], primarily driven by the significantly elevated IEP (28% vs 10%) and Birth-Age 3 (10% versus 0) services in the JME group ($P < 0.05$).

CBCL and BRIEF scales

CBCL Total Competence, Internalizing Problems, and Externalizing Problems scales yielded a significant overall main effect, F(1,108) = 9.40, $P < 0.001$, partial $\eta^2 = 0.21$. Significant group differences were found for Total Competence, F(1,108) = 17.08, $P < 0.001$; Internalizing Problems, F(1,108) = 15.29, $P < 0.001$; and Externalizing Problems, F(1,108) = 17.90, $P < 0.001$, such that JME youth exhibited lower Total Competence and more behavioral problems compared with controls. CBCL means are summarized in Table 2 and Figure 2.

BRIEF MIT and BRI yielded a significant overall main effect, F(1,107) = 9.86, $P < 0.001$, partial $\eta^2 = 0.16$. Significant group differences were found for MIT, F(1,107) = 18.98, $P < 0.001$, and BRI, F(1,107) = 15.15, $P < 0.001$, indicating that executive dysfunction was greater in JME youth compared with controls. BRIEF means are summarized in Table 2 and Figure 2.

Psychiatric status

Prevalence of any current Axis I diagnosis was significantly higher for children with JME compared with controls (54% versus 23%), [χ^2 (1, N = 111) = 10.89, $P = 0.001$]. Prevalence of current ADHD and depression diagnosis was also significantly higher for children with JME compared with controls (27% vs 7%), [χ^2 (1, N = 111) = 8.12, $P < 0.01$]; (27% vs 1%), [χ^2 (1, N = 111) = 17.30, $P < 0.001$]. There were no significant group differences for children with JME and controls on current rates of anxiety. Of the 41 children with JME, a total of 21 children (51%) showed evidence of a psychiatric diagnosis before epilepsy diagnosis. Axis I diagnosis rates are summarized in Table 1 and Figure 3.

TABLE 2.
Factor Scores, CBCL, and BRIEF

Measures	JME (M, S.D.)	Control (M, S.D.)
Factor scores		
Attention	−0.71 (1.76)	−0.07 (0.79)*
Executive	−0.68 (1.28)	0.09 (1.05)†
Perceptual	−0.66 (1.24)	0.03 (0.73)†
Speed	−0.46 (0.95)	−0.10 (0.75)*
Verbal	−0.53 (1.33)	0.02 (1.05)*
CBCL scales		
Total Competence	44.71 (10.14)	52.36 (8.92)†
Internalizing Problems	55.73 (12.57)	47.22 (9.70)†
Externalizing Problems	53.90 (11.87)	45.19 (9.50)†
BRIEF Scales		
MIT	58.05 (13.69)	48.38 (9.43)†
BRI	54.45 (12.82)	46.17 (9.27)†

Abbreviations:
BRI = Behavior Regulation Index
BRIEF = Behavior Rating Inventory of Executive Function
CBCL = Child Behavior Checklist
JME = Juvenile myoclonic epilepsy
MIT = Meta Cognition Index
* $P < 0.05$.
† $P < 0.01$.

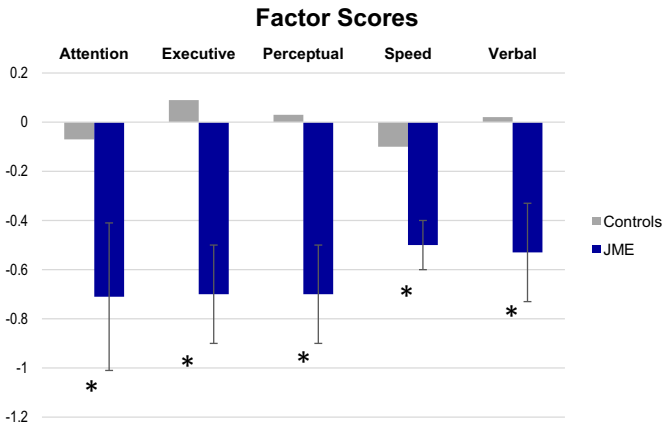

FIGURE 1. Factor scores for each cognitive domain. *$P < 0.05$. The color version of this figure is available in the online edition.

