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Electroencephalogram discharges in atypical cognitive development

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Abstract

In order to investigate the significance of electroencephalogram discharges and their treatment we retrospectively reviewed the charts of 22 children with atypical cognitive development that did not respond to standard educational therapy and demonstrated discharges on electroencephalogram. Most children demonstrated no obvious symptoms of seizures and developmental regression and/or fluctuations were uncommon. The majority of children demonstrated a language and attention disorder and autism symptomatology and had multifocal discharges on electroencephalograms. Of the 20 patients treated with antiepileptic medications, 70% demonstrated definite improvement within one clinic visit. This study suggests that children with electroencephalogram discharges and developmental cognitive disorders demonstrate a unique pattern of symptomatology and discharges on electroencephalography. This study suggests that children with developmental cognitive disorders that do not respond to standard therapy may benefit from screening with an electroencephalogram and a trial of antiepileptic medication if discharges are detected.

Keywords

speech delay; attention deficit; pervasive developmental disorder; electroencephalography; magnetoencephalography; electroencephalogram discharges

Introduction

The significance of electroencephalogram discharges on cognitive and behavioral development has been debated. Electroencephalogram discharges have a high incidence in several neurodevelopmental disorders, such as autism spectrum disorder and Asperger syndrome, even when a diagnosable seizure disorder is absent.^{1,2} This has led some to suggest that these discharges could be correlated with abnormal behavioral and cognitive development. However, discharges are commonly found in children who have benign childhood epileptic disorders such as benign rolandic epilepsy of childhood. Children with benign rolandic epilepsy of childhood, for the most part, demonstrate normal cognitive development despite frequent discharges on the electroencephalogram. This has raised doubt to the association of discharges with abnormal behavioral and/or cognitive development.

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This study has not been presented or published previously.

In some cases benign rolandic epilepsy of childhood can be associated with cognitive disturbances.^{3,4} Several reports have examined cases with electroencephalographic characteristics of benign rolandic epilepsy of childhood who also have cognitive or achievement deficits.⁵ Using magnetoencephalography, studies have suggested that discharge location may be related to specific behavioral and cognitive abnormalities. Wolff et al.⁶ demonstrated that children with discharges in the left perisylvian area scored lower in tests of language whereas children with discharges in the occipital cortex scored lower in tests involving visual transformation. Such data is consistent with a larger study by Lewine et al.⁷ who demonstrated that children with traditional Landau-Kleffner syndrome demonstrated primary discharges only in the left temporoparietal area. Lewine et al.⁷ also demonstrated that children with pervasive developmental disorder demonstrated additional discharges outside the left temporoparietal area and manifested a multifocal pattern of discharges.

Several studies have demonstrated that a subset of children with developmental disorders manifest abnormal electroencephalographic studies and in some studies abnormal electroencephalograms were reported to be more likely in children with cognitive regression⁸. However, studies have not examined whether children with discharges, as a group, (1) represent a specific clinical phenotype, (2) manifest a specific electroencephalographic pattern, or (3) respond to anti-epileptic drug treatment. Identifying neurological or cognitive characteristics that are specific to children with electroencephalographic discharges would help determine which children require an electroencephalogram to identify discharges. Identifying specific electroencephalographic characteristics of discharges would be of great value for identifying candidates in whom discharges may be associated with abnormal cognitive and behavioral development. Documenting significant improvement in cognition with initiation of anti-epileptic drug treatment would help validate the notion that electroencephalogram discharges are clinically significant and treatable.

In this study we investigate a series of children who presented to our pediatric neurology clinic with cognitive delays, including abnormalities of speech, social function, attention, learning or memory, did not respond to standard educational interventions and demonstrated discharges on electroencephalography. All children had more than two electroencephalograms allowing us to compare the consistency in electroencephalographic findings across studies. To address the lack of information on electroencephalogram discharges, as outlined above, we (1) reviewed the presenting and general cognitive symptoms, (2) examined the consistency in electroencephalographic findings and correlated the discharges with cognitive symptoms, and (3) determined whether anti-epileptic drug treatment was associated with cognitive improvement.

Methods

Participants presented to the University of Texas Health Science Center at Houston Child and Adolescent Neurology Clinic for evaluation. One of the first two authors evaluated patients with a neurological history and physical examination. Specific questions addressed cognitive development, any developmental regression and fluctuations, and signs of seizures including staring episodes and other subtle episodes of seizures. Specific information was abstracted from independent educational, psychological or neuropsychological evaluations. Specifically, it was determined whether the patients met criteria for developmental disorders in receptive and expressive language, reading and/or attention. An evaluation for delays in social development, including symptoms related to autism spectrum disorder, was abstracted from the outside evaluations and conducted by the examiner using Diagnostic Statistical Manual-IV-Text Revision (DSM-IV-TR) criteria. For patients who had an intellectual quotient determined, none were in the mental retardation range.

All patients underwent at least two electroencephalography studies. Studies included routine electroencephalograms, outpatient ambulatory electroencephalograms and 23-hour continuous video-electroencephalographic monitoring in the epilepsy monitoring unit at Children's Memorial Hermann Hospital, Houston, Texas. The international 10–20 electrode placement system was used for all electroencephalograms but sedation was not. A board certified epileptologist read all electroencephalographs. Additional electroencephalograms were ordered depending on the clinical course of the child and electroencephalographic type was guided by standard clinical judgment. All patients underwent magnetic resonance imaging using epilepsy and focal cortical dysplasia protocols.

Twelve children (55%) underwent magnetic source imaging (4-D Neuroimaging, San Diego, Calif). Sources of magnetoencephalographic activity were modeled as single equivalent current dipoles, and their locations were estimated and projected onto the patient's magnetic resonance image for epileptiform dipole localization. An electroencephalogram was conducted as part of the magnetoencephalography protocol.

Initiation of anti-epileptic drug therapy was offered to all patients during their clinical evaluation. The timing of the initiation of therapy was a combination of clinical recommendations and the parents' wishes. The decision whether or not to initiate an anti-epileptic drug and whether to perform the initial electroencephalogram followed a general guideline. Younger patients (N=11, mean age 5 years 0 months, SD 10m) were first prescribed standardized educational therapy and followed clinically for several months to years (mean 1y 6m, SD 4m) to determine if they would respond to such therapy before anti-epileptic medication was prescribed. Older patients (N=9, mean age 9y 2m, SD 3y 9m) who had several years of educational therapy despite no improvement were prescribed anti-epileptic medication upon a positive electroencephalogram study.

The particular anti-epileptic drug chosen was determined in consultation with parents after discussing the risks and benefits of each anti-epileptic drug. The patient's treatment response in cognition was assessed in an unblinded manner by the parents', educators and/or therapists as well as the clinician. A five point scale was used to assess treatment response: (1) definite improvement, (2) possible improvement, (3) no change, (4) possible worsening and (5) definite worsening. All parties assessing the child (i.e., parents, educators, therapists, and clinician) needed to agree on improvement. If the parties did not agree, the worst response was recorded. Lack of improvement typically resulted in change in anti-epileptic drug therapy and/or repeat electroencephalogram. Comorbid attention disorders were treated with standardized medications, usually amphetamine salts.

The study was conducted in accordance with the Institutional Review Board regulations for the protection of human subjects of our institution.

Results

Patient Characteristics (Table S.1)

There were slightly more males (55%) than female children (45%). Age of presentation range from 1y 11m to 11y 1m with an average age of 5y 11.5 m (SD=2y 9.8m). Only 9% had a history of seizures and 4.5% had a history of an abnormal electroencephalogram. Twenty-six percent of magnetic resonance imaging scans were abnormal with left hippocampus abnormalities accounted for 80%.

Presenting Complaint (Table 1)

The most common presenting complaint was speech and/or language disorder (68%) with few of these patients admitting to language regression (7%) or fluctuation (20%). Learning

disability, including reading disability, was the second most common presenting complaint (23%) with few of these patients admitting to fluctuations (20%). Memory problems, including word finding difficulties, was the third most common presenting complaint (18%) with half describing fluctuation. Eighteen percent presented with atypical paroxysmal symptoms and one patient presented with more classic episodes of seizures (see Table S.1).

Comorbid cognitive disorders (Table 2)

Attention problems was the common comorbid disorder (73%) with 25% of these patients having mild attention problems that did not qualify for attention deficit disorder with or without hyperactivity and 75% having moderate to severe attention problems that qualified for the attention deficit disorder with or without hyperactivity diagnosis. At least one symptom of autism was present in 59% of patients with 8% of these patients demonstrating echolalia, 46% being diagnosed with mild pervasive developmental disorder, 23% diagnosed with pervasive developmental disorder-not otherwise specified and 8% diagnosed with high-functioning autism. Of the seven children that did not present with a speech or language disorder, 71% had a history of speech or language disorder. Overall 91% of patients had a history of a speech or language disorder.

Of the patients not presenting with paroxysmal episodes, 53% were found to have subtle symptoms of paroxysms, with staring episodes being the most common symptom. Of all patients, 64% were found to either have paroxysmal episodes on presentation or on detailed questioning.

Electroencephalograms: Relationship Between Abnormalities and Electroencephalogram Type

A total of 82 electroencephalogram studies were performed across all patients. Most (77%) initial electroencephalograms demonstrated discharges. Normal initial studies were found in 29% of routine electroencephalograms, 33% of the ambulatory electroencephalographic studies and 0% of epilepsy monitoring unit studies. When the patient was not receiving anti-epileptic medications discharges were present on epilepsy monitoring unit studies and electroencephalograms performed during magnetoencephalography 100% of the time, while discharges were less likely on routine electroencephalograms (74%) and ambulatory electroencephalograms (63%). Of the abnormal electroencephalograms, sharp wave were the predominant discharge type (61%) while focal spike and slow wave (10%) and spike and wave (8%) occurred less often. Focal (11%) and generalized (7.5%) slowing were also seen. A clinical correlation with the electroencephalogram discharges was only detected in one patient. This represents a clinical correlation in 1% all electroencephalographic studies and 2% of all extended studied electroencephalographic studies.

Electroencephalogram: Discharge Lateralization and Localization Consistency

Most patients (86%) demonstrated discharges on at least two electroencephalograms studies. Of these patients, 95% patients demonstrated focal or multifocal discharges consistently. Consistent lateralization of focal or multifocal discharges was only seen in 53% of these patients or in 45% of patients overall. Of the patient who demonstrated consistent lateralization of focal or multifocal discharges, most (60% or 27% of all patients) demonstrated bilateral discharges. Overall, only 25% of the patients demonstrated consistent discharge localization.

Electroencephalogram Discharge Lateralization: Correlation with Symptoms

Here we consider the ten patients who demonstrated consistent lateralization of discharges. The patient with pervasive developmental disorder demonstrated right hemisphere discharges. Out of the four patients with attention deficit hyperactivity disorder, three and one patient(s)

demonstrated bilateral and right hemisphere discharges, respectively. Of the two patients with a diagnosis of reading disability, one demonstrated right hemisphere discharges while the other demonstrated bilateral discharges. Of the four patients with isolated speech disorder, half had left hemisphere discharges while the others demonstrated bilateral discharges.

Magnetoencephalography Discharge Localization and Correlation with Symptoms

Source localization of magnetoencephalography spikes was performed in 12 patients but one patient demonstrated no discharges and another demonstrated inconsistent findings over two magnetoencephalography scans. The remaining ten patients were considered. The two patients diagnosed with pervasive developmental disorder demonstrated left hemisphere discharges. Of the six patients diagnosed with attention deficit hyperactivity disorder four, one and one demonstrated left lateralized, right lateralized and bilateral discharges, respectively. Of the four patients with a diagnosis of reading disability two, one and one demonstrated left hemisphere, right hemisphere and bilateral discharges, respectively.

Five of the ten patients with consistent electroencephalographic discharge lateralization had magnetoencephalography studies. Lateralization of source localized magnetoencephalography spikes matched lateralization of electroencephalograph discharges in only 40%. Only one of these patients had repeated electroencephalograms with consistent localization. The localization of electroencephalogram discharges, right parietal, matched the location of magnetoencephalography discharges, right supramarginal gyrus.

Antiepileptic Treatment

Table S.4 outlines each patient's clinical course and their response to anti-epileptic treatment. Overall 91% of the patients were treated with anti-epileptic drugs. Of these, 15% also were prescribed stimulants. Most patients were only treated with one anti-epileptic drug while 20% required a second anti-epileptic drug trial and 5% required a third anti-epileptic drug trial. One child was concurrently treated with two anti-epileptic drugs. Anti-epileptic medication were changed or added for several reasons: no improvement or limited improvement was seen with treatment (N=2), definite improvement occurred in some areas of cognition but other areas of cognition and behavior were still below what would be expected for age (N=3), and regression occurred approximately 10 months after response to a low dose of an anti-epileptic medication (N=1). The distribution of the anti-epileptic drugs is outlined in Table 3.

Table 4 outlines the clinical response to anti-epileptic drug treatment. Overall most (80%) patients responded to anti-epileptic drug treatment either initially or after increasing the anti-epileptic drug dose. Of the two patients not treated with anti-epileptic drugs, development in one eventually improved while the other did not. Although we do not have a control group, 55% of the patients treated with anti-epileptic medications were followed untreated for months to years before initiation of anti-epileptic therapy, thus providing a partial crossover control group. As seen in Table 4, most (81%) of these patients improved with anti-epileptic drug treatment, either initially or after an increase in anti-epileptic drug dose. Anti-epileptic drug treatment was withdrawn in two patients who initially responded significantly. Both patients developed significantly regression following anti-epileptic drug withdrawal and improved with reinstituting the anti-epileptic drug.

We examined the change in electroencephalogram with change in clinical response to anti-epileptic treatment. This was complicated since most electroencephalograms were performed several years after response to anti-epileptic medication in order to determine if the child could be discontinued from the anti-epileptic medication or in some cases when the child had a regression following withdrawal of the anti-epileptic medication. Electroencephalograms were performed on 11 children who definitely responded clinically while they were on medication

and demonstrated clinical improvement. Of these children, 64% of these children demonstrated normalization of the electroencephalogram while 18% demonstrated improvement of discharge frequency on the electroencephalogram and 18% demonstrated no improvement of the number of discharges on the electroencephalogram. Of the two patients that did not demonstrate no definite clinical response, the electroencephalogram normalized for one while the other did not show any significant change in discharges.

Discussion

We have reviewed a case series of 22 patients with developmental cognitive disorders that were refractory to standard educational interventions who were subsequently found to have electroencephalogram discharges. Most of these children were treated with anti-epileptic drugs in an open-labeled manner. We use this review to answer three important questions.

Do children with electroencephalogram discharges demonstrated a specific clinical phenotype?

Our sample demonstrates distinct characteristics. First, unlike idiopathic speech, language or reading disability, we do not find a particular male prevalence. Second, although the average age of presentation was almost 6 years of age, somewhat later than Landau-Kleffner syndrome, several children presented considerably younger than 3 years of age. Third, very few children presented with or had a history of paroxysmal episodes and of the remainder only about half admitted to subtle paroxysmal symptoms. For those children that presented with cognitive disturbances, few admitted to regression or fluctuations. Thus, although these classic paroxysmal symptoms are important to elicit in the history, the lack of these symptoms does not rule out potentially clinically significant discharges. Fourth, although most anatomic magnetic resonance imaging scans were normal, subtle left hippocampus abnormalities, mostly mild atrophy, were found in several of the patients, suggesting that this finding may be significant, if found. Review of these patients demonstrated that their symptomatology or electroencephalographic characteristics were not different than other patients. Fifth, the great majority of the patients (91%), whether or not it was their presenting complaint, had a speech or language disorder. Sixth, a high proportion of children (73%) had attention problem, with over half (55%) of the having symptoms severe enough to meet criteria for attention deficit with or without hyperactivity disorder. Seventh, the majority of the patients (59%) demonstrated some core autism symptoms, although most of the time these were limited and did not substantiate a diagnosis of autism disorder. Thus, this study seems to substantiate a unique clinical phenotype associated with electroencephalographic discharges. The patients in our study demonstrate a history of speech delay with clear symptoms of attention difficulties and some, but not many, symptoms of autism.

Classic epileptic encephalopathies, specifically Landau-Kleffner syndrome and continuous spike and wave during slow wave during sleep, are characterized by status epilepticus during sleep, undergo regression in receptive language after 3 years of age and manifest behavioral comorbidities that include hyperactivity, aggressiveness and depression.^{9,10} Clearly the patients described in this study have similarities and differences with these classic syndromes.

Is there an electroencephalograph discharge signature?

Focal discharges on at least two electroencephalographs were seen in the great majority of the patients (82%). However, consistent discharge lateralization was only seen in 45% of the overall sample and only 17% of the patients demonstrated lateralization to a single hemisphere. Although we attempted to correlate discharge lateralization with symptomatology, the inconsistency in discharge lateralization resulted in a small number of patients on which to base this evaluation, making it difficult to make any conclusions. The fact that most discharges

were focal (79%) but were either inconsistently lateralized to a hemisphere or consistently found to be bilateral suggests a multifocal discharge pattern. This is substantiated by the magnetoencephalography data which demonstrates bilateral discharges in several patients and inconsistent lateralization in one patient across two studies. These data are consistent with Lewine et al.⁷ who demonstrated that children with pervasive developmental disorder demonstrated multifocal neuromagnetic discharges.

Does treatment of discharges with anti-epileptic drugs influence development?

Treatment of children with electroencephalographic discharges is controversial, most likely due to the fact that the significance of such discharges is unclear, resulting in an unclear risk to benefit ratio. This is underscored by the fact that children with Landau-Kleffner syndrome, a related disorder with a more definite association between discharges and cognitive disability, do not typically respond robustly to standard anti-epileptic drug treatment.^{9,10} A great majority of patients whom we offered an anti-epileptic drug trial responded robustly. A smaller number responded only after increasing the anti-epileptic drug dose. Two patients underwent regression with withdrawal of the anti-epileptic drug treatment, further substantiating the utility of anti-epileptic drug treatment by re-challenge methodology. Interestingly, discharges did not always disappear with anti-epileptic treatment. This parallels our clinical experience. It is possible that this represents children who have responded to anti-epileptic medications as a placebo. It is also possible that the anti-epileptic medication has limited the spread of the discharges to other cortical areas, thereby reduced electrographic disturbance in important adjacent cortical regions. Overall these data provide intriguing findings which warrant further study.

Study Limitations

This study was not designed to be a prevalence study, thus it is unknown how many children with developmental challenges are affected clinically by electroencephalographic discharges. The sample of patients evaluated in this study was subject to referral bias. Furthermore, although we tried to apply a standard criterion to all patients for electroencephalographic screening, the decision to screen and treat the child was performed in collaboration with the child's parents. This might suggest that the parents that accepted the protocol were more likely to expect the protocol to have a positive effect. This raises the possibility of a significant placebo effect. However, the positive effect of anti-epileptic drugs was markedly larger than the 19% placebo effect¹¹ in anti-epileptic drug studies examining children and many children improved only with anti-epileptic drug treatment despite being followed for many years. Clearly, a prospective double-blind placebo controlled study with objective language assessments will be needed to validate the treatment data presented. Such an effort would be important and significant, since if simple anti-epileptic drug treatment positively affects selected children, it could have a substantial help the most difficult to treat children.

Conclusions

In this paper we have reviewed a case series of 22 patients with electroencephalogram discharges and developmental cognitive disorders that were refractory to standard educational interventions. As a group, these children appear to have a distinct behavioral and cognitive phenotype characterized by language delay, moderate-to-severe attention difficulties, and autism symptoms. Regression and fluctuation in cognition and symptoms of seizures, even subtle symptoms, were not common. As a group, these children appeared to respond positively to anti-epileptic drugs. Although this study is limited in its design, this preliminary data suggests that there is a subpopulation of children that are refractory to standard educational treatment that may benefit from referral to a pediatric neurologist for further evaluation and an electroencephalographic study to identify discharges. The great majority of the patients that we studied did not have confirmed clinical or electrographic seizures. Without a documented

seizure it is not clear whether or not these children fall into an epileptiform or encephalopathy syndrome. Future studies to determine which subset of children with discharges may benefit from anti-epileptic drug treatment will be critical, since long-term treatment with some anti-epileptic drugs may results in adverse cognitive and psychiatric effects.^{12,13}

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Presenting Complaints

		% of Subcategory	% of All Patients
Language			68% (15/22)
	Regression	7% (1/15)	4.5% (1/22)
	Fluctuations	20% (3/15)	14% (3/22)
Learning			23% (5/22)
	Fluctuations	20% (1/5)	4.5% (1/22)
Memory			18% (4/22)
	Fluctuations	50% (2/4)	9% (2/22)
Paroxysmal			18% (4/22)
Seizure			4.5% (1/22)

Table 2

Developmental Cognitive Disorders

		% of Subcategory	% of All Patients
	Attention Problems		73% (16/22)
	Mild	25% (4/16)	18% (4/22)
	Attention disorder with or without hyperactivity	75% (12/16)	55% (12/22)
	Autism Symptomatology		59% (13/22)
	Echolalia	8% (1/13)	4.5% (1/22)
	Mild pervasive developmental disorder	46% (6/13)	27% (6/22)
	Pervasive developmental disorder-not otherwise specified	23% (3/13)	14% (3/22)
	High functioning autism spectrum disorder	8% (1/13)	4.5% (1/22)
	Speech or Language Disorder		91% (20/22)
	No Obvious Paroxysmal Symptoms		77% (17/22)
	Subtle Symptoms	53% (9/17)	41% (9/22)
	Staring	89% (8/9)	36% (8/22)

Table 3

Treated with AED	91%
Carbamazepine	31%
Valproic Acid	19%
Oxcarbazepine	19%
Ethosuximide	8%
Lamotrigine	8%
Levetiracetam	4%
IVIG	4%
Treated with Stimulant	15%

Table 4

Clinical Response to AED Treatment.

	All Patients	Delayed Treatment
Definite Improvement within One Clinic Visit	70%	72%
Definite Improvement with Increasing AED Dose	10%	9%
Possible Improvement	5%	9%
No Improvement	15%	9%