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Epilepsy and the Gut: Perpetrator or Victim?

The Gut and Epilepsy

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Abstract

The brain and the gut are linked together with a complex, bi-path link known as the gut-brain axis through the central and enteric nervous systems. So, the brain directly affects and controls the gut through various neurocrine and endocrine processes, and the gut impacts the brain *via* different mechanisms. Epilepsy is a CNS disorder with abnormal brain activity, causing repeated seizures due to a transient excessive or synchronous alteration in the brain's electrical activity. Due to the strong relationship between the enteric and the central nervous systems, gastrointestinal dysfunction may increase the risk of epilepsy. Meanwhile, about 2.5% of patients with epilepsy were misdiagnosed as gastrointestinal disorders, especially in children below the age of one year. Gut dysbiosis also has a significant role in epileptogenesis. Epilepsy, in turn, affects the gastrointestinal tract in different forms, such as abdominal aura, epilepsy with abdominal pain, and the adverse effects of medications on the gut and the gut microbiota. epilepsy with abdominal pain, a type of temporal lobe epilepsy, is an uncommon cause of abdominal pain. Epilepsy also can present with postictal states with gastrointestinal manifestations such as postictal hypersalivation, hyperphagia, or compulsive water drinking. At the same time, antiseizure medications have many gastrointestinal side effects.

On the other hand, some antiseizure medications may improve some gastrointestinal diseases. Many gut manipulations were used successfully to manage epilepsy. Prebiotics, probiotics, synbiotics, postbiotics, a ketogenic diet, fecal microbiota transplantation, and vagus nerve stimulation were used successfully to treat some patients with epilepsy. Other manipulations such as omental transposition are still in need of more studies. This narrative review will discuss the different ways in which the gut and epilepsy affect each other.

Key Words: Epilepsy; epilepsy with abdominal pain; Gut, Gastrointestinal Diseases; Gut-Brain-Microbiota Axis; Abdominal Aura; Ketogenic Diet; Abdominal Migraine

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Core Tip: The brain and the gut have an intense but complex interaction through a strong relationship between the enteric and the central nervous systems. Epilepsy and the gut may affect each other in diverse ways. At the same time, about 2.5% of patients with epilepsy are misdiagnosed as gastrointestinal disorders, especially at an early age. Gut dysbiosis also has a significant role in epileptogenesis. Epilepsy, in turn, affects the gastrointestinal tract in different forms, such as abdominal aura, epilepsy with abdominal pain, and the adverse effects of antiseizure medications on the gut and the gut microbiota. At the same time, many gut manipulations successfully managed some cases of epilepsy.

INTRODUCTION

The human body organs and systems interact with each other in harmony. However, the interaction between the brain and the gut is overly complex, forming a two-way link known as the gut-brain axis through the central and the enteric nervous system. The enteric nervous system (ENS) is the most crucial autonomic nervous system component. It has common structural and functional similarities with the brain, consequently named the second brain, forming 90-95% of total body serotonin [1]. It is uniquely prepared with intrinsic microcircuits to orchestrate the gastrointestinal functions independent of the central nervous system (CNS) control [2]. The brain directly affects the stomach and intestines and controls the gut through various neurocrine and endocrine processes [3].

On the other hand, the gut impacts the brain *via* different mechanisms, including neuropeptides and neurotransmitters release such as leptin and serotonin, vagus nerve activation, immune signaling through controlling the release of secretory IgA, affecting the integrity of mucous membrane barrier through Zonulin protein, and local production of short-chain fatty acids such as butyrate by gut microbiota [4]. The gut-

brain axis explains the effects of the emotional and cognitive centers of the brain and its control over peripheral intestinal functions. It also describes how a chronic painful abdominal condition such as irritable bowel syndrome can affect the cognitive and psychological function of the body [5]. Many neurological disorders—including hereditary, metabolic, infectious, vascular, inflammatory, and metabolic diseases—may affect the brain and gastrointestinal tract. Consequently, the clinical neurological or gastrointestinal findings may assist confirm the diagnosis or reducing the differential diagnosis [6]. This review sheds some light on the relationship between epilepsy, a common neurological disorder, and its effects on the abdomen and vice versa.