Discussion

It is now recognized that JME can be associated with a host of neurobehavioral comorbidities including cognitive deficits,[8-20] difficulties in social competence, behavioral complications or psychiatric diagnoses,[23-30] and academic struggles, all of which could lead to need for supportive services, with increased risk for poor long-term psychosocial outcomes.[11,29,48]

Most previous research has focused on persons with established and treated JME and investigated predictors of comorbidities based on clinical seizure features such as epilepsy duration, seizure frequency, and severity.[6,11,16,20] A small number of studies have suggested that these comorbidities may be present much earlier in the course of the disease including children with new-onset and drug-naive JME.[8,19] These articles have tended to focus on a subset of comorbidities. Here we studied children with new- or recent-onset JME and comprehensively characterized a number of potential problematic comorbidities, which included formal assessment of cognitive function, structured review of need for supportive academic services, parent reports of behavior and EF, and formal structured psychiatric interview and diagnosis. We also examined whether academic and psychiatric issues antedated the onset, diagnosis, and treatment of seizures.

Our findings show that cognitive anomalies are not limited to particular cognitive domains such as EF, but instead cognition is more generally adversely affected, consistent with some previous findings.[40] This pattern is also consistent with that observed in youth with other epilepsy syndromes, such as temporal lobe epilepsy.[44] One unique difference is that the percentage of children with JME and cognitive anomalies is lower and less severe than would be observed in other epilepsy syndromes.[54] Our study also evaluated the need for supportive academic services including formal IEP. Children with JME do indeed utilize academic accommodation options more frequently than controls, including qualifying for IEP services. The results regarding provision of academic services indicate that the cognitive anomalies found likely have clear clinical (academic) consequences. In addition, some of these academic issues were identified antecedent to the onset of epilepsy

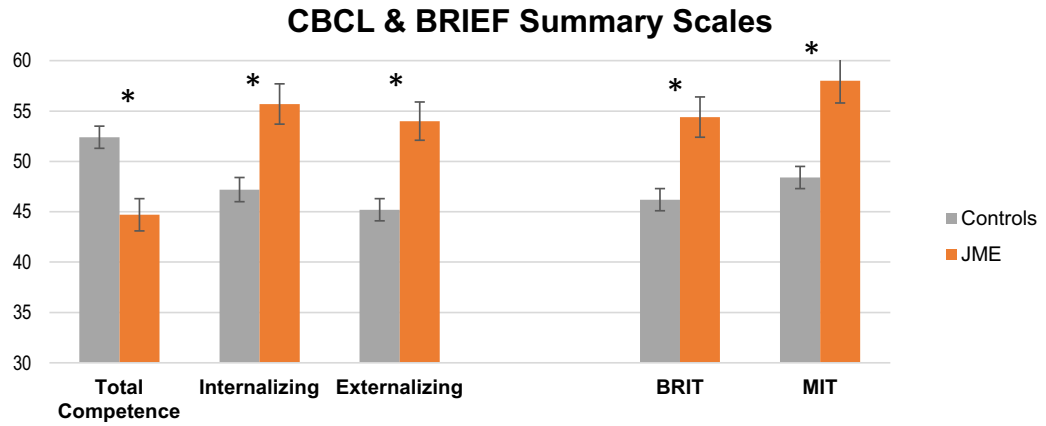

FIGURE 2. Child Behavior Checklist (CBCL) and Behavior Rating Inventory of Executive Function (BRIEF) summary scales, $^{*}P < 0.05$. The color version of this figure is available in the online edition.

and treatment, suggesting that factors independent of epilepsy itself may be contributing to these issues.

