Factors Associated With Seizure Onset in Children With Autism Spectrum Disorder

Jamie K. Capal, MD,[a,b] Eric A. Macklin, PhD,[c,d] Frances Lu, MPH,[c] Gregory Barnes, MD[e]

abstract

BACKGROUND AND OBJECTIVES: Children with autism spectrum disorder (ASD) have a higher prevalence of epilepsy compared with general populations. In this pilot study, we prospectively identified baseline risk factors for the development of seizures in individuals with ASD and also identified characteristics sensitive to seizure onset up to 6 years after enrollment in the Autism Speaks Autism Treatment Network.

METHODS: Children with ASD and no history of seizures at baseline who either experienced onset of seizures after enrollment in the Autism Treatment Network or remained seizure free were included in the analysis.

RESULTS: Among 472 qualifying children, 22 (4.7%) experienced onset of seizures after enrollment. Individuals who developed seizures after enrollment exhibited lower scores at baseline on all domains of the Vineland Adaptive Behavior Scales, greater hyperactivity on the Aberrant Behavior Checklist (25.4 ± 11.8 vs 19.2 ± 11.1; $P = .018$), and lower physical quality of life scores on the Pediatric Quality of Life Inventory (60.1 ± 24.2 vs 76.0 ± 18.2; $P < .001$). Comparing change in scores from entry to call-back, adjusting for age, sex, length of follow-up, and baseline Vineland II composite score, individuals who developed seizures experienced declines in daily living skills (−8.38; 95% confidence interval −14.50 to −2.50; $P = .005$). Adjusting for baseline age, sex, and length of follow-up, baseline Vineland II composite score was predictive of seizure development (risk ratio = 0.95 per unit Vineland II composite score, 95% confidence interval 0.92 to 0.99; $P = .007$).

CONCLUSIONS: Individuals with ASD at risk for seizures exhibited changes in adaptive functioning and behavior.

[a]*Department of Neurology, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio;* [b]*Department of Pediatrics, College of Medicine, University of Cincinnati, Cincinnati, Ohio;* [c]*Biostatistics Center, Massachusetts General Hospital, Boston, Massachusetts;* [d]*Department of Medicine, Harvard Medical School, Harvard University, Boston, Massachusetts; and* [e]*Departments of Neurology and Pediatrics, University of Louisville Autism Center, Louisville, Kentucky*

Drs Capal and Barnes conceptualized and designed the study and drafted the initial manuscript; Dr Macklin conceptualized and designed the study, conducted the initial analysis, and drafted the methods section of the initial manuscript; Ms Lu collected data and provided significant contribution to the study design; and all authors reviewed and revised the manuscript, approved the final manuscript as submitted, and agree to be accountable for all aspects of the work.

DOI: https://doi.org/10.1542/peds.2019-18950

Accepted for publication Jan 27, 2020

WHAT'S KNOWN ON THIS SUBJECT: Children with autism spectrum disorder (ASD) have a higher prevalence of epilepsy compared with the general population. Comorbid ASD and epilepsy have been associated with worse adaptive functioning, behavior, and quality of life.

WHAT THIS STUDY ADDS: Those individuals with ASD at risk for seizures (before onset of seizures) have lower adaptive functioning. Onset of seizures is associated with decreased adaptive functioning, increased irritability and stereotypies, plus possible lower school and social functioning.

To cite: Capal JK, Macklin EA, Lu F, et al. Factors Associated With Seizure Onset in Children With Autism Spectrum Disorder. *Pediatrics.* 2020;145(s1):e201918950

Autism spectrum disorder (ASD) is defined as impairments in social communication and interaction combined with restricted and repetitive patterns of behavior emerging early in development[1] with a prevalence of 1 in 59.[2,3] Epilepsy commonly occurs in individuals with ASD with a prevalence ranging from 2.4% to 46%[4–8] vs 0.4% to 0.8% in the general population.[9] Conversely, rates of comorbid ASD in patients with epilepsy are also higher,[5,10,11] suggesting a common neurodevelopmental pathway.

Several risk factors for the development of epilepsy in ASD have been reported in the literature, in particular poor intellectual functioning.[10,12,13] In a meta-analysis of 10 studies, the prevalence of epilepsy in children with ASD <12 years of age with intellectual disability (ID) was higher (21%) than in those without (8%).[10] This study also revealed a higher prevalence of epilepsy even in individuals with ASD without ID. Therefore, ASD itself is associated with higher rates of epilepsy compared to the general population. A cross-sectional analysis of a large sample of children with ASD and epilepsy revealed that epilepsy was associated with older age, lower cognitive ability, poorer adaptive and language functioning, a history of developmental regression, and more severe ASD symptoms.[7] However, after controlling for IQ (reported only as either above or below 70), only older age and lower cognitive ability were independently associated with epilepsy. In addition, syndromic ASD caused by certain single-gene disorders, such as tuberous sclerosis complex (TSC), fragile X, phosphatase and tensin homolog, and Phelan-McDermid, have higher rates of associated ID and epilepsy.[14–21]

Regardless of risk factors, comorbid ASD and epilepsy have been associated with worse adaptive functioning, behavior, and quality of life.[13,22–24] In a large cross-sectional study of children with ASD, the authors found that children with both ASD and epilepsy exhibited greater impairment when compared with children with ASD and no epilepsy.[23] This relationship was mostly explained by low IQ. However, when accounting for IQ, children with both ASD and epilepsy exhibited more irritability and hyperactivity symptoms on the Aberrant Behavior Checklist–Community (ABC).[23] In a separate study comparing children with ASD with and without epilepsy, the authors found that children with both ASD and epilepsy had more impaired daily living skills, motor skills, and challenging behaviors.[25] The clinical impact of seizure development on the phenotype of ASD is not well understood. The long-term impact of disrupted neuronal activity on ASD symptoms and medical comorbidities is also unknown.

