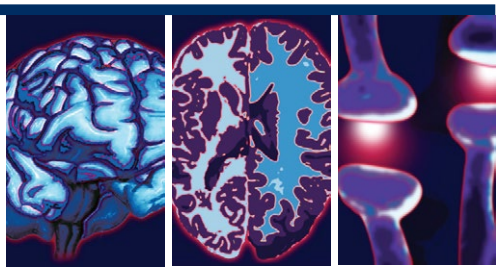
Review



# Comorbidities of Refractory Epilepsy and the Update Mechanism

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**Abstract**

Epilepsy is still an issue that perplexes the epileptologists worldwide, with a reported impact on 50 million populations. With the reconceptualization of epilepsy as a disease of brain networks, it is great timing to rethink epilepsy and those associated comorbidities, including cognitive and behavioral comorbidities, psychiatric comorbidities, cardiovascular disease and migraine. In this review, we introduce the state of the art of these comorbidities of refractory epilepsy, including etiology, epidemiology, manifestation and mechanism. As essential comorbidities of epilepsy share the network consistent with epilepsy, a series of recent studies of comorbidities of epilepsy supply a new perspective on epileptic network. It is possible to accelerate the progression of epilepsy by translating those exciting advances in epileptic network into routine clinical practice.

**Keywords:**

Epilepsy, Comorbidities, Mechanism, Cognitive, Psychiatric, Cardiovascular, Migraine

## Introduction

Epilepsy is a disorder of unprovoked seizures, diagnosing by at least one unprovoked seizure and high risk for another [1]. The majority of patients with refractory epilepsy, which is up to 30% of epilepsy, will suffer a lifetime burden that horrible seizures deteriorate the quality of life with cognitive, psychiatric and (or) other comorbidities [2]. As epilepsy has been regarded as a disease of brain networks, those associated comorbidities, such as cognitive and behavioral comorbidities, psychiatric comorbidities, cardiovascular disease and migraine, are great starting point and refresher for epileptic network [3-8]. Unfortunately, the exact underlying etiology of those comorbidities is not clear. The epilepsy associated comorbidities are often underestimated, consequently, undertreated. Furthermore, cognitive deficits always remain despite seizure greatly control [9]. Increased attention and early management of associated comorbidities is of great significance to improve the quality of life and maximize the opportunity for patients to re-integrate the society. In terms of mechanism, associated comorbidities can be divided into essential comorbidities and secondary comorbidities, according to whether sharing certain same mechanism of seizures [10]. In this review, we focus on comorbidities of refractory epilepsy, discussing their etiology, category, manifestation and current progression of mechanism.

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## ■ Cognitive and behavioral comorbidities

The cognitive and behavioral comorbidities are more common in refractory epilepsy than those with "pharmaco-sensitive" epilepsy. The common cognitive and behavioral comorbidities, including learning disorders, social cognition disorders and attention deficit-hyperactivity disorder (ADHD), always have a huge influence on the quality of life, even greater than does epilepsy. The etiology of cognitive and behavioral comorbidities still remains unclear.

The refractory epilepsy has explicit impact on pediatric neurodevelopment, especially intellectual disability and learning function. A community-based study showed that children with epilepsy had lower overall cognition function than those without [11], whereas another study revealed onset age <5 years and symptomatic epilepsy were associated with low cognition function [12]. In aspect of associated learning disorders, they are often found at the onset, and always described as subtle, consequently, difficult to recognize. Both working memory and processing speed are sensitive markers of impaired learning function, can be used as a screening tool for learning disorders [13]. Regardless of AED use, underlying syndrome and remission status, children with epilepsy often have unsatisfied performance in writing, reading and mathematics, even they are within normal range of IQ [11,14]. Generalized epilepsy is often giving a worse performance in arithmetic test than focal epilepsy [15].

In fact, the definition of social cognition is included autism spectrum disorder (ASD), but often less severe than ASD. The prevalence of epilepsy, both adults and adolescents, with ASD is 20%, at the other hand, 8% of those with epilepsy have ASD, or social cognition deficit less severe than autism [16]. There are serials of studies revealing a higher rate of epilepsy in ASD than general population [17-19].

Patients with refractory epilepsy have a higher rate of attention-deficit/hyperactivity disorder (ADHD), with a reported prevalence ranged from 28% to 70% [20], whereas 5-10% in general population [21]. Combined subtype of ADHD is believed to be more common in developmental ADHD, whereas Inattentive ADHD is more common in children with epilepsy [22]. Several epileptic manifestations are positively related to attention skills, such as location of epileptogenic zone, epilepsy duration, frequency, age of onset and the number of AEDs [23].

