

Autism Spectrum Disorder: Correlation between aberrant behaviors, EEG abnormalities and seizures

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Abstract

The relationship between epilepsy, epileptiform discharges, cognitive, language and behavioral symptoms is not clearly understood. Since difficulties with socialization and maladaptive behaviors are found in children with Autism Spectrum Disorder (ASD), we inquired whether epileptiform activity and seizures are associated with adverse behavioral manifestations in this population. We reviewed our EEG database between 1999-2006, and identified 123 children with ASD. EEG abnormalities were found in 39 children (31%). A control group of age and gender matched ASD children with normal EEG's was obtained. Packets of questionnaires including the Vineland Adaptive Behavior Scale II (VABS), Aberrant Behavior Checklist (ABC) and the Childhood Autism Rating Scale (CARS) were sent by mail. Out of 21 packets received, 11 had normal and 10 had abnormal EEG's. There were no statistically significant differences in behavior between the two groups. Statistical analysis of discharge location and frequency did not reveal a significant trend. However, children with ASD and seizures had statistically significant lower scores in VABS daily living (P=0.009) and socialization (P=0.007) as compared to those without seizures. ASD children with seizures had higher ABC levels of hyperactivity and irritability. Differences in irritability scores nearly reached statistical significance (P=0.058). There was no significant difference in the degree of CARS autism rating between the groups. Our study did not reveal statistically significant differences in behaviors between ASD children with and without EEG abnormalities. However, ASD children with seizures revealed significantly worse behaviors as compared to counterparts without seizures.

Introduction

Autism spectrum disorder (ASD) is a syn-

onym for the DSM IV category of Pervasive Developmental Disorder. Behavioral criteria have been developed to define this category of disorders, in which there are variable degrees of abnormal communicative intent, social reciprocity and interaction, and repetitive and stereotyped patterns of behavior, interests and activities with onset before three years of age.1 Since the time autism was first described in 1943 by Dr. Leo Kanner, many reports have linked ASD and epilepsy. Seizures are common and occur in approximately 20-30% of patients diagnosed with the more symptomatic subset of individuals with ASD.24 Most studies do not distinguish between autism and ASD where fewer of the defining criteria are present. A bimodal distribution of seizures has been described, with a peak before five years of age and an additional peak after 10 years.3 The risk of epilepsy in autism appears to be associated with the degree of mental retardation,5 and the severity of symptoms of autism itself.1 Epilepsy may be seen more frequently in individuals with ASD who have lower receptive language abilities.1

The relationship between epilepsy, epileptiform discharges without clinical seizures and cognitive language and behavioral symptoms is not clearly understood.6 The documentation of epileptiform EEG abnormalities varies from 10.3-72.4% of patients with ASD in some studies to 4-42%3 and subclinical abnormalities in 6.1%-31%.24 Prolonged EEG studies including slow wave sleep may demonstrate abnormalities in additional cases.6 While it is recognized that certain seizure syndromes are associated with cognitive and behavioral impairment, it is not clear whether the seizures are causative for the cognitive changes or whether the seizures and cognitive aberrations reflect a similar underlying neuropathology.7 Attention has been brought to subclinical epileptiform abnormalities on EEG and it has been hypothesized that these may cause cognitive, language and/or behavioral changes.^{2,7} Landau Kleffner syndrome (LKS), an acquired aphasia, is associated with clinical seizures or an abnormal EEG. The epileptiform discharges seen on EEG are seen bilaterally, mainly over the temporo-parietal regions. Acquired aphasia in a child who had fluent speech is the hallmark of this condition. Clinical seizures are not seen in 25% of cases prior to the EEG. The loss of language is thought to be due to active epileptiform activity arising from the eloquent language cortex. Verbal auditory agnosia associated with epileptiform EEG abnormalities has been reported to occur also in developmental dysphasia and autism.6

It has been suggested that the dysfunction of the specific neuronal network that accounts for the behavioral syndrome of autism may be due to a wide variety of insults to the developing brain, and that such insults are likely to Correspondence: Michelle Hartley-McAndrew, Women and Children's Hospital of Buffalo, Department of Neurology, 219 Bryant Street, Buffalo, NY 14222, USA. E-mail: mhmcandrew@theini.org

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affect more than one single neuronal network.8 For example, studies have shown that much of the neural basis for autism lies in abnormalities in brain size, aspects of the limbic system, functionally related regions of the orbitomedial prefrontal cortex and visual associations of the temporal lobe.9 Given that difficulties with socialization and aggressive behaviors are often found in children with ASD, we inquired whether the presence of aberrant behaviors may indicate underlying cerebral irritability or abnormal structural network that gives rise to epileptiform discharges. In an attempt to objectively measure behavior differences between those with and without epileptiform EEG abnormalities, we compared standardized assessments of functional and atypical behavior in children with ASD with and without abnormal EEG's.