Data on individuals with ASD and epilepsy are confounded by many factors, with the majority of studies performed via retrospective analyses. The Autism Speaks Autism Treatment Network (ATN) has created a registry of ~7000 children and adolescents with ASD with the goal of better understanding the relationship between ASD and associated medical comorbidities as well as the impact on neurodevelopmental functioning. A subset of these children and adolescents was called back for a follow-up assessment. In this article, we identify baseline characteristics and the longitudinal changes in function, behavior, sleep, and quality of life associated with development of seizures in children with ASD using data from the ATN and Call-Back Assessment study.

METHODS

Study Design

The Autism Treatment Network Registry Call-Back Assessment (RCBA) study was a longitudinal cohort study of children and adolescents with ASD. Individuals were included in the study if (1) they originally enrolled in the ATN from January 2011 through December 2013 at 1 of 12 sites in the United States and Canada that participated in the RCBA; (2) they met *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*,[26] criteria for autism, Asperger syndrome, or pervasive developmental disorder not otherwise specified; and (3) who had complete data for *Vineland Adaptive Behavior Scales, Second Edition* (Vineland II). Individuals from a 13th site who enrolled in the ATN from September 2015 through November 2016 and who met *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*,[1] criteria for ASD were also eligible for inclusion in the RCBA. Inclusion criteria for the ATN included age 2 years 0 months through 17 years 6 months. There were no exclusion criteria for enrollment.

Among eligible individuals at the first 12 sites (initially restricted to enrollees from January 2011 through December 2012), blocks of 65 participants from each site were identified at random by the coordinating center at Massachusetts General Hospital. Site coordinators selected participants in a randomly generated sequence for participation in the RCBA. Assent from the child or adolescent was obtained as well, as required by the review board at each site. Additional blocks were generated for sites if >15 from the original block could not be located, declined consent to the RCBA, or were determined to be ineligible on the basis of information not known at the time of their selection by the data coordinating center. Because of limited enrollment at 8 sites,

eligibility criteria were relaxed to accept individuals who had originally enrolled in the ATN through December 2013. At the 13th site, all participants enrolled in the ATN were eligible to enroll in the RCBA 9 to 15 months after registry enrollment.

Number of Participants and Method of Selection

A total of 7164 children and adolescents with ASD had enrolled in the ATN by August 31, 2017, from which the pool of eligible RCBA subjects was generated. Of those, 2200 potentially eligible ATN participants were identified, and 658 completed an RCBA assessment. Of those, 559 did not have a diagnosis of seizure disorder or any reported history of seizures at the time of ATN entry. Twenty-nine individuals were excluded because of conflicting history, and 58 were excluded because of lack of adequate follow-up. The final sample included 472 RCBA participants without a seizure disorder or any reported history of seizures at the time of ATN entry who could be classified at the end of at least 2.5 years of follow-up as either individuals who reported development of seizures subsequent to ATN entry or individuals without development of seizures subsequent to ATN entry.

Assessments

Consented participants in the RCBA returned for a clinic visit or completed assessments by phone. The following standardized assessments were administered: Vineland II, survey interview,[27] ABC,[28,29] Child Behavior Checklist (CBCL),[30] Child Sleep Habits Questionnaire (CSHQ),[31] and Pediatric Quality of Life Inventory (PedsQL).[32] Baseline IQ scores were collected on individuals who had obtained testing, which included the Stanford-Binet Intelligence Scales, Mullen Scales of Early Learning, Weschler Intelligence Scale for Children, Bayley Scales of Infant Development, and the Differential Abilities Scales. Scores were reported as standard scores with a mean of 100 and SD of 15. In addition, parents were asked to report on the presence of gastrointestinal symptoms, asthma, allergies, autoimmune disorders, and history of seizures. The site investigator reviewed participants' medical histories, recorded current medications, and conducted a physical examination if the visit occurred in person.

Statistical Analysis

Baseline characteristics were compared between participants who did or did not experience onset of seizures after ATN enrollment by Fisher's exact test and *t* test. Inference from *t* tests was confirmed by Wilcoxon rank test to protect against the influence of outliers. Change from enrollment to follow-up in Vineland II, ABC, CBCL, CSHQ, and PedsQL were compared between participants who did or did not experience onset of seizures after ATN enrollment by multivariate linear regression, adjusting for age at enrollment, sex, baseline Vineland II composite score, and length of follow-up. Age, sex, and baseline Vineland II, ABC, CBCL, CSHQ, and PedsQL scores were tested as predictors of seizure onset by using a binomial generalized linear model with log link, adjusting for age at enrollment, sex, baseline Vineland II composite score, and length of follow-up (as an offset after log transformation). Analyses were performed by using SAS version 9.4 (SAS Institute, Inc, Cary, NC). Inference is based on 2-tailed tests. Comparisonwise *P* values are reported without correction for multiple comparison given the small sample size of children who experienced onset of seizures with nominal significance declared for $P < .05$. For reference, with 19 measures tested, $P < .003$ would be required for familywise significance on the basis of a Bonferroni correction for multiple comparisons.