I- EPILEPSY AND SEIZURE DISORDERS IN GASTROINTESTINAL DISORDERS:

Epilepsy is a CNS disorder with abnormal brain epileptic activity, causing repeated seizures or periods of sudden abnormal motor or sensory behavior and sometimes impaired or even loss of consciousness due to a transient excessive or synchronous alteration in the brain's electrical activity. Any part of the brain can be affected by epileptic activity, especially the mesial part of the temporal lobes [7]. Epilepsy is a common neurological condition, affecting about 5-10% of the population at a particular time of their life and about 0.5-1% of children. It can affect any age or gender and all races [8].

According to the etiology, there are four main types of epilepsy: idiopathic, symptomatic, provoked, and cryptogenic, resulting from genetic, structural/metabolic, immunological, infectious, or unknown causes. Idiopathic epilepsy is pure epilepsy resulting from a single gene disorder or complex inheritance. Symptomatic epilepsy has predominately genetic or developmental causation such as childhood epilepsy syndromes, progressive myoclonic epilepsies, neurocutaneous syndromes, other single-gene neurologic disorders, chromosomal disorders, developmental cerebral structure anomalies, perinatal and infantile causes, cerebral trauma, tumor, or infection, cerebrovascular disorders, cerebral immunologic disorders, or degenerative brain

diseases. Provoked epilepsy could arise from provocation factors like fever or menses or reflex epilepsy such as photosensitive or reading epilepsies. Cryptogenic epilepsies are "unknown" and more common in adults than in the pediatric age [9,10]. Due to the strong relationship between the enteric and the central nervous systems, gastrointestinal dysfunction can be seen in neurological disorders, and neurological dysfunction can be seen in gastrointestinal disorders [11]. About 2.5% of patients with epilepsy were misdiagnosed as gastrointestinal disorders, especially in children below the age of one year [12].

Gastroesophageal Reflux and Gastroesophageal Reflux Disease (GERD):

Gastroesophageal reflux disease (GERD) is a common childhood disorder. It can simulate epileptic seizures and may be misdiagnosed as epilepsy. Sandifer Syndrome is a distinct clinical entity presented with GER, irritability, and abnormal movements of the head and body with spasmodic contractions of the neck. It may appear as paroxysms with abnormal neurobehavioral like crying, irritability, torticollis, head/eye version, and extensor spasm of the neck with dystonic posturing. These paroxysms may simulate epilepsy and can be misdiagnosed with specific types of epilepsy, particularly infantile spasms [13].

On the other hand, epilepsy can be missed as GERD. Sweetman *et al* reported a gelastic seizure due to hypothalamic hamartomas misdiagnosed as GERD [14]. Eating epilepsy is a type of feeding-related reflex focal epilepsy. It may be misdiagnosed as GERD, especially in very young infants [15]. Eating epilepsy should be considered if the history, clinical examination, and investigations for GER and apparent life-threatening events are absent [16].

Meanwhile, GERD is a common comorbidity in children with neurological problems such as cerebral palsy, frequently complicated with epilepsy. Early-onset neurological disease, abnormal EEGs, and the presence of mitochondrial disorder are significant risk factors for severe GERD [17]. The presence of GERD in such patients may jeopardize their management and mimic refractory seizures [18]. Asymptomatic gastroesophageal reflux can induce laryngospasm during sleep. This nocturnal laryngospasm causes

Non-Rapid Eye Movement (NREM) parasomnias which clinically simulate Sleep-Related Hypermotor Epilepsy (SHE). Video-electroencephalogram (vEEG) can differentiate between the two conditions [19]. The nocturnal choking sensation is a scary condition that may complicate insular epilepsy, nocturnal laryngospasm, and gastro-oesophageal reflux [20]. Acid reflux can induce obstructive laryngospasm and subsequent respiratory arrest, a probable mechanism of sudden unexpected death in epileptic patients. Proper GERD management and antiseizure medication significantly improve the prognosis [21].

