

# Epilepsy and Autism Comorbidity – Up-To-Date Review

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**Abstract:** *This article aims to present an up-to-date viewpoint regarding epilepsy and autism comorbidity. Extensive research in neurobiology and genetic studies have showed significant proof of a common foundation of genetic factors and pathophysiological pathways in both, epilepsy and autism. We present some clinical implications regarding evidence-based approaches to diagnosis and management in patients with this comorbidity. Methodology: The authors have reviewed multiple studies and articles authored by experts and respected scientist in the field up to the year 2015. These consist in genetic, neurobiological, neuropathophysiological, and electroencephalographic studies combined with clinical data. Clinically-oriented results and implications were extracted and used to present practice recommendations with the strongest evidence support. A detailed list of the material used can be found in the reference sector. The correlation between ASD, neurologic dysfunction and epilepsy suggests an underlying encephalopathy presenting with a combination of neurologic abnormalities, including clinical epileptiform activity. The estimated rate of comorbidity varies between 20–25% of the whole spectrum. Several biological pathways appear to be involved in both disease processes, including gene transcription regulation, cellular growth, synaptic channel function, and maintenance of synaptic structure. The American Academy of Neurology and the Child Neurology Society practice parameters state that there is inadequate evidence to recommend an EEG study in all individuals with autism. In the absence of clinical epilepsy, treatment of EEG epileptiform activity with AEDs has not been demonstrated to reverse the symptoms of ASD.*

**Keywords:** epilepsy; autism; co morbidity; Electroencephalography; Fragile X syndrome; tuberous sclerosis complex

## 1. Introduction

Epilepsy in autism spectrum disorders has been the subject of increasing interest and it is one of the additional problems to be dealt with in these patients. The association between epilepsy and autism has been extensively described and documented during the past decade due to its therapeutic approach and clinical importance. The rate of comorbidity varies depending upon the age and type of disorder and currently the conservative estimate of comorbidity cases is 20–25% of the whole spectrum. Major risk factors for seizure occurrence are mental retardation and additional neurological disorders, as well as some specific associated medical conditions. (1)

The association between autism and specific epileptiform electroencephalography (EEG) abnormalities is not firmly established; neither is the prevalence of epileptiform abnormalities in the broader range of pervasive developmental disorders (PDDs).

There is an increased prevalence of both epilepsy and abnormal potentially epileptogenic activity in children with PDDs. About 10% of children given a diagnosis of autism are found to have either a paroxysmal EEG pattern, as seen in acquired epileptic aphasia (Landau–Kleffner syndrome), or electrical status epilepticus during sleep, as seen in some children with childhood disintegrative disorder. (2)

The correlation between ASD, neurologic dysfunction and epilepsy suggests an underlying encephalopathy presenting with a combination of neurologic abnormalities, including clinical epileptiform activity. Other lines of evidence suggest that epilepsy itself is a risk factor for autism, independent of other central nervous system dysfunction. For example, among children with tuberous sclerosis complex, seizures, especially infantile spasms, are an

independent risk factor for autism, suggesting a specific pathophysiologic role for epilepsy in development of ASD (3). However, the mechanisms responsible for increased seizure susceptibility in ASD are largely unknown. Clues to neural hyperexcitability in the autistic brain might be derived from disorders in which single gene mutations cause both epilepsy and an autistic phenotype, such as fragile X syndrome and tuberous sclerosis complex. (4)

## 2. Electroencephalographic (EEG) findings in ASD

All types of seizures have been detected in autism with some differences emerging in relationship to the population examined. Simple and complex partial seizures, atypical absences, tonic-clonic and myoclonic seizures have all been reported. There is no specificity to seizure type to be expected in children and adolescents with autism. Thus, the clinical approach is essential in recognizing any of these types of epileptic disorders. (1, 5, 6)

Requesting EEG studies for children with autism only, is not routine practice. EEG is not recommended in the practice parameters for autism, either by pediatricians or by the Psychiatric Associations of America, unless there is evidence of clinical seizures or regression or a high index of suspicion for epilepsy. (2)

While normal EEGs are frequently seen, multiple types of EEG abnormalities have been described in patients with ASD, especially focal spikes. In early EEG-autism studies the definition of EEG “abnormality” was broader than currently accepted and included not only epileptiform features (e.g., spikes and spike-wave discharges) but also less clearly abnormal features such as “diffuse theta” “low-voltage fast” and “amorphous background”. (7)

Recent EEG studies of children with ASD, using contemporary definitions of abnormality, especially paroxysmal epileptiform activity (spike, spike-wave, poly-spikes, and poly-spikes and waves), support earlier observations although with a lesser prevalence. It is notable that there are often focal epileptiform abnormalities reminiscent of localization related epilepsy, including benign focal epilepsies of childhood.

In 1995, a study of EEG findings in 106 people with autism ranging from 3 to 31 years of age noted that the majority (57.5%) had neither epilepsy nor “paroxysmal activity” (that is, epileptiform activity). (8) However, a history of epilepsy was not necessary for the presence of EEG abnormalities. Twenty (18.9%) did not have seizures but did have focal spikes primarily in central, parietal, and temporal regions including central temporal spikes in nine, as seen in benign epilepsy of childhood with central-temporal spikes (BECTS). They also noted photo paroxysmal activity in several patients.

Another study reported EEG results in 42 children with developmental disorders consistent with ASD, none of whom had a history of epilepsy. (9) Occipital spikes like those seen in benign occipital epilepsy of childhood were seen on video-EEG monitoring in seven cases (17%).

Others have noted a significant incidence of centro-temporal spikes in autistic children without language regression, independent of the presence of epilepsy. (10)

Approximately one-third of children with ASD present as toddlers or preschool children with insidious regression in language, behavior, social, and play skills, that is, autistic regression. A smaller percentage of autistic children will experience late severe regression, usually between 2 and 10 years, defined as disintegrative disorder. The high frequency of associated focal EEG abnormalities suggests a link between abnormal brain electrical activity and autistic regression. (11)

Several explanations for this concurrence have been suggested: (12)

- The two conditions are independent.
- The epilepsy and ASD are both different clinical manifestations of the same brain pathology (e.g., fragile X syndrome).
- Epilepsy or related process occurring early in development interfere with developing function of the brain, in the case of ASD, focused on brain networks associated with communications and social function (e.g., West syndrome)
- Focal CNS pathology that affects limbic systems can produce ASD and trigger epilepsy which in turn aggravates the autistic symptoms (e.g., hamartomas in tuberous sclerosis).
- Epilepsy or an “epileptic process” produces a specific sensory or cognitive dysfunction with “autistic withdrawal” in a “vulnerable child.”

### **Neurobiological and pathophysiological co-occurrences in disorders with overlapping epileptic and autistic features. (Fragile X-syndrome, Tuberous Sclerosis Complex, Rett Syndrome)**

There is an increasing recognition of clinical overlap in patients presenting with epilepsy and autism spectrum disorder (ASD), and a great deal of new information is available regarding the genetic causes of both disorders. The risk of epilepsy is increased in both idiopathic and syndromic forms of ASD, suggesting that there might be common pathophysiological alterations that lead to decreased seizure threshold. Several biological pathways appear to be involved in both disease processes, including gene transcription regulation, cellular growth, synaptic channel function, and maintenance of synaptic structure. (13, 14)

Although much of idiopathic ASD is likely to be multi-genetic, a small but increasing proportion of persons with ASD have been identified with specific gene mutations; some single gene defects are associated with both ASD and seizures. For example, *fragile X syndrome (FXS)* is caused by mutation of the fragile X mental retardation 1 (*FMR1*) gene, leading to specific dysmorphic features and mental retardation. Epilepsy occurs in 10–20% of individuals with FXS and tends to be mild, resembling rolandic epilepsy both clinically and electrographically. (23)

Both the learning impairment and seizure propensity in FXS are hypothesized to be related to abnormal regulation of metabotropic glutamate receptor-mediated neurotransmission. (14, 15)

FXS arises when a CGG-repeat tract in the 5' noncoding region of *FMR1* exceeds 200 repeats (i.e., the “full mutation” range), at which point the gene becomes hypermethylated and transcriptionally silent. (4, 16) The absence of the *FMR1* fragile X mental retardation protein (FMRP), is responsible for the clinical phenotype and physical features, which include prominent ears, long face, high-arched palate, macro-orchidism, and hyper-extensible finger joints. (4, 17)