Materials and Methods

This study was approved by the pediatric institutional review board at the Women and





Table 1. Results of parental questionnaires indicating patient age, EEG result, presence of anti-epileptic medication, behavior modification medications, questionnaire scores and history of seizures.

Gender	Age (yr)) EEG	AED	Behavior meds	CARS	Irritability	Hyperactivity	Daily living	Socialization	Maladaptive behavior index	History of seizures
F	15	Normal	-	-	33.5	74%	>98	58	42	24	-
M	11	Normal	-	-	41.5	55%	74%	48	38	19	-
M	7	Normal	-	-	36	50%	<50%	71	80	19	-
F	8	Normal	+	+	31	91%	89%	73	75	21	-
M	7	Normal	-	+	34	75%	93%	69	71	23	-
M	11	Normal	-	-	39.5	84%	<50%	89	69	22	-
M	7	Normal	-	-	38	92%	74%	59	53	21	-
F	9	Normal	-	+	36	>98%	73%	69	68	22	-
M	10	Normal	-	+	34	80%	89%	55	59	22	-
M	11	Normal	-	+	28	<50%	52%	81	82	16	-
M	23	Normal	+	+	30	92%	60%	40	33	24	+
M	9	Abnormal	+	+	40	>98%	75%	71	68	22	+
M	23	Abnormal	+	+	30	87%	83%	31	25	20	+
M	16	Abnormal	-	-	30.5	<50%	<50%	65	80	17	-
M	7	Abnormal	-	+	34	72%	76%	103	80	21	-
M	11	Abnormal	+	-	35.5	60%	52%	47	36	17	+
M	19	Abnormal	-	+	30.5	70%	84%	119	78	22	-
M	13	Abnormal	+	-	37.5	98%	75%	66	61	22	+
M	11	Abnormal	-	-	35	80%	65%	85	91	22	-
F	18	Abnormal	+	+	35.5	96%	93%	59	58	22	+
M	15	Abnormal	-	+	33	70%	<50%	99	73	20	-

Table 2. Description and indications of EEG performed in children with Autism Spectrum Disorder.

Gender	EEG features	Localization	State	Frequency of discharge	es Indication
Male	Normal	-	Awake/sleep	-	Staring
Female	Normal	-	Awake	-	Shaking episode
Male	Normal	-	Awake/sleep	-	Automatisms, staring
Male	Sharp Wave	Rt centro-temporal/BFED	Awake/sleep	>20x/minute	Rule out seizure
Male	Spike and wave complexes	Generalized max bifrontal	Awake/sleep	>5x in record	Staring
Male	Normal	-	Sleep	-	Staring
Female	Normal	-	Awake/sleep	-	Violent behaviors
Male	Normal	-	Awake/sleep	-	Staring
Female	Normal	-	Sleep	-	Temper tantrums
Male	Normal	-	Awake/sleep	-	Automatisms
Male	Normal	-	Awake/sleep	-	Arousal from and movement in sleep
Male	Spikes	Right central	Sleep	-	Autism work up
Male	Spike and wave complexes	Generalized	Awake	Once in the record	History of blackouts
Male	Sharp wave	Left occipital-parietal	Awake	10-20x/minute	Autism work up
Male	Polyspike and wave/ spike and wave complexes	Multiregional and generalized max bifrontal	Awake/sleep	>20x/minute	History of GTC seizure
Male	Normal	-	Awake/sleep	-	Body jerks
Male	Sharp wave	Left occipital	Awake/sleep	5-10 x/record	History of absence and GTC seizure
Male	Continuous slow, Sharp wave, Spike and wave complexes	Left posterior hemisphere slow, Multiregional sharp and spike wave complexes	Awake/sleep	1-5 x/minute	History of GTC seizure
Female	Continuous slow	Generalized max bifrontal	Awake	-	"Drop seizures"
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Male	Sharp wave	Left centro-parietal	Sleep	10-20 x/minute	Seizure with right arm shake





