

Autism and Epilepsy: Practical points that clinicians should aware of

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Typical Clinical Scenarios

Case 1: A 15-year-old high functioning autistic boy with normal IQ was found to have episode of eyes rolling upwards followed by rhythmic body shaking and was unresponsive for 2 minutes. Ten hours after symptom onset, EEG study was performed and reported as normal. One week later, during playing soccer, he had another attack with similar pattern. Physical examination was unremarkable. Second EEG study was normal. He has no history of head injury. Family history was negative for seizure disorder. No developmental regression is mentioned. *Should we prescribe antiepileptic drugs for this child?*

Case 2: A 7-year 2-month-old autistic girl with severe developmental delays who has developed 'bizarre behaviors' described as head nodding and rapid eye blinking during listening to radio over a two week period. During sleep, she sometimes wakes up in the middle of the night and makes loud noises for 10 minutes before falling asleep again. These behaviors are unusual and have never occurred before. Regular medications included risperidone, methylphenidate, and zinc supplements. *Are those 'bizarre, unusual behaviors' epilepsy or just stereotypic movements that are commonly found in autistic children?*

Case 3: A 5-year-old autistic girl with epilepsy. Her seizures (generalized tonic-clonic) are well-controlled by valproic acid. She has had regular rehabilitation and physical therapy for motor and speech delay. Overall milestones are gradually improved. One day after being rebuked by a friend at school, she stopped speaking, not making any sound. However, she is able to follow verbal instruction as usual. Parents are frightened and bring her to pediatrician for proper opinion. *Has she developed language regression? Could this symptom be a subclinical seizure or just a behavioral reaction?*

Case 4: A 10-year-old high functioning autistic boy is brought to clinic due to excessive drowsiness over two weeks. Actually his sleep duration is usually of 6-8 hours a day but has increased to 12-16 hours a day. Teachers have also reported to parents regarding his frequent falling asleep in the classroom. Normally, he is a good disciplined child and is always admired by parents, teachers and friends. Academic performance is average. He is a school tennis athlete. There is neither fever, history of head injury nor drug use during this episode. Physical examination is normal. Blood tests for CBC, electrolytes, sugar, BUN, Cr, liver function, thyroid function, and ammonia level are normal. CT scan of the brain shows negative study. *Shall we consider 'non-convulsive seizure' as the cause of excessive sleepiness in this patient?*

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Outline:

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2. Epilepsy in autism
 - 2.1 Prevalence and risk factors
 - 2.2 Types of seizures in autism
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3. Treatments of epilepsy in autism and autistic regression
4. Conclusion

Introduction

Autistic spectrum disorder (ASD) is the umbrella term for life-long developmental disorders of brain in childhood comprising (1) autistic disorder or classic autism, (2) pervasive developmental disorder, not otherwise specified (PDD-NOS) or atypical autism, (3) Asperger’s disorder, (4) Rett’s disorder, and (5) childhood disintegrative disorder.^{1,2} The three core areas of malfunction of ASD are (i) impairments in social interaction, (ii) impairments in verbal and non-verbal communication and (iii) restricted, repetitive or stereotyped behaviors, interests and activities.³ The prevalence of ASD is considered to be approximately 4 to 10 per 10,000 children from the 1980s and early 1990s, whereas recent studies have reported prevalence of 30 to 50 per 10,000 children.⁴ Highlighted on autistic disorder, the prevalence for classic autism representing the narrow phenotype is 0.1 – 0.3% and 0.3 – 0.6% for the broader ASDs.⁵ Clinical signs of ASD are frequently present at 3 years of age and recent prospective studies in toddlers indicate that abnormalities in social, communication and play behavior that may represent early indicators of autism can be detected as early as 14 months of age.⁶

Recent data indicate that the ‘autism epidemic’ is not real, and definitely not due to vaccines.⁷