RESULTS

Patient Characteristics

Participants were followed for a mean of 3.7 ± 0.6 years (range: 2.5–5.8 years). Of the 472 children and adolescents included in this analysis, 22 patients (4.7%) had no history of seizures before enrollment in the study but reported seizures at the call-back assessment (see Table 1 for patient demographics). The ratio of boys to girls was ~4.8:1 in the group without seizures and 2.7:1 in the group with seizure development. In the group that developed seizures, 11 (50%) had 1 to 5 seizures, 2 (9.1%) had 11 or more seizures, and 9 (40.9%) did not have any seizures in the 3 months before RCBA. Only 41% reported using antiepileptic medications (18% oxcarbazepine, 18% valproic acid, and 13% lamotrigine, with 2 individuals reporting use of both oxcarbazepine or valproic acid and lamotrigine).

Genetic testing results, including karyotype (111 patients), fragile X (207 patients), and chromosomal microarray (190), were available. No significant differences in genetic test results were seen between individuals with and without seizures. Baseline IQ data were available for 381 patients (81%). A higher percentage of individuals with development of seizures (53%) had IQs <70 compared with the group without seizures (43%), but this difference was not significant. Mean IQ for individuals without seizures was 75.9 ± 22.4 vs 68.1 ± 21.8 in those who developed

TABLE 1 Patient Demographics and Baseline Characteristics

	Overall (*N* = 472)	No Seizure Onset (*n* = 450)	With Seizure Onset (*n* = 22)	*P*
Sex				.25
Male	388 (82.2%)	372 (82.7%)	16 (73%)	—
Female	84 (18%)	78 (17%)	6 (27%)	—
Ethnicity				.43
Non-Hispanic	414 (91.2%)	395 (91.4%)	19 (86%)	—
Hispanic	40 (9%)	37 (9%)	3 (14%)	—
Missing	18	18	0	—
Race				.38
White	369 (80.4%)	350 (80.1%)	19 (86%)	—
African American	31 (7%)	31 (7%)	0	—
Asian American	21 (5%)	21 (5%)	0	—
Other or multiracial	38 (8%)	35 (8%)	3 (14%)	—
Missing	13	13	0	—
Age at consent into registry	5.9 (3.15)	5.88 (3.13)	6.3 (3.51)	.54
2–5 y	292 (61.9%)	278 (61.8%)	14 (64%)	.80
6–9 y	127 (27%)	122 (27%)	5 (23%)	—
10–15 y	53 (11%)	50 (11%)	3 (14%)	—
Age at RCBA visit, y	9.643 (3.2)	9.62 (3.17)	10.2 (3.62)	.38
Years of follow-up	3.74 (0.57)	3.73 (0.56)	3.93 (0.71)	.12
IQ				.44
≥70	216 (56.7%)	209 (57.1%)	7 (47%)	—
<70	165 (43%)	157 (42.9%)	8 (53%)	—
Missing	91	84	7	—
Calibrated ADOS severity score	7.06 (2.1)	7.08 (2.1)	6.50 (2.1)	.22
BMI	17.7 (4.0)	17.7 (4.0)	17.7 (4.4)	.99
Head circumference, cm	54.1 (2.7)	54.1 (2.6)	54.1 (3.5)	.93

Values reported are *n* (%) or mean (SD). ADOS, Autism Diagnostic Observation Schedule; —, not applicable.

seizures (P = .19). The calibrated Autism Diagnostic Observation Schedule severity score, BMI, and head circumference were not significantly different between groups.

There were no significant differences between individuals with and without development of seizures in medical history variables collected, including environmental or food allergies, gastrointestinal disturbances, asthma, atopic dermatitis, inflammatory bowel disease, autoimmune thyroiditis, type I diabetes, or other autoimmune disorders.

Cognitive and Behavioral Measures

Cognitive and behavioral measures captured at registration and at pre- and postseizure onset are summarized in Table 2. Adjusted estimates of change in cognitive and behavioral measures are summarized in Table 3.

Vineland II

Individuals with subsequent development of seizures exhibited significantly lower scores on all domains of the Vineland II at entry compared with those who did not develop seizures, although only communication scores were significant with correction for multiple comparisons. At call-back, all domains continued to be lower in the individuals who developed seizures with the exception of motor skills. When comparing change in scores from entry to call-back, adjusting for age, sex, length of follow-up, and baseline Vineland II composite score (which was used as an estimate of cognitive functioning), individuals who developed seizures experienced declines in all domains, with large declines in daily living skills and overall composite scores. Only change in daily living skills was significantly different from in individuals who did not develop seizures (Table 3).