Peptic Ulcer:

Peptic ulcers are up to eight times more prevalent in patients with epilepsy than in the general population [22]. At the same time, epilepsy can be misdiagnosed as a peptic ulcer, as reported by Magon P [23]. At the same time, a perforated peptic ulcer may provoke or complicate a generalized tonic-clonic seizure. Consequently, we should pay careful attention to the vital sign during seizure episodes. Omeprazole is a proton pump inhibitor effectively used to treat peptic ulcers. It has effective anticonvulsant activity through carbonic anhydrase inhibition but with rapid tolerance [24].

Celiac Disease:

Celiac disease is a well-known systemic autoimmune disease characterized by gluten-induced autoimmune intestinal villous atrophy, malabsorption, and various systemic and gastrointestinal symptoms. The older the patient with celiac disease is, the more the prevalence of systemic symptoms not related to the gastrointestinal tract, including the neurological symptoms [25]. About 10% of patients with celiac disease develop neurological complications, including seizures. At the same time, about 0.78 to 9.1% of patients with epilepsy develop celiac disease [26,27]. The exact mechanism of neurological manifestations is poorly understood, probably related to immune mechanisms. This hypothesis is advocated by the presence of anti-Purkinje cell and anti-ganglioside antibodies in patients with celiac disease who developed neurological manifestations [28]. Another possible hypothesis is neurological damage due to deficiencies of the neurotrophic and neuroprotective vitamins (e.g., vitamin D, vitamin E, thiamine, and

vitamin B12) resulting from the malabsorption associated with celiac disease [29]. The prevalence of drug-resistant epilepsy is more common in children who have celiac disease as comorbidity. Most patients with celiac disease and epilepsy have been cured with adherence to a gluten-free diet. Adherence to a gluten-free diet and adequate antiseizure medications can also reduce the seizure frequency and severity in patients with celiac disease and drug-resistant epilepsy [30].

Gut Dysbiosis:

Gut dysbiosis strongly relates to autoimmune diseases, which are closely linked with epilepsy, suggesting an association between epilepsy and gut dysbiosis [3]. Huang *et al* showed that mild gastroenteritis precedes the development of benign infantile convulsions. This temporal relation links the infection-induced gut dysbiosis with epileptogenesis [31]. Şafak *et al* found a significant increase in Fusobacteria species prevalence in patients with epilepsy (10.6%) but not in the healthy control. This considerable shift and drift in the intestinal microbiota and the subsequent gut dysbiosis may be present in certain epilepsy types [32]. Meanwhile, the gut microbiome differs in patients with drug-resistant epilepsy (e.g., *Cronobacter, Bacteroides, Bifidobacterium,* and *Erysipelatoclostridium*) from patients with drug-sensitive epilepsy with an abnormally increased richness of rare flora. On the other hand, patients with drug-sensitive epilepsy have a gut microbiome composition like the healthy controls, enforcing the evidence of effects of gut dysbiosis in the development of epilepsy and drug-resistant epilepsy [33,34].

7

Irritable Bowel Syndrome:

Irritable bowel syndrome (IBS) is a constellation of symptoms occurring together, such as repeated abdominal pain and changes in bowel habits, such as diarrhea, constipation, or both. It affects about 7-21% of the population [35]. IBS is associated with increasing the incidence of epilepsy, particularly temporal lobe epilepsy. A large population-based cohort study by Chen *et al* showed that IBS increases the epilepsy risk with a cumulative incidence of epilepsy of 2.54/1000 person-years *vs* 1.86/1000 person-years in the cohort without IBS with an adjusted hazard ratio of 1.30 [36]. Studies also showed

that the incidence of irritable bowel syndrome increases five times in patients with epilepsy than in controls [37]. There is also an increased incidence of functional gastrointestinal disorders, including IBS, in children with epilepsy than in matching control [38]. epilepsy with abdominal pain could also be misdiagnosed as IBS [39]. The cumulative data from these studies showed the bidirectional link between IBS and epilepsy. The exact cause of this increase in epilepsy risk is not known. It is probably related to the shared pathophysiological mechanisms and risk factors such as disturbed brain-gut axis, microbiota imbalance of the gastrointestinal tract, increased incidence of dietary allergies, neuroimmune interactions, and mucosal inflammatory mediators' deregulation in the gastrointestinal tract [40-42]. Patients with epilepsy who have IBS as comorbidity have an increased rate of depressive and anxiety disorders [43]. If IBS is present in patients with drug-resistant epilepsy, most of the seizures occur during the period of altered bowel movements [44].