## ■ Psychiatric comorbidities

In this part, we review the recent progression on epidemiology of common psychiatric comorbidities of refractory epilepsy, depression and anxiety. In terms of mood disorders, depression is common but often misdiagnosed, with 23.1% prevalence reported by a recent meta-analysis [24]. According to a study on Canadian patients, the prevalence of epilepsy patients with depression is about 30%, and patients with epilepsy are more likely to express anxiety than individuals without epilepsy [25]. The cause of psychiatric comorbidities still remains unknown [26]. Psychiatric comorbidities, associated with poor prognosis, decreased medical adhesion and increased medical cost, have even a greater hazard on the quality of life than seizures do [26]. Psychiatric comorbidities are often difficult to diagnose, as it is tough to distinguish depression and anxiety from the side effects of antiepileptic drugs. Even when depression or anxiety draws attention, epileptologists are possible to consider that mood as a natural response of uncomfortable feelings imposed by epilepsy.

## ■ Other associated comorbidities

The category of comorbidities of epilepsy is various. Cardiovascular comorbidities of epilepsy include various arrhythmias, structural cardiac disease, transient myocardial ischemia and the Takotsubo syndrome. Most patients with epilepsy have arrhythmias, but often without manifestations. It is worth to mention that ictal asystole has been always considered to be the mechanism of sudden unexpected death in epilepsy (SUDEP).

The relationship between migraine and epilepsy is still controversial. Patients with epilepsy have a higher risk for developing migraine [27], and vice versa, individuals with migraine are at higher risk of epilepsy [28]. Although the etiology and mechanism is not clear, migraine is associated with epilepsy, especially benign childhood epilepsy with Centro-temporal spikes (BECTS) [29].

## ■ The update mechanism

In aspect of cognitive and behavioral comorbidities, the ion channel dysfunction caused by genetic mutations contributes to epilepsy, disturbing different brain network depend on specific distribution. For example,

decreased excitability of GABAergic cerebellar Purkinje cells caused by SCN1A mutation not only contributes to seizure but also can be linked with learning and behavioral dysfunction [30]. Epilepsy and cognitive comorbidities attribute to interictal frequent epileptiform discharges, which impair synaptic plasticity, neurogenesis and memory retrieval by inhibition of action potential firing through spine loss in pyramidal cells in hippocampal CA3 [31].

Interestingly, epilepsy and ASD share mechanism in level of gene, protein, neurotransmitters, ion channel and synapse. In terms of gene level, DEPDC5, NPRL3 and MTOR have been elucidated that associated with epilepsy and ASD [32-34]. The mutation of subunit of the sodium channel gene, SCN1A, is often found in both patients with dravet syndrome and ASD families [35,36]. In patients with epilepsy, decreased level of GABA contributes to epileptogenesis, whereas GABAA binding sites have been found to be reduced in ASD individuals [37]. In addition, neurexin and synapsin dysfunction can be implicated in epilepsy and ASD comorbidity [38,39]. These findings suggest that the neurobiological and genetic mechanisms of epilepsy and ASD can be reasonably regarded as shared.

Ictal asystole is the most common cardiovascular comorbidity, and attributes to epilepsy activity initiating the autonomic networks, such as cingulate gyrus and amygdala [40].

For both migraine comorbidity and epilepsy, neuronal hyper excitability is thought to be key point to initiate. In migraine the hyper excitabilities of pyramidal cells result in decreased cortical propagation which in turn generates the pain and aura [41]. Furthermore, the relationship between migraine and epilepsy can also be supported by the evidence that, valproate and topiramate are effective for migraine prevention [42]. Serials of genetic mutations have been reported to be shared in both epilepsy and migraine, such as CACNA1A, ATP1A2, PRRT2, encoding calcium channel, sodium/potassium pump and axonal protein [6].

## Conclusion

With the rapid development of neuroscience, the mechanism of epileptogenensis still remains uncertain. The research of comorbidities of epilepsy reveals a new perspective on epileptogenesis. As epilepsy is regarded as a disease of brain network, the manifestation of comorbidities implies which network is involved. The core of exploring the relationship between epilepsy and those associated comorbidities is to identify similarities and differences of neurobiological and genetic mechanism of populations with epilepsy-only or other disorders-only. Consequently, it is hopeful that several new markers and precise treatment will emerge in the future.

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