ABC

Individuals with subsequent development of seizures exhibited elevation of scores in the hyperactivity subscale at entry compared with individuals who did not develop seizures. No other ABC domains differed at baseline. At call-back, irritability and stereotypy were elevated in those who developed seizures versus those without seizures. When comparing change in scores from entry to call-back, no significant differences were seen when adjusting for age, sex, length of follow-up, and cognitive functioning. In addition, none of the baseline or call-back comparisons were significant after correction for multiple comparisons.

CSHQ

No significant differences were seen in scores at entry, call-back, or in change from entry to call-back.

PedsQL

Individuals with subsequent development of seizures exhibited lower physical functioning scores and total scale score compared with individuals without seizure development. At call-back, social function score, school functioning score, psychosocial health score, and total score were all lower in those who had developed seizures, with differences in school functioning and psychosocial health scores significant after multiple comparisons correction. Physical functioning score continued to be lower, but the difference was not significant. When adjusting for age, sex, length of follow-up, and cognitive functioning, significant declines

TABLE 2 Cognitive and Behavioral Measures at Registry Entry and Call-Back Visit

	At Registry Entry			At Call-Back Visit		
	Non-Seizure Group (n = 450)	Seizure Group (n = 22)	P	Non-Seizure Group (n = 450)	Seizure Group (n = 22)	P
Vineland II						
Communication standard score	75.4 (15.6)	64.9 (12.0)	.002	75.8 (16.8)	62.3 (11.4)	<.001
Daily living skills standard score	76.1 (13.4)	69.2 (11.8)	.019	76.1 (15.8)	62.7 (12.3)	<.001
Socialization standard score	70.9 (11.1)	65.1 (11.0)	.018	71.9 (14.9)	62.4 (13.6)	.004
Motor skills standard score	81.4 (14.1)	73.7 (11.1)	.016	86.7 (18.2)	80.2 (21.6)	.19
Composite standard score	72.4 (11.2)	65.6 (9.0)	.007	71.0 (17.0)	59.6 (10.9)	.002
ABC						
Irritability	13.6 (9.5)	16.8 (9.3)	.16	11.0 (9.0)	16.1 (10.1)	.01
Lethargy	11.0 (8.0)	13.1 (7.4)	.28	8.5 (7.2)	10.7 (6.0)	.16
Stereotypy	5.2 (4.7)	7.4 (3.7)	.05	4.4 (4.3)	6.5 (3.8)	.03
Hyperactivity	19.2 (11.1)	25.4 (11.8)	.02	15.9 (10.8)	18.7 (10.4)	.24
Inappropriate speech	3.5 (3.0)	2.9 (3.1)	.37	3.4 (3.0)	3.4 (2.9)	.89
CBCL						
Internalizing problems T score	62.6 (9.6)	63.7 (9.9)	.616	59.5 (10.1)	59.7 (11.8)	.923
Externalizing problems T score	58.9 (11.0)	63.0 (10.9)	.10	55.9 (10.8)	61.7 (11.5)	.020
CSHQ total score	45.3 (8.5)	48.5 (10.3)	.10	454.8 (8.7)	45.4 (10.0)	.80
PedsQL						
Physical functioning score	76.0 (18.2)	60.1 (24.2)	<.001	70.6 (20.6)	62.5 (21.0)	.08
Emotional functioning score	66.3 (20.2)	64.5 (25.5)	.69	65.8 (19.3)	64.1 (24.4)	.70
Social functioning score	53.9 (22.2)	49.9 (22.3)	.42	56.9 (22.4)	43.6 (24.3)	.008
School functioning score	63.5 (19.9)	57.8 (25.8)	.20	61.0 (19.1)	46.2 (19.8)	<.001
Psychosocial health score	61.2 (16.0)	56.9 (20.8)	.22	61.3 (16.3)	51.3 (17.2)	.006
Total scale score	66.6 (14.8)	58.2 (20.8)	.01	64.5 (16.1)	55.2 (16.4)	.01

Values reported are mean (SD). T scores are standardized scores with a mean of 50 and a standard deviation of 10 based on normative samples stratified by age and gender.[33]

were observed among individuals with seizure development in school functioning and psychosocial health, although only the decrease in school functioning was greater than that among individuals who did not develop seizures.

Adjusting for age, sex, and length of follow-up, lower baseline Vineland II composite score predicted a greater risk of seizures (risk ratio = 0.95 per unit Vineland II composite score, 95% confidence interval [CI] 0.92 to 0.99; P = .007). No other baseline characteristics predicted development of seizures after also adjusting for Vineland II composite score, although ABC hyperactivity score was weakly associated.

DISCUSSION

Autism and epilepsy are neurologic disorders with highly genetic etiologies.[4,34–39] Multiple meta-analyses and smaller studies have identified ID as a consistent risk factor for seizures. In addition, ID may form a background on which epilepsy is part of the mosaic of other characteristics present in many, but not all, individuals with ASD and recurrent seizures. In this study, we identify further characteristics of those at risk for seizures in ASD, including lower adaptive functioning, hyperactivity, and lower physical functioning. Onset of seizure development is associated with further changes of clinical characteristics, including lowering of adaptive functioning, more irritability and stereotypy, and lowering of school and social function.