Inflammatory Bowel Diseases:

Inflammatory bowel diseases (IBD) are chronic autoimmune and immune-mediated inflammatory disorders affecting the digestive system with gastrointestinal and systemic manifestations, including the central and peripheral nervous systems. IBDs include ulcerative colitis, Crohn's disease, and unclassified IBD [45]. Neurological complications occur in 0.25% to 47.5%. of patients with IBDs. Seizures of all types, including status epilepticus, can be observed during the clinical course of IBDs, especially in severe cases [46]. Many underlying mechanisms explain the occurrence of seizures in IBDs. These mechanisms include autoimmune-mediated neuroinflammation, gut dysbiosis with brain-gut-microbiota axis dysfunction, the associated nutritional deficiencies, especially thiamine and vitamin B12, increased incidence of infections, arterial and venous thromboembolism, and possible side effects of medications especially sulfasalazine, metronidazole, steroids, tumor necrosis factor-α (TNF-α) inhibitors, and anti-integrin antibodies [47]. Seizures in patients with IBDs indicate the need to rule out a cranial thromboembolic event [48].

Gastrointestinal Disorders in Children with Autism:

Gastrointestinal disorders occur in 46%-84% of children with autism. The most common GI problems observed in children with autism are motility disorders such as chronic constipation or diarrhea, nausea, vomiting, gastroesophageal reflux or disease, chronic flatulence, abdominal discomfort, ulcers, inflammatory bowel disease, colitis, food allergies or intolerance, and failure to thrive. The severity of autism strongly correlates positively with gastrointestinal symptoms [49]. Meanwhile, abnormal EEG is present in 60% of children with autism (compared to 6-7% of typically developed children), while epilepsy is present in 10% to 30% of children with autism. Children with autism have a high rate of celiac disease and gut dysbiosis, which increases the incidence of epilepsy [50].

Situation-related Seizures (Convulsions associated with Gastrointestinal infections CwG):

Gastrointestinal infections were first reported to cause epileptiform activity development by Japanese researcher Morooka in 1982 and were called "situation-related seizures" [51]. It occurred in a previously healthy child who developed nonfebrile convulsions following mild gastroenteritis and mild dehydration for 1–5 days without apparent acid intoxication or electrolyte imbalance. It usually occurs during the winter, mainly by the rotavirus, which can reach the brain and cause encephalitis, cerebropathy, or convulsions [52]. The convulsions may present as single or multiple attacks of generalized tonic-clonic or focal seizure with characteristic normal interictal EEG, normal electrolytes, serum glucose, and cerebrospinal fluid (CSF). Stool analysis may test positive for rotavirus, norovirus, adenovirus, sapovirus, and coxsackievirus. It occurs in young children with an immature nervous system, like febrile convulsions [53]. Unfortunately, the prevalence of this type of convulsion is on the rise and has not been affected by the introduction of rotavirus vaccination [54]. The etiology and pathophysiology are not yet thoroughly explained. However, it could be related to direct microbial invasion of the CNS due to the indirect effects of specific mediators triggered by gastrointestinal infections [55]. This type of seizure has a favorable

prognosis with infrequent relapse and typically normal development without the need for long-term antiseizure therapy [56].

II-EFFECTS OF EPILEPSY ON THE GUT:

As the brain has a bidirectional relationship with the gut, neurological disorders may impact the gastrointestinal tract. Examples of this impact include the occurrence of sialorrhea, anorexia, dysphagia, gastroparesis, motility disorders such as diarrhea, intestinal pseudo-obstruction, constipation, and fecal incontinence [57]. