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Clinical features and drug-resistance in pediatric epilepsy with co-occurring autism: A retrospective comparative cohort study

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ABSTRACT

Objective: We conducted a retrospective comparative cohort study to determine the phenotypic and real-world management differences in children with epilepsy and co-occurring autism as compared to those without autism.
Methods: Clinical variables, EEG, brain MRI, genetic results, medical and non-medical treatment were compared between 156 children with both epilepsy and autism, 156 randomly selected and 156 demographically matched children with epilepsy only. Logistic regression analyses were conducted to determine predictors of drug-resistant epilepsy (DRE).
Results: As compared to the'matched' cohort, more patients with autism had generalized motor seizures although not statistically significant after Benjamini-Hochberg correction (54.5%, vs 42.3%, p = .0314); they had a lower rate of electroclinical syndromes (12.8%, vs 30.1%, p = .0002). There were more incidental MRI findings but less positive MRI findings to explain their epilepsy in children with autism (26.3%, vs 13.8% and 14.3%, vs 34.2%, respectively; p = .0003). In addition, LEV, LTG, and VPA were the most common ASMs prescribed to children with autism, as opposed to LEV, OXC, and LTG in children without autism. No difference in the major EEG abnormalities was observed. Although the rates of DRE were similar (24.8%, vs 26.6%, p = .7203), we identified two clinical and five electrographic correlates with DRE in children with both epilepsy and autism and a final prediction modeling of DRE that included EEG ictal findings, focal onset seizures, generalized motor seizures, abnormal EEG background, age of epilepsy onset, and history of SE, which were distinct from those in children without autism.
Significance: Our study indicates that detailed seizure history and EEG findings are the most important evaluation and prediction tools for the development of DRE in children with epilepsy and co-occurring autism. Further studies of epilepsy in specific autism subgroups based on their etiology and clinical severity are warranted.

1. Introduction

There is a long-observed yet complex association between epilepsy and autism [1–7]. Disorders due to copy number variations (CNVs) such as 16p11.2 deletion and 15q11.13 deletion, or single gene mutations such as Fragile X syndrome, Tuberous Sclerosis Complex, and Rett syndrome predispose patients to both autism and epilepsy as clinical phenotypes, which likely represents an epiphenomenon rather than a causative relationship [8–10]. Furthermore, children with epilepsy due to channelopathies and 'mTORpathies' seem to have a high risk of developing autism [8,11]. The rates of epilepsy in individuals with autism range from 6-27% and are associated with older age, lower cognitive ability, poorer adaptive and language functioning, a history of developmental regression, and more severe autism symptoms [12–14]. Multiple studies have attempted to characterize EEG patterns in individuals with autism with and without epilepsy. There have also been various percentages of interictal epileptiform discharges (IEDs) reported among individuals with autism who do not have epilepsy [15–18]. However, it is not clear whether there are

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region-specific EEG biomarkers in patients with autism regardless of comorbid epilepsy.

Depending on different studies, both generalized onset tonic-clonic seizures [6,19] and focal onset (or partial) seizures [20–23] were reported to be the most common seizure types in patients with co-occurring autism. Moreover, it remains unknown if patients with autism have a different response or tolerability to conventional antiseizure medications (ASMs). The pooled prevalence of drug-resistant epilepsy (DRE) is known to be 25% in the pediatric population and 14.6% in adult/mixed-age studies. Abnormal EEG, status epilepticus (SE), symptomatic etiology, multiple seizure types, febrile seizures, and polymorphisms of the ABCB1 gene were identified as potential predictors or correlates of DRE [24–26]. The prevalence of DRE in a cohort of pediatric patients with idiopathic autism was reported as 33.9% [27]. However, studies analyzing electroclinical risk factors associated with DRE in the autism population are lacking. The objective of our study was to identify distinctive epilepsy features in children with both autism and epilepsy and analyze risk factors that predict the risk of DRE in patients with these comorbidities.

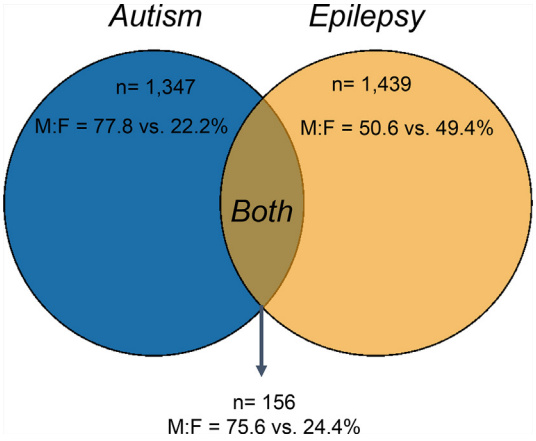

Fig. 1. Patient cohorts identified in EMR based on ICD-10 codes for autism and epilepsy. The male-to-female ratio in all patients with autism (n = 1,347) is 77.8 versus 22.2%, as compared to 50.6 versus 49.4% in all patients with epilepsy (n = 1,439). This ratio is 75.6 versus 24.4% in patients with both diagnoses of autism and epilepsy (n = 156).

2. Patients and methods

2.1. Study design and ethic approval

This retrospective chart review was completed at the outpatient pediatric neurology clinic of Hasbro Children's Hospital in Providence, RI. The study was approved by the Lifespan Institutional Review Boards (IRB, 1720212-3).

2.2. Patient cohorts

We searched the electronic medical records (EMR) within the time frame from April 1, 2015, to March 31, 2020. Our inclusion criteria were age 1–18 years [28–29], diagnosis of autism (ICD-10 code F84.0) and/or of epilepsy (ICD-10 code G40*), and at least 6 months of outpatient follow-up for epilepsy management. We categorized the search results into 3 cohorts of patients: epilepsy, autism, and both epilepsy and autism. The study cohort includes 156 patients with both epilepsy and autism conditions (Fig. 1). Next, we generated two control cohorts from all patients with epilepsy only (n = 1,283), either randomly or demographically matched, named 'random' and 'matched' cohorts. The 'matched' cohort was generated by matching sex, race/ethnicity, and age at the last follow-up to the study cohort. Patients with unknown or refused to answer race/ethnicity information among those with epilepsy only were excluded for matching. The rationale to generate a 'matched' cohort lies in the well-known male predominance of autism diagnosis. Each control cohort had 156 patients.

2.3. Data collection

Clinical data collected by chart review included demographic data (age, sex, race, and ethnicity), epilepsy history, electroencephalogram (EEG) features, magnetic resonance imaging (MRI) data, genetic reports, and ASMs. For epilepsy history, we collected the age of epilepsy onset, seizure semiology, drug resistance, and status epilepticus (SE). Seizure semiology was recorded based on the ILAE 2017 classification of seizure types [30]. We broke down EEG features into background activity, interictal epileptiform discharges (IEDs), ictal findings, and electroclinical epilepsy syndrome. The subcategories of background activities were normal for age, focal slowing, generalized slowing, or other encephalopathic patterns such as burst suppression, hypsarrhythmia, and electrical status epilepticus during sleep (ESES). IEDs were further classified as focal, multifocal, generalized discharges, paroxysmal fast activity, periodic or rhythmic patterns, or absent epileptiform discharges. Multifocal is defined as independent discharges occurring in both hemispheres, arising from at least 3 distinct locations based on the international 10–20 system. We also collected further information on EEG ictal findings including focal onset, generalized onset, electrodecremental pattern, electrographic or electroclinical. The brain MRI results were classified as normal, positive findings that explain the etiology of epilepsy, or incidental/non-specific. The positive findings were further grouped as brain malformation, vascular insult, hypoxic-ischemic encephalopathy (HIE) or anoxic injury, infectious sequelae, neoplasm/brain tumor, temporal/hippocampal sclerosis, and others. The genetic testing results included chromosomal microarray analysis (CMA), epilepsy gene panels, and whole exome sequencing (WES). We also collected information on medical and non-medical treatments such as vagus nerve stimulator (VNS), responsive neurostimulator (RNS), dietary therapy, and epilepsy surgery. Both the current and past ASMs (excluding rescue medications) were recorded. Data was collected into a password-protected REDCap database. Each participant was assigned a global unique identifier (GUID) and de-identified data was extracted as a Microsoft Excel CSV file for group analyses.

2.4. Statistical analysis

Statistical analyses were conducted using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA). We compared the frequency of clinical features between the study cohort and the control, including the 'random' and demographically 'matched' epilepsy cohorts. Categorical data, presented as percentages or rates, was analyzed by the Chi-square test or Fisher's exact test to assess the significance of correlation. Continuous variables such as the age of epilepsy onset were presented as median with interquartile range (IQR) and analyzed by t-test. A p-value < .05 was considered statistically significant. When there was a concern for multiple comparisons (Table 2, S1, and S2), Benjamini-Hochberg correction was applied based on a false discovery rate of 0.2.

We performed univariable logistic regression to assess independent variables associated with DRE in the study versus 'matched' control cohorts. The strength of associations was expressed as an odds ratio (OR) with a 95% confidence interval (CI) and statistical significance set at $p < .05$. Variables with a p-value $\leq .15$ in univariable analysis were then included in the multivariable logistic

regression model unless variables considered highly collinear (e.g., focal slowing, generalized slowing, and abnormal EEG background). The multivariable logistic regression was performed following a backward elimination process with a cutoff p-value < .2. Discrimination was assessed by the area under the curve (AUC) of a receiver operator characteristics (ROC) curve.

3. Results

3.1. Male predominance in the pediatric cohort of co-occurring epilepsy and autism.

We identified 1,439 patients with a diagnosis of epilepsy and 1,347 patients with autism between April 1st, 2015, and March 31st, 2020. There were 156 children with co-occurring epilepsy and autism. The male-to-female ratio (3.1:1) in the study cohort (118 males, 38 females) showed a slight predilection for females as compared to the entire autism cohort (1,048 males, 299 females, 3.5:1) (Fig. 1).

3.2. Electroclinical features between children with versus without co-occurring autism

To investigate the potential difference in epilepsy features and management between children with both epilepsy and autism versus those without autism, we compared data from the 'random' and demographically 'matched' epilepsy control cohorts. As a result of matching, the 'matched' cohort showed a male-to-female ratio (117 males, 39 females) similar to the study cohort and the 'random' epilepsy represented the sex distribution (79 males, 77 females) of the entire epilepsy cohort (Table 1). When compared to the 'random' epilepsy cohort, the study cohort showed lower rates in focal onset seizures (43.6 vs 52.6%, p = 0.1127, significant after Benjamini-Hochberg correction), focal motor seizures (28.9 vs 39.7%, p = .0426), focal aware or unaware seizures (17.3 vs 30.1%, p = .0078), multiphasic seizures (7.7 vs 17.3%, p = .0102), and classified electroclinical epilepsy syndromes (12.8 vs 22.4%, p = .0258), but higher rates in generalized onset seizures (66.0 vs 51.3%, p = .0082), generalized motor seizures (54.5 vs 35.3%, p = .0006), and focal non-motor seizures (9.6 vs 3.2%, p = .0208). There was no significant difference comparing ages at epilepsy onset (5.3, IQR 2.0–10.2 vs 4.6, IQR 1.0–8.3, in years) or rates of DRE (24.8 vs 18.0%). However, when compared to the demographically 'matched' cohort, the study cohort only showed a lower rate of classified epilepsy syndrome (12.8 vs 30.1%, p = .0002); though the study cohort showed a higher tendency for generalized motor seizures (54.5 vs 42.3%, p = .0314) there was lack of significance following Benjamini-Hochberg correction). There was no difference in age of epilepsy onset (5.3, IQR 2.0–10.2 vs 5.0, IQR 1.5–9.3, in years), rate of DRE (24.8 vs 26.6%, p = .7203), generalized onset seizures (66.0 vs 57.1%, p = .1033), focal onset seizures (43.6 vs 44.9%, p = .8197), generalized non-motor seizures (24.4 vs 23.7%, p = .8946), focal motor seizures (28.9 vs 28.9%, p = 1.000), focal non-motor seizures (9.6 vs 7.7%, p = .5458), focal awareness (intact or impaired) seizures (17.3 vs 23.7%, p = .1609), and multiphasic seizures (7.7 vs 10.3%, p = .4282) between the study and 'matched' cohorts. We did not observe a significant difference in the incidence of SE either (17.3% in the study cohort, vs 15.4% in the 'random' cohort, vs 20.8% in the 'matched cohort', p = .6612 and p = .4543, respectively) (Table 2). These results have demonstrated that children with both epilepsy and autism were less likely to be classified as one of the electroclinical epilepsy syndromes and they have a higher tendency for generalized motor seizures in comparison to those without autism.

At least one brain MRI report was available for 133 (85.3%) patients in the study cohort, 132 (84.6%) patients in the 'random' epilepsy cohort, and 123 (78.9%) patients in the 'matched' epilepsy cohort. Seventy-nine (79, 59.4%) patients in the study cohort, 77 (58.3%) in the 'random' epilepsy cohort, and 64 (52%) patients in the 'matched' cohort had a normal MRI of the brain. As compared to both control cohorts, the study cohort had a lower rate of positive MRI findings that explain the etiology of their epilepsies (14.3% in the study cohort, vs 28.0% in the 'random' cohort, vs 34.2% in the 'matched' cohort) and a higher rate of non-specific/incidental findings (26.3% in the study cohort, vs 13.6% in the 'random' cohort', vs 13.8% in the 'matched' cohort, p = .0036 and p = .0003, respectively). The most common positive findings in each cohort were brain malformations. Vascular insults, HIE or anoxic injury, infectious sequelae, and neoplastic lesions tended to occur more frequently in the control cohorts although the number of patients in each subcategory was too small (<15) for statistical analyses (Table 3).

At least one EEG report was available for 145 (92.9%) patients in the study cohort, 149 (95.5%) patients in the 'random' epilepsy cohort, and 144 (92.3%) patients in the 'matched' epilepsy cohort. Although there was no difference among these rates, the average number of EEG studies for each patient was lower in the study cohort as compared to the 'matched' cohort (data not shown), suggesting that patients with autism had a considerably lower procedure tolerability than those without autism. There was no difference between the study cohort and control cohorts in all three major categories or the subcategories, including background abnormalities (e.g., generalized, focal slowing, burst suppression, hypsarrhythmia, or ESES as background abnormalities), different types of IEDs (focal, generalized IEDs, multifocal, paroxysmal fast activity, periodic or rhythmic patterns), and ictal findings. Even though multifocal and focal IEDs were less frequently seen in the study cohort when compared to the 'random' cohort (12.5 vs 21.5%, p = .0412 on multifocal; and 36.6 vs 46.3%, p = .0896 on focal IEDs, following Benjamini-Hochberg correction), it was not different from the 'matched' epilepsy cohort (12.5 vs 12.5%, p = 1.00; 36.6 vs 46.5%, p = .0853, respectively) (**Table S1**). Among the 145 patients in the study cohort, there were 26 (17.9%) patients with normal EEG and 17 (11.7%) patients with background abnormality however no IEDs. Of note, 73 (50.3%) patients had generalized and/or multifocal IEDs; and focal IEDs (with or without co-existing generalized IEDs) were present in 53 patients (Fig. 2**a**). Among the focal IEDs, 34 (64.2%) were in the temporal lobe followed by 25 (47.2%) frontal, 13 (24.5%) central, 11 (20.8%) occipital, and 8 (15.1%) parietal lobe (Fig. 2**b**). While 22 (41.5%) patients with bilateral focal IEDs, 16 (30.2%) patients had left-sided only, and 15 (28.3%) patients with right-sided only IEDs, indicating lack of hemispheric dominance in the distribution of focal IEDs (Fig. 2**c**).

We then compared current and past ASMs taken by patients among different cohorts. More patients in the study cohort reported currently taking lamotrigine (LTG) and zonisamide (ZNS) than in the 'random' epilepsy cohort (21.2 vs 12.2%, p = .0334 and 10.9 vs 4.5%, p = .0336, respectively). This finding was not seen when comparing the study cohort to the 'matched' cohort. The percentage of patients taking levetiracetam (LEV), valproate (VPA), oxcarbazepine (OXC), and topiramate (TPM) as current ASMs did not differ between the study cohort and either control cohort. The percentage of patients taking LEV, VPA, OXC, and LTG as past ASMs was also similar between the study and control cohorts. Of note, LEV (33.3%), LTG (21.2%), and VPA (12.8%) were the three current ASMs most commonly taken in patients with both epilepsy and autism as opposed to LEV (36.5%), OXC (18.0%), LTG (14.7%) in the 'matched' cohort. OXC seemed to be less commonly prescribed for children with autism although a direct

Table 1
Demographic data for patients with co-occurring epilepsy and autism in comparison with the 'random' or demographically 'matched' epilepsy-only cohorts. Significant *p*-values (<.05) are bolded.

Demographic Data	Autism and epilepsy n (%)	Epilepsy, 'random' n (%)	*p*-value	Epilepsy, 'matched' n (%)	*p*-value
Total cohort	156	156		156	
Sex			**<.0001**		.8955
Male	118 (75.6)	79 (50.6)		117 (75.0)	
Female	38 (24.4)	77 (49.4)		39 (25.0)	
Race			.1656		.8041
White	111 (71.2)	95 (60.9)		107 (68.6)	
Black/African American	12 (7.7)	22 (14.1)		14 (9.0)	
Asian	3 (1.9)	2 (1.28)		3 (1.9)	
American Indian/Alaskan native	0	0		2 (1.3)	
Other	30 (19.2)	37 (23.7)		30 (19.2)	
Ethnicity			.0672		.8988
Hispanic/Latino	42 (26.92)	28 (18.0)		43 (27.6)	
Non-Hispanic/Latino	114 (73.08)	126 (80.77)		113 (72.44)	
Unknown or missing	0	2 (1.28)		0	
Age at last follow-up (years)	15.01 (IQR 10.45–17.70)	11.05 (IQR 7.21–15.64)	**<.0001**	13.77 (IQR 10.58–17.67)	.2956

Abbreviations: IQR, interquartile range.

Table 2
Clinical features and seizure semiology in patients with co-occurring epilepsy and autism as compared to the 'random' or demographically 'matched' epilepsy-only cohorts. Significant clinical features are bolded after Benjamini-Hochberg correction based on a false discovery rate of 0.2 (*p*-value calculated from chi-square or Fisher's exact test).