ASD Individuals at Risk for Seizures May Be a Distinct Population

The prospective collection of data and random selection of participants from the larger ATN cohort permits an unbiased characterization of individuals with ASD before the development of seizures. Results of this exploratory study suggest that individuals with ASD prospectively followed before the age of seizure development are already distinct from their age- and sex-matched compatriots. Previous studies have documented that those with ASD, ID, and epilepsy have lower motor function, social and/or adaptive function, poorer communication (or are less verbal), more repetitive behaviors, and more hyperactivity.[7,23] This study suggests that it is not the seizures and/or neuronal activity that are responsible for more severe symptoms. Careful studies of developmental trajectory in the synapsin I and Contactin Associated Protein 2 mutant mice, animal models of autism and epilepsy, support this hypothesis. For example, impaired social behavior preceded both seizure activity on EEG and clinical seizures of the mutant mice.[40,41]

TABLE 3 Estimated Change in Cognitive and Behavioral Measures, Adjusting for Age, Sex, Length of Follow-up, and Baseline Vineland II Composite Score

	No Seizure Onset (n = 450)		With Seizure Onset (n = 22)		Group Difference	
	Estimate (95% CI)	P	Estimate (95% CI)	P	Estimate (95% CI)	P
Vineland Adaptive Behavior Scales						
Communication standard score	0.80 (−0.54 to 2.13)	.24	−4.41 (−10.31 to 1.49)	.14	−5.21 (−11.27 to 0.85)	.09
Daily living skills standard score	0.40 (−0.90 to 1.69)	.55	−7.98 (−13.71 to −2.25)	.006	−8.38 (−14.25 to −2.50)	.005
Socialization standard score	1.45 (0.20 to 2.70)	.02	−3.26 (−8.81 to 2.29)	.25	−4.71 (−10.40 to 0.99)	.11
Motor skills standard score	2.58 (0.35 to 4.81)	.02	−6.24 (−15.45 to 2.97)	.18	−8.82 (−18.32 to 0.68)	.07
Composite standard score	−1.34 (−2.80 to 0.12)	.07	−7.76 (−14.21 to −1.31)	.02	−6.42 (−13.04 to 0.20)	.06
ABC						
Irritability	−2.83 (−3.78 to −1.88)	<.001	−1.33 (−5.66 to 3.00)	.55	1.49 (−2.95 to 5.94)	.51
Lethargy	−2.65 (−3.48 to −1.82)	<.001	−2.33 (−6.11 to 1.45)	.23	0.32 (−3.55 to 4.20)	.87
Stereotypy	−0.81 (−1.25 to −0.38)	<.001	−0.71 (−2.70 to 1.29)	.49	0.11 (−1.94 to 2.15)	.92
Hyperactivity	−3.78 (−4.93 to −2.63)	<.001	−6.00 (−11.24 to −0.77)	.03	−2.23 (−7.60 to 3.14)	.42
Inappropriate speech	−0.19 (−0.50 to 0.11)	.22	−0.12 (−1.56 to 1.31)	.87	0.07 (−1.40 to 1.54)	.92
CBCL						
Internalizing problems T score	−3.26 (−4.20 to −2.31)	<.001	−2.76 (−7.11 to 1.59)	.21	0.49 (−3.96 to 4.95)	.83
Externalizing problems T score	−3.42 (−4.43 to −2.42)	<.001	−0.97 (−5.61 to 3.66)	.68	2.45 (−2.30 to 7.20)	.31
CSHQ total score	−0.38 (−1.32 to 0.55)	.42	−1.07 (−4.65 to 2.51)	.56	−0.69 (−4.39 to 3.02)	.72
PedsQL						
Physical functioning score	−5.24 (−7.35 to −3.13)	<.001	2.96 (−6.34 to 12.26)	.53	8.20 (−1.35 to 17.75)	.09
Emotional functioning score	−0.44 (−2.51 to 1.64)	.68	−1.34 (−10.47 to 7.79)	.77	−0.90 (−10.28 to 8.48)	.85
Social functioning score	3.37 (0.99 to 5.74)	.006	−7.41 (−17.86 to 3.04)	.16	−10.77 (−21.51 to −0.04)	.05
School functioning score	−3.29 (−5.61 to −0.97)	.006	−13.64 (−22.97 to −4.31)	.004	−10.35 (−19.98 to −0.72)	.04
Psychosocial health score	−0.01 (−1.60 to 1.59)	.99	−7.10 (−14.14 to −0.05)	.05	−7.09 (−14.32 to 0.14)	.05
Total scale score	−2.11 (−3.61 to −0.60)	.006	−3.65 (−10.28 to 2.99)	.28	−1.54 (−8.35 to 5.27)	.66

P values <.003 would be significant after multiple comparison correction given 19 measures tested. T scores are standardized scores with a mean of 50 and a standard deviation of 10 based on normative samples stratified by age and gender.[33]

Adaptive Functioning as a Predictor of Seizure Onset

The Vineland II composite score, a close correlate with IQ, has previously been shown to be strongly associated with risk for epilepsy in a multiplex ASD sample.[4] Probands with Vineland adaptive composite scores <70 were 3 times as likely to have epilepsy as those with composite scores ≥70. In this study, Vineland II composite score was the only significant predictor of seizures after adjusting for age, sex, and length of follow-up. Interestingly, biomarkers such as sex, BMI, and head circumference shown to be predictive of seizures in ASD were not predictive of seizures in this cohort.[10,42–44] Associations of these biomarkers with epilepsy risk in ASD may be greater for adolescents.[42]