Children's Hospital of Buffalo. The EEG database at the Women and Children's Hospital of Buffalo was reviewed and out of 22,715 EEG's performed between 1999-2006, 123 were found to be of children with ASD. The terms searched included "Autism", "Asperger's syndrome", "PDD" and "pervasive developmental disorder". Diagnoses along the autism spectrum were confirmed by parental report of prior clinevaluations from Developmental Pediatricians and ADOS testing where DSM IV criteria were met. EEG abnormalities included both epileptiform and non-epileptiform abnormalities. Inclusion criteria included: primary autism spectrum disorder and age over four years. Exclusion criteria included any concomitant disorder that would have accounted for the autistic features (e.g., Rett syndrome, Tuberous sclerosis, Fragile X syndrome, Landau Keffner syndrome). A telephone introduction to the study was made to 78 families prior to the mailing of questionnaires. The families were asked to complete and return the Vineland Adaptive Behavior Scale II (VABS) and the Aberrant Behavior Checklist (ABC) and were later interviewed by telephone. On telephone interview follow-up, the Childhood Autism Rating Scale (CARS) was administered to support the diagnosis of autism spectrum disorder. This method was used in a study in 2008 by Eaves¹⁰ when studying young adult outcomes in autism spectrum disorder. VABS subdomain scores of interest for this analysis were daily living, socialization and maladaptive behaviors. Scores noted on the ABC included hyperactivity and irritability, since our aim was to evaluate the most disruptive behaviors. The CARS has been shown to have a high degree of concordance with clinical diagnoses, thus providing value in its continuous score to indicate severity.11 Though not diagnostic, it supports the clinical diagnosis of ASD and scores the degree of autistic behavior. EEG abnormalities and behaviors were analyzed using ANOVA (analysis of variance between groups) on SPSS and ANCOVA (analysis of covariance).

Results

Abnormal EEG's had both epileptiform and non-epileptiform abnormalities, for example one patient had non-specific slowing of the record. EEG abnormalities were found in 39 children (31%) with ASD. A control group of age and gender matched controls also noted to have ASD with normal EEG's were obtained in order to compare behaviors between groups. Four EEG's were obtained from long term monitoring studies and 17 were outpatient EEG's. Sleep was achieved in 81% (17) of the EEG recordings. Of the records with only awake pat-

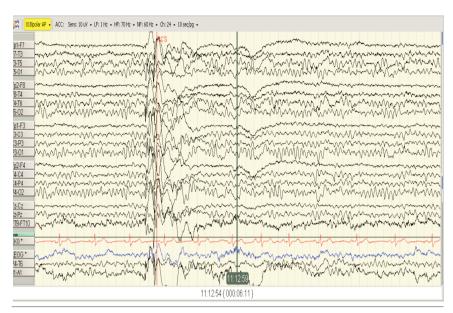


Figure 1. Example of infrequent generalized spike and wave discharges.



Figure 2. Example of frequent right sided discharges.

terns seen, 75% were abnormal. Completed questionnaires were returned by 27 families. One was excluded as the criteria of autism spectrum disorder were not met, another was excluded because of age (<4 years) and four could not be reached for telephone interview. The total number of patients included in the study was 21. Of the 21 children appropriate for inclusion, 10 had abnormal EEGs and 11 had normal EEGs. In the group with abnormal EEGs, one was female, five were on antiepileptic medication and six were on behavior modification medication. In the normal EEG group with normal EEGs, three were female, two were on anti-epileptic medications and six were on behavior modification medication

(Table 1).

The indications for EEG testing included ruling out questionable seizure activity, such as staring, shaking episodes and automatisms (Table 2). EEG abnormalities consisted mainly of interictal epileptiform activity in multiple distributions including from the left and right hemispheres, the occipital, centro-temporal, centro-parietal and bifrontal regions, in addition to generalized discharges. A single EEG revealed significant generalized slowing (Table 2).

Comparison of daily living scores, as measured by the VABS, revealed no significant difference in mean scores between those with abnormal EEG and those with normal EEG,



with mean scores of 74.50 ± 27.01 with abnormal EEG and 64.73 ± 14.36 with normal EEG (P=0.307), while the expected average score in the general population is 100 (range 70-130). Socialization scores in the abnormal EEG group had a mean of 65.00 ± 20.47 and 60.91 ± 17.18 in the normal EEG group (P=0.627). Mean maladaptive behavior scores was 20.50 ± 2.01 in the abnormal EEG group, and was 21.18 ± 2.40 in the normal EEG group (P=0.492).