Autism has a strong genetic basis and this neurodevelopmental disorder is the most clearly genetically influenced of all developmental disorders, including so-called ‘idiopathic autism’ without known etiology or comorbidity. A number of nuclear and mitochondrial genetic linkages have been identified – proof that different genes cause autism in unrelated affected individuals. Studies suggest that polygenic influences (i.e. multiple interacting genes) together with environmental/gene interactions are responsible for individual phenotypes.^{8,9} In addition to genetic studies, recent work on the immunology of autism suggests that there are specific serum antibodies in mothers of children with autism that recognize prenatally expressed brain antigen.¹⁰ Moreover, abnormalities of synaptic structure and brain function are at the forefront of current investigations of the brain basis of autism. The now well accepted alterations in cortical minicolumns with selective scarcity of gabaergic interneurons may be relevant to hyperexcitability to sensory stimuli, increased seizure susceptibility, and systemic comorbidities in autism.¹¹⁻¹³

Epilepsy in autism

Prevalence and risk factors

Epilepsy is defined as two unprovoked seizures of any type; therefore, febrile seizures (the most prevalent seizure of early childhood) and seizures in the course of acute trauma, infection, or metabolic illness are not classified as epilepsy. The prevalence of epilepsy among all children is estimated at 2 – 3%, compared with some 30% in autism.¹⁴ A bimodal age distribution of seizures is reported in autism. One peak occurs in infancy before age 5 years and the other in adolescence after age 10 years.¹⁵ The severity of cognitive impairment and the presence of cerebral palsy or other motor deficits (Table 1) are the specific risk factors for epilepsy in children with ASD.¹⁶

Table 1: Cumulative probability of development of epilepsy in subgroups of children with autism as a function of age and severity of the underlying brain dysfunction¹⁶

Diagnostic group	Number of cases	Age		
		1 year	5 years	10 years
Autism alone	160	0.02	0.02	0.08
Autism with severe mental retardation but no cerebral palsy	56	0.07	0.16	0.27
Autism with severe mental retardation and cerebral palsy	21	0.29	0.35	0.67

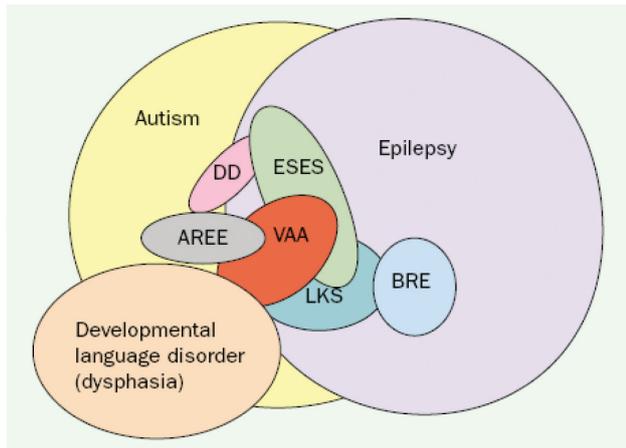


Figure 1: Overlaps between autism with or without epilepsy and other disorders of children with or without language regression. Although an attempt has been made to suggest the relative prevalence of each disorder by the size of its oval, the sizes of the symbols and overlaps should not be taken literally because they were constrained by the need to show the multiple overlaps clearly (e.g., developmental language disorder should be larger, ESES smaller). AREE, autistic regression with an epileptiform EEG; BRE, benign rolandic epilepsy; DD, disintegrative disorder; VAA, verbal auditory agnosia.¹⁴

Types of seizures in autism

All seizure types can be associated with autism. The most prevalent seizure types found in a Swedish study were complex partial, atypical absence, myoclonic, and tonic-clonic seizures, whereas, generalized tonic-clonic and atypical absence seizures were the most common seizure type in a large American cohort.^{16, 17} Overt clinical seizures do not cause difficulty in diagnosis whereas subclinical, known as subtle or nonconvulsive, seizures may present with variety of under-recognized symptoms including complex, bizarre behaviors or unexplained deterioration level of consciousness. These symptoms could be underrecognized, particularly in autistic children with moderate-to-severe developmental delay. Subclinical epilepsy in this population are often overlooked and misdiagnosed. Moreover, until recently, more studies evidence the overlaps between autism with or without epilepsy as shown in Figure 1.