The etiology of comorbid ID, ASD, and epilepsy is complex and likely involves both biological and environmental factors. Several pathophysiologic mechanisms have been proposed: (1) accidental co-occurrence of ID, ASD, and epilepsy, (2) altered organization of minicolumns associated with defects in local gamma aminobutyric acid circuits and their gamma aminobutyric acid type A receptors, (3) common genetic or neurodevelopmental factors, and (4) induction of autistic behaviors by early-life epilepsy, such as infantile spasms. The latter hypothesis, although definitely relevant to specific disorders, such as TSC and Dravet syndrome, is less likely in our current population. Indeed, ID is an integral part of each disorder. Genetic disorders of high effect size (TSC, fragile X, phosphatase and tensin homolog, Phelan-McDermid) are high risk for the co-occurrence of ID, epilepsy, and ASD.[14–21] Careful prospective tracking of neural development of at-risk ASD populations may provide the data needed to evaluate these pathophysiological mechanisms.

Limitations of the Study

As an observational study, the associations identified in our analysis are hypothesis generating and should not be interpreted to imply causation. The small number of patients with onset of seizures (n = 22) reduced our power to detect associations. Future studies could be improved by applying a more rigorous definition of epilepsy and more complete description of epilepsy reports, including description of seizure semiology (type[s] and frequency), MRI results, EEG results, comorbidities, and response to antiepileptic drugs.[45] The age range of subjects in this study was skewed toward younger ages. Future studies would be improved by including broader age ranges to determine more fully the roles of sex, age, macrocephaly, and BMI as biomarkers for seizures in ASD.[10,42] This study also lacked data on prenatal environmental exposures associated with epilepsy risk. Finally, most measures reported here are parental

reported measures, which may not accurately predict seizure-sensitive phenotypes.[46] We also lack comprehensive IQ data on each subject. New direct measures, such as the National Institutes of Health Toolbox Cognition Battery, may more accurately define parameters sensitive to onset of seizures.[47]

CONCLUSIONS

ASDs are known to be associated with an increased risk of seizures. Prospective studies of genetic, histopathological, EEG, imaging studies, and extensive clinical phenotyping comparing individuals with ASD with and without epilepsy are needed to delineate well-defined clinical subpopulations and specific pathogenic mechanisms of ASD and epilepsy comorbidity. With caveats, this prospective pilot study represents a pragmatic first step toward identification of this subgroup. Those individuals with ASD at risk for seizures (before onset of seizures) have lower adaptive functioning. Onset of seizures is associated with decreased adaptive functioning, increased irritability and stereotypies, plus possible lower school and social functioning. In this prospective sample, only the Vineland adaptive composite score was a significant independent predictor for the development of seizures. Given the limited information in the literature on comorbid ASD and epilepsy, this study lays the groundwork for further investigation in this area.

ABBREVIATIONS

ABC: Aberrant Behavior Checklist–Community
ASD: autism spectrum disorder
ATN: Autism Treatment Network
CBCL: Child Behavior Checklist
CI: confidence interval
CSHQ: Child Sleep Habits Questionnaire
ID: intellectual disability
PedsQL: Pediatric Quality of Life Inventory
RCBA: Autism Treatment Network Registry Call-Back Assessment
TSC: tuberous sclerosis complex
Vineland II: *Vineland Adaptive Behavior Scales, Second Edition*

Address correspondence to Jamie K. Capal, MD, Department of Neurology, Cincinnati Children's Hospital Medical Center, MLC 2015, 3333 Burnet Ave, Cincinnati, OH 45229. E-mail: jamie.capal@cchmc.org

PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

FINANCIAL DISCLOSURE: The authors have indicated they have no financial relationships relevant to this article to disclose.

FUNDING: The Autism Treatment Network (ATN) was supported by Autism Speaks and cooperative agreement UA3 MC11054 through the US Department of Health and Human Services, Health Resources and Services Administration, Maternal and Child Health Research Program to the Massachusetts General Hospital. This work was conducted through the Autism Speaks ATN. This information or content and conclusions are those of the authors and should not be construed as the official position or policy of nor should any endorsements be inferred by the Health Resources and Services Administration, US Department of Health and Human Services, the US government, or Autism Speaks. This work was conducted through the Autism Speaks ATN serving as the Autism Intervention Research Network on Physical Health.

POTENTIAL CONFLICT OF INTEREST: Dr Macklin serves on data and safety monitoring committees for Acorda Therapeutics, Novartis Pharmaceuticals, and Shire Human Genetics Therapies and consults for Myolex, Inc, and Lavin Consulting. Dr Barnes has received a clinical trial research grant from GW Pharmaceuticals, which does not impact this work. Dr Capal consults for Roche Pharmaceuticals, which does not impact this work; the other authors have indicated they have no potential conflicts of interest to disclose.