When holding anti-epileptic medication as constant in the different domains, the difference in scores with regard to daily living became significant (P=0.033). Socialization and maladaptive behavior differences did not appear significant with P=0.162 and 0.39, respectively. Behavior modification medications did not predict dependent variables and were not included in the covariant analysis. In comparing measurements from the ABC, mean for irritability was 79.10±16.60 in the abnormal EEG group and 76.45±17.59 in the normal EEG group, which were not statistically significant (P=0.828). Means for the hyperactivity scale were 70.30±15.38 in the group with abnormal EEG and 72.91±17.91 for the group with normal EEGs (P=0.53). CARS means were 34.15±3.25 in the abnormal EEG group and 34.68 ± 4.08 in the normal EEG group (P=0.74).

EEG discharge frequency was defined as infrequent with discharges 5 or less times per minute and frequent discharges were 5-20 times per minute (Figures 1 and 2). Discharge frequency was compared with VABS subsets and did not reveal statistically significant differences in scores of daily living, socialization and maladaptive behavior. Individual comparisons were not made as to avoid type 1 error between the two groups. Scores of irritability and hyperactivity as measured by the ABC, in comparison to discharge frequencies also did not reveal a significant correlation. The CARS score was not statistically associated with the discharge frequency (Figure 3). Scores of daily living, socialization and maladaptive behavior were not significantly different with regard to location of EEG abnormalities. The same was also true of irritability and hyperactivity scores. Localization of EEG abnormalities did not have any significant association with the CARS scores as well (Figure 4). The small samples size may not be sensitive to real differences that a larger, prospective study with additional diagnostic evaluations could reveal.

Further analyses were performed on the ASD group with EEG abnormalities. We compared those without seizures to those with seizures and found statistically significant differences in behavior. Children without seizures had a mean of 94.50 ± 20.33 in daily living and those with seizures had a mean of 54.80 ± 16.07 (P=0.009) on the VABS. Socialization scores were also significantly

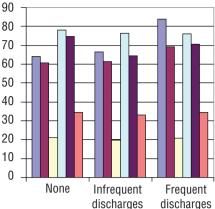
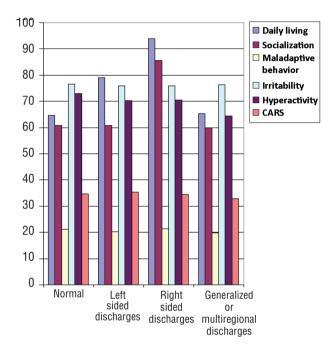




Figure 3. Comparison of Vineland Adaptive Behavior Scale and Aberrant Behavior Checklist subset scores and CARS scores with frequency of epileptiform discharges (Daily living P=0.3, Socialization P=0.4, Maladaptive behavior P=0.7, Irritability P=0.5, Hyperactivity P=0.8, CARS P=0.8)



4. Figure Comparison of discharge location with Vineland Adaptive Adaptive Behavior Scale. **Behavior** Aberrant Checklist subset and CARS scores (Daily living scores P=0.3, Socialization P=0.4, Maladaptive behavior P=0.7. P=1.0, Irritability Hyperactivity P=0.9, CARS P=0.8).

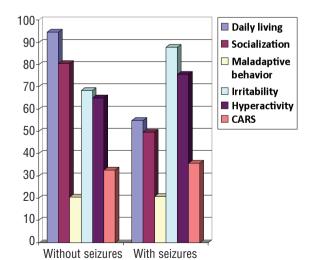


Figure 5. Comparison of Vineland Adaptive Behavior scales, Aberrant Behavior Checklist subset scores and CARS scores in ASD patients with epileptiform abnormalities without seizures and with seizures living (Daily P = 0.009Socialization P = 0.007Maladaptive behavior **Irritability** P=0.886, P=0.058, Hyperactivity P=0.302, CARS P=0.139).

lower with means of 80.40 ± 6.58 and 49.60 ± 18.23 in groups without and with seizures, respectively (P=0.007). Comparing maladaptive scores between the two groups resulted in means of 20.40 ± 2.07 in the with-

out-seizure group and 20.60 ± 2.19 in the withseizure group (P=0.886). Examination of subsets of the ABC, identified differences in irritability means that did not reach statistical significance with mean of 68.40 ± 11.08 in the





without-seizure group compared to 87.80 ± 16.19 in the with-seizure group (P=0.058). Mean hyperactivity scores were 65.00 ± 15.26 and 75.60 ± 15.13 in the without-seizure and with-seizure groups, respectively (P=0.302). CARS scores were again not significantly different between the two groups, with a mean of 32.60 ± 2.06 in the without-seizure group and 35.70 ± 3.68 in the with-seizure group, respectively (P=0.139) (Figure 5).

