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Epilepsy and GI Disorders

Halil Kocamaz and Sedat Işıkay

Abstract

The gastrointestinal system communicates with the brain by way of vagus nerve fibers and the gut-brain axis. There is a well-known relationship between autoimmune diseases and epileptogenesis, and this may explain the involvement of gut microbiota in the course of epilepsy. Many seizures which are described, depending the severity and/or duration, as benign or epilepsy may be related and based on gastrointestinal origin. Epilepsy and related neurological symptoms may alert the clinician to additional life-threatening conditions and complications during the course of gastrointestinal system-based chronic disease such as inflammatory bowel disease and celiac disease. Since the gut is the only part of inner body exposed to environment, novel therapeutic options that target gut microbiata may be promising in many diseases including epilepsy.

Keywords: autoimmune, electrolyte, epilepsy, gastrointestinal, gut

1. Introduction

The enteric nervous system (ENS), located in the wall of the bowel, is also known as the "second brain." The ENS exhibits a wide similarity to the brain, both structurally and functionally. Its neuronal structure is not cemented by collagen and Schwann cells but by glial astrocytes of the central nervous system (CNS). It has similar complex functions to the brain and contains various neurotransmitters [1]. The gastrointestinal system communicates with the brain through vagus nerve fibers and the gut-brain axis. The interaction between the CNS and ENS is known as the gut-brain axis. This axis is mainly regulated by gut microbiota and related neurotransmitters such as 5-hydroxytryptamine (5-HT), also known as serotonin [2]. The common features in terms of function between the ENS and the CNS are reflected in the context of disorder, in that gastrointestinal dysfunction may be seen in neurological diseases, and neurological dysfunction may become evident in gastrointestinal disease processes [3]. Painful abdominal cramping, nausea, and cyclical vomiting syndrome are related to childhood epilepsy, and also in adults, abdominal symptoms are usually associated with idiopathic complex partial or secondary generalized seizures [4]. The ketogenic diet has beneficial effects on intractable seizures, and has been shown to affect the gut microbiota [5]. The gut microbiota and the immune system are interrelated [6]. Gut bacteria balance affects the development of autoimmune disorders. For instance, changing the balance of *Firmicutes* and *Bacteroidetes* in gut microbiota may promote autoimmune disorders such as type 1 diabetes mellitus [7]. The balance in the gut microbiota is also linked to the pro- and anti-inflammatory immune responses [8]. There is a well-known relationship between autoimmune diseases and epileptogenesis, and this may explain the involvement of gut microbiota in the course of epilepsy. The incidence

of epilepsy differs between developed and developing countries, similarly to the differences observed in the gut microbiota [9]. Autoimmune diseases occur when the immune system exhibits redundant responses against the tissues of its own body. The etiology of autoimmune disease is still unclear, but some potential factors such as the environment, genetic predisposition, vaccines, an unbalanced diet, and immune disorders have been implicated [10, 11]. A large number of epilepsy cases have an autoimmune-related basis, and adjunctive immunotherapy has beneficial effects in such cases [12]. Some serum autoantibodies are also epileptogenic, and immunomodulatory therapy may attenuate the progression of some epilepsy syndromes [13]. In this context, gut microbiota-targeted therapy may be useful in the treatment of certain types of epilepsy syndromes by altering gut-related immunity and the gut-brain axis, which is also controlled by neurotransmitters. One case report stated that fecal microbiota transplantation cured refractory epilepsy in concomitant Crohn's disease [14].

2. GI disorders could be accompanied by epilepsy or seizures

Electrolyte imbalances resulting from acute or chronic vomiting and diarrhea may trigger severe seizures, especially in early childhood. Acute and profound electrolyte imbalances may lead to life-threatening neurological deterioration and intractable seizures [15]. Electrolyte imbalance and dehydration disrupt the regular voltage gradient across cellular membranes and lead to neuronal excitability following impaired neuronal discharge and epileptiform activities. Altered plasma osmolality is also substantially involved in the progression of abnormal neuronal discharge and disturbed brain metabolism. Electrolyte imbalance-related seizures are self-limited and do not commonly lead to morphological changes in the CNS if treated promptly and adequately. Epileptiform activities are commonly seen in patients with sodium abnormalities, hypocalcemia, and hypomagnesemia [16]. Seizures are related to electrolyte imbalance that usually presents as tonic-clonic type, although focal and other types may also be seen. Patients with electrolyte imbalance-related seizure frequently have a concomitant history of vomiting and diarrhea [17]. In order to identify the cause of seizures, prompt analyses of serum electrolytes and glucose levels should be performed in patients with first seizure at any age [18]. Hyponatremia is defined as a sodium level of less than 135 mEq/L. Acute hyponatremia (decreased sodium levels within a matter of hours) is mainly related to severe neurological deterioration including intractable seizures. Cerebral edema and cerebral herniation may be present as major life-threatening complications, particularly if serum sodium levels decrease to 120 mEq/L within a few hours [19]. Many clinical conditions and drugs may be responsible for hyponatremia, but antiepileptic drugs (AED) such as carbamazepine (CBZ), oxcarbazepine (OXC), and eslicarbazepine (ESL) should be remembered as causative drugs for developing hyponatremia due to inappropriate antidiuretic hormone syndrome [20]. Hyponatremia usually occurs as a nonspecific wave slowing in EEG. Other EEG abnormalities include triphasic waves, high amplitude delta activity bursts, and central high amplitude delta waves with paroxysms. Interestingly, hypernatremia (when sodium levels exceed 145 mEq/L) may be seen as a consequence of tonic-clonic seizures. The pathological mechanism involved in hypernatremia after seizures depends on muscle contraction-related extracellular water depletion. Hypernatremia causes high intracellular osmolality of brain cells and shrinkage of the brain. The correction of hypernatremia should be gradual in order not to promote severe seizures. Hypocalcemia is defined as a

plasma calcium level under 8.5 mg/dL, or an ionized calcium concentration less than 4 m/dL. Sodium and potassium abnormalities are more common in gastroenteritis, and hypocalcemia may also be seen during the course of gastroenteritis [21]. The clinical manifestations of hypocalcemia are related to the degree of hypocalcemia and the rate of decrease in serum calcium concentrations. The main clinical manifestation of hypocalcemia is neuromuscular excitability and tetany, although acute hypocalcemia may result in tonic-clonic, focal motor, and rarely absent seizures [22]. The major causes of hypocalcemia are vitamin D deficiency and drugs. Antiepileptic drugs (AEDs) such as phenobarbital, phenytoin, carbamazepine, and primidone may disrupt the absorption of intestinal calcium and lead to hypocalcemic symptoms, including seizures [23]. Hypocalcemia-related seizures can be easily treated with calcium therapy, and anticonvulsive therapy is not usually necessary [24].

Gastrointestinal infections are another cause of the development of epileptiform activities. There is a known relationship between diarrhea and seizures, especially in early childhood. Convulsion with mild gastroenteritis (CwG) was first reported in 1982 by the Japanese researcher Morooka, and is also known as "situation-related seizures" [25]. The diagnostic criteria for CwG were defined as follows [26]:

1. The child was previously healthy.

2. Nonfebrile convulsions accompanied by mild gastroenteritis, possible mild dehydration, absence of apparent acid intoxication, and electrolyte imbalance.

3. Convulsions mainly occurring during winter, and the gastroenteritis may persist for 1–5 days.

4. Convulsions may manifest as single or multiple episodes of generalized tonic-clonic seizure (GTCS).

5. Normal interictal electroencephalogram (EEG).

6. Normal serum electrolytes, serum glucose, and cerebrospinal fluid (CSF) with stool antigen test positive for rotavirus.

7. Favorable prognosis with rare relapse and unimpeded development.

CwG is primarily caused by rotavirus, norovirus, sapovirus, adenovirus, and coxsakie virus. Convulsions usually occur between the first and sixth day after the initial symptoms of gastroenteritis. The principal agent determined in cases of CwG is rotavirus. The mechanisms involved in CwG are still unknown [27]. Since CwG only appears in early childhood, it has been hypothesized to be related to the immature nervous system, similarly to febrile convulsions. Rotavirus can directly reach the central nervous system and cause cerebropathy, encephalitis, or convulsions [28]. Children with CwG do not require antiepileptic treatment. CWG has a short and benign course, with most episodes ending within 24 hours. Acute treatment with antiepileptic should be considered in patients with two or more convulsions [29]. Bacterial agents such as *Shigella* species are also related to neurological manifestations, including seizures. The pathophysiological mechanism of *Shigella*-related seizures has not been elucidated. Shiga toxin availability has been shown not to be essential for neurological complication [30]. Cytokines and host-immune responses are related to neurological complication during the

course of disease [31]. Hyponatremia and hypoglycemia are also another factor for developing *Shigella*-related seizures and other neurological complications. *Shigella* infections are usually serious and life-threatening particularly in the case of extraintestinal and systemic involvement in developing countries. *Shigella* dysentery type 1 frequently leads to neurological complications. Appropriate treatment of *Shigella* infections with antibiotics will prevent recurrent seizures and neurological deterioration [32].

Abdominal epilepsy (*AE*) is characterized by a paroxysmal episode of abdominal pain, various abdominal symptoms, electroencephalogram (EEG) abnormalities, and favorable response to AEDs. AE is commonly seen in childhood although there have been reports of adults with AE [33]. Gastrointestinal symptoms associated with AE include abdominal pain, nausea, and vomiting, and patients may also have concomitant neurological symptoms, such as postictal lethargy, drowsiness, headache, blindness, paresthesia, and convulsions [34]. The pathophysiology of AE is not well understood, but several hypotheses have been suggested including the one which holds that abdominal epilepsy results from abnormal brain activity in the temporal lobe involving the amygdala. The amygdala then transmits activities to the gastrointestinal tract via direct projections to the dorsal motor nucleus of the vagus nerve through which gastrointestinal symptoms are felt to localized [35].

There are four diagnostic criteria for AE in the context of noninflammatory, neoplastic, metabolic, or anatomic abnormalities.

These are:

a. Otherwise unexplained, paroxysmal gastrointestinal complaints.

b. Symptoms arising from CNS disturbance.

c. An abnormal EEG with findings specific for a seizure disorder.

d. Improvement with anticonvulsant medication.

The most important differential for AE is abdominal migraine. In patients presenting with headache, it is very difficult to differentiate AE and abdominal migraine because symptoms usually overlap. Duration of the symptoms may be used to differentiate the two; being longer in migraine than in AE [36]. EEG is usually abnormal in AE and may confirm the diagnosis of AE. There is no recommended special AED therapy for abdominal epilepsy. Most of the patients may respond to single-drug therapy [37].

Inflammatory bowel disease: seizures may be seen as a clinical manifestation during the course of inflammatory bowel disease (IBD) particularly in severe cases. All types of seizures including status epilepticus have been reported. Thromboembolic events and various vitamin deficiencies such as thiamine and vitamin B12 are mostly responsible for seizures in IBD [38]. In case of seizure, a patient with IBD should be evaluated for a cranial thromboembolic event.

Celiac disease is characterized by malabsorption and gastrointestinal symptoms due to the intestinal villus injury. Approximately 10% of patients with celiac disease exhibit neurological manifestations including seizures [39]. The frequency of celiac disease in individuals with epilepsy ranges from 0.78 to 9.1% [40]. It has been suggested that vitamin deficiencies play an important role in the association between epilepsy and celiac disease because vitamins have neurotrophic and neuroprotective effects [41]. Immune mechanisms are also implicated in the pathogenesis of epileptic disorders in celiac disease. In support of this hypothesis, anti-Purkinje cell

and anti-ganglioside antibodies have been determined in celiac disease patients with neurological dysfunction. Most of epileptic patients with celiac disease have been cured after adopting a gluten-free diet [42].

3. Gastrointestinal problems associated with antiepileptic drugs

AEDs have a relatively narrow therapeutic index, and their adverse effects can impact on any organ or system. Some 10–30% of patients with epilepsy discontinue their first prescribed AED due to adverse effects and intolerance [43]. Many AEDs cause gastrointestinal side effects. Multi-AEDs in particular may increase the potential side effects in intractable seizures. The most common AED-related side effects are vomiting and nausea [44]. Some important adverse gastrointestinal side effects of AEDs are mentioned below.

Valproic acid (*VA*) may cause gastrointestinal side effects such as nausea, diarrhea, abdominal pain, and vomiting. This problem may be seen particularly when the initial doses are taken. The meal time ingestion and slow release form of the drug will be tolerated by most patients [45]. Acute pancreatitis is also related to VA ingestion, and the clinician should suspect this in case of severe abdominal pain during VA therapy. Hepatotoxicity is a life-threatening condition related to VA therapy. Patients with organic brain disease, treated with several antiepileptic drugs, and younger than 2 years old have the highest risk for developing hepatotoxicity during VA treatment. Liver function tests, ammonia, and other tests are not reliable for assessing VA-related hepatotoxicity. However, clinical symptoms such as vomiting, nausea, anorexia, and lethargy may be an indicator of fatal hepatotoxicity [46].

Benzodiazepines are commonly prescribed drugs particularly in childhood epileptic syndromes. Although they exhibit sedation-related adverse effects, benzodiazepines are usually well tolerated in the gastrointestinal system and do not lead to hepatic damage unless combined with other AEDs [47].

Carbamazepine (*CBZ*) is well tolerated in the gastrointestinal system, but idiosyncratic reaction due to CBZ might be related to granulomatous hepatitis, fever, and rash [48].

Ethosuximide (*ESM*) has reversible, adverse gastrointestinal effects, such as abdominal discomfort, vomiting, diarrhea, and hiccups, but these can all be prevented if ESM is taken after meals [49].

Felbamate and *topiramate* (*TPM*) may cause anorexia, thus promoting weight loss, and there are reports of fatal hepatotoxicity due to felbamate [50, 51].

4. Conclusions

Gastrointestinal system manifestations may be a milestone of many neurological diseases, including epilepsy and benign seizures. Epilepsy and related neurological symptoms may alert the clinician to the presence of additional life-threatening conditions and complications during the course of gastrointestinal-based chronic disease such as inflammatory bowel disease and celiac disease. Since the gut is the only part of inner body exposed to environment, novel therapeutic options that target gut microbiata may be promising in many diseases including epilepsy.

Conflict of interest

The authors have no conflict of interest to report.

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