REFERENCES

1. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders: DSM-5. 5th ed. Washington, DC: American Psychiatric Association; 2013
2. Baio J, Wiggins L, Christensen DL, et al. Prevalence of autism spectrum disorder among children aged 8 years - Autism and Developmental Disabilities Monitoring Network, 11 sites, United States, 2014. *MMWR Surveill Summ.* 2018;67(6):1–23
3. Developmental Disabilities Monitoring Network Surveillance Year 2010 Principal Investigators; Centers for Disease Control and Prevention (CDC). Prevalence of autism spectrum disorder among children aged 8 years - Autism and Developmental Disabilities Monitoring Network, 11 sites, United States, 2010. *MMWR Surveill Summ.* 2014;63(2):1–21
4. Amiet C, Gourfinkel-An I, Laurent C, et al. Epilepsy in simplex autism pedigrees is much lower than the rate in multiplex autism pedigrees. *Biol Psychiatry.* 2013; 74(3):e3–e4
5. Hughes JR, Melyn M. EEG and seizures in autistic children and adolescents: further findings with therapeutic implications. *Clin EEG Neurosci.* 2005; 36(1):15–20
6. Jokiranta E, Sourander A, Suominen A, Timonen-Soivio L, Brown AS, Sillanpää M. Epilepsy among children and

adolescents with autism spectrum disorders: a population-based study. *J Autism Dev Disord*. 2014;44(10):2547–2557

7. Viscidi EW, Triche EW, Pescosolido MF, et al. Clinical characteristics of children with autism spectrum disorder and co-occurring epilepsy. *PLoS One*. 2013;8(7):e67797
8. Kohane IS, McMurry A, Weber G, et al. The co-morbidity burden of children and young adults with autism spectrum disorders. *PLoS One*. 2012;7(4):e33224
9. Fisher RS, Acevedo C, Arzimanoglou A, et al. ILAE official report: a practical clinical definition of epilepsy. *Epilepsia*. 2014;55(4):475–482
10. Amiet C, Gourfinkel-An I, Bouzamondo A, et al. Epilepsy in autism is associated with intellectual disability and gender: evidence from a meta-analysis. *Biol Psychiatry*. 2008;64(7):577–582
11. Strasser L, Downes M, Kung J, Cross JH, De Haan M. Prevalence and risk factors for autism spectrum disorder in epilepsy: a systematic review and meta-analysis. *Dev Med Child Neurol*. 2018;60(1):19–29
12. Woolfenden S, Sarkozy V, Ridley G, Coory M, Williams K. A systematic review of two outcomes in autism spectrum disorder - epilepsy and mortality. *Dev Med Child Neurol*. 2012;54(4):306–312
13. Trauner DA. Behavioral correlates of epileptiform abnormalities in autism. *Epilepsy Behav*. 2015;47:163–166
14. Betancur C, Buxbaum JD. SHANK3 haploinsufficiency: a "common" but underdiagnosed highly penetrant monogenic cause of autism spectrum disorders. *Mol Autism*. 2013;4(1):17
15. Bolton PF, Park RJ, Higgins JNP, Griffiths PD, Pickles A. Neuro-epileptic determinants of autism spectrum disorders in tuberous sclerosis complex. *Brain*. 2002;125(Pt 6):1247–1255
16. Butler MG, Dasouki MJ, Zhou XP, et al. Subset of individuals with autism spectrum disorders and extreme macrocephaly associated with germline PTEN tumour suppressor gene mutations. *J Med Genet*. 2005;42(4):318–321
17. Buxbaum JD, Cai G, Chaste P, et al. Mutation screening of the PTEN gene in patients with autism spectrum disorders and macrocephaly. *Am J Med Genet B Neuropsychiatr Genet*. 2007;144B(4):484–491
18. Capal JK, Bernardino-Cuesta B, Horn PS, et al; TACERN Study Group. Influence of seizures on early development in tuberous sclerosis complex. *Epilepsy Behav*. 2017;70(pt A):245–252
19. Jeste SS, Varcin KJ, Hellemann GS, et al. Symptom profiles of autism spectrum disorder in tuberous sclerosis complex. *Neurology*. 2016;87(8):766–772
20. Niu M, Han Y, Dy ABC, et al. Autism symptoms in fragile X syndrome. *J Child Neurol*. 2017;32(10):903–909
21. Thurman AJ, McDuffie A, Kover ST, Hagerman RJ, Abbeduto L. Autism symptomatology in boys with fragile X syndrome: a cross sectional developmental trajectories comparison with nonsyndromic autism spectrum disorder. *J Autism Dev Disord*. 2015;45(9):2816–2832
22. Danielsson S, Gillberg IC, Billstedt E, Gillberg C, Olsson I. Epilepsy in young adults with autism: a prospective population-based follow-up study of 120 individuals diagnosed in childhood. *Epilepsia*. 2005;46(6):918–923
23. Viscidi EW, Johnson AL, Spence SJ, Buka SL, Morrow EM, Triche EW. The association between epilepsy and autism symptoms and maladaptive behaviors in children with autism spectrum disorder. *Autism*. 2014;18(8):996–1006
24. Hara H. Autism and epilepsy: a retrospective follow-up study. *Brain Dev*. 2007;29(8):486–490
25. Turk J, Bax M, Williams C, Amin P, Eriksson M, Gillberg C. Autism spectrum disorder in children with and without epilepsy: impact on social functioning and communication. *Acta Paediatr*. 2009;98(4):675–681
26. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders: DSM-IV. 4th ed. Washington, DC: American Psychiatric Association; 1994
27. Sparrow SS, Cicchetti DV, Balla DA. Vineland Adaptive Behavior Scales: Second Edition (Vineland II), Survey Interview Form/Caregiver Rating Form. 2nd ed. Livonia, MN: Pearson Assessments; 2005
28. Aman MG, Singh NN, Stewart AW, Field CJ. The Aberrant Behavior Checklist: a behavior rating scale for the assessment of treatment effects. *Am J Ment Defic*. 1985;89(5):485–491
29. Aman MG, Singh NN. Aberrant Behavior Checklist Manual. East Aurora, NY: Slosson Educational Publications; 1986
30. Kaat AJ, Lecavalier L, Aman MG. Validity of the Aberrant Behavior Checklist in children with autism spectrum disorder. *J Autism Dev Disord*. 2014;44(5):1103–1116
31. Markovich AN, Gendron MA, Corkum PV. Validating the Children's Sleep Habits Questionnaire against polysomnography and actigraphy in school-aged children. *Front Psychiatry*. 2015;5:188
32. Varni JW, Seid M, Kurtin PS. PedsQL 4.0: reliability and validity of the Pediatric Quality of Life Inventory version 4.0 Generic Core Scales in healthy and patient populations. *Med Care*. 2001;39(8):800–812
33. Achenbach TM, Rescorla LA. *Manual for the ASEBA School-Age Forms & Profiles*. Burlington, VT: University of Vermont Research Center for Children, Youth, & Families; 2001
34. Abrahams BS, Geschwind DH. Advances in autism genetics: on the threshold of a new neurobiology. *Nat Rev Genet*. 2008;9(5):341–355
35. El Achkar CM, Spence SJ. Clinical characteristics of children and young adults with co-occurring autism spectrum disorder and epilepsy. *Epilepsy Behav*. 2015;47:183–190
36. Levy D, Ronemus M, Yamrom B, et al. Rare de novo and transmitted copy-number variation in autistic spectrum disorders. *Neuron*. 2011;70(5):886–897
37. Manning M, Hudgins L; Professional Practice and Guidelines Committee. Array-based technology and recommendations for utilization in medical genetics practice for detection of chromosomal abnormalities. *Genet Med*. 2010;12(11):742–745
38. Marshall CR, Noor A, Vincent JB, et al. Structural variation of chromosomes in

