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Overlap Between Epilepsy and Neurodevelopmental Disorders: Insights from Clinical and Genetic Studies

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Abstract: Patients with epilepsy often experience comorbid cognitive and behavioral problems. These problems are often caused by neurodevelopmental disorders such as autism spectrum disorder and attention-deficit hyperactivity disorder. Although the etiology of epilepsy is unclear in many patients, there is increasing evidence for the existence of genetic traits common to both epilepsy and

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neurodevelopmental disorders. These include chromosomal abnormalities, copy number variations, and single gene diseases. This chapter examines several genetic disorders that may underlie epilepsy and several neurodevelopmental disorders. There is substantial evidence that the same gene mutations are associated with both epilepsy and neurodevelopmental disorders. Alternative biological models are considered that could explain the association and causal links between the two disorders. It is likely that epilepsy and neurodevelopmental disorders both lie on a single continuum, and that greater understanding of the overlap between these disorders and epilepsy would help to provide more tailored interventions.

Keywords: attention-deficit hyperactivity disorder; autism spectrum disorder; epilepsy; genetics; neurodevelopmental disorder

INTRODUCTION

Epilepsy is characterized by recurrent seizures caused by intense electrical excitation of neurons in the brain, and can occur regardless of age, sex, or race. Epilepsy is a common disease, with an incidence of 61.44 per 100,000 person-years (95% confidence interval [CI] 50.75–74.38) and a lifetime prevalence of 7.60 per 1,000 persons (95% CI 6.17–9.38) in many countries (1). The epilepsy classification published by the International League Against Epilepsy in 2017 categorizes epilepsy into three levels (2). At the first level, seizures are broadly classified into focal, generalized, and unknown onset. At the second level, epilepsy is categorized into four main types: focal epilepsy, generalized epilepsy, combined focal and generalized epilepsy, and unknown epilepsy. The third level defines epilepsy in terms of epilepsy syndrome, when a specific syndrome diagnosis is possible. The etiologic categories of epilepsy are structural, genetic, infectious, metabolic, immune, and unknown. Despite the widespread use of advanced diagnostic techniques such as magnetic resonance imaging, the etiology of epilepsy in most patients remains unclear. However, with recent advances in gene sequencing technology, there is growing evidence that genetics plays an important role in the development of epilepsy (3). Important comorbidities of epilepsy include cognitive and behavioral disorders. In some patients, such comorbidities may have a greater effect than the epilepsy (4, 5) and may severely affect daily life. The disorders that most often cause cognitive and behavioral impairments are neurodevelopmental disorders. In the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), neurodevelopmental disorders as a diagnostic category are defined as a group of conditions with onset in the developmental period, inducing deficits that produce impairments of functioning (6). Neurodevelopmental disorders include autism spectrum disorder (ASD), attention-deficit hyperactivity disorder (ADHD), and intellectual disabilities. Many studies, particularly in the field of genetics, have reported that neurodevelopmental disorders have a common biological background (7). A substantial number of cases of neurodevelopmental comorbidities occur in clinical practice (8). The diagnostic criteria of earlier versions of the DSM (e.g., DSM-IV) did not include combinations of neurodevelopmental disorders, such as the combination of ASD and ADHD. However, DSM-5 recognizes the

diagnosis of combined ASD and ADHD. The concept of neurodevelopmental disorders in the International Classification of Diseases 11th Revision (ICD-11), published in 2018, generally aligns with that of DSM-5, and ICD-11 also recognizes the comorbidity between ASD and ADHD. These developments highlight the importance of considering the substantial overlap between neurodevelopmental disorders, at least in their clinical aspects. Furthermore, some researchers have proposed that these neurodevelopmental disorders are on a dimensional continuum, rather than being separate diagnostic categories (9).