Subclinical epilepsy & autistic regression

The clinical diagnosis of epilepsy in autism is complicated by the fact that subclinical complex absences may be mistaken for other childhood behaviors such as failing to respond to one's name or to participate in an activity introduced by someone else. The unusual repetitive behaviors, such as tic-like movement, common in children with autism can be difficult to distinguish clinically from seizures. For clinicians faced with an autistic child who has no clinical convulsive seizures and an abnormal electroencephalogram (EEG), to prove a link between epilepsy and autism is difficult, especially if there is history of regression and the EEG is epileptiform. Some studies suggest that epileptiform discharges on EEG without clinical seizures can cause behavioral and cognitive impairment.^{18, 19}

In an open trial of valproic acid of 176 children with autism, 80 normalized on EEG and 30 more showed EEG improvement compared with the first EEG.²⁰

This positive outcome offers hope that treatment of these subclinical abnormalities may act to prophylactically prevent future clinical seizure development. However, there is no current consensus on whether treatment of EEG abnormalities may influence development. Commencing anticonvulsant to autistic children with abnormal EEG, particularly in autistic regression, without clinical seizures is still debated and remains unanswered.

EEG findings in autistic patients

Children with autism may have normal EEG patterns that do give leave concern to parents and physicians. Conversely, abnormal EEG finding always raises questions to physicians, regarding definite diagnosis of epilepsy, especially for autistic children who do not have clinical seizures and those with regression.

Descriptions of EEG abnormalities have included not only epileptiform discharges (e.g. spikes, spike and wave, polyspikes, sharp wave discharges) but also less clearly abnormal features, such as "diffuse theta", "low-voltage fast" and "amorphous background" which have been mentioned in many literatures. The fact is that the incidence of EEG abnormalities in nonepileptic children with autism has ranged from 6 to 83% but 46 to 59% with clinical seizures.^{20, 21} The EEG abnormalities include both generalized and focal abnormalities. The epileptiform activity is usually multifocal. Epilepsy is significantly more frequent in autistic youngsters with a history of regression compared with those without regression.²²

The relation of clinical and subclinical epilepsy to autistic behavioral and language regression is intriguing but unresolved. Clinicians should consider investigating with EEGs, particularly children with history of regression, or fluctuations in language function, or new unfavorable behaviors. Several studies suggest that prolonged overnight EEG recordings have the highest yield

Table 2: General frequency of behavioral and psychiatric side effects of AEDs²⁵

AED	Behavioral side effects ^a		Psychiatric side effects ^b	
	Negative behavior	Positive behavior	Depression	Psychosis
Barbiturates (phenobarbital)	+++	-	+++	-
Benzodiazepine	+++	-	-	-
Carbamazepine	+	+++	+	-
Gabapentin	+	-	-	-
Lamotrigine	+	+++	-	+
Levetiracetam	+	+	-	+
Oxcarbamazepine	+	-	-	-
Phenytoin	+	-	-	-
Topiramate	+	+	-	+
Valproic acid	+	+++	-	-
Vigabatrin	+	-	-	+
Zonisamide	+	-	-	++

^a Negative and positive behavior: -, rare or not reported; +, 0-20%; ++, 21-40%; +++, >40%.

^b Psychiatric side effects: -, rare or not reported; +, 1-3%; ++, 4-10%; +++, >10%.

to assess the presence of subclinical epileptiform activity. Although there is controversy as to whether the epileptiform discharges are causally related to the language deficit or regression, the identification of such abnormalities offers possible therapeutic intervention.²³

Treatments of epilepsy in autism and autistic regression

Medical treatment

The treatment of the seizures in autism is neither particularly difficult nor different from treatment of seizures in other children with epilepsy.²⁴ Seizure types, EEG findings, and related illness history will guide neurologist in choosing proper antiepileptic drug (AED). Crucial point of AED selection in autistic children is that clinician should avoid using medication that may aggravate seizure attack. Moreover, adverse effects of some AEDs causing negative behavior or psychiatric symptoms should also be considered.²⁵ (Table 2) There are reports that the language of limited numbers of children with autism or autistic regression has improved in response to anticonvulsants, especially valproic acid, ethosuximide (not available in Thailand), and benzodiazepines.²⁶ Improvements have also been reported in patients treated with corticotrophin, steroids, or immunoglobulins.²⁷⁻³⁰

There are several clinical reports of the use of valproic acid in children with autism with or without clinical seizures but with epileptiform discharges on the EEG.^{20, 31-33} In an open trial of valproic acid, 10 of 14 individuals that completed the trial showed improvement in core symptoms and the associated affective instability, impulsivity, and aggression, and all patients with abnormal EEG or seizure history were rated as responders.³⁴

