Review

Prevalence, Significance and Clinical Characteristics of Seizures, Epilepsy and Subclinical Electrical Activity in Autism

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This manuscript reviews epilepsy, seizures and/or subclinical electrical discharges (SEDs) in individuals with autism spectrum disorder (ASD), including prevalence of epilepsy and SEDs, clinical characteristics of this ASD subgroup and seizure types. The prevalence of epilepsy in ASD is higher than the prevalence of epilepsy in typically developing individuals and depends on age and gender as well as comorbid genetic, metabolic and intellectual abnormalities. Studies suggest that, in ASD, the prevalence of clinical seizures increases with age and that adults with ASD and epilepsy have greater behavioral and cognitive problem as well as elevated mortality. Temporal and frontal lobe epilepsies as well as electrical status epilepticus during sleep syndromes share characteristics with ASD yet these syndromes are rarely diagnosed in ASD. The prevalence of SEDs is very high in ASD. Studies suggest that SEDs and epilepsy share common underlying neuropathology but that children with epilepsy have greater cognitive and behavioral impairments than those with SEDs. Studies, mostly on children with epilepsy, provide evidence that SEDs are related to cognitive impairment. One study suggests that the patterns of temporal and frontal SEDs are related to the ASD diagnosis. These studies are consistent with the cognitive and behavioral abnormalities associated with temporal and frontal lobe epilepsies. This adds support for that fact that SEDs are significant. However, carefully controlled studies on the significance of SEDs in ASD are lacking.

1. INTRODUCTION

This manuscript reviews the features of individuals with autism spectrum disorder (ASD) that have co-morbid epilepsy, seizures and/or electroencephalograpic (EEG) abnormalities. Features reviewed include the prevalence of epilepsy and EEG abnormalities, the clinical characteristics of individuals with ASD and epilepsy and/or EEG abnormalities, and the particular types of seizures associated with ASD. The significance of EEG abnormalities in various neurological and neurodevelopmental conditions is also reviewed. Finally key points of this review that may further the understanding, treatment and management of individuals with ASD are highlighted.

Prevalence

Individuals with ASD have been reported to have a 3- to 22-fold higher rate of developing epilepsy as compared to typically developing individuals.[1] While 1-2% of children in the general population develop epilepsy, the prevalence of epilepsy in ASD is much higher with estimates varying widely from 5% to 38%.[1-5] The wide variation in prevalence estimates is probably due to particular characteristics of the patient sample since the prevalence of epilepsy in ASD is dependent on individual characteristics and comorbid medical conditions. Some,[6,7] but not all,[5] studies have reported a higher prevalence of epilepsy in females with ASD. Variations in the age range of the patient sample may be particularly important, as studies with older ASD individuals tend to report a higher prevalence of epilepsy as compared to studies with younger ASD individuals.[2]

The prevalence of epilepsy in ASD depends on comorbid cognitive, neurological and genetic disorders.[2] The prevalence of epilepsy is high in progressive neurological disorders, such as Rett syndrome, disorders associated with single gene defects, such as Fragile X, disorders associated with congenital brain malformations and metabolic disorders.[8-11] The prevalence of epilepsy is elevated in the context of comorbid intellectual disability and/or cerebral palsy.[2] In fact, a meta-analysis suggests that the prevalence of epilepsy in ASD is strongly related to the level of intellectual impairment.[12] Several studies suggest that epilepsy is more prevalent in children with more severe ASD symptoms.[13] Nevertheless, even individuals with ASD without underlying comorbid disorders or severe symptoms have a higher prevalence of epilepsy as compared to the general population.

The relationship between epilepsy and ASD is complex.[14] For example, many children with ASD manifest epileptiform abnormalities on EEG despite a lack of clinical seizures. In most cases, these EEG abnormalities do not meet criteria for electrographic seizures.[15] Since subclinical epileptiform discharges may not be associated with clinical or electrographic seizures, it is not clear that these EEG abnormalities should even be referred to as epileptiform. Indeed, Frye et al6 suggested that these EEG abnormalities should simply be referred to as subclinical electrical discharges (SEDs) since any reference to epilepsy or an ictal or interictal period may be inaccurate without a documented clinical or electrographic ictus. Despite the semantics associated with naming these abnormalities, it is clear that these discharges may be significant in ASD as the prevalence of these abnormalities is high in ASD, varying from 30%[16] to 61%[17] in studies that have used long-term EEG monitoring and varying from 82%[18] to 100%[19] in studies that have used magnetoencephalography (MEG). Less than 3% of children without ASD manifest such EEG abnormalities.[15]

It is clear that the prevalence of seizures and SEDs is higher in individuals with ASD as compared to the general population. Epilepsy appears to be more prevalent when individuals with ASD have comorbid genetic and medical conditions. This fact may help identify children with ASD who have an undiagnosed underlying comorbid condition as the diagnosis of epilepsy may lead to a more focused diagnostic workup.