Interestingly, neurodevelopmental disorders and epilepsy often co-occur. The incidence of neurodevelopmental disorders in patients with epilepsy is higher than that in the general population, and the incidence of ADHD varies from 11% to 46% (10-13). One study showed that children with epilepsy had a fully adjusted incidence rate ratio of 2.72 (95% CI 2.53–2.91) for ADHD compared with children without epilepsy (14). In addition, 18-30% of children with epilepsy meet the criteria for ASD (15, 16). The frequency of epilepsy complications in neurodevelopmental disorders is also high, ranging from 8-77% of patients with ADHD (17), and approximately 5-46% of ASD patients have epilepsy (15).

The combination of epilepsy and neurodevelopmental disorders has several characteristics. One is the distribution of epilepsy onset. Patients with ASD show two peaks of epilepsy onset, one in infancy and the other around puberty, with most cases occurring around puberty (18). Presumably, the former group develops epilepsy in childhood as a result of the presence of a common neuropathophysiological antecedent that causes epilepsy and neurodevelopmental disorders; in the latter group, the accumulation of abnormal brain functions that cause neurodevelopmental disorder may trigger seizures. Another feature is that both epilepsy and neurodevelopmental disorders are prone to electroencephalogram (EEG) abnormalities. EEG abnormalities are often observed in epilepsy patients, and are found in 4-86% of ASD patients (15) and 16-30% of ADHD patients (19–21). These EEG abnormalities are strongly associated with earlier epilepsy onset, inattentive subtype, and intellectual disability (21, 22). The presence of epileptic discharges in EEG correlates with cognitive decline, as reported in patients with Alzheimer's disease (23). Epilepsy or epileptic EEG changes may exacerbate neurodevelopmental disorders. It is important to recognize that these relationships between epilepsy and neurodevelopmental diseases are not reciprocally exclusive or unidirectional. Recognizing the co-occurrence of these disorders and understanding the mechanisms by which they interact could lead to individualized treatment and better management. This chapter provides an overview of the genetic disorders that commonly cause epilepsy and neurodevelopmental disorders, and proposes an etiological perspective on epilepsy and neurodevelopmental disorders as lying on a continuous biological spectrum.

THE GENETIC BACKGROUNDS OF NEURODEVELOPMENTAL DISORDERS AND EPILEPSY

In recent years, owing to the rapid progress of genome technologies, several genetic traits have been identified that cause both neurodevelopmental disorders

and epilepsy. The most frequently reported traits include chromosomal abnormalities, copy number variations (CNVs), and single gene diseases. The following are typical examples of each of these conditions.

Chromosomal abnormalities and copy number variations

Chromosomal variations and anomalies can be broadly divided into numerical and structural aberrations. There are several types of numerical abnormalities, including monosomy, in which there is only one chromosome when there should be two; trisomy, in which there are three chromosomes; and tetrasomy, in which there are four chromosomes. Structural chromosomal abnormalities include translocations and inversions, partial deletions and duplications, ringed circular chromosomes, and isochromosomes with only a long or short arm. These structural variants affect the number of stretches of DNA that are replicated. In some people, the original two copies may be reduced to one copy, or conversely tripled or quadrupled; these abnormalities are called copy number variations (CNVs). CNVs can affect gene expression levels, although they are also found in healthy individuals. There is some evidence that CNVs affect comorbid epilepsy and neurodevelopmental disorders. For instance, the following CNVs are known to be associated with ASD, intellectual disability, and/or epilepsy: 2p16.1-p15 duplication, 6p25.3-p25.1 duplication, 8p23.3-p23.1 deletion, 9p24.3-p23 deletion, 10q11.22-q11.23 duplication, 12p13.33-13.2 duplication, 13q34 deletion, and 16p13.2 duplication (24). Regarding other CNVs, the 15q11-q13, 22q11.2, and 16p11.2 loci are associated with ASD, and patients with ASD who have CNVs have a higher rate of epilepsy complications (25). In addition to the above regions, the three genomic regions 5q14.3, 11q23.2, and 7p22.3 are known to contribute to psychiatric disorders, including ASD and ADHD (26). Of these regions, 5q14.3 and 7p22.3 are also associated with epilepsy (27, 28). In the following, we use examples to discuss typical chromosome number abnormalities and CNVs.