Surgical treatment

Epilepsy surgery, such as surgical transection of epileptogenic foci, is mostly indicated to patients with intractable epilepsy. A few reports of children with autistic regression and clinical seizures revealed that epilepsy surgery affects positive outcomes for seizure control. Those studies hardly emphasized effectiveness of epilepsy surgery toward autistic symptom.³⁵⁻³⁷ One study stated that both language regression and behaviors were improved by using multiple subpial transections in 12 of 18 children with autistic regression, multifocal epileptiform EEGs, and subtle seizures (e.g. staring episodes, rapid eye blinking) without overt clinical seizures³⁸ However, this study raises the question as to whether the use of such a potentially life-threatening intervention in autistic children who do not have intrac-

table epilepsy is either medically logical and/or ethical. In summary, more systematic studies are required for developing guidelines of surgical treatment among autistic children either with or without clinical epilepsy.

Conclusion

Epilepsy in autism is not uncommon. The prevalence of epilepsy found in autistic children is up to 10 times higher compared with general pediatric population (30% vs. 2-3%). Autism and epilepsy co-occur in some genetic disorders that follow a Mendelian pattern of inheritance. These disorders may therefore share a common neurochemical substrate that is targeted by the psychotropic mechanism of action of several antiepileptic drugs. Diagnosis of epilepsy in autism is sometimes complicated. Convulsive seizures are not difficult to diagnose and clinicians may have no doubt to start antiepileptic drugs. In contrast, non-convulsive (or subclinical) seizure is under-recognized and this condition is often an overlooked diagnosis in children with autism. Autistic children with language regression or new peculiar behaviors cause more difficulty in diagnosis of epilepsy. Moreover, subtle symptoms such as intermittent eye blinking, tic-like symptoms or fluctuation of emotion may cause parents and clinicians to doubt whether those symptoms are indeed real seizures. In such scenarios, investigating with prolonged overnight EEG recording will provide the highest yield in detecting the presence of subclinical epileptiform discharges that may be causally related to language regression or other related symptoms. Despite there being no current consensus on whether treatment of EEG abnormalities may influence development, recent positive outcomes from copious clinical studies are more promising and offer possible therapeutic intervention, such as the option to use AED or corticosteroids. Adverse effect of some AEDs that might create adverse behavior or psychiatric symptom should be avoided.

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Questions of Autism and Epilepsy

- Q1.** Autistic spectrum disorder (ASD) known as pervasive developmental disorder is the umbrella term for life-long developmental disorder of brain in childhood. Which one is not classified into subtype of ASD?
- A. Asperger's syndrome
 - B. Autistic disorder (classic autism)
 - C. Fragile X syndrome
 - D. Childhood disintegrative disorder
 - E. Rett's syndrome
- Q2.** Which subtype of ASD has the highest risk of epilepsy?
- A. Autistic disorder
 - B. Asperger's syndrome
 - C. Pervasive developmental disorder, not otherwise specified (atypical autism)
 - D. Childhood disintegrative disorder
 - E. Rett's syndrome
- Q3.** Parents of a-previously healthy 5-year-old-boy, noticed that he stopped talking for three days without loss of consciousness. There was neither history of school problem, head injury nor taking any medication. On physical examination, he was alert and able to follow verbal instruction appropriately. Otherwise were unremarkable. Investigations including CBC, electrolytes, screening for toxic substances, liver function test normal. Hearing tests and MRI study of the brain were normal. EEG study showed predominantly bilateral temporal (mainly posterior temporal) spikes or spike-wave discharges that are activated by sleep. What is the most likely diagnosis of sudden aphasia of this child?
- A. Autistic regression
 - B. Rett's syndrome
 - C. Conversion disorder
 - D. Landau-Kleffner syndrome
 - E. Depression disorder of childhood
- Q4.** EEG study is a very useful investigation in confirmation of 'subclinical seizures' in patient who do not develop overt convulsive symptoms. Of the children described below, who should we be suspicious that they might have experienced subclinical seizures?
- A. A 10-year-old high functioning autistic boy with intermittent deterioration of language skill for one month.
 - B. A 7-year-2-month-old autistic girl with new unusual behaviors such as head nodding and rapid eye blinking during listening to radio for two weeks.
 - C. A 5-year-10-month-old autistic girl with sudden waking up during the night and mumbling and walking around for 5 minutes before returning to bed. (Parents considered these symptoms as sleep walking.
 - D. A, B, C
 - E. A and C
- Q5.** To avoid adverse reactions affecting negative behavior and psychiatric symptoms, choosing the proper antiepileptic drugs (AED) for autistic children with epilepsy should be strongly considered. Which AED cause less unfavorable behavioral side effects and usually promote positive behaviors?
- A. Midazolam (Dormicum®)
 - B. Valproic acid (Depakine®)
 - C. Topiramate (Topamax®)
 - D. Levetiracetam (Keppra®)
 - E. All of above