Approximately 85% of males and 25% of females experience cognitive impairment (IQ < 70); nearly all patients have behavioral problems, with males tending to present with attention deficit hyperactivity disorder (ADHD) and aggression, while females are more prone to shyness and social withdrawal. (4, 18)

Individuals with CGG expansions in the pre-mutation range (55–200 CGG repeats) display a range of clinical features, including behavioral and cognitive involvement in childhood and a late-adult-onset neurodegenerative disorder, fragile X-associated tremor/ataxia syndrome (FXTAS). The prevalence of seizures in individuals with the pre-mutation is reported to be more than 20%.

Another disorder in which epilepsy and autism commonly coexist is *tuberous sclerosis complex (TSC)*. In TSC, mutation of *TSC1* or *TSC2* genes involved in the control of cell growth and differentiation (mammalian target of rapamycin (mTOR) pathway) leads to neuropathological lesions (tubers) that are highly epileptogenic and strongly associated with cognitive defects and autism. Recent studies

show promising improvement in seizures and cognitive deficits in TSC animal models when the mTOR pathway is inhibited. (14, 19)

**MECP2-related disorder (formerly Rett syndrome)**  
MECP2-related disorder predominantly affects females and is characterized by intellectual disability, postnatal microcephaly, loss of spoken language and stereotypic hand movements. Onset of symptoms and regression typically occur at 6 to 18 months of age after a period of apparently normal development. Individuals with MECP2-related disorder demonstrate autistic symptoms as well as distinct features that include respiratory rhythm abnormalities, gait impairment, and cardiac complications.

Among individuals with MECP2 deficiency, 50–90% are reported to have seizures. Seizure type is variable, age of onset is rarely before 2 years of age and severity of seizures appears to decline after adolescence. Specific MECP2 mutations (p. T158M and p. R106W) were more highly associated with epilepsy.

MECP2 is primarily a transcriptional activator during brain development. The consequences of mutations in MECP2 include abnormal downstream regulation of multiple gene targets, and loss of MECP2 function reduces GABAergic transmission and impaired glutamatergic drive in specific populations of inhibitory interneurons. There is evidence from mouse models that restoration of gene function reversed some of the neurodevelopmental deficits even after symptoms had emerged. (13)

#### **Evidence-based recommendations: Clinical approach to diagnosis and management. Does it differ from current guidelines used in isolated disorders?**

While the electrophysiologic abnormalities associated with ASD provide insight into the pathophysiology of this group of disorders, the utility of routine EEG in diagnosis has not been demonstrated. The American Academy of Neurology and the Child Neurology Society practice parameter states that there is inadequate evidence to recommend an EEG study in all individuals with autism (20). However, an EEG, in particular a sleep-deprived EEG with appropriate sampling of slow-wave sleep, may be appropriate if there is “a history of clinical seizures or suspicion of subclinical seizures, and a history of regression (clinically significant loss of social and communicative function) at any age, but especially in toddlers and preschoolers.”

No well-designed, controlled trials have defined a role for antiepileptic drug therapy as specific treatment for the symptoms of ASD. In the absence of clinical epilepsy, treatment of EEG epileptiform activity with AEDs has not been demonstrated to reverse the symptoms of ASD. Therapies, such as surgery (including multiple subpial transaction), ketogenic diet and vagus nerve stimulation remain of unproven benefit. (11)

At present, there have been only a limited number of clinical reports on the effectiveness of valproate in reducing hyperactivity, instability and impulsivity in children with autism and abnormal electroencephalograms. (1, 21)

Affective symptoms often add to autistic features and medications with mood stabilizing action may be used. Anticonvulsants are again first line options and they may be used with the double aim of treating epileptiform abnormalities and mood disturbances. It is known that valproate is also recognized as a mood stabilizing agent and its use is on the increase. **In conclusion**, the effectiveness of anticonvulsants as mood stabilizers in children with autism, with and without paroxysmal abnormalities, needs to be clarified. (1,21,22)

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