We also found that parents report that children with new- or recent-onset JME exhibit behavioral problems related to dysexecutive function more frequently than controls. These children also exhibit decreased competence with increased internalizing and externalizing problems at the time of JME diagnosis. These behavioral concerns in the academic (school) setting may appear to exacerbate the underlying academic issues that the patient with new- or recent-onset JME may have. In addition, children with new-onset JME have a higher rate of Axis I diagnoses compared with controls, again with a substantial subset of children having evidence of these complications antecedent to epilepsy onset. Assessing both reported behavioral concerns and psychiatric diagnoses in the same population gives perspective on how the psychiatric comorbidities of the disorder may have direct clinical consequences that may already affect the day-to-day activities of these patients before the chronic effects of medication and seizures.

Our findings also shed light on the potential neurodevelopmental origins of cognitive and psychiatric comorbidities associated with JME. An assessment of siblings of these patients with JME could provide further insight into the potential heritable factors associated with these comorbidities. Studies have shown that there may be neurobehavioral phenotypes of JME.[49,50] These genetic or heritable links appear to not extend any further than first-degree relatives, which is why cousins were used in this study as healthy controls. Specific analysis of these potential phenotypes would begin to delineate those who may be more likely to show these cognitive and psychiatric comorbidities.

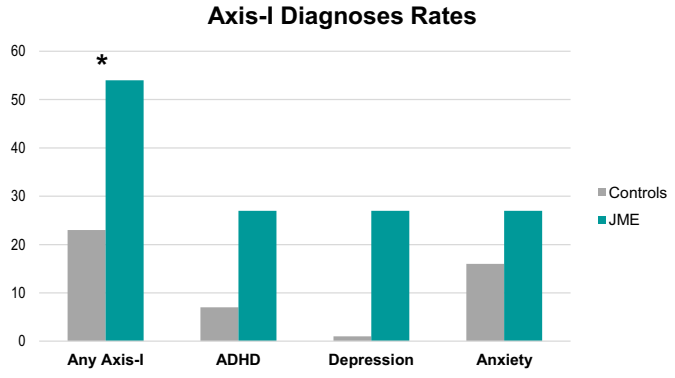

FIGURE 3. Axis I diagnosis rates. $^{*}P < 0.05$. The color version of this figure is available in the online edition.

This study is limited by the cross-sectional design. A longitudinal design with the prospective course of the disorder would be better suited to delineate how early comorbidities affect long-term psychosocial and academic outcomes. Our study is also limited by the clinical nature of the sample. A population-based sample would be ideal to improve the generalizability of the findings. In addition, all but one patient in this study had been started on medication. There is still a possibility that medication or sedating effects may have played a small role in the findings. Finally, even though the subjective findings are congruent with the objective findings, the self-report nature of some of the tests can introduce subjective or recall bias.

This is the first comprehensive documentation of clear clinical implications of the cognitive and psychiatric comorbidities associated with new- or recent-onset JME before the chronic effects of seizures and medications. Our study indicates that children with JME are at significant risk early in the disorder and that comorbidities should be identified as early as possible to optimize the patient with JME's academic and behavioral progress. In light of the problematic long-term social outcomes,[11,29,48] early identification and intervention would be beneficial to potentially reduce the known lasting consequences. Delays in intervention may be avoided by assessing academic and behavioral concerns before epilepsy onset and treatment with the goal to provide the necessary academic services immediately after diagnosis. Further research will illuminate if interventions do indeed improve academic and psychosocial outcomes in the long term.

This investigation presented the average or modal patterns and rates of neurobehavioral complications in a group of children with JME. Larger-scale investigations to identify underlying phenotypes within JME are needed. That is, like other epilepsy syndromes,[55] there is likely a subset of children with JME who show minimal neurobehavioral complications, a subset that is heavily burdened, and other subsets that may be more cognitively or behaviorally affected.[56-58] This important next step, the clinical (if any) correlates, and their longitudinal courses will be important in targeting or personalizing services for youth with JME at the most optimal time.

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