Answers of Autism and Epilepsy

Answer 1: C) Fragile X syndrome is a common cause of mental retardation in children. Autistic features occur in about 25% of patients with fragile X syndrome. Patients with the fragile X anomaly often show a different kind of social and communicative deficit, and, in some cases, a distinct pattern of extreme social anxiety. Classic phenotypes of children with fragile X syndrome include long, prominent mandible, large ears, macroorchidism (testicular size more than 30 ml). Other physical signs such as pectus excavatum and hyperextensibility of finger joints could also be demonstrated. Detection of repeated CGG at the 5' end of FMR1 gene at chromosome Xq27.3 by chromosome study, DNA PCR, and/or Southern blot hybridization is useful for diagnostic confirmation.

Answer 2: E) The risk of epilepsy in children with Rett's syndrome is more than 90%. Childhood disintegrative disorder is the second common subtype of ASD that the risk of epilepsy may be as high as 70%. Autistic disorder (classic autism) particularly in autistic regression is reported that the risk of epilepsy is 2 to 10 times higher than general pediatric population. The likelihood for having epilepsy in Asperger's syndrome is 5-10% in early childhood. Pervasive developmental disorder, not otherwise specified (PDD-NOS, or atypical autism) could have epilepsy and the risk of epilepsy is probably linked to the severity of the underlying brain dysfunction.

Answer 3: D) Language arrest or language regression in childhood can occur in isolation, in the setting of a more global autistic regression, or in the acquired epileptic aphasias known as Landau-Kleffner syndrome (LKS). This disorder is commonly found in boys with the ratio of 2:1. LKS typically presents with speech disturbance between the ages of 3 and 8 years in a child who has already developed age-appropriate language production. The onset can be subacute, steady, or stuttering and initially consists of a loss of understanding of spoken language. In severe instances, the child becomes entirely mute and may not respond to nonverbal sounds as well. LKS is characterized by the following: (1) seizures that are relatively easy to treat and self-limited, (2) acquired aphasia, (3) an EEG showing epileptiform discharges, usually over one or both temporal regions, and (4) no definitive brain pathology that can explain the behavioral symptoms and some degree of improvement when the epileptic condition resolves. The key clinical features of this syndrome are loss of language in association with either epileptiform EEG activity or clinical seizures.

Answer 4: D) Diagnosis of subclinical seizures in children with autism is sometimes complicated. Clinicians should consider investigating with EEGs, particularly children with history of either language or behavior regression, or fluctuations in language function, or new unusual behaviors. Subclinical seizures should be initially excluded from sleep disorder; nocturnal frontal lobe epilepsy or temporal lobe epilepsy could be manifested by complex, repetitive behaviors during sleep that hardly distinguish from sleep disorder. Overnight EEG record provides the highest yield in detecting the presence of subclinical epileptiform discharges that may causally related to those symptoms.

Answer 5: B) Valproic acid is a broad spectrum antiepileptic drug indicating in most types of seizure. Besides epilepsy, valproic acid also has two off-label uses: (1) preventing migraine headaches, and (2) treating 'mania' part of bipolar disorder. Moreover, valproic acid could be used in patient with violent behavior and those with movement disorder e.g. Sydenham's chorea. The best-known and most-feared serious reaction is liver failure. This disorder usually occurs within the first 6 months of treatment. The risk of liver failure is much higher in children under 2 years of age, especially if they also take other seizure medicine or already have other serious disorders. Physicians seldom prescribe valproic acid for those with the highest risk. People with liver disease should not take valproic acid. Neither should anyone who has shown an allergy to valproic acid or another valproate medicine in the past.