Clinical features	Autism and epilepsy n (%)	Epilepsy, 'random' n (%)	*p*-value	Epilepsy, 'matched' n (%)	*p*-value
Total cohort	156	156		156	
Age of epilepsy onset (years)	5.3 (IQR 2.0–10.2)	4.6 (IQR 1.0–8.3)	.0667	5.0 (IQR 1.5–9.3)	.2102
DRE?	3 missing		.1390	2 missing	.7203
Yes	38 (24.8)	28 (18.0)		41 (26.6)	
No	115 (75.2)	128 (82.0)		113 (73.4)	
History of SE?	23 missing		.6612	7 missing	.4543
Yes	23 (17.3)	24 (15.4)		31 (20.8)	
No	110 (82.7)	132 (84.6)		118 (79.2)	
Seizure semiology					
Generalized onset	103 (66.0)	80 (51.3)	**.0082**	89 (57.1)	.1033
Focal onset	68 (43.6)	82 (52.6)	**.1127**	70 (44.9)	.8197
Unknown onset	6 (3.9)	7 (4.5)	.7769	8 (5.13)	.5844
Generalized motor	85 (54.5)	55 (35.3)	**.0006**	66 (42.3)	.0314
Generalized non-motor	38 (24.4)	33 (21.2)	.4996	37 (23.7)	.8946
Focal motor	45 (28.9)	62 (39.7)	**.0426**	45 (28.9)	1.000
Focal non-motor	15 (9.6)	5 (3.2)	**.0208**	12 (7.7)	.5458
Focal awareness (intact or impaired)	27 (17.3)	47 (30.1)	**.0078**	37 (23.7)	.1609
Multiple phases (including 2ry generalization)	12 (7.7)	27 (17.3)	**.0102**	16 (10.3)	.4282
Epilepsy syndromes	20 (12.8)	35 (22.4)	**.0258**	47 (30.1)	**.0002**

Abbreviations: DRE, drug-resistant epilepsy; SE, status epileptics; IQR, interquartile range.

Table 3
Brain MRI results in patients with co-occurring epilepsy and autism as compared to the 'random' or demographically 'matched' epilepsy-only cohorts. Significant *p*-values (<.05) are bolded.

MRI brain findings	Autism and epilepsy n (%)	Epilepsy, 'random' n (%)	*p*-value	Epilepsy, 'matched' n (%)	*p*-value
Total cohort	156	156		156	
MRI brain obtained	133 (85.3)	132 (84.6)	.8742	123 (78.9)	.1401
MRI results			**.0036**		**.0003**
Normal	79 (59.4)	77 (58.3)		64 (52.0)	
Positive (explain epilepsy)	19 (14.3)	37 (28.0)		42 (34.2)	
Non-specific (incidental)	35 (26.3)	18 (13.6)		17 (13.8)	
If positive,			NA		NA
Brain malformation	11 (8.3)	12 (9.1)		14 (11.4)	
Vascular insult	6 (4.5)	8 (6.1)		9 (5.8)	
HIE or anoxic injury	0	12 (9.1)		4 (3.3)	
Infectious sequelae	1 (0.8)	8 (6.1)		4 (3.3)	
Neoplastic/brain tumor	0	0		5 (4.1)	
Temporal/hippocampal sclerosis	2 (1.5)	1 (0.8)		2 (1.6)	
Other	1 (0.8)	4 (3.0)		8 (6.5)	

Abbreviations: NA, not applicable (n < 15).

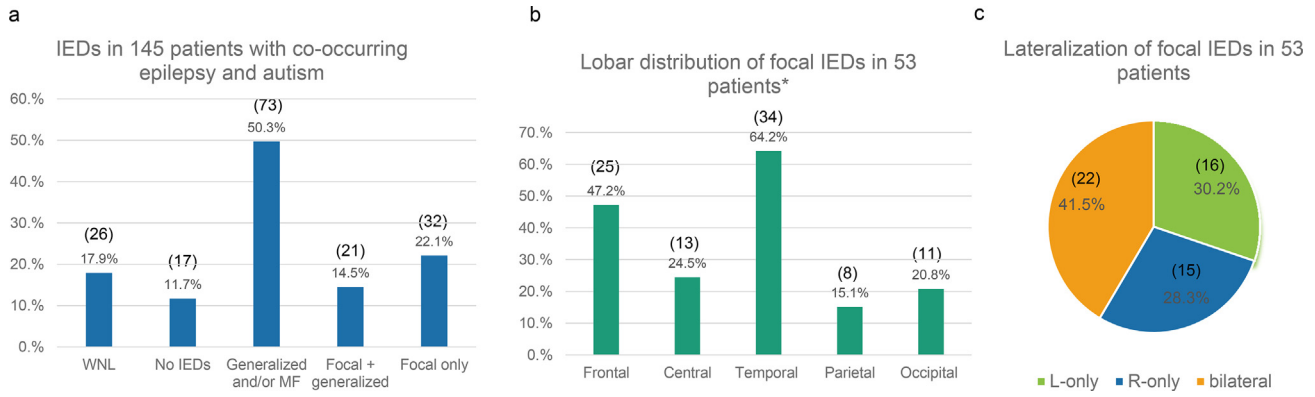

Fig. 2. a, Percentages of patients with generalized, multifocal (MF), and focal IEDs among the 145 patients with co-occurring epilepsy and autism who underwent at least one EEG study. IEDs, interictal epileptiform discharges; WNL, within normal limit. b, Lobar distribution (percentages) of focal IEDs identified in 53 patients after excluding those with MF IEDs. *indicates missing data in one patient. c, Percentages of patients with bilateral, left-sided (L-) only, or right-sided (R-) only IEDs in the 53 patients.

comparison to the 'matched' cohort did not yield a statistical significance (11.5 vs 18.0%, p = .1103) (**Table S2**).

Not surprisingly, there was a higher percentage of patients with autism who had received CMA than those without autism (47.4% in the study cohort, vs 16.0% in the 'random' cohort, vs 18.0% in the 'matched' epilepsy cohort, p < .0001 for each comparison). However, there was no difference in the diagnostic yield of CMA among the cohorts (37.8% in the study cohort, vs 32.0% in the 'random' epilepsy cohort, vs 53.6% in the 'matched' epilepsy cohort). When compared to the 'matched' cohort, more patients with autism received WES analysis (10.3% vs 4.5%, p = .0493) and were more likely to have a first-degree relative with autism (9.6% vs 1.3%, p = .0047). The rates of epilepsy gene panel testing were unexpectedly low in all three cohorts (~6%) (**Table S3**).

3.3. Risk factors and prediction modeling of DRE in children with both epilepsy and autism

The prevalence of DRE in the study cohort, 'random' and 'matched' cohorts were similar (24.8 vs 18.0 vs 26.6%, respectively) (Table 2). We then focused on the study cohort and identified two clinical and five electrographic variables independently associated with DRE in the univariable regression analysis. These were age of epilepsy onset <2 years (OR 7.87, 95% CI [2.34–26.52], p = .0009), history of SE (OR 5.17, 95% CI [1.90–14.06], p = .0013), abnormal EEG background (OR 4.60, 95% CI [2.70–10.23], p = .0002), generalized slowing (OR 5.72, 95% CI [2.40–13.55], p < .0001), focal slowing (OR 2.61, 95% CI [1.18–5.78], p = .0181), multifocal IEDs (OR 5.51, 95% CI [1.93–15.77], p = .0015), and EEG ictal finding (OR 4.45, 95% CI [1.91–10.37], p = .0005) (Table 4). In the final multivariable logistic regression modeling, EEG ictal findings (OR 8.37, 95% CI [2.36–29.74], p = .001), focal onset seizures (OR 7.91, 95% CI [1.84–33.98], p = .0054), generalized motor seizures (OR 6.80, 95% CI [1.57–29.39], p = .0103), abnormal EEG background (OR 4.13, 95% CI [1.39–12.33], p = .0110), and history of SE (OR 2.77, 95% CI [0.77–9.92], p = .1169) increased the odds of DRE, whereas an older age onset of epilepsy decreased the odds of DRE (OR 0.87, 95% CI 90.77–1.00), p = .0506) (Table 5). The final DRE prediction model including these 6 electroclinical variables yielded an area under the receiver operating characteristic curve (AUC score) of 0.88 (Fig. S1**a**). There was no difference in the multivariable logistic regression between children with versus without DRE for the other factors including generalized and multifocal IEDs. By contrast, risk factors for DRE in the 'matched' epilepsy cohort were abnormal EEG background, generalized IEDs, age of epilepsy onset, multifocal IEDs, EEG ictal findings, and history of SE (**Table S4**) as shown in the multivariable logistic regression modeling with an AUC score of 0.89 (Fig. S1**b**).

Table 4
Results from univariable analyses showing electroclinical features associated with DRE in children with co-occurring epilepsy and autism (n = 38, 24.8%). Significant p-values (<.05) are bolded.

Variables	OR (95% CI)	p-value
Sex (female vs male)	0.83 (0.34–2.01)	.6783
Ethnicity (Hisp vs non-Hisp)	0.53 (0.24–1.16)	.1099
Age of epilepsy onset (years)		
< 2 yo (vs > 10 yo)	7.87 (2.34–26.52)	**.0009**
2-5 yo (vs > 10 yo)	3.50 (0.98–12.43)	.0529
5-10 yo (vs > 10 yo)	1.54 (0.40–5.96)	.5286
Semiology		
Generalized onset	1.55 (0.69–3.51)	.2921
Focal onset	1.99 (0.95–4.19)	.0684
Generalized motor	2.13 (0.98–4.62)	.0561
Generalized non-motor	0.92 (0.39–2.17)	.8496
Focal motor	1.47 (0.67–3.24)	.3356
Focal non-motor	0.90 (0.23–3.46)	.8780
Focal awareness (intact or impaired)	1.44 (0.57–3.64)	.4437
History of SE	5.17 (1.90–14.06)	**.0013**
Epilepsy syndrome	1.35 (0.48–3.81)	.5675
EEG abnormalities		
Abnormal background	4.60 (2.70–10.23)	**.0002**
Generalized slowing	5.71 (2.40–13.55)	**<.0001**
Focal slowing	2.61 (1.18–5.78)	**.0181**
Generalized IEDs	1.78 (0.84–3.77)	.1337
Focal IEDs	1.35 (0.65–2.81)	.4274
Multifocal IEDs	5.51 (1.93–15.77)	**.0015**
Ictal finding	4.45 (1.91–10.37)	**.0005**
Positive MRI brain	1.66 (0.55–5.01)	.3716
Positive CMA result	2.00 (0.75–5.37)	.1689
Family history of epilepsy	0.71 (0.22–2.28)	.5681
Family history of autism	1.71 (0.54–5.39)	.3624

Abbreviations: OR, odds ratio; CI, confidence interval; DRE, drug-resistant epilepsy; IED, interictal epileptiform discharges; MRI, magnetic resonance imaging; CMA, chromosomal microarray analysis; SE, status epileptics.

Table 5
Results from multivariable logistic regression modeling after a backward selection process. Significant p-values (<.05) are bolded.

Variables	**OR (95% CI)**	***p*-value**
EEG Ictal finding	8.37 (2.36–29.74)	**.0010**
Focal onset seizure	7.91 (1.84–33.98)	**.0054**
Generalized motor seizure	6.60 (1.57–29.39)	**.0103**
Abnormal EEG background	4.13 (1.39–12.33)	**.0110**
Age of onset	0.87 (0.77–1.00)	.0506
History Of SE	2.77 (0.77–9.91)	.1169

Abbreviations: OR, odds ratio; CI, confidence interval; EEG, electroencephalogram; SE, status epileptics.

4. Discussion

While the sex ratio in the epilepsy cohort (n = 1,439) is nearly equal (M:F = 1.02:1), that in the autism cohort (n = 1,347) demonstrates an extreme male predominance (M:F = 3.5:1) that is similar to the published data [31]. The study cohort's male-to-female ratio of 3.1:1 is close to that of all autism patients. This similarity suggests that the factors that predispose males to develop autism play a similar role in children with both epilepsy and autism. Additionally, the slightly lower male-to-female ratio in the study cohort as compared to the entire autism cohort indicates that the epileptogenic process has a slight predilection towards females with autism.

Creating 'random' and 'matched' control groups to compare with the study group is instrumental to determining the epilepsy phenotype in autism. When demographically matched, the rate of DRE in children with autism is 24.8%, which is similar to those without autism (26.6%) (Table 2). This rate is overall consistent with the cumulative incidence of DRE of 25.0% based on a meta-analysis of previous pediatric studies [24]. We have identified 2 clinical associations (age of epilepsy onset <2 years and history of SE) and 5 electrographic correlates of DRE (abnormal EEG background, generalized slowing, focal slowing, multifocal IEDs, and ictal findings). A prediction modeling includes EEG ictal findings, focal onset seizures, generalized motor seizures, abnormal EEG background, and history of SE which increase the odds of DRE, whereas older age of epilepsy onset decreases the odds of DRE. By contrast, generalized and multifocal IEDs in children with co-occurring epilepsy and autism are not as significant DRE predictors as for children without autism (**Table S4**). Our study indicates that detailed seizure history taking and EEG findings remain among the most important risk stratification for developing DRE in children with co-occurring autism. We assume that epilepsy genetics also plays a pivotal role in risk stratification despite the lack of differences in DRE rate reported between the positive and negative genetic test groups in the study of Chinese children with co-occurring epilepsy and autism [8]. This remains to be investigated when more clinical genetics data are available for analysis.

Our comparative study also indicates that patients with autism have an increased tendency for generalized motor seizures and a lower rate in classified electroclinical syndromes as compared to those without autism. Yet it is possible that the treating neurologist could have been hesitant to assign a 'benign' electroclinical syndrome to a patient with preexisting autism. Interestingly, we have found that LEV, LTG, and VPA are the top three most commonly prescribed ASMs as opposed to LEV, OXC, and LTG for children with epilepsy only. These results suggested that OXC might be less commonly prescribed for patients with co-occurring epilepsy and autism than for those in the 'matched' cohort, even though the direct comparison has not yielded statistical significance (**Table S2**). This ranking difference is in part consistent with the finding of more generalized motor seizures seen in children with autism (Table 2). On the other hand, the comparable frequency of taking LEV in our study cohort suggests that children with autism may tolerate LEV, especially when pyridoxine can be included in the treatment regimen [32], although we do not have the LEV discontinuation or pyridoxine utilization data in the current study.

Our study demonstrates no difference in the rates of EEG background abnormalities, IEDs, or ictal findings between children with autism and those without autism. The subcategories of background abnormalities and types of IEDs are also similar between children with autism and those without autism (**Table S1**), suggesting a lack of EEG biomarkers in patients with both conditions. Rossi and colleagues found that focal and multifocal paroxysmal EEG activity, particularly in the centro-parieto-temporal regions, was present in over 90% of a cohort of subjects with autism and EEG abnormalities and over 80% in a cohort of subjects with autism and epilepsy [20]. Some recent studies reported that focal IEDs were most commonly seen in temporal regions of patients with both autism and epilepsy versus patients with autism and no epilepsy, but an abnormal EEG [16,19]. We have identified approximately 50% of children with both epilepsy and autism having generalized and/or multifocal IEDs as well as >36% having focal IEDs on their EEGs; however, these percentages are similar to those without autism. While temporal and frontal lobes are the most common regions containing the focal IEDs, we have found no evidence of hemispheric dominance. Interestingly, autism is known for a lack of normal left–right asymmetry in structure and function [33–34]. Our result further suggests a lack of hemispheric asymmetry in terms of epileptogenic network or EEG biomarker for children with autism independent of epileptogenesis. In this study, we have not collected the EEG data for children with autism only and so the rate and nature of EEG abnormalities in those children are yet to be studied.

In our cohorts, more children with autism have non-specific MRI findings but fewer with positive findings that explain the etiology of their epilepsy as compared to those without autism. In the subcategories of positive findings, children with autism have lower rates of vascular insult, HIE or anoxic injury, and infectious sequelae, suggesting that a significant portion of epilepsy in children with co-occurring autism is idiopathic or genetic in nature. The role of brain MRI or other neuroimaging in the clinical assessment of patients with co-occurring autism and epilepsy remains unclear [35]. It is also unknown if focal epileptiform discharges seen in these patients have a concordant or causative MRI finding (e.g., focal cortical dysplasia, mesial temporal sclerosis). More advanced imaging modalities such as positron emission tomography (PET), diffusion tensor imaging (DTI), functional MRI, and magnetoencephalography (MEG) may offer a better sensitivity of detection than conventional MRI. Chromosomal microarray analysis remains the first-tier genetic testing for children with developmental delays. As expected, 47.4% of patients in our study cohort had CMA obtained as opposed to only 18% of children in the 'matched' cohort. However, the diagnostic yield of CMA was not different. More patients with autism have undergone WES analysis than those without autism. Unexpectedly, only a small portion (~6%) of each cohort underwent an epilepsy gene panel study (**Table S3**). This is likely due to limited referrals or access to these tests in our center up to the beginning of 2020.

The strength of our study is that we have generated two epilepsy control cohorts in order to investigate potential phenotypic and management differences in their epilepsies between children with autism versus those without autism. We have conducted deep phenotyping according to the ILAE (2017) classification of seizure types and also included classified EEG features for the DRE risk stratification. Our study has limitations. First, a retrospective study design that relies on chart review has limitations related to history recall, EEG inter-rater variability, and documenting discrepancies among providers. The accuracy of classifying each patient's seizure semiology varies based on the complexity of the event and the amount of detail describing the seizure. Secondly, a retrospective study may not keep up with data in current practice for a fast-evolving field. For example, our cohorts have low rates of epilepsy gene panel studies. Thirdly, we have not recorded data on the temporal relationship between ages of autism diagnosis and epilepsy onset, or the severity of autism in this study. In addition, it is possible that some patients with a historical diagnosis of Asperger syndrome and/or Pervasive Developmental Disorder are not included in our study cohort.

5. Conclusion

Our comparative study on the epilepsy phenotype has revealed that generalized motor seizures are the most common seizure type in children with co-occurring autism. These children are less likely to have brain MRI findings that explain their epilepsies or to be classified as electroclinical epilepsy syndromes. The cumulative prevalence of DRE in children with co-occurring autism is 24.8% and our study highlights several demographics, clinical and electrographic characteristics observed in children with autism and co-occurring epilepsy that may contribute to further prognostic characterization of this cohort of patients. However, autism is an etiologically and clinically heterogeneous group of neurodevelopmental disorders. Based on our results, further studies on epilepsy in subgroups of autism based on its etiology (e.g., syndromic vs non-syndromic) or clinical severity (e.g., regression vs no regression) are warranted.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.yebeh.2023.109228.

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