Trisomy 21 (Down syndrome)

The most well-known numerical chromosomal aberration is trisomy 21, known as Down syndrome (DS). Its incidence ranges from 1 in 319 to 1 in 1,000 live births, depending on maternal age (29, 30). The prevalence of epilepsy in DS patients is approximately 8-13% (31, 32). Of affected individuals, 40% have seizures in early childhood and another 40% experience seizures after their 30s. Regarding epileptic seizure type, 47% of individuals with DS and epilepsy have partial seizures, 32% have infantile spasms or West syndrome, and 21% experience generalized tonic-clonic seizures (32, 33). It is widely known that patients with DS often have comorbid intellectual disabilities and that 7-19% of such patients meet the criteria for ASD (34–38). It has been also reported that 43% of DS patients have comorbid ADHD (39). Notably, in patients with DS, only autism and epilepsy are known to be associated with cognitive function decline; physical comorbidities have no association with cognitive outcomes (40). Several hypotheses have been proposed to explain the increased susceptibility to epilepsy and neurodevelopmental disorders in DS. These include congenital structural abnormalities of the brain, including abnormal cortical lamination, persistent fetal dendritic morphology, and underdevelopment of synaptic profiles (33, 41).

Chromosome 15q11-q13 duplication syndrome

Maternal duplication of chromosome 15q11-q13, the region responsible for Prader-Willi and Angelman syndromes, is the most common chromosomal abnormality (0.5%–3%) in patients with ASD (42, 43). This region, known as the imprinting region, is phenotypically variable depending on whether the etiologic allele is of paternal or maternal origin. Patients with maternal 15q11-q13 duplication have a high incidence of childhood seizures (44). Paternal duplication is associated with a variety of phenotypes, including sleep disorders such as parasomnias. Up to 50% of affected individuals with paternal duplication also have autistic traits, but these traits are more common in patients with maternal duplication (45). Developmental delay/intellectual disability, ASD, and ADHD are frequently observed in cases of duplication of the *CHRNA7* gene, which encodes a protein that mediates fast signal transmission at synapses and is located in 15q13.3 (46). Several genes that encode γ-aminobutyric acid receptor subunits (*GABRA5*, *GABRB3*, *GABRG3*) are located in the 15q11-q13 region, and it has been hypothesized that dysregulation of inhibitory synapses mediates the etiology of the epilepsy and ASD phenotypes (47).

22q11.2 deletion and duplication syndrome

Manifestations of 22q11.2 deletion syndrome (OMIM #611867) include congenital cardiac disease, cleft palate, characteristic facial features, reduced parathyroid gland size (causing hypocalcemia), absence or dysplasia of the thymus gland (causing immunodeficiency), and psychiatric manifestations such as intellectual disability, ADHD, schizophrenia, and ASD. The physical symptoms of patients with 22q11.2 duplication syndrome (OMIM #608363) include hypotonia and growth retardation leading to short stature. Psychiatric symptoms include intellectual disability, learning disability, and ASD. Studies of 22q11.2 deletion syndrome and epilepsy have shown that focal seizures are the most common epilepsy type, followed by genetic generalized epilepsy, mainly juvenile myoclonic epilepsy (48, 49). The 22q11.2 deletion is associated with a high incidence of schizophrenia, but is also frequently associated with neurodevelopmental disorders. The complication rate of ADHD is 16-37% and that of ASD 13-27% (50). The following candidate genes have been identified as responsible for neurological symptoms in 22q11.2 deletion syndrome (51): *RTN4R*, which encodes a protein that mediates axonal growth inhibition (52), *DGCR8*, the transcript of which is involved in the early stages of microRNA biogenesis (53), *COMT*, which encodes a protein that inactivates catecholamine neurotransmitters in cortical neurons (54), and *PRODH*, which encodes a protein involved in L-glutamate synthesis.

Single gene diseases

Single gene diseases such as fragile X syndrome (FXS), tuberous sclerosis (TSC), myocyte enhancer factor 2 (*MEF2C*)-related disorders, and methyl-CpG binding protein 2 (*MECP2*)-related disorders (Rett syndrome and *MECP2* duplication syndrome) are associated with complications including epilepsy, intellectual disability, ASD, and/or ADHD. The following genes are also associated with ASD,

intellectual disability, and/or epilepsy: *NRXN1*, *SCN1A*, *SCN2A*, *SYNGAP1*, *RELN*, *CNTNAP2*, *SMARCA2*, *PTEN*, *CACNA1C*, *COL4A1*, *UB3A*, *ABAT*, *BCKDK*, *RBFOX1*, *NF1*, *SHANK3*, *CDKL5*, *SYN1*, and *KIAA2022* (15,24,55).

Fragile X syndrome

FXS (OMIM #300623) is an X chromosome-linked mental retardation syndrome characterized by craniofacial features (long face, prominent forehead, large ears, long palpebral fissures, and prominence of the jaw) and psychiatric symptoms such as mental retardation, ASD, and ADHD (56). FXS is caused by CGG trinucleotide repeat expansion in the 5′ UTR of the *FMR1* gene. Fewer than 54 CGG repeats in the *FMR1* gene are normal; 55–200 CGG repeats are permutation sizes that can cause X-associated tremor/ataxia syndrome and fragile X-associated primary ovarian insufficiency. More than 200 CGG repeats constitutes a full mutation, which causes FXS (57). Epilepsy has been reported in approximately 10-20% of FXS patients. The seizure pattern in FXS typically resembles that of childhood benign focal epilepsy. Of individuals with FXS without clinical seizures, 23% show centrotemporal spikes on EEG (58). Complications of neurodevelopmental disorders have been frequently reported in patients with FXS. Of such patients, 54-59% meet the diagnostic behavioral criteria for ADHD based on parent or teacher reports (59). Approximately 60% of male patients with FXS have ASD, and approximately 2-5% of all individuals diagnosed with ASD have FXS (60, 61).

According to a review by Bagni and Zukin, proposed developmental mechanisms for these neurological symptoms in FXS patients include reduced expression of γ-aminobutyric acid type A receptors in the hippocampus, reduced frequency and amplitude of miniature and spontaneous inhibitory postsynaptic currents in the mature amygdala, developmental delay of inhibitory networks, excitatory–inhibitory ratio imbalance of neuron networks, and dysregulation of mammalian target of rapamycin (mTOR) and mitogen-activated protein kinase/extracellular signal-regulated kinase signaling cascades (62).

Tuberous sclerosis complex

TSC1 (OMIM # 191100) and TSC2 (# 613254) are autosomal dominant multisystem diseases characterized by multiple hamartomas in various organ systems including the brain, heart, lungs, skin, and kidneys. The causative genes are *TSC1* and *TSC2*, respectively (63). These genes encode hamartin and tuberin, respectively, which are proteins involved in the regulation of mTOR. Most patients with TSC are affected by epilepsy (64–66). In one retrospective chart review of 291 TCS patients, 38% had a previous history of infantile spasms, 85% had a seizure history, and 54% had seizures of multiple types, not including infantile spasms (66). Another study found that pediatric seizures occurred in approximately 20-38% of patients with TSC, and generally had a poor prognosis (67). Intellectual disability (68), ASD (69), and ADHD (70) are other complications of TSC. An estimated 20-60% of TSC patients have ASD, and it occurs with almost equal frequency in both sexes (71). Up to 50% of TSC patients have ADHD, and it is 10 times more common in such patients than in the general population (72).

mTOR signaling is not only a pivotal regulator of cell growth, proliferation, cell cycle, ribosome biogenesis, autophagy, protein synthesis, and the actin cytoskeleton, but also modulates protein synthesis, which plays a central role in synaptic plasticity (62). Interestingly, mTOR dysregulation has also been observed in mouse models of FXS, in ASD patients with 15q11-q13 duplication, and in mouse models overexpressing *Cyfip1*, a homolog of a gene located in the human 15q11-q13 region whose coding protein interacts with synaptic functional regulator FMR1 (62).