autism spectrum disorder. *Am J Hum Genet*. 2008;82(2):477–488

39. Sebat J, Lakshmi B, Malhotra D, et al. Strong association of de novo copy number mutations with autism. *Science*. 2007;316(5823):445–449

40. Greco B, Managò F, Tucci V, Kao HT, Valtorta F, Benfenati F. Autism-related behavioral abnormalities in synapsin knockout mice. *Behav Brain Res*. 2013; 251:65–74

41. Peñagarikano O, Abrahams BS, Herman EI, et al. Absence of CNTNAP2 leads to epilepsy, neuronal migration abnormalities, and core autism-related deficits. *Cell*. 2011; 147(1):235–246

42. Valvo G, Baldini S, Brachini F, et al. Somatic overgrowth predisposes to seizures in autism spectrum disorders. *PLoS One*. 2013;8(9):e75015

43. Blackmon K, Bluvstein J, MacAllister WS, et al. Treatment resistant epilepsy in autism spectrum disorder: increased risk for females. *Autism Res*. 2016;9(2): 311–320

44. Hazlett HC, Gu H, Munsell BC, et al; IBIS Network; Clinical Sites; Data Coordinating Center; Image Processing Core; Statistical Analysis. Early brain development in infants at high risk for autism spectrum disorder. *Nature*. 2017;542(7641):348–351

45. Beretta S, Carone D, Zanchi C, et al; PRO-LONG Study Group. Long-term applicability of the new ILAE definition of epilepsy. Results from the PRO-LONG Study. *Epilepsia*. 2017;58(9): 1518–1523

46. Warren Z, Vehorn A, Dohrmann E, Nicholson A, Sutcliffe JS, Veenstra-Vanderweele J. Accuracy of phenotyping children with autism based on parent report: what specifically do we gain phenotyping "rapidly"? *Autism Res*. 2012;5(1):31–38

47. Schork AJ, Brown TT, Hagler DJ, et al; Pediatric Imaging, Neurocognition and Genetics Study. Polygenic risk for psychiatric disorders correlates with executive function in typical development. *Genes Brain Behav*. 2019; 18(4):e12480

Factors Associated With Seizure Onset in Children With Autism Spectrum Disorder

Jamie K. Capal, Eric A. Macklin, Frances Lu and Gregory Barnes

Pediatrics 2020;145;S117
DOI: 10.1542/peds.2019-1895O

PEDIATRICS®
OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

Factors Associated With Seizure Onset in Children With Autism Spectrum Disorder

Jamie K. Capal, Eric A. Macklin, Frances Lu and Gregory Barnes

Pediatrics 2020;145;S117
DOI: 10.1542/peds.2019-1895O