2. CLINICAL CHARACTERISTICS

Seizures starting early in life may be related to the development of ASD as 19% of children with the onset of seizures before the first year of life developed ASD with intellectual disability.[20] Infants with epileptic encephalopathies have a high rate of ASD with intellectual and motor disabilities.[21] ASD is also related to infantile onset epilepsy, especially if there are associated infantile spasms, brain injury, congenial brain malformations or genetic syndromes.[20,22,23]

One study suggests that the onset of clinical seizures has a bimodal age distribution with one peak before age 5 and another in adolescence.[1] Other studies have suggested that SEDs are more prevalent in childhood while clinical seizures and the diagnosis of epilepsy becomes increasingly prevalent with age.[24] This notion is consistent with follow-up studies of adults with ASD where the prevalence of clinical seizures is 25% to 38% and studies which suggest that most clinical seizures start after 10 years of age.[25] Also, adults with ASD and epilepsy may be more severely affected as they receive more psychotropic medications and have lower intelligence, adaptive behavior, and social maturity scores as compared to adults with ASD but not epilepsy.[4,5]

Children with epilepsy and ASD may comprise a subgroup of ASD children with more severe medical disorders, cognitive delays and distinct behavioral characteristics (**Table 1**). Children with ASD and epilepsy are more likely to have developmental delays, cerebral palsy and intellectual

disability, however, they also have better eye control and tend to be less aloof, passive and hyperfocused than children with ASD without epilepsy.[2,7,26] Studies have also suggested that SEDs are associated with more severe speech and intellectual impairment in children with ASD.[25,27,28] In addition, individuals with ASD and epilepsy tend not to have a family history of epilepsy unlike idiopathic epilepsy, but have a broad phenotype of ASD in the family.[25]

Table 1. Characteristics of individuals with ASD and seizures as compared to individuals of the same group with ASD without seizures.

Children
Similar number of Males and Females Affected
More likely to have
Co-morbid medical conditions
Developmental Delays
Cerebral palsy
Mental retardation
Less like to have/be
Poor eye control
Aloof
Passive
Adults
More likely to have:
Psychotropic medications prescribed
Lower intelligence
Lower adaptive behavior
Lower social maturity

Several neuroimaging studies have examined individuals with ASD and epilepsy. The most well-known related structural brain abnormalities related to ASD are those associated with tuberous sclerosis, particularly if the cortical tubers are located in the temporal or insular areas.[29,30] Specific structural abnormalities, including abnormal gray and white matter volumes and maturation as well as disruptions in neuronal migration, are common to both epilepsy and ASD[31] and neuroimaging abnormalities appear to be associated with treatment-resistant epilepsy in individuals with ASD.[32] Functional neuroimaging with single-photon emission computed tomography has demonstrated a mixed pattern of hyperperfusion and hypoperfusion corresponding to epileptiform foci.[33,34]

The diagnosis of autistic epileptiform regression (AER) describes the association between autistic regression and seizures or SEDs.[35,36] The evidence for AER as a clear clinical entity is inconsistent. Some studies suggest that clinical seizures and/or SEDs are more prevalent in children with regression,[16,37,38] as compared to children without regression but other studies have not verified this finding.[17,36] One study found that children with AER had lower intellect and that regression occurred either later (> 24 months) or earlier (< 18 months) in AER as compared to ASD children with regression but not AER.[37]

A few studies have examined whether children with ASD and SEDs have the same level of disability as children with ASD and clinical seizures. In a rather large study death rates were 8.3 times higher for ASD individuals with epilepsy as

compared to those with ASD but no epilepsy.[38] Another study demonstrated that, by far, seizures were the highest factor affecting standardized mortality for individuals with ASD, both with or without intellectual disability. Interestingly, these high rates almost exclusively occurred Parmeggiani et al[24] divided 345 children with ASD into three groups: those without epilepsy or SEDs, those with SEDs but not epilepsy and those with epilepsy. Children with SEDs were more likely to have autistic regression, an abnormal neurological examination and cerebral lesions than children without epilepsy or SEDs but not children with epilepsy, suggesting that the children with SEDs but not epilepsy are similar to the children with epilepsy on measures of neurological disability. In a study of 205 children with ASD, children with AER and epilepsy but not those with only SEDs without epilepsy, were more likely to be intellectually impaired.37 Similarly, in a small study of children with ASD, children with epilepsy demonstrate lower scores on the socialization and daily living scales of the Vineland Adaptive Behavior Scale and higher levels of hyperactivity on the Aberrant Behavior Checklist as compared to children with SEDs but not epilepsy or ASD controls.[39] These studies suggest that factors related to the underlying neuropathology may be shared between children with epilepsy and those with SEDs without epilepsy but that children with epilepsy may have greater cognitive and behavioral impairments than those with SEDs without epilepsy. Clearly further research is needed to characterize these ASD subgroups. Such research could help in the understanding of the neurological basis of cognitive and behavioral impairment in ASD.

Epilepsy might have more serious consequences than other co-morbid medical disorders associated with ASD. For example, in California during 2007 and 2009, crude after 20 years of age.[40] This is consistent with studies that find an age related increase in epilepsy prevalence in individuals with ASD, signaling that the long-term study of epilepsy and seizures in ASD individuals is an important area of future research, especially for adults with ASD.

3. SEIZURE TYPES

Children with ASD are unique in the variety of common and uncommon types of seizures and epilepsy. Every clinical seizure type has been noted in ASD[2,41] but there is no consensus on the most prevalent seizure type. Different studies have suggested that different seizures are the most prevalent, including complex partial, atypical absence, myoclonic and tonic-clonic seizures,[42] generalized tonic-clonic and atypical absence seizures,[41] generalized tonic-clonic,[25] complex-partial seizures with centro-temporal spikes[43] and partial and partial-complex seizures.[4,44] Although clinical motor seizures are prevalent in ASD, non-motor seizures are probably also prevalent, although the prevalence of such subtle paroxysm has not been studied in detail in individuals with ASD.

Few studies have compared the characteristics of seizures in children with ASD to the characteristics of seizures in typically developing children. Matsuo et al[45] found that 42% of 86 patients with childhood-onset cryptogenic partial

complex epilepsy carried the diagnosis of ASD. Children with ASD, as compared to those without ASD, had more frequent seizures that were less likely to remit over time, but the seizures were less likely to generalize. Frontal discharges were more frequently found on EEG in the ASD group as compared to the non-ASD group.[45]

3.1. The Importance of the Temporal and Frontal Lobes

Epileptiform disturbances in the temporal and the frontal lobes are associated with abnormalities in language, social interactions and behavioral regulation - core ASD symptoms. Below we review studies that highlight the brain-behavior correlations of temporal and frontal lobe epilepsy and ASD.

3.1.1.   Temporal Lobe Epilepsy
The temporal lobes are essential for language and social function.[46] Disorders associated with temporal lobe seizures have been associated with ASD. For example, temporal lobe tubers associated with Tuberous Sclerosis, which are epileptogenic, are associated with the development of ASD.[30,47] Language and social skills fail to develop in epilepsy syndromes that affect the temporal lobes and start early in life such as in infants with bilateral hippocampal sclerosis or bilateral temporal lobe hypoplasia[48,49] and in children with cortical dysplasia-focal epilepsy syndrome with focal dysplasias in the temporal lobe.[50] Epileptiform disturbance of right temporal lobe may be important in the development of ASD features. For example, ASD features have been described in a child with Landau-Kleffner Syndrome (LKS)-like syndrome and a right temporal ganglioglioma.[51] Children with ASD and temporal lobe epilepsy are more likely to have right temporal lobe lesions[52,53] and, within children with ASD, right temporal lobe EEG abnormalities appear to be associated with abnormal prosody.[54] However, epileptiform disturbances in the left temporal lobe are not specifically related to ASD as frequent left temporal lobe SEDs seen in LKS are not associated with ASD features.[18]

Overall, these data suggest that temporal lobe abnormalities may be related to the development of ASD features. Further research is needed to determine whether it is the age of onset of temporal lobe disturbances or right temporal lobe disturbances specifically that are associated with ASD features in individuals with epilepsy. In addition, many reports of ASD features in individuals with temporal lobe epilepsy note comorbid structural lesions, so it is not clear whether structural abnormalities of the temporal lobe are needed in addition to seizures in order to develop ASD features.

3.1.2.   Frontal Lobe Epilepsy
Patients with frontal lobe epilepsy demonstrate behavioral abnormalities similar to those seen in individuals with ASD, including echolalia, stereotypic motor movements, motor coordination and planning deficits, reduced attention span, and difficulties with response inhibition.[55] In addition, children with frontal lobe epilepsy present with seizures that manifest as ASD type behaviors, including labile mood, sudden agitation, unexpected quietness, subtle change in

awareness, and repetitive and stereotypic movements.[56] Individuals with frontal lobe epilepsy have non-behavioral symptoms that are commonly found in ASD such as deficits in the appreciation of humor, perception of facial expression and eye gaze expression.[55] In addition, SEDs are more frequent in the frontal regions in children with ASD.[57] These data may suggest that frontal epileptiform disturbances can result in ASD-type behaviors and could have a relationship to the pathogenesis of ASD in children with ASD and seizures or SEDs.

4. SUBCLINICAL ELECTRICAL DISCHARGES (SEDS)

In order to gain an understanding of the clinical significance of SEDs in ASD, the association of SEDs with epilepsy and neurodevelopmental disorders is discussed. For the most part, the significance of SEDs is poorly defined, not so much because they have not been studied, but because their significance in relation to cognition and behavior is complex. Some of the strongest evidence that SEDs might have a significant effect on cognition is derived from the phenomenon of electrical status epilepticus during sleep (ESES). ESES is a disorder where frequent SEDs result in a marked regression in language, cognition and behavior that is reminiscent of ASD. Since ESES can be used as a model to understand the effect of SEDs on cognitive development, ESES is discussed first. We then discuss the studies that have examined whether SEDs adversely impact cognition in non-ASD populations. Lastly, we discuss the potential impact of SEDs on the cognitive and behavioral abnormalities associated with ASD.

4.1. Electrical Status Epilepticus during Sleep

ESES is often used as a model to understand AER and SEDs in ASD. In fact, children with ESES are sometimes diagnosed as having ASD. ESES is an EEG pattern in which epileptiform discharges occur during a significant proportion of sleep. ESES is comprised of two epilepsy syndromes, LKS and Continuous Spike-wave Activity during Slow-wave Sleep (CSWS).

In classic LKS (also known as acquired epileptiform aphasia), language, social and cognitive development is normal until approximately 5 years of age when children experience severe language regression without regression in non-linguistic skills.58 The EEG of children with LKS is characterized by frequent SEDs in the left temporal lobe, primarily during sleep. It is believed that the frequent SEDs disrupt the left perisylvian neural networks responsible for language.[18,59] Despite the very frequent SEDs, 25% of LKS patients never develop clinical seizures. Although LKS is similar to regressive-type ASD in that its onset is herald by the loss of previously acquired language skills, the language regression associated with LKS typically occurs later in childhood (i.e., after three years of age) as compared to children with autistic regression (i.e., typically in the second year of life). In addition, since children with LKS only have regression in language skills, they do not meet the criteria for ASD. Despite these differences, it is easy to see that LKS can be used to understand how SEDs can disrupt developing

neural networks that support cognition. Of course, given that the cognitive disturbances in ASD affect many cognitive areas, one would suspect that epileptiform discharges associated with ASD behavior would affect more regions of the brain than just the left temporal lobe. As we will discuss below, SEDs abnormalities associated with ASD have a more widespread pattern in the brain.

CSWS is associated with an abrupt regression of previously acquired skills, usually after 3 years of age, with more severe intellectual and behavioral impairments as compared to LKS. Children with CSWS do not always have ASD, but children with a frontal variant of CSWS frequently have ASD features.[60] Children with an onset of ASD features along with ESES are more commonly diagnosed with CSWS rather than LKS. Tuchman[61] points out that the age of onset of LKS and CSWS is older than the maximal age for the diagnosis of autistic disorder and, thus, the diagnosis in such cases is more consistent with childhood disintegrative disorder, a separate ASD diagnosis in which regression in skills occurs after 3 years of age. However, at least one study has reported that 20% of ASD children with late-onset epilepsy manifested CSWS on EEG.[62] Nevertheless, studies that have reviewed the prevalence of EEG abnormalities in children with ASD failed to report a high prevalence of CSWS or traditional LKS, supporting the idea, that, in general, ESES is probably rare in ASD.

4.2. Subclinical Electrical Discharges and Cognitive Function

In this section, studies that examine the cognitive effects of SEDs will be discussed in order to illustrate the evidence associating SEDs and cognitive deficiencies. Controversy regarding the cognitive impact of SEDs has been ongoing for decades. Some of this controversy stems from the fact that SEDs are seen in 2-3% of typically developing children without epilepsy[15] and that children with benign rolandic epilepsy of childhood (BREC), a syndrome with very frequent SEDs in the centrotemporal region of the brain, are not generally believed to have cognitive problems. However, over the last two decades evidence has been growing that SEDs in some children with BREC are associated with cognitive dysfunction.[63-65] This evidence is discussed in Section 5.2.1. In addition, the growing evidence for the detrimental cognitive effects of SEDs in childhood epilepsy is reviewed in Section 5.2.2. Evidence supporting the association between SEDs and cognitive impairments in non-epileptic children, especially in children with neurodevelopmental disorders, is discussed in Section 5.2.3. Lastly, the evidence for the significance of SEDs in ASD is reviewed in Section 5.2.4. Overall, we believe that the evidence presented provides support for the idea that SEDs may contribute to abnormal cognition and behavior in a wide variety of neurodevelopmental disorders, including children with ASD.

4.2.1. Subclinical Electrical Discharges in Benign Rolandic Epilepsy of Childhood

Children with BREC have frequent SEDs originating from the rolandic fissure and centrotemporal brain areas. The

rolandic fissure separates the primary motor and sensory strips of the cortex. Hence seizures in BREC sometimes involve focal motor or somatosensory manifestations. Clinical seizures in BREC are often mild, focal, occur during sleep and occur infrequently despite frequent SEDs. In the large majority of cases, the seizures resolve with age. Because of the low morbidity and excellent prognosis, this syndrome is considered, for the most part, benign.

Interestingly, the first report of developmental cognitive disturbances in children with BREC dates back almost 40 years. In a small case series, Beaumanoir et al described cognitive dysfunction in several children with BREC.[66] More recent reports have provided wide estimates of the prevalence of cognitive dysfunction in children with BREC. Indeed, prevalence estimated range from 9%[67] to 65%[68] with the specific cognitive disturbances documented across studies ranging widely and including problems with speech, reading, comprehension, spelling, attention, memory, fluency and visual-motor coordination.

Many authors have questioned whether SEDs in children with BREC are directly related to cognitive dysfunction. Demonstrating cognitive dysfunction in individuals with BREC does not provide a causal link between SEDs and cognitive dysfunction. Indeed, other psychological and physiological explanations for the cognitive abnormalities associated with BREC have been suggested. Learning and behavioral abnormalities have been attributed to parental overprotection[69] and sleep fragmentation as a result of frequent SEDs during sleep.[70] In order to link SEDs in BREC to cognitive disturbances, studies have taken several approaches, including examining the correlation between the SED location and cognitive disturbance, measuring cognition during periods of active SEDs vs no SEDs in the same children, and associating the SED severity and the effect of treatment with cognitive performance. The most relevant studies are reviewed below.

Studies have followed the cognitive and behavioral outcomes of children with BREC and SEDs longitudinally. D'Alessandro et al found that children with active SEDs manifested subtle cognitive delays when they were young but that these delays resolved when the children were free of seizures and SEDs for 4 years.[71] Metz-Lutz et al[72] found that over half of children with BREC demonstrated problems with memory, attention and learning within the first 6 months of the onset of their first seizure. When retested 18 months later, the children whose SEDs completely resolved demonstrated better cognitive performance than the children who still continued to show SEDs. Other studies have failed to find a relationship between SED improvement and the resolution of cognitive problems in children with BREC.[73]

A confounding factor that can affect cognitive performance in children with epilepsy is antiepileptic drug (AED) treatment. Children with more active epilepsy or SEDs are more likely to receive AED treatment than children with resolved epilepsy. At least one study has demonstrated improvements in cognitive performance as a consequence of

AED treatment in children with BREC. Baglietto et al[74] found that AED treatment resulting in SED improvement during sleep was associated with improvement in neuropsychological measures of intelligence, short-term memory and attention.

Studies have linked the location of SEDs to specific cognitive limitations in children with BREC. In an early small study, Beaumanoir et al[66] found that left hemisphere SEDs were related to poor performance on a recognition test while right hemisphere SEDs were related to poor performance on the Bender test, a test of visual motor coordination. Piccirilli et al[75] compared 14 children with left-hemisphere SEDs to 8 children with right-hemispheric SEDs on a verbal repetition-finger tapping interference task. This interference task revealed that children with left-hemispheric SEDs had evidence of language processing in the right-hemisphere suggesting atypical language lateralization. D'Alessandro et al found that attention, language, and visual motor coordination were worse in children with BREC with bilateral SEDs than those with only right- or left-hemispheric SEDs.[71] Piccirilli et al[76] compared 14 children with left-hemisphere SEDs, 14 children with a right-hemisphere SEDs, 15 children with bilateral SEDs and 15 control children on a cancellation task that required high attention demands; children with right-hemisphere and bilateral SEDs performed worse than children with left-hemisphere SEDs and controls, suggesting that SED disturbances of the right-hemisphere interfered with attention control. Some have not found associations between lateralization of SEDs and specific cognitive disturbances.[77]

Studies have also used MEG, a technique which provides better spike localization than an EEG, to investigate whether the cortical location of SEDs in children with BREC were related to specific cognitive disturbances. Using MEG Wolff et al[78] demonstrated that SEDs in the left perisylvian area were related to lower performance on language tests whereas SEDs in the occipital cortex were associated with lower performance on tests involving visual transformation.

Studies have also linked the frequency and severity of SEDs with cognitive dysfunction in children with BREC. Weglage et al[79] found that children with frequent SEDs demonstrated lower full-scale and performance intelligence quotients that children with less frequent SEDs. Staden et al[68] found that a higher percentage of children with language problems had very frequent SEDs as compared to those without language problems and Fonseca et al[80] demonstrated that children with reading problems had more frequent SEDs than those without reading problems. Northcott et al[77] demonstrated that the frequency of SEDs during drowsiness or sleep correlated with phonological, word association, memory and attention skills. Others have not been able to link the frequency of SEDs to cognitive function.[81]

Thus, although the SEDs seen in children with BREC were once thought to be benign, there is ample evidence that these SEDs may be related to co-morbid problems in language, attention and cognition. Studies have demonstrated

improvement in cognition with resolution of SEDs, and have linked SED lateralization, location and frequency to cognitive deficits in children with BREC. Of course, it is possible that underlying neuropathology could cause both SEDs and cognitive dysfunction, in which case SEDs may simply be a biomarker for such neuropathology. Interestingly, the effect of SEDs on sleep fragmentation is likely to be important, but is poorly studied. Although the effect of AEDs on cognition is a factor that can be hard to control, one study has demonstrated that AED treatment that improves SEDs also improves cognitive function.[74] Clearly, these studies demonstrate that SEDs have an important relationship to cognitive development in children with BREC and deserve more intense study.

4.2.2. Subclinical Electrical Discharges in Childhood Epilepsy

Like BREC, other childhood epilepsies demonstrate SEDs even if they are not considered part of a specific syndrome. Many studies have examined SEDs in children with epilepsy and have demonstrated evidence that SEDs are related to cognitive dysfunction. These studies are reviewed below.

Several studies have associated SED frequency with cognitive defects. Over a 4 year period, Aldenkamp et al[82] examined the performance of 199 children with normal intellect and MRIs and subtle seizures, cognitive fluctuations, or frequent SEDs, including short electrographic seizures, on a computerized cognitive test system. Children with SEDs in > 1% of the EEG during a complex visual motor task performed significantly worse as compared to children that demonstrated SEDs in < 1% of the EEG. Children that demonstrated electrographic seizures on EEG during a task were found to score significantly worse on a wide range of visual motor, language and memory tasks as compared to those children that did not demonstrate electrographic seizures on EEG. Poor performance on cognitive tasks for children with frequent SEDs has been confirmed by other studies. Aldenkamp et al[83] studied children with focal epilepsy with active SEDs as compared to children with focal epilepsy without active SEDs. The children with active SEDs performed worse than children without active SEDs on the computerized visual searching task, but not on standard neuropsychological tests.

Studies have examined the acute effects of SEDs while controlling for the underlying epilepsy diagnosis. In a large well-designed study of factors leading to underachievement in children with epilepsy, Aldenkamp et al[84] found that frequent SEDs were related to decreased vigilance after carefully controlling for epilepsy type and AED treatment. In another study, Aldenkamp and Arends[85] studied 152 children with SEDs with and without epilepsy. While the type of epilepsy and whether or not they had epilepsy contributed to long-term cognitive function, such as educational achievement, the acute effect of SEDs affected more dynamic cognitive processes such as alertness and processing speed. These authors proposed that a persistent disturbance in dynamic cognitive processes over time could have an eventual impact on more long-term cognitive function such

as educational achievement and intelligence.

These data appear to support the idea that SEDs and short electrographic seizures can influence cognitive performance, especially for tasks that require high information processing demands. However, in another study Aldenkamp et al[86] compared children with epilepsy with and without SEDs and those with ongoing subtle electrographic seizures to non-epileptic control children; only the group with ongoing subtle electrographic seizures, but not the children with SEDs, demonstrated problems on intelligence subtests and a test of complex information processing as compared to controls. Thus, this latter study suggests that the electrographic seizures rather than isolated SEDs were responsible for the cognitive disturbances.

The strongest evidence that SEDs can adversely affect cognition in children with epilepsy is provided by studies that show that AED treatment that suppresses SEDs improves cognitive function. Evidence supporting this idea comes from a case series[87] and two double-blind placebo-controlled studies examining the effect of lamotrigine on SEDs and behavior and cognition.[88,89] These studies suggest that cognition and behavior of patients with SEDs can be improved by AED treatment in carefully controlled clinical trials.

Clearly there is evidence that SEDs and electrographic seizures can cause cognitive disturbances in children with epilepsy. Studies have demonstrated that active SEDs are associated with poor performance on visual tasks including visual motor and visual search tasks, attention processes including vigilance and alertness as well as processing speed. In contrast, electrographic seizures appear to be associated with more profound cognitive disturbances, including performance problems on intelligence testing and complex information processing tests.

Probably some of the most compelling evidence that SEDs are related to cognitive dysfunction is from clinical-trials that demonstrated improvement in cognitive and behavior with AED treatment. These studies also suggest that long-term cognitive outcomes including intelligence and achievement might be related to the underlying neuropathological processes that more directly related to epilepsy including persistence disturbances of SEDs over time. However, these studies fall short because they have not correlated the cortical location of the SEDs or electrographic seizures with the particular cognitive deficits. Clearly the studies reviewed in this section suggest that SEDs are associated with cognitive disturbances in childhood epilepsy and deserve closer consideration and study.

4.2.3. Subclinical Electrical Discharges in Neurodevelopmental Disorders

There is a surprisingly high prevalence of SEDs in children with neurodevelopmental and/or neurobehavioral problems that do not manifest clear clinical seizures. Such problems include attention-deficit disorders,[90,91] selective mutism,[92] dyslexia,[6] learning difficulties[6,93] as well as non-specific

cognitive and behavioral problems including unexplained cognitive fluctuations,[6,82] sudden decline in school performance,[94] and behavioral regression.[36] Rather than ask whether SEDs are present or not in specific neurodevelopmental syndromes, Frye et al[6] examined the clinical characteristics of children with SEDs and neurodevelopmental disorders. In general, it was found that almost all of the children had a history of expressive-receptive language disorder and a substantial number of children had features of attention deficit-hyperactivity disorder and ASD although they frequently did not fulfill full criteria for either disorder.

Interestingly, it is not clear whether the cognitive and behavioral problems found in children with epilepsy and SEDs are any different than children with SEDs without epilepsy. For example, Weglage et al[79] found no difference between 20 children with SEDs and partial seizures as compared to 20 children with SEDs without seizures on a broad range of neuropsychological tests even though both groups performed worse than age, sex and socioeconomic matched controls.

It is not clear that SEDs are consistently localized to a certain focal brain area in neurodevelopmental disorders. For example, both focal and generalized SEDs were found in equal number in patients with attention-deficit disorders.[91] In another study, Frye et al[6] found that SEDs changed lateralization from EEG study to EEG study in the majority of cases, suggesting that SEDs were multifocal.

The strongest evidence that SEDs can adversely affect cognition in children with neurodevelopmental disorders can be derived from treatment studies. Evidence supporting this idea comes from case series[6,92,95] and an open-label clinical trial.[96] A small double-blind placebo controlled cross-over trial did not support this notion but used supratherapeutic valproic acid levels for treatment thereby potentially resulting in adverse cognitive effects from the AED treatment.[97]

Overall, it is clear that there is evidence for the existence of SEDs in various neurodevelopmental disorders. However, unlike the studies on SEDs in epilepsy, there is a lack of systematic study of the specific cognitive effects of SEDs, although one study suggests that there is a very high rate of expressive-receptive language disorder associated with SEDs in individuals with neurodevelopmental disorders. The few studies that have looked at cortical localization for these discharges seem to suggest a multifocal or generalized discharge pattern. Evidence to support the notion that AED treatment improves cognition is somewhat mixed but generally supportive, although more rigorous studies are needed. Further systematic studies are needed in children with neurodevelopmental disorders. The mixed results from treatment studies may suggest that the therapeutic dose window for AEDs may be narrower for children with neurodevelopmental or neurobehavioral disorders without epilepsy as compared to those with epilepsy. Clearly further research will be required to answer these important questions.

4.2.4. Subclinical Electrical Discharges in Autism Spectrum Disorder

Children with ASD may have a specific distribution of SEDs. Yasuhara[98] reviewed 1014 ASD patients, 37% with a diagnosis of epilepsy, that had sleep EEGs approximately every 6 months for at least 3 years. SEDs were found in 86% of patients with about two-thirds of these discharges located in the frontal lobes. Other studies examining children with ASD have also reported high rates of SEDs localized to the frontal lobes[44] (~ 50%) but other researchers have found high rates of SEDs in the central and temporal areas.[24] However, this latter study excluded patients with multifocal discharges from their analysis.

The cortical distribution of SEDs may be related to whether a child has the diagnosis of LKS, pervasive developmental disorders-not otherwise specified (PDD-NOS) or autistic disorder (AD). Using MEG, Lewine et al[18] compared SEDs in children with classic LKS to children with regressive-type ASD, including PDD-NOS and AD. The primary source of the SEDs was the left peri-Sylvian area for patients with classic LKS. While some children with regressive-type ASD also demonstrated primary generators of the SEDs within the left peri-Sylvian area, similar to the LKS patients, they also had SEDs outside the left peri-Sylvian area, thus demonstrating a multifocal pattern of SEDs. The distribution of SEDs was related to the ASD diagnosis. Children with PDD-NOS demonstrated SEDs in both the left and right peri-Sylvian areas while children with AD demonstrated SEDs in the frontal lobes in addition to the peri-Sylvian areas. This distribution of SEDs should not be surprising as temporal lobe epilepsy (see **Section 4.1.1**) is associated with problems in the development of language and social skills while frontal lobe epilepsy is associated with ASD-type behaviors (see **Section 4.1.2**). The patterns outlined by Lewine et al[18] also suggest that severe ASD symptoms (i.e., AD) are associated with more widespread SEDs (both frontal and bilateral peri-Sylvian) than those with less severe ASD symptom (i.e., PDD-NOS) that appear to have less widespread SEDs (bilateral peri-Sylvian).

The neurophysiological, cognitive and behavioral effect of AED treatment on children with ASD and SEDs has not been well studied. Two open-label studies noted a high rate of SED improvement with AED treatment[6,17] but did not measure effect on cognition or behavior. One study demonstrated amelioration of ASD symptoms with AED treatment in 8% of 72 individuals with ASD and childhood-onset partial complex seizures but the study did not examine SEDs.[44]

Some clinicians have described ASD children with SEDs as having "atypical LKS." However, characteristic of ASD children with SEDs are distinct from classic LKS, suggesting that SEDs associated with ASD should not be described in reference to LKS and that the "atypical LKS" diagnosis is probably not valid for children with ASD.[35] For example, children with LKS primarily have isolated language regression without ASD symptoms, regress after 3 years of age and have SEDs isolated to the left peri-Sylvian region.

Such a notion is consistent with the MEG study by Lewine et al18 which demonstrates that the SED pattern in PDD-NOS and AD is distinct from those with classic LKS as the ASD groups tend to have a multifocal SED pattern that includes SEDs outside of the left peri-Sylvian region. This suggests that another diagnosis specific to children with ASD and SEDs needs to be developed.

Unfortunately there are only a handful of studies on SEDs in ASD. It is clear that a significant proportion of children with ASD manifest SEDs and children with ASD appear to have a particular multifocal SED pattern. Limited uncontrolled studies support the beneficial effects of AED treatment on children with SEDs and ASD. No study has examined the effect of AEDs on cognition and behavior in children with ASD and SEDs. Since other studies have demonstrated favorable cognitive and behavioral effects of AED treatment in children with SEDs and epilepsy and other neurodevelopmental disorders, it is probably wise to study AEDs treatment in children with ASD and SEDs in a controlled fashion in the near future.

5.3. The Significance of Subclinical Electrical Discharges in Autism Spectrum Disorder

While SEDs can result in cognitive disturbances, it is possible that the underlying neuropathology that causes the SEDs can also result in the same cognitive disturbances. Even if strong evidence existed that treating the SEDs resulted in cognitive improvement, it is highly probable that underlying neuropathology co-exists and contributes to the ASD symptoms and SEDs. This view emphasizes that treatment of SEDs may only be part of the treatment solution. Deonna and Roulet[35] provide a nice discussion of the possible relationships between SEDs and the cognitive defects manifested in ASD. As they discuss, neuropathology that results in ASD could trigger epilepsy or epilepsy could arise independently as a result of the neuropathology. Epilepsy (and presumably SEDs) could aggravate ASD symptoms, interfere with the development of specific brain networks involved in communication and social behavior and/or cause specific sensory or cognitive dysfunction. Thus, epilepsy (and presumably SEDs) could work in concert with the neuropathology causing ASD to substantially impair cognitive function and, presumably, recovery. Further research is needed to determine the extent to which clinical epilepsy, SEDs and underlying neuropathology contributes to the development of ASD symptoms. Clearly this is a ripe area for further research and a potential avenue for providing treatments that can, at least in part, reduce or alleviate some of the cognitive and behavioral symptoms associated with ASD.

6. SUMMARY

Seizures, epilepsy and EEG abnormalities are highly prevalent in individuals with ASD. The prevalence is related to underlying comorbid medical and intellectual disabilities that are commonly found in children with ASD. The risk of seizures and epilepsy increases with age in individuals with ASD. Adults with ASD and epilepsy may have more severe comorbid medical, behavioral and cognitive problems than adults with ASD who do not have epilepsy. Seizures are a leading cause of mortality in adult with ASD. This provides significant evidence that seizures are both important in individuals with ASD and require further study, especially in adults with ASD.

Almost every type of seizure has been reported to occur in individuals with ASD but many reports suggest that complex partial seizures are the most prevalent seizure type in individuals with ASD. Individuals with ASD also have a high prevalence of electroencephalographic epileptiform abnormalities, which we refer to as subclinical electrical discharges (SEDs). It may be that individuals with ASD have a unique multifocal distribution of SEDs that includes the temporal and frontal cortical areas. The significance of SEDs and their relation to the underlying neuropathology is not well studied, but evidence from studies on individuals without ASD suggests that SEDs could cause or worsen cognitive and behavioral symptoms associated with ASD, and that treatment may be beneficial. Further research is needed in this area.

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