MEF2C-related disorders

Patients with loss of function mutations and *MEF2C* deletions were first reported to have severe intellectual disability, epilepsy, and atypical movements in 2010 (73). This disorder is also known as neurodevelopmental disorder with hypotonia, stereotypic hand movements, and impaired language, or chromosome 5q14.3 deletion syndrome (OMIM #613443). Epilepsy in patients with *MEF2C*-related disorders is variable: 20% of patients have infantile spasms, 33% have myoclonic epilepsy of infantile onset, and 24% have generalized epilepsy of childhood onset. However, 23% have no epilepsy (74). Some patients have autistic features (75), and genetic variant analysis has shown that *MEF2C* is a risk gene for ADHD (76). *Mef2c* haploinsufficiency mice, a model of human *MEF2C* haploinsufficiency, exhibit autistic-like behaviors associated with decreased neurogenesis, increased neuronal apoptosis, and an increased ratio of excitatory–inhibitory balance in the hippocampus (77). In another mouse model of ASD induced by fetal valproate exposure, *Mefc2* expression in the embryonic brain was reduced, suggesting that this gene may be important for fetal brain development (78). Notably, the symptoms characteristic of ASD in these haploinsufficiency mice were ameliorated by postnatal administration of NitroSynapsin, a modified form of memantine (77). These findings suggest that the identification of mechanisms of autism pathogenesis may lead to the development of therapeutic agents for ASD.

MECP2-related disorders

Loss of function variants in *MECP2* are known to cause MeCP2 deficiency, which contributes to the pathogenesis of classical Rett syndrome (OMIM # 312750). There are various manifestations of Rett syndrome, including partial or complete loss of acquired purposeful hand skills, loss of spoken language or other language skills, gait abnormalities, stereotypic hand movements, breathing disturbances when awake, abnormal muscle tone, peripheral vasomotor disturbances, scoliosis/kyphosis, and growth retardation (79). *MECP2* duplication syndrome (OMIM # 300260) is a severe X-linked mental retardation syndrome first described by Lubs et al. in 1999 (80). In addition to the characteristic facial features, the clinical manifestations of this disease include absent speech, loss of ambulation, microcephaly, and recurrent infections; psychiatric symptoms include autistic-like features and epilepsy, which are observed in more than half of patients (81). Epileptic seizures associated with *MECP2* duplication syndrome are usually treatment refractory and comprise epileptic encephalopathy. Lennox–Gastaut syndrome occurs in 55% of *MECP2* duplication syndrome patients (82). It has been

reported that almost all boys with *MECP2* duplication syndrome have characteristics similar to idiopathic ASD when evaluated with the Autism Diagnostic Observation Schedule (83). A study of *Mecp2*-null mice has shown that MeCP2 is involved in upward regulation of transcription of various genes in the hypothalamus, including *MEF2C* (84).

MODELS OF OVERLAP BETWEEN EPILEPSY AND NEURODEVELOPMENTAL DISORDERS

As described above, epilepsy and neurodevelopmental disorders such as ASD and ADHD co-occur in many disorders owing to mutations in the same gene(s). Three biological interpretive models provide possible explanations for this association: (i) neurodevelopmental and epileptic phenotypes arise from the same genetic risk and biological pathways; (ii) neurodevelopmental-like symptoms arise as secondary symptoms of epileptic seizures; and (iii) the two phenotypes arise independently by chance without causality. Interestingly, some epilepsy syndromes (e.g., infantile spasms and Lennox–Gastaut syndrome), appear to be risk factors for later diagnosis of ASD (18). This indicates that, at least for some epilepsy syndromes, neurodevelopmental-like symptoms may be caused by epileptic seizures. However, it remains unclear which of these biological models best explains the co-occurrence of neurodevelopmental disorders and epilepsy, and which model is most appropriate for each genetic disorder. The neurobiological basis of neurodevelopmental disorders comprises many biological dimensions, including genes, epigenomes, cells, brain function, behavior, and clinical manifestations. The biological background of epilepsy and neurodevelopmental disorders comprises complex multifactorial interactions across these multiple biological dimensions (85) (Figure 1). The model in Figure 1 assumes that the core clinical symptoms (represented at the top of the model) are not common across disease categories, whereas the disease risk genes (at the bottom of the model) are shared by multiple psychiatric disorders. This model also suggests that mutations of the same disease risk gene may result in different clinical phenotypes according to the outcome of the interactions between biological dimensions.

In recent years, a variety of new methods have enabled the comprehensive analysis of biological factors known as omics data analysis. This has produced some unexpected findings and contributed to the acquisition of new knowledge. Comprehensive studies that focus on the elucidation of the connections and feedback mechanisms between biological dimensions are called transomics or multiomics analyses (86, 87). Such analyses are needed to comprehensively examine the possibility of biological overlap between neurodevelopmental disorders and epileptic seizures. However, few studies have directly examined the overlap between the different dimensions, and this remains an important issue for future investigation.

Currently, psychiatric diagnoses are usually defined categorically. However, interest has recently increased in the concept that mental illness exists on a spectrum or continuum ranging from health to disease. For example, in the case of neurodevelopmental disorders, DSM-5 introduced the concept of ASD.

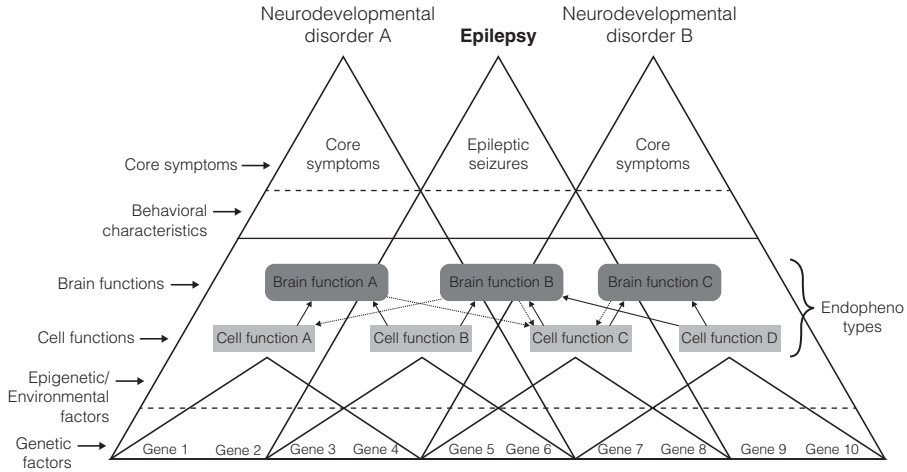

Figure 1. The neurobiological basis of neurodevelopmental disorders and epilepsy. It comprises several biological dimensions, including genes, epigenomes, cells, brain functions, behaviors, and clinical symptom levels. The relationship between a particular biological dimension and other biological dimensions may be characterized by complex multifactorial interactions. This model shows that core clinical symptoms are not common to each disease category, whereas disease risk genes are common to multiple psychiatric disorders.

Therefore, the clinical and genetic overlap between neurodevelopmental disorders and epileptic seizures suggests the need to re-examine the possibility that these disorders can be defined along a single spectrum.

CONCLUSION

In this chapter, we reviewed recent findings related to the co-occurrence of neurodevelopmental disorders and epilepsy. Future analyses will contribute to a growing body of knowledge, as previously unidentified pathological mechanisms common to both diseases are identified. Evidence for a biological overlap between these diseases is likely to lead to a comprehensive understanding of these disorders and the future discovery of new therapeutic targets.

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