Chapter

Epilepsy: A Common Co-Morbidity in ASD

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Abstract

ASD and epilepsy, two common co-occurrent conditions, may appear in a developing brain in various genetic and non- genetic syndromes. The fact that multiple genetic and epigenetic factors, metabolic diseases, environmental factors and epileptic encephalopathies are related to the causation of both ASD and epilepsy indicate the presence of some common underlying pathophysiologic mechanisms. Although many questions are yet to be answered, recent studies suggest that synaptic aberrant connectivity and disruption of the delicate balance between neuronal excitation and inhibition (E/I imbalance) leads to various aspects of neuronal dysfunction. The presence of intellectual disability increases the likelihood of co-morbid ASD and epilepsy and all these associations greatly affect the quality of life of these children as well as their families. Therefore, understanding the genetic, cellular and molecular basis of relationship between these common co-morbid conditions is fundamental in planning appropriate and prompt management of these children. Future researches will as such continue to address the pathophysiology underlying the genetic, chromosomal, metabolic-mitochondrial disorders and environmental factors related to these co-morbidities as well as preventing them. Thus, it will lay the base of focused investigations and targeted management in this field.

Keywords: ASD, epilepsy, co-morbidity, intellectual disability, genetics, metabolic

1. Introduction

Autism spectrum disorder (ASD) is a complex neurodevelopmental disorder characterized by deficits in social-communication interaction and restricted and repetitive behaviors [1]. It covers a wide variation in clinical presentation, symptom severity, and cognitive ability. These symptoms are present from early years of life.

Epilepsy is characterized by an enduring tendency to produce epileptic seizures and practically defined as having two untriggered seizures occurring at least 24 hours apart [2]. Associated comorbidities are very common in ASD. Among them, epilepsy is an important medical condition that could affect the lives of persons with ASD. Kanner's original paper in 1943 describing 11 children with "autistic disturbances of affective contact," included one child with history of seizures and abnormal electroencephalogram (EEG) [3]. Since then, the relationship of autism to epilepsy has been an area of interest for scientists for decades.

Association between autism and epilepsy has now been recognized and well established. Prevalence of epilepsy in autism ranged from 5–46% in quite a large number of studies [4–10] which exceeds than that of the general population

(0.6–1%) [11–12]. This wide range is likely due to heterogeneity of groups being studied, particularly with regard to cognitive functioning of the participants, sample age range, sex and inclusion or exclusion of other co-occurring medical conditions [8].

In addition, methodological differences used for diagnosing ASD also lead to these differences in prevalence rate. In the earlier studies, only severe autism associated with a high rate of intellectual disability (ID) and a high rate of epilepsy were included, whereas more recent studies that have used the current broader "ASD" criteria (DSM-5) might lead to a lower rate of ID and a lower rate of epilepsy.

Several factors have been associated with a greater risk for developing epilepsy. Among them, ID is the single most common risk factor. Amiet et al., in a meta-analysis on epilepsy in autism encompassing articles from 1963–2006 demonstrated a relationship between epilepsy in autism with ID and gender. Here epilepsy was present in 21.5% of subjects with autism who also had ID and 8% of subjects without ID [9].

Previous studies in the ASD population have found that idiopathic ASD (i.e., no known cause) had a lower risk of developing epilepsy than those with syndromic autism (i.e., associated with underlying neural/genetic abnormalities) [13]. Pavone et al. found epilepsy in only 7.4% with idiopathic ASD compared to 55% of patients with syndromic ASD [14]. These findings match with the hypothesis that one abnormal neural dysfunction may make the brain more susceptible to another neurological dysfunction [15]. This also supports the hypothesis that epilepsy, ID and ASD may all be the result of a mutual underlying neurological condition. Equally, children with epilepsy also have an increased risk for being diagnosed with ASD [8, 16].

Besides, on average, autistic adults with epilepsy have, less cognitive ability and weaker daily living skills than their autistic peers who do not have seizures [17, 18]. There is also a strong influence on the quality of life and well-being in children with epilepsy.

Because of these facts, clinicians and researchers have worked to understand how epilepsy and ASD can relate to each other. Studying the two disorders in combination may help in understanding their genetic, molecular, and cellular mechanisms that are critical in the field of appropriate management of the both [19, 20].

2. Age of onset of epilepsy

Differing results have been found regarding the age of onset of epilepsy in ASD. Most of the researchers found seizure onset during early childhood [5, 21, 22]. However, Bolton et al. in a long-term follow-up study of 150 individuals with autism, found epilepsy onset in the majority of cases over 10 years and some in adulthood [7], this also agrees with few other studies [6, 23]. While others found, two peaks in the age distribution of seizure onset in autism, one in early childhood and a another in adolescence [13, 24]. Epilepsy persists in adulthood in up to 80%, with remission in about 16% in ASD.

3. Sex

Reports have suggested that females with autism have higher rates of epilepsy than males [6, 8, 13, 16, 22, 25, 26]. Amiet's study reported prevalence of epilepsy, in autistic females 34.5% versus 18.5% in autistic males [9]. Studies have reported a more frequent association of epilepsy in persons with ID than without ID [6, 9]. Since females

with autism tend to have more severe ID compared to males [9, 27], greater ID severity might be a possible cause for this high prevalence of epilepsy in autistic females [28].

4. ID and epilepsy in autism

Intellectual disability (ID), referring to general intelligence and adaptive functioning below −2 standard deviations for population norms, occurs in about 38% of children with ASD [29].

A key concept that has developed during the past 40 years is the strong association between intellectual disability and a higher prevalence of epilepsy in individuals with ASD [25]. Amiet et al. carried out a meta-analysis from published reports between 1963 and 2006 on autism and epilepsy to assess the relative risk of epilepsy in autism with respect to ID [9]. The pooled prevalence of epilepsy with and without ID was highly significant (21.5% versus 8% respectively). This study also highlighted on the association of increasing ID severity on the prevalence of epilepsy in autism [9, 30].

Other authors also have argued that intelligence mediates the relationship between autism and epilepsy [17, 26, 30–34], and lower the intellectual ability, the higher the prevalence of epilepsy and autism. According to Viscidi et al. al, low IQ is the best predictor of epilepsy in children and also commented that the presence of ID can guide prognosis and alert physicians regarding who are at increased risk for epilepsy [6]. A recent study on 6975 children by Jasua et al. with ASD found ID alone as an independent predictor for the increased prevalence of epilepsy [19, 20].

The high rate of co-occurrence of ID, epilepsy and ASD suggests potentially shared underlying mechanisms. All three could result from the same pathophysiologic mechanisms. Therefore, it may be more likely to occur in genetic conditions that lead to abnormal excitability and disrupted synaptic plasticity, such as fragile X syndrome, neuroligin 2 mutations, Rett syndrome, tuberous sclerosis complex, cyclin-dependent kinase-like 5 (CDKL5) mutations, and "interneuronopathies" resulting from aristaless-related homeobox, X-linked (ARX), all of which include ASDs, IDs, and epilepsy [35].

5. Etiology and pathogenesis

The high co-occurrence of autism and epilepsy has led to the speculation that there are some common mechanisms linking these two types of disorders. But a singular *pathophysiological* mechanism responsible for the seizures and autistic phenotype is unlikely. Scientists have stressed mainly upon the genetic factors as the most common contribution for this co-occurrence followed by environmental and metabolic conditions.

Buckley and Holmes have conceptualized ASD and epilepsy both as disorders of aberrant connectivity caused by multiple genetic and environmental factors [36]. Chromosomal abnormalities [37], metabolic conditions [38, 39], environmental factors, e.g., maternal rubella during pregnancy [40], and brain damage via neonatal jaundice are examples that have been recognized as predisposing to both epilepsy and autism [41].

5.1 Genetic factors and syndromes

ASD and epilepsy are both described in various genetic syndromes, which includes single and common gene mutations as well as undiscovered rare mutations

and copy number variations [36, 42]. Both ASD and epilepsy can be understood as disorders of synaptic plasticity, where the same pathological mechanisms result in developmental imbalances of excitation and inhibition in the developing brain.

This genetically-derived abnormal plasticity can result in both ASD and epilepsy. Examples are fragile X, Rett syndrome, tuberous sclerosis complex (TSC), CDKL5 mutations, neuroligin mutations, "interneuronopathies" that results from X-linked aristaless-related homeobox (ARX) and Neuropilin 2 (NRP2) gene mutations. Moreover, the process of epileptogenesis and/or spontaneous seizures may result in maladaptive synaptic plasticity and produce imbalances of excitation and inhibition. All these processes might contribute to behavioral and learning difficulties. Alterations in receptors, signaling molecules or neurotropins may also result in synaptic abnormalities. Early-life seizures due to genetic conditions may be associated with both ASD and epilepsy (**Figure 1**).

Synaptic plasticity is the process whereby, the connections between 2 neurons of the synapses, get strengthened by experiencing or practicing. When these connections (i.e., synapses) are activated, AMPA receptors mediated by depolarization blocks release of magnesium and helps in entry of calcium through the NMDA receptors. This stimulates calcium dependent activation of kinases and other signaling pathways and enhances gene transcription and trafficking of receptors. This results in faster and stronger synaptic connections. This is known as long-term

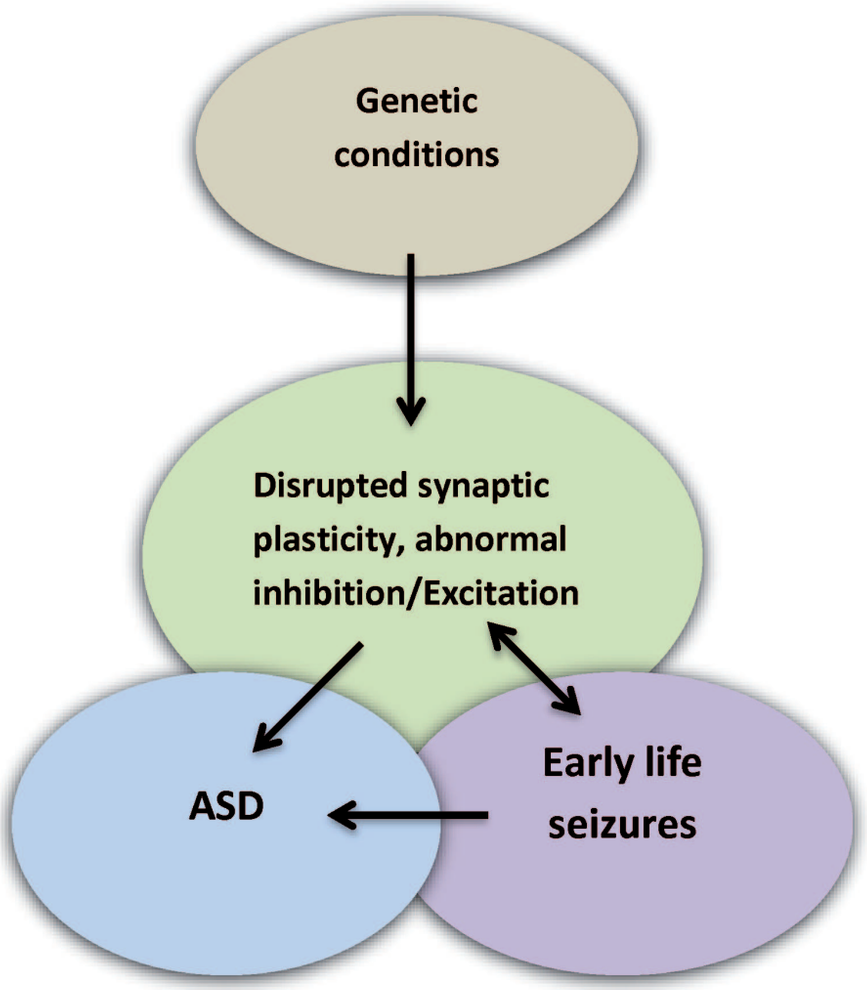

Figure 1.
Abnormal excitability and disrupted synaptic plasticity in the developing brain result in both ASD and Epilepsy. This abnormal plasticity can result from different genetic conditions. Early life seizures during early post-natal development may also alter synaptic plasticity and results in ASD. Mechanisms lie in alterations in receptors, signaling molecules or neurotrophins.

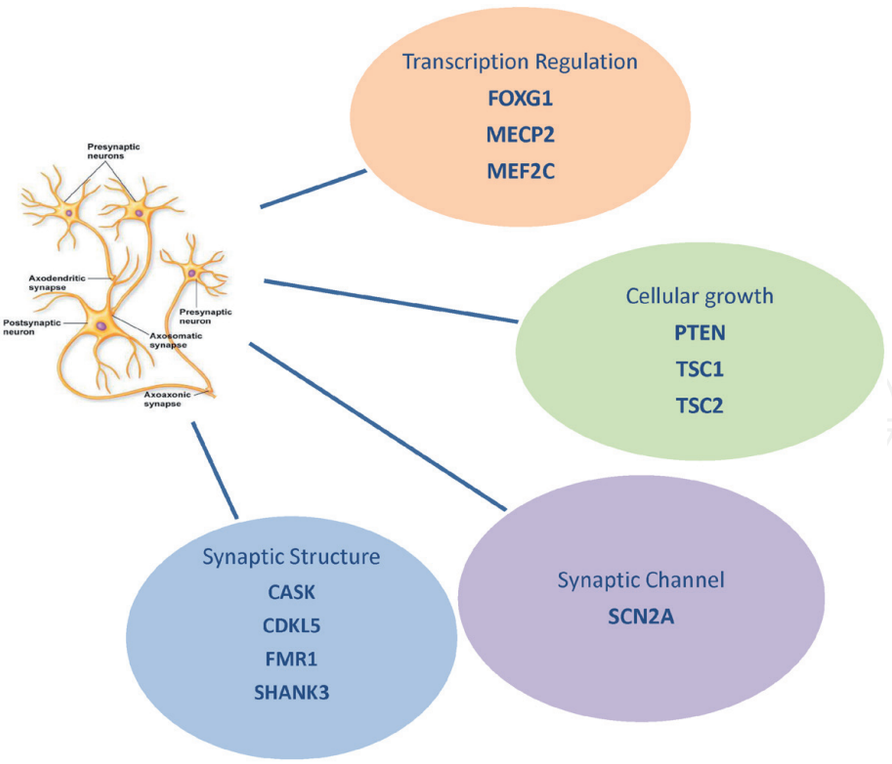

Figure 2.
Four important biological pathways for neuronal development and function common to autism spectrum disorder and epilepsy, that includes transcriptional regulation (FOXG1, MECP2 and MEF2C), cellular growth (PTEN, TSC1, and TSC2), synaptic channels (SCN2A), and synaptic structure (CASK, CDKL5, FMR1, and SHANK3).

potentiation and, is believed be the cellular basis of learning. In some of the genetic conditions associated with autism and epilepsy, variety of genes are disrupted upon which synaptic plasticity depends. These include cyclin-dependent kinase-like 5 (CDKL5) in West syndrome, MeCP2 in Rett syndrome, FMRP in fragile X mental retardation syndrome, mTOR in tuberous sclerosis, and reelin in lissencephaly.

Knowledge of copy number variation and single gene disorders that are disturbed in these two developmental disorders include gene transcriptional regulation; cellular growth and proliferation; and synapse development, stability, and function. An overview of biological common pathway of ASD and epilepsy are shown in **Figure 2**.

5.1.1 Single gene disorders

5.1.1.1 Fragile X syndrome

Fragile X syndrome (FXS) is the most frequent form of genetic disorder causing ID and often presents with ASD and epilepsy. It occurs when a triplet repeat (CGG) expansion leads to inactivation of the FMR1 gene which is responsible for coding of FMRP- fragile X mental retardation protein. FMRP is associated with and regulates various mRNA related to development and functions of dendritic spines, axons and synapses, formation and wiring of neuronal circuits and plasticity of brain. It also regulates metabotropic glutamate receptor (mGluR)-induced long-term depression (LTD). As the "mGluR theory of fragile X" postulates that FMRP and group I metabotropic glutamate receptors (mGluRs) play oppositional roles at the level of synaptic function, loss of FMRP function and activation of mGluRs lead to excessive AMPA receptor internalization, exaggerated LTD and therefore, disrupted synaptic activity. Bianchi et al. provided compelling evidence that a voltage-gated

inward current, ImGluR (V), is the cellular basis for the epileptogenic behavior induced by activation of the mGluR5 receptor [43, 44]. In addition, dysregulation of glutamergic neurons in FXS can disrupt the normal actions of inhibitory GABAergic neurons, and downregulation of GABA receptor subunits and altered expression of a number of enzymes involved in the metabolism of GABA. Identification of this mechanism could contribute to hyperexcitability and epilepsy in the fragile X syndrome [45].

Physical features include prominent ears, long face, macrocephaly, and macroorchidism. The cognitive profile includes hyperactivity, anxiety, tactile defensiveness, gaze avoidance, and socialization difficulties. Epilepsy is reported in approximately 10–20% of individuals with FXS [46]. Seizure patterns in FXS typically resemble benign focal epilepsy of childhood (BFEC). Moreover, 23% of individuals with FXS without clinical seizures demonstrated centrotemporal spikes on EEG.

5.1.1.2 Tuberous sclerosis complex

Tuberous sclerosis complex (TSC) is an autosomal dominant disorder that results from mutations in the *TSC1* or *TSC2* genes [47]. Although skin, kidney, heart, eye, and lung can be affected, involvement of the brain is associated with most significant morbidity. Central nervous system is consistently involved, with 90% of individuals affected showing structural abnormalities, and almost all having some degree of CNS clinical manifestations [48].

TSC1 and *TSC2* genes, found in chromosomes 9 and 16, are responsible for encoding two proteins namely hamartin and tuberin respectively. They bind together to form a protein complex which in turn regulates the mammalian target of rapamycin (mTOR). The loss of function mutation in either of the two genes results in overactivity in mTOR signaling cascade with consequent disinhibition of protein synthesis and cell growth. A simplified diagram in **Figure 3** shows the activation of mTOR cascade [48]. This shows the underlying brain dysfunction resulting in susceptibility to epilepsy, autism and cognitive impairment.

Cortical tubers constitute the hallmark of the disease and are pathognomonic of cerebral TSC. The number and localization of cortical tubers may account for the variability of the neurological phenotype observed in TSC patients [49]. Autism appears to be more common in infants with frontal and temporal tubers, and it has been suggested that an early dysfunction in the associative areas owing to the location of cortical tuber may be responsible for the autistic features [49]. Tuberin, the product of TSC2 gene is expressed to a large extent in frontal and temporal regions of brain- the areas that are responsible for the behavioral phenotypes of the autistic disorder [50].

Epilepsy is the most common presenting symptom in tuberous sclerosis complex. In up to 80% to 90% of persons with TSC, seizures will develop during their lifetime, with the onset most frequently in childhood. Approximately one-third develop infantile spasms. Almost all seizure types can be seen in persons with tuberous sclerosis complex, including tonic, clonic, tonic–clonic, atonic, myoclonic, atypical absence, partial, and complex partial. Only “pure” absence seizures are not observed [51].

Epilepsy in TSC is often medically intractable. The treatment of seizures in TSC is often difficult but efficacy of Vigabatrin in children has proved to have best results.

Although mutations in both TSC1 and TSC2 are associated with development of autism, TSC2 mutation has greater likelihood of developing ASD [52]. Again, early-onset and difficult to control infantile spasms, especially if there is an epileptic focus in a temporal lobe, carry an increased likelihood of getting ASD in a

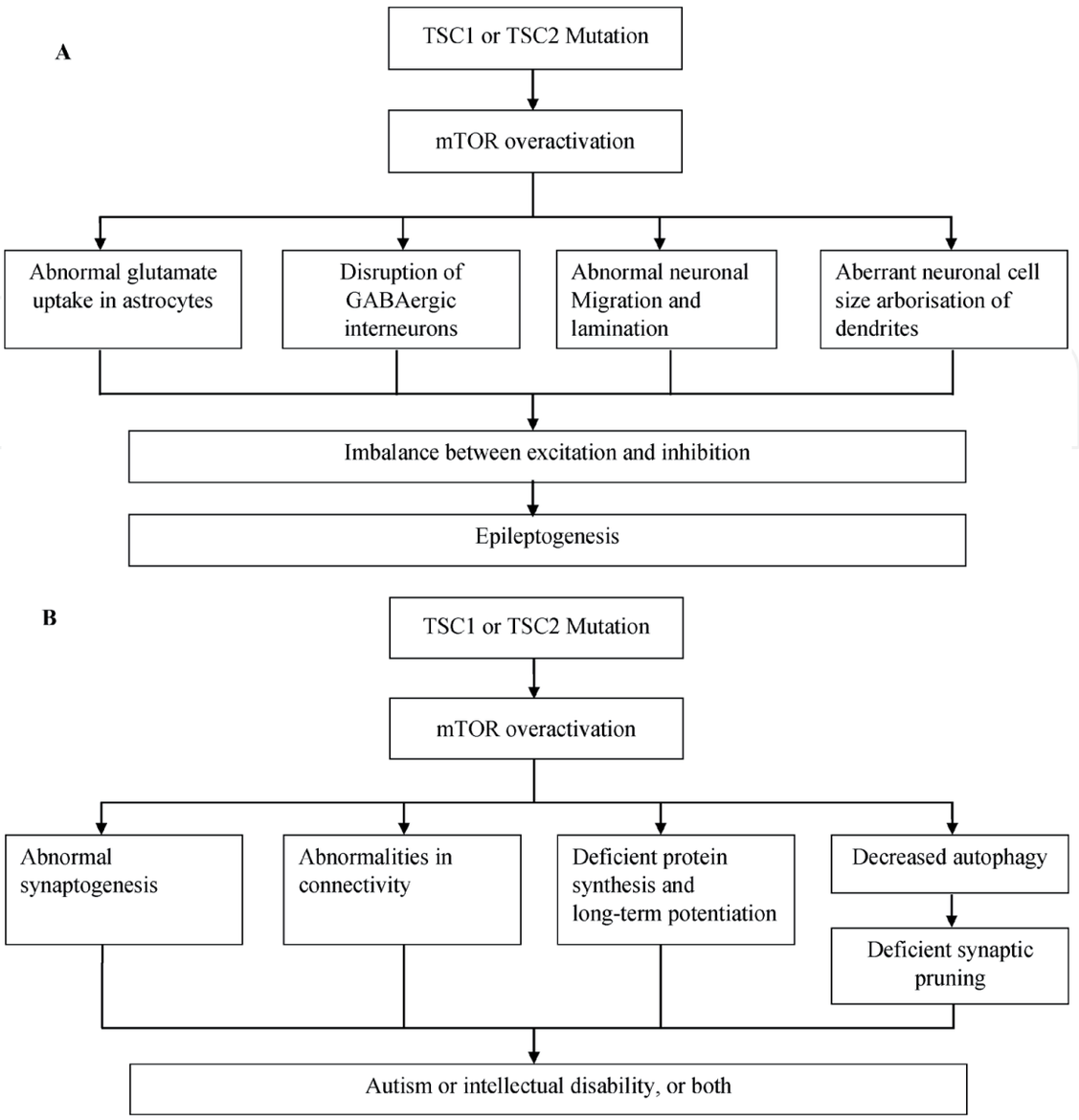

Figure 3.
Schematic representation of the potential roles of mTOR overactivation in determining the neurological and neuropsychiatric manifestations of tuberous sclerosis. (A) mTOR overactivation can dysregulate the balance between neuronal excitation and inhibition, leading to epileptogenesis. (B) mTOR overactivation can alter synaptogenesis and synaptic pruning, connectivity, and long-term potentiation, leading to an increased susceptibility to autism or intellectual disability, or both. mTOR=mammalian target of rapamycin. Courtesy of: Curatolo P, Moavero Vries P J. Neurological and neuropsychiatric aspects of tuberous sclerosis complex. Lancet Neurol 2015; 14: 733–45.

child. Because early onset of infantile spasms and associated hypsarrhythmia may have a malignant effect on brain development in infants with TSC, the importance to search for ways to anticipate the onset of infantile spasms before they become apparent as seizures is very important [53].

Rapamycin normalizes the dysregulated mTOR pathway, and recent clinical trials have demonstrated its efficacy in various TSC manifestations, suggesting the possibility that rapamycin may have benefit in the treatment of TSC brain disease.

5.1.2 PTEN

PTEN is a tumor suppressor gene that encodes a phosphatase affecting G1 cell cycle arrest and inhibiting the PI3K–AKT–mTOR pathway, which has roles in controlling cell growth, survival and proliferation [54, 55]. ASD and macrocephaly and have been reported in children with germline PTEN mutations. PTEN-related

ASD is, therefore, emerging as one of a group of megalencephaly disorders associated with dysregulation of the PI3K–AKT–mTOR pathway [56]. In patients with PTEN mutations, seizures have been reported, in whom focal cortical dysplasia has also been reported [57]. Epilepsy seems to be a part of the phenotype for many of the megalencephaly disorders that are associated with impaired regulation of the PI3K–AKT–mTOR pathway [56] but the exact roles of mutations in these specific genes with and their relation to seizures and ASDs are not clarified.

5.1.2.1 MECP2-related disorder (Rett syndrome)

MECP2-related disorder, result of an X- linked loss- of- function mutation of MECP2, starts presenting with regression typically at 6 to 18 months of age after a period of apparently normal development. Females are predominantly affected with this disorder which is manifested with ID, postnatal microcephaly, loss of spoken language, and stereotypic hand movements. Besides autistic symptoms individuals with MECP2-related disorder may present other symptoms like respiratory rhythm abnormalities, gait impairment, and cardiac complications as well. Approximately 50–90% of children are reported to have seizures, the type of which is variable [58]. The age of onset of seizure is rarely before 2 years of age, and the severity appears to decline after adolescence.

MeCP2 acts, at least in part, as a transcriptional repressor during brain development. And it may be required to reduce aberrant transcriptional events, thus allowing the transcriptional machinery to function efficiently. In addition, it has been suggested to have a function in synaptogenesis or maintenance of neuronal function. The onset of Rett syndrome at 6 to 18 months, coincides with a period of widespread synaptogenesis in the human brain [59], which is compatible with the view that RTT could be caused by failure to form synapses appropriately. Evidence supporting a role for MeCP2 in synapse formation includes altered glutamatergic synapse numbers in vitro and in vivo and changes to neuronal morphology in some brain regions. These findings suggest that long-term changes occur in neuronal networks in the MeCP2-deficient brain [60].

5.1.2.2 CDKL5-related disorder

CDKL5-related disorders are X-linked condition, manifest early in life with epilepsy, usually infantile spasms, postnatal microcephaly and severe neurodevelopmental problems. Girls with mutations in CDKL5 display various ASD features including abnormal social interactions, repetitive movements, and absent speech. However, the developmental disability and the epilepsy phenotype associated with this condition are much greater than those typically seen in children with classical forms of ASD.

CDKL5 is a key-limiting factor in regulating synapse formation. To exert its role CDKL5 binds and phosphorylates the cell adhesion molecule NGL-1. This phosphorylation event ensures a stable association between NGL-1 and PSD95 (key candidates in ASD pathogenesis) in glutamatergic post synapses during dendrite spine development and generates significant role in stabilizing the postsynaptic membrane [61].

5.1.2.3 FOXG1-related disorders

FOXG1-related disorders are associated with epilepsy, severe ID, absent speech with autistic features. Children may present with duplications on chromosome 14q12 or mutations of FOXG1. Children with duplication of 14q12 often present

with infantile spasm followed by ID with autistic features [62]. These patients may also present postnatal microcephaly, morphologic abnormalities of corpus callosum and choreiform movements. The mean age at epilepsy onset for children with deletions/loss-of function mutations of FOXG1 is 22 months. FOXG1 is a brain-specific transcriptional repressor protein that regulates neurogenesis.

5.1.2.4 MEF2C-related disorder

These are extremely rare genetic disorder caused by a in the *MEF2C* gene. This mutation, often a deletion, leads to the dysfunction of MEF2C protein which is essential to the proper functioning of the neurological system in addition to other systems.

Patients with mutations and deletions of MEF2C on chromosome 5q14.3 may present with severe ID, epilepsy, and stereotypic movements. Autistic features have been recognized with some overlap with features found in MECP2-related disorder with a very small deletion encompassing the MEF2C gene [63]. This The epilepsy found in individuals with MEF2C-related disorder can be variable, with 20% presenting with infantile spasms, 33% presenting with infant-onset myoclonic epilepsy, 24% presenting with childhood onset generalized epilepsy. *MEF2C* is essential for early neurogenesis, neuronal migration and differentiation.

5.1.2.5 CASK-related disorders

CASK-related disorders are genetically defined neurodevelopmental syndromes that includes ASD, ID, ADHD as well as epilepsies. CASK encodes for calcium/calmodulin-dependent serine protein kinase (CASK), located on chromosome Xp11.4, in which pathogenic variants underlie a range of NDDs.

Mutations affecting CASK were first described in cases with microcephaly with pontine and cerebellar hypoplasia (MICPCH), followed by the identification in cases with X-linked ID (XL-ID), developmental delay (DD), and ASD. But ASD diagnosis here is difficult because of the presence of the severity of impairment and ID.

CASK is expressed with high expression in the developing human brain and has a role in synapse formation and cortical development. Reduced CASK protein levels affect presynaptic development and decrease inhibitory pre-synapse size, which might have consequences to E/I balance in developing neural circuitries. Aberrant E/I balance, and synaptogenesis are two common biological pathways that underlies the NDDs of different genetic origin.

5.1.2.6 Other conditions with genetic abnormalities

There are few syndromes which are not always present with autism and epilepsy both. But where, genetic mutation in combination with environmental risk factors can result in the appearance of autism and epilepsy. The responsible genes are CNTNAP2, RELN, SYNGAP1, SYN1, NRXN1, BCKDK, RBFOX1 and SCN1A, SCN2.

5.1.3 Genomic copy number variants

5.1.3.1 15q11-q13 duplication syndrome

15q11-q13 duplication syndrome is characterized by developmental delay (DD), epilepsy, and autism.

Individuals with this syndrome have features of both PWS and AS which are caused by deletions spanning this region. Muscle hypotonia is observed in almost all individuals with Dup15q syndrome, and can be severe. ID and feeding difficulties are common. Joint hyperextensibility and drooling accompanies the hypotonia in most individual.

Seizures affect approximately 60% of children with Dup15q syndrome, with the typical onset occurring before age 5 years. A high incidence of infantile spasm with later progression to Lennox–Gastaut syndrome (LGS) has also been reported [64]. However, multiple seizure types including tonic, atonic, tonic–clonic, myoclonic, complex partial, and atypical absence have also been reported. These seizures can be intractable.

A majority of individuals with Dup15q syndrome meet the diagnostic criteria for autism. Expressive language is typically severely impacted, and may even be absent. Behavioral difficulties like ADHD, anxiety, and frustration leading to tantrums are sometimes associated in some affected individuals.

Dup15q syndrome is caused by presence of at least one extra maternally derived copy of the Prader-Willi/Angelman critical region (PWACR) within chromosome 15q11.2-q13.1. Duplications may vary in size but must contain the PWACR to be causative of dup15q syndrome. This duplicated region encodes for GABRA5, GABRB3, and GABRG3 of the GABA receptor subunit allow one to hypothesize the inhibitory-synapses mediated dysregulation as the pathogenesis of the epilepsy and ASD phenotypes found in this disorder [65].

5.1.3.2 Trisomy 21 (Down syndrome)

Trisomy 21 or Down syndrome (DS) is a genetic condition in which a child is born with an extra copy of their 21st chromosome. It is usually associated with characteristic facial features, mild to moderate ID, and few associated congenital anomalies. Previous thinking held that autism is rare in DS. But the fact is that, it is estimated that autism in individuals with Down syndrome is 10–25 times more common than in the typical population [66]. However, this diagnosis often comes much later than it would for an otherwise typical child. This might be due to the presence of associated ID. The prevalence of epilepsy in patients with DS is approximately 1–13%. Infantile spasm (IS) is most frequently found seizure and represents 4.5–47% of these children [67]. Lennox–Gastaut syndrome (LGS), reflex seizures and others such as partial and generalized tonic clonic seizures have also been described in children with DS. A high rate of EEG abnormalities has been reported in DS, even among children without epilepsy [67].

Important mechanisms of epileptogenesis in DS are due to alteration of neuronal or synaptic anatomy resulting from fewer inhibitory inter-neurons, decreased neuronal density and membrane channel dysfunction due to altered membrane potassium permeability, decreased voltage threshold for spike generation.

5.1.3.3 Other copy number variants (CNVs)

Certain pathogenic copy number variants are highly associated with ASD and epilepsy. Deletions of 15q11.2, 16p11.2, and duplication of 16p13.11 have been detected with high frequency in individuals with ASD [68].

5.1.3.4 Phelan–McDermid syndrome (22q13 deletion syndrome)

Phelan-McDermid syndrome (PMS) is a rare genetic condition caused by deletion of 22q13.3 containing the SHANK3 gene. The genetic changes that cause PMS

vary from person to person and so do the clinical features. PMS can appear de novo or be inherited from a parent (20%) who carries a related genetic defect. A broad spectrum of medical, intellectual and behavioral challenges can arise from the symptoms of PMS; however, ID at varying stages, delayed or absent speech, motor delays, low muscle tone, symptoms of ASD and epilepsy have been found to be some of the most regularly observed traits of people with PMS. Some have reported a benign course of generalized tonic–clonic or myoclonic seizures with typical EEG features.

Current research specifies the inability of the single functioning copy of *SHANK3* to produce sufficient Shank3 protein for normal functioning. This may be responsible for most of the neurologic symptoms associated with this disorder. A larger series found seizures to be three times more common when the de novo deletion occurred on the maternally rather than paternally inherited chromosome 22 [69].

5.2 Environmental and epigenetic

5.2.1 Environmental fctors

Although genetic factors are clearly involved in ASD risk, they cannot fully account for all the cases. It is likely that a combination of autism-related genes and specific environmental factors might act as risk factors that triggers the development of autism. A population-based case–control study done in India found several environmental factors for example, the living conditions of family members, infection during pregnancy and preeclampsia, that could trigger development of the autism disorder [70]. Schmidt 2014 reviewed the environmental factors associated with autism, some of which may also be associated with epilepsy [71]. They reported consistent results for an association of higher maternal intake of certain supplements with reduction in ASD risk, with the strongest evidence for folic acid supplements [71, 72]. If a mother is exposed to a relevant environmental toxin and her offspring has a genetic predisposition, the combined effect might result in development of ASD, and carries a risk of epilepsy as well.

Intrauterine infection, e.g., maternal rubella during pregnancy has long been associated with a high risk of ID, autism and epilepsy in the offspring [40]. Use of antiepileptic drug sodium valproate during pregnancy can also affect brain development of the fetus, leading to ID and autism [71]. Rybakowski et al., emphasized that factors occurring already before conception like age of the parents, family autoimmune factors and maternal metabolic factors like obesity, diabetes, hypertension play important roles [72]. Many authors reported of factors occurring during pregnancy, such as bleeding throughout the pregnancy, multiple pregnancy, intrauterine infections (TORCH, bacterial, other) and maternal hypothyroidism. Arterial hypertension during pregnancy seems important, along with pre-eclampsia and eclampsia, severe anemia, smoking during the pregnancy [71, 73], maternal stress during pregnancy etc. Among other factors preterm delivery, low birth weight, intrauterine growth retardation and hypoxic ischaemic encephalopathy are mentioned. Among neonatal factors, the most commonly mentioned are: intraventricular bleeding, hyperbilirubinemia and congenital defects. While all these are responsible for development of ASD, more research is needed to know the association of epilepsy in these cases. However, environmental risk factors do not solely cover the exposure to toxins but include all changes other than those on a DNA–level, such as maternal nutrition, infection during pregnancy, and prematurity as well as parental age at conception.

5.3 Metabolic disorders associated with epilepsy in ASD

Many metabolic disorders may be associated with ASD and epilepsy. Among them, conditions like mitochondrial disease and dysfunction and abnormalities in cerebral folate metabolism are the common associations. Many of these conditions can lead to brain damage if inadequately treated. Frye provided a strong argument for treating any underlying metabolic disorders, both for ameliorating autism and epilepsy [74]. He also added the importance of understanding metabolic and genetic biomarkers. If these disorders can be detected early in life or even prenatally, treatment can be started at the earliest possible time. Identifying metabolic defects might help using standard known or novel treatments in children with epilepsy.

These metabolic disorders have diverse classic presentations, so basing a diagnostic strategy on the search for one or two specific key symptoms is inappropriate.

However, mitochondrial disease is of particular interest in children with ASD since it is being increasingly recognized as a cause of epilepsy in individuals with ASD [74, 75].

5.3.1 Disorders of energy metabolism

Several disorders affecting energy metabolism have been documented in ASD, including mitochondrial disorders and creatine deficiency syndromes. The prevalence of mitochondrial abnormalities appears to be very high in ASD [75].

Disorders of creatine metabolism have also been reported in children with ASD and epilepsy [76].

The general presentation of children with disorders of creatine metabolism includes developmental delay, regression, ASD features, ID, receptive and expressive language disorders, and seizures.

5.3.2 Disorders of cholesterol metabolism

Smith–Lemli–Opitz syndrome (SLOS) is a congenital disorder of cholesterol metabolism caused by mutations in both DHCR7 genes. Metabolically, children with SLOS demonstrate elevated concentrations of 7-dehydrocholesterol and reduced cholesterol concentrations in the blood. Interestingly, 50%–75% of children with this disorder meet the criteria for ASD [77]. This disorder is may be associated with seizures along with their other clinical presentations [78].

5.3.3 Disorders of vitamin metabolism

These include disorders of folate, pyridoxine, biotin, and carnitine metabolism. Children with cerebral folate deficiency (CFD) are commonly diagnosed with epilepsy and/or ASD [78].

Since the folate transport system is energy-dependent, a wide variety of mitochondrial diseases and novel forms of mitochondrial dysfunction related to ASD [79] have been associated with CFD.

Pyridoxine and its active form pyridoxal-5-phosphate play major roles in metabolism of glutamic acid to GABA acting as a cofactor. Pyridoxal-5-phosphate depletion reduces glutamic acid decarboxylase activity, resulting in a reduction in GABA synthesis. In children with ASD, several studies have reported significant improvement in behavior and cognition attributable to combined therapy with magnesium and pyridoxine [80].

5.3.4 Disorders of γ-aminobutyric acid metabolism

Succinic semialdehyde dehydrogenase deficiency is a rare disorder of GABA metabolism that results from a mutation in both ALDH5A1 genes. Neurological manifestations may include seizures, and ASD features among others.

5.3.5 Disorders of pyrimidine and purine metabolism

Children with ASD and comorbid seizures have been described to have disorders of purine and pyrimidine metabolism. Patients show a variable combination of mental retardation, epilepsy, ASD features, and cerebellar vermis hypoplasia.

5.3.6 Disorders of amino acid metabolism

Disorders in the metabolism of phenylalanine, have been described in children with ASD and comorbid epilepsy. Phenylketonuria is an autosomal recessive inborn error of phenylalanine metabolism resulting from deficiency of phenylalanine hydroxylase secondary to a mutation in the PAH gene on chromosome 12q23.2. Children with PKU who go untreated or who do not adhere to the diet adequately may demonstrate poor growth, poor skin pigmentation, microcephaly, seizures, spasticity, ataxia, aggressive behavior, hyperactivity, ASD features, global developmental delay, and/or severe intellectual impairment. Recently an inactivating mutation in the branched-chain ketoacid dehydrogenase kinase was described to be associated with autism, epilepsy, and intellectual disability in three families with two children each who were products of first-cousin consanguinity.

5.3.7 Mitochondrial dysfunction associated with epilepsy in ASD

A recent meta-analysis found that 5% of children with ASD met the criteria for classic mitochondrial disease, while as many as 30% of children with ASD may manifest mitochondrial dysfunction.

Prevalence of abnormal mitochondrial function in immune cells derived from children with ASD is exceedingly high.

A meta-analysis found that, overall, 41% of children with ASD and documented mitochondrial disease are reported to have seizures.

Mitochondrial dysfunction has also been reported in many genetic syndromes associated with ASD and epilepsy. For example, in Rett syndrome, Phelan–McDermid syndrome, 15q11-q13 duplication syndrome, Angelman syndrome and Down syndrome, mitochondrial dysfunction may underlie the phenotype of ASD with epilepsy, regardless of the underlying cause.

Abnormalities in mitochondrial function can lead to abnormal development in brain circuits, resulting in both neurodevelopmental disorders and epilepsy through several mechanisms. Abnormalities in mitochondrial biomarkers have also been found in the brains of individuals with ASD. Thus, it is very likely that changes in mitochondrial function in the brain affect neural transmission and function in children with ASD. Neural synapses that are areas of high energy consumption and are especially dependent on mitochondrial function may be one of the mechanisms for developing these developmental disorders. Recent studies have suggested that oxidative stress may be involved in the development of epilepsy.

Studies have found connection between reactive oxygen species and mitochondrial dysfunction in brain tissue from individuals with ASD. This may be another mechanism where mitochondrial dysfunction can lead to the development of epilepsy in ASD.

Immune dysfunction is found to be implicated in the development of epilepsy, and evidence of cellular and humoral immune dysfunction has also been implicated in ASD. Thus, studies suggest abnormalities in immune cell function result in seizures in ASD.

Another physiological abnormality that is becoming increasingly recognized in both ASD and epilepsy is the dysregulation of calcium [81]. On the other hand, epilepsy may be a common symptom of metabolic disorders and be a clue that a metabolic disorder may be the underlying etiology of the neurodevelopmental abnormalities in children with epilepsy and ASD. One advantage of investigating and diagnosing metabolic disorders is that treatments for many of these metabolic disorders are available.

6. Epilepsy syndromes with ASD as frequent neurodevelopmental sequelae

Several specific epilepsy syndromes with early onset epilepsy show an autistic behavior, some also appear to be the risk factor for later diagnosis of ASD. If they are identified appropriately and treated, behavioral improvement which is radical in some of the cases can be seen. In these cases, epilepsy originates in the brain networks responsible for communication and interactions. These include infantile spasms and Lennox–Gastaut syndrome. More recently, clinical overlap has been observed in cases with continuous slow waves during sleep (CSWS) and Landau–Kleffner syndrome and ASD [82].

6.1 West syndrome (WS)

WS is an epileptic encephalopathy characterized by infantile spasm/epileptic spasms, an EEG pattern of hypsarrhythmia and cognitive stagnation or regression. They usually occur before 2 years of age. Genetic causes are present in many of them and abnormalities in several brain developmental pathways are noted.

ASD may develop in a few of them. However, an association between TSC and duplications of FOXG1 have been reported consistently.

6.2 Lennox–Gastaut syndrome (LGS)

LGS is a childhood-onset epilepsy, which is characterized by constellation of several distinct types of seizures and electroclinical features of diffuse slow spike waves and generalized paroxysmal fast activity in sleep. Prevalence of ASD in LGS is rare, although ASD has been reported in patient with LGS resulting from duplications of maternal 15q11q13 [83].

6.3 Landau–Kleffner syndrome (LKS)/continuous spikes and slow waves during slow sleep (CSWS)

LKS is an epilepsy-aphasia syndrome that is characterized by regression in language and characteristic CSWS on EEG-termed as electrical status epilepticus of slow sleep (ESES). Several children who had been diagnosed with ASD were noted to have a predominant language deficit. Stereotypies and withdrawal are also common in LKS, but whether these children also have deficits in social reciprocity is not clear. The association may be more related to severe receptive language deficit. Copy number variants have been detected in patients with LKS who also have associated ASD [84], and, most recently, GRIN2A mutation have been identified in patients with epilepsy-aphasia phenotypes [85].

7. Regression in Autism

Developmental regression is present in approximately one-third of children with ASD [86] and is believed to have an association with epilepsy. The relationship between regression and epilepsy in ASD has therefore long been of interest because of the hope that some developmental regression in idiopathic ASD could be caused by epilepsy and be reversible through using anti-seizure therapies [87].

The overlap of language and autistic regression to epilepsy, EEG epileptiform activity, sleep, and to epileptic encephalopathies such as LKS continue to be controversial areas of research and of clinical interest because of the close clinical resemblance to autism.

LKS or acquired epileptic aphasia may present as a developmental language regression followed by autistic-like social-communicative phenotype. LKS usually presents between 3 and 7 years of age with loss of language skill in children who were previously normal and most but not all affected children have convulsive seizures. In case on early LKS, it becomes difficult to differentiate it from ASD clinically and the diagnosis is done mainly on EEG finding and response to anti-seizure treatment. The EEG in the awakened state often has a normal background with seizures of various types in LKS. During sleep, it is characterized by epileptic discharges throughout the sleep-electrical status epilepticus (ESES) on EEG that may affect cognitive processing. In children with autistic regression, both language and behavior in association with significant social deficits occur between 18 and 24 months compared to usually only language regression in LKS, which is more dramatic and the social deficits are less severe than those with autism [88]. McVicar et al. in their study reported that children with isolated language regression have a higher frequency of epileptiform discharges and seizures than children with both language and autistic (i.e., social and behavioral) regression [89].

An extensive review, in 2002 on epileptiform neurocognitive disorders linked with speech/language deterioration concluded that "acquired epileptiform aphasia (AEA) can be conceptualized on a spectrum with other epileptiform neurocognitive disorders that may share pathophysiological features". They also added that "without better documentation of potential factors around the time of the regression, it will be difficult to identify the fundamental factors that differentiate these conditions, their response to treatment and long-term prognosis" [90].

CSWS, an epileptic syndrome of that is associated with EEG pattern of ESES may present with regression in global skills that overlaps with autism [91]. However, the differences in age of regression, type of regression, frequency of epilepsy and EEG abnormalities suggest that these are distinct phenotypes.

Nonconvulsive status epilepticus (NCSE) may also have features that have a strong similarity to autism. The child may exhibit poor reciprocal social interaction, poor verbal and nonverbal communication. But with effective treatment, the features of autism disappear.

Magnetoencephalography has identified precise location of the source of these epileptic EEG discharges. The finding from this investigation shows that focal spike waves (FSW) in the perisylvian region and located in the superior temporal gyrus may cause auditory and verbal agnosia (LKS). When FSW predominate in the prefrontal regions, a cognitive regression with features of CSWS, when in cortical areas like the superior temporal sulcus or the fusiform gyrus involving the networks relating emotions to higher-level visual representations could interfere with the developing capacity to recognize the emotional signals of faces, that are typically deficient in autism.

Other epileptic disorders, like refractory partial epilepsies of frontal or temporal origin like the Benign epilepsy with centrotemporal spikes (BECTS)also interfere

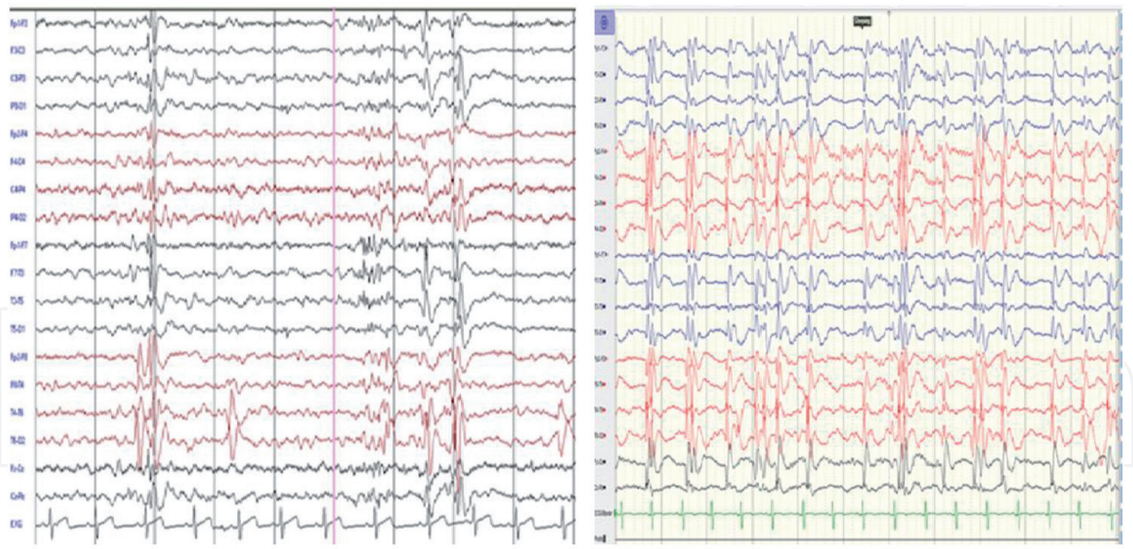

Figure 4.
Electroencephalogram finding of a (A) 4 years 6 months old boy with LKS, and regression of speech for one year showing spike and waves over frontal central and temporal regions (B) 7 year old girl with regression of speech and cognitive function in a case of CSWS showing ESES, generalized spike waves in all the channels.

with developing language networks and/or other circuits involving the "social brain" such as the amygdala, cingulate and orbitofrontal cortex and account or contribute to language and autistic regression. Other examples are Focal dysplasias, hippocampal sclerosis, congenital tumors or tuberous sclerosis and hypothalamic hamartomas.

In addition, an increasing number of genetic and metabolic encephalopathies with severe developmental problems are now recognized with autistic regression where epilepsy may aggravate the regression.

It is also found that approximately 20% of children with autistic regression without epilepsy may have an abnormal EEG, the majority with spikes or spike-and-wave discharges [92]. Although this abnormal EEG is found usually after the regression, there is no evidence of a causal relationship between the epileptiform abnormalities and the regression [93].

Figure 4 shows EEG of LKS in awake and CSWS in sleep with ESES.

8. Autism in epilepsy

A meta-analysis of 19 studies showed a pooled ASD prevalence of 6.3% in individuals with epilepsy, which is considerably higher than the reported prevalence of 0.75% to 1.1% in the general population [94]. Tuchman et al. reported approximately 30% of children with epilepsy have autism and/or intellectual or developmental disabilities [95]. Several studies have shown that children with epilepsy have an increased risk of being diagnosed with ASD [8, 16, 22]. A higher prevalence was found for studies with younger age groups, ID, and specific epilepsy syndromes (West syndrome, Dravet syndrome).

Epilepsy and autism both can arise from abnormal excitability and disrupted synaptic plasticity in the developing brain. This abnormal plasticity can also result from genetic conditions.

Early-life seizures can produce a variety of cellular and molecular changes in the hippocampus, including short-term enhancement of excitation and long-term enhancement of inhibitory neurotransmission and reductions in excitatory

neurotransmission [35]. All these early seizures also have numerous disruptive effects on neural development, including abnormal synaptic reorganization, and cortical interneuron dysfunction [96, 97]. This in turn disrupts the construction of cortical networks necessary for acquiring certain skills during development, and may predispose an individual towards developing ASD [15]. Further, risk of both epilepsy and ASD is elevated in numerous genetic disorders as mentioned previously, such as Rett syndrome, fragile X syndrome, and tuberous sclerosis complex [37].

Lukmaji et al. emphasized the importance of screening for autism in persons with epilepsy, and vice versa, to appropriately tailor treatment decisions and improve patient outcomes [28]. As in their systematic review revealed the occurrence of autism in persons with epilepsy and epilepsy in persons with autism to be higher than the previously reported independent occurrence of each of these conditions in the general population.

9. EEG abnormalities

ASD are associated with increased incidence of EEG abnormalities. EEG epileptiform abnormalities were found at a range of 35% to 86% in ASD individuals with epilepsy [9, 21, 98] and up to 28.6% [21] to 60% [9] in individuals without epilepsy. These discharges are often more common when there is history of autistic regression, even if there is no history of seizures or epilepsy [99]. In addition to epileptiform discharges, non-epileptiform discharges were also found in ASD, these were- disorganized and slowing of background rhythm, asymmetry etc. [100]. But epileptiform EEGs seemed to be more common than nonepileptiform abnormalities in most of the studies [101–105].

Abnormal EEG is considered as a biomarker of cortical dysfunction [8, 100] and provide evidence that autism is a neurobiological disorder [106]. Interictal discharges are thought to interfere with normal neural processing which may further impair cognitive function [17, 18, 100]. The clinical importance of epileptiform discharges without overt seizures are not clear, but they may also cause behavioral and cognitive problems [99].

EEG should be considered in children with clinical or suspected seizures and, in all the children where autism is questionable and a clinical suspicion of LKS is present. Performing a sleep-EEG was highly recommended by Pacheva et al. in all patients to prevent underdiagnosis of ESES and LKS [21]. The authors also mentioned the need of timely treatment to get improved behavior and cognition in patients with ESES. Fernandez et al. also concluded in that a treatment trial with AED is justified in patients with epileptic encephalopathies and cognitive dysfunction/regression, that could be related to epileptiform discharges [107]. Children with LKS may also have an autistic-like regression that extends to behaviors beyond language [87]. Presence of epileptiform EEG abnormalities even in the absence of clinical seizure found in LKS and ESES is a controversial problem [108, 109].

10. Management of individuals with both epilepsy and autism

Both the conditions should be managed individually. This depends upon the causes if present, especially in case of epilepsy. First of all, the cause of epilepsy in autism should be investigated appropriately. It has to be ensured that the autistic features are not the result of ESES or frequent epileptiform discharges [110].

The diagnosis of epilepsy become more difficult in autism, especially if there is accompanying intellectual disability because history taking in these cases becomes more difficult.

The treatment of epilepsy in ASD is based on the general principles of treatment of epileptic seizures with traditional antiepileptic drugs (AEDs). Usually, valproate, lamotrigine and levetiracetam are used as the most effective and tolerable AEDs for individuals with ASD [74]. But levetiracetam can have negative effects on mood and behavior and be associated with deterioration in children, whereas lamotrigine tends to be a mood-leveling antiepileptic drug and Topiramate can be associated with word-finding difficulties [110].

The discovery of the role of neuronal autoantibodies has been one of the most exciting developments in the recent years. These antibodies can result in seizures, loss of skills, (sometimes a dramatic loss), behavioral changes and even psychosis. Effective immunotherapy can, in at least some cases, reverse all these changes [111, 112]. This is an area which requires further consideration.

New therapeutic options were suggested for ASD and epilepsy, based on the opinion that gene defects could determine all the symptoms of these disorders. This also includes modulators of GABA A receptors, GABA agonists, modulators of GABA metabolism, glutamate receptor antagonists, insulin-like growth factor 1 and m-TOR inhibitors for ASD-epilepsy comorbidity [113]. M-TOR inhibitors like Everolimus (Rapamycin) and Sirolimus have positive results in patients with TSC, ASD and PTEN-related disorders. After treatment with conventional GABAnergic agonists, a paradoxical result was reported in ASD [101]. In addition, ASD with epilepsy having 15q11.2 duplication, effectiveness of benzodiazepines was reported to be lowered [114].

In addition to the treatment, the usual management of autism should be continued.

10.1 Management of additional comorbidities in the presence of both epilepsy and autism

10.1.1 Attention deficit hyperactivity disorder

ADHD is common in children with autism and in children and adolescent with epilepsy. Diagnosing ADHD in epilepsy sometimes becomes difficult, because some of the children with epilepsy present with features of ADHD. This is due to frequent epileptiform discharge. In those cases, treating these epileptic discharges with AEDs will alleviate these symptoms. Few children with epilepsy may have inattention, hyperactivity and distractibility as a result of antiepileptic medication, as for example, treatment with phenobarbitone, benzodiazepine or vigabatrin [110]. So, review of antiepilepetic medication is very important before diagnosing the child as having ADHD.

Epilepsy is a highly variable condition and after treatment with AED, there might be is no change in seizure or even there is high frequency of seizure and since ADHD medication is started, it may be incorrectly concluded that this increase in seizures is because of the ADHD treatment.

There are two groups of medication currently used to treat ADHD: stimulants (methylphenidate, amphetamine) and non-stimulants (Atomoxetine, alpha-2 agonists). When children with symptoms of ADHD require medication, current guidelines recommend starting with a trial of a stimulant like methylphenidate. If this first stimulant does not prove to be effective, the alternative stimulant is then used [115]. If stimulants are not effective or cause intolerable adverse effects, then nonstimulants like atomoxetine, alpha-2 agonists, and antidepressants are used.

Methylphenidate is the most commonly used medicine for ADHD. Large observational studies conducted in children and adolescents with epilepsy have found that ADHD medications in general and stimulants like methylphenidate are not associated with increased risk of seizures [116]. Use of low and moderate doses of methylphenidate has been observed in reduction of seizure frequency and severity along with improved quality of life in a Brazilian study done in 2015 [117]. However, it is important to monitor seizure frequency in the first few weeks and months after prescribing methylphenidate [116] as there are still questions regarding use of this drug in epilepsy.

Guidance for identification and treatment of individuals with attention deficit/hyperactivity disorder and ASD based upon expert consensus in the UK in 2020 [118] emphasized on non-pharmacological interventions and care management, including psychoeducation, carer interventions, behavioral/environmental and Cognitive Behavioral Therapy (CBT) approaches and educational interventions, followed by pharmacological treatments. They have commented that in children, pharmacological intervention should be preceded by behavioral observation and psychological intervention as the first-line treatment. And if psychological/environmental interventions fail in children, then ADHD medication may be helpful for treating symptoms of inattention. Medication should be used in a 'low and slow' approach as people with both ADHD with epilepsy may be more treatment resistant and more prone to develop side effects to medication. Medication should be given for the shortest time possible and side effects should be monitored carefully.

Researchers also mentioned about the relative little evidence, on using other ADHD treatments, such as atomoxetine, guanfacine and clonidine in children with autism, having both epilepsy and ADHD [110]. However, several research papers and reviews found no clear evidence about exacerbation of seizures with these medications. Besag et al., in their paper summarized, about 30% of children with epilepsy had ADHD and about 70% among those with epilepsy and ADHD benefited from treatment of their ADHD symptoms with methylphenidate [119].

10.1.2 Anxiety

Anxiety is commonly found in young people with autism and epilepsy. Children with epilepsy with co-morbid psychiatric disorders like — ADHD, depression, and anxiety disorders, end up with significant compromise in academic performance and social skills, leading to deterioration in the Quality of life [120].

Risperidone and Aripiprazole in low dose can improve the behavior in children with autism. The mechanism is probably through decreasing anxiety. But the dose used should be very low because of the risk of seizure exacerbation with high doses of these antipsychotic drugs. On the other hand, the antiepileptic drugs like carbamazepine, phenobarbital and phenytoin may decrease the blood levels of antipsychotic drugs and a larger dose of antipsychotics may be required who are taking these AEDs. The management goals in pediatric epilepsy with anxiety disorders are — adequate seizure control, optimization of the functioning of the child and keeping the patient in best and simple pharmaco-therapeutic regimen [121].

The clinician should avoid an antiepileptic drug which is having side effects like behavioral problems.

Behavioral therapy should be the first-line approach to managing anxiety. Despite the effectiveness of selective serotonin reuptake inhibitors in decreasing anxiety in adults and teenagers there is a lack of evidence for a beneficial role of these drugs in treating anxiety in children with autism, according to a Cochrane review.

10.1.3 Sleep

Sleep disturbances are very common in children with autism. Epilepsy and sleep have reciprocal relationships. In some of the cases, sleep facilitates seizures and, in some seizures, adversely affects sleep architecture. If sleep problems are present, possibility of nocturnal seizures should it is eliminated. In that case careful history and if required antiepileptic medication should be tried. And if the sleep disturbance is not due to nocturnal seizures, melatonin is the drug of choice [110]. There is no good evidence of exacerbating seizures using melatonin. Animal work suggests that melatonin might have an antiepileptic effect. Identification and management of sleep disorders may improve seizure control and challenging behaviors of autism

11. Future direction

No single unifying ASD–epilepsy phenotype is there till now but understanding possible commonalities in subgroups of children with an ASD– epilepsy phenotype should help us in understanding the pathophysiology of both ASD and epilepsy [110].

Prospective, population-based studies are recommended, whenever there is any history of regression [110]. These studies should include investigations like genetic and chromosomal studies, searching for metabolic/mitochondrial disorders, EEG including sleep EEG and also testing for possible neuronal antibodies.

Environmental factors, prenatal factors such as maternal exposure to infection, toxic chemicals, pollution, alcohol and drugs should be searched for as these are the risk factors of autism and they might also cause epilepsy. A history of exposure to antiepileptic drugs like maternal valproate and learning problems/probable autism in the offspring and thorough obstetric and neonatal factors should also be an essential part of the history-taking.

12. Conclusions

Epilepsy is a common co-occurrence in children and persons with ASD. Determining the bidirectional prevalence of autism and epilepsy is important. Understanding the specific effects of the genes/metabolic/environmental pathways affected may give a better insight into the pathogenesis of the developmental problems. ID is also an important association in epilepsy and ASD. Multiple interrelated factors are there in the pathogenesis of ASD-epilepsy connection. Further, understanding these comorbidities will have a profound effect on the management of these challenging patient populations. For example, it has been found that autistic symptoms can be minimized when epilepsy is being treated in patients with both the conditions. Well-managed epilepsy, autism, and associated comorbidities can significantly improve the quality of life in both patient and caregiver. Further population-based studies and investigations including genetic, and, metabolic, in addition to EEG are needed, especially in case of regression in order to detect both these conditions in the early years of life.

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