Discussion

It has been documented that epilepsy is associated with a variety of cognitive and behavioral manifestations.12 Some interictal behavioral disturbances may actually represent unrecognized seizures.4 These observations result in the hypothesis that epileptiform discharges without clinical seizures could cause behavioral, cognitive and language impairments in children with ASD.6 Since studies suggest that up to one third of children with ASD develop epilepsy, 2,3,4,6 this study was undertaken to determine whether children with ASD with abnormal EEGs with or without seizures, have more significantly impaired behavior. The data did not reveal significant differences in behaviors between children with ASD with and without EEG abnormalities. This finding remained when behavior modifying medication use was controlled for by ANCOVA. The VABS measures skills in communication, daily living, socialization, motor skills and maladaptive behavior. In this study, the VABS was used to measure adaptive and socialization behaviors. Even in children with ASD with typical cognitive abilities, VABS scores are depressed.13 Although the differences between mean scores in daily living and socialization domains were not significant, they seemed to trend higher in the abnormal EEG population. This is not an expected finding and is likely due to the small sample size. Although an interesting consideration is perhaps that this may support the fact that only the population of higher functioning children with ASD and epileptiform abnormalities are able to successfully tolerate the EEG testing.

The ABC gives account of behavior in five domains (hyperactivity, irritability, lethargy, stereotypic behavior, inappropriate speech). In order to attend to those behaviors that are troublesome or impair daily activity, hyperactivity and irritability scores were focused. Those with EEG abnormalities performed better in the hyperactivity domain (lower score indicates less hyperactive behavior). Again, perhaps EEG abnormalities are more easily detected and technically feasible on patients who are less hyperactive. However, those with abnormal EEGs had more irritability. Another

notable finding of this study was the results of the CARS, a scale that documents the presence of symptoms of autism. There was virtually no difference in the CARS score between those with normal and abnormal EEGs. Aiming to further explore the lack of statistical difference between the two groups, both discharges location (left, right, generalized) and frequency were analyzed. Again, no statistically significant pattern or trend was seen to attribute to differences in behavior. Our study demonstrated that children with ASD, EEG abnormalities and seizures have significant differences in behaviors from those with abnormal EEG but without seizures. This confirms the results of previous studies revealing that patients with seizures have more challenging behavior, especially in areas of aggression.14 However, to our knowledge, this pattern has not been previously described in individuals with autism. Our findings also tend to support the study of Hrdlicka et al.5 in which behavior, specifically autistic regression is significantly associated with the presence of epilepsy and not with the presence of epileptiform abnormalities on EEG. Limitations of this study include the small sample size. Given the low return rate (34.6%), families who volunteered for this study may have represented a subgroup with additional concerns regarding behavior. No other sources of behavioral data, such as direct observation or school reports were used to corroborate parent reports of adaptive and maladaptive behaviors. Social stressors may be increased in those families who are facing seizure management in addition to ASD, thus making a less peaceful home environment and leading to a perception of more difficult child behavior. A technical limitation to the interpretation of this study is that although 17 of the 21 (81%) EEGs included sleep, the majority of EEG recordings were outpatient EEGs with only four >24 hour recordings in the analysis. Previous studies have shown that prolonged sleep EEGs increase the yield of EEG abnormalities in people with autism.15 Treatment of EEG abnormalities has typically been up to the clinical judgment and experience of the clinician caring for the autistic child. There are no published practice parameters of established guidelines.16 Behavioral benefits could be obtained with medications. Most anti-epileptic drugs have either mood stabilizing qualities or sedation effects; as such, the behavior improvement noted could be due to improvement of the seizure activity or primary improvement in the behavior. Our study suggests that treatment of the epileptiform abnormalities with the aim to improve behavior may not be warranted. Previous studies support the notion of withholding treatment of EEG abnormalities without clinical seizures. The possibility that a proactive approach toward the treatement of abnormalities could be preventative in the development of later epilepsy is yet unknown. Is Another point of debate is whether screening EEGs in children with autism at the time of diagnosis are necessary. Our study did support the AAP Technical Report It that advises that only those children with seizure-like episodes or those whose behaviors are suggestive for seizures should receive EEG. It should also be added that since children with Landau Kleffner syndrome may mimic findings of idipathic autism, any child with features suggestive of acquired epileptic aphasia, with loss or regression of speech and language should be evaluated to exclude this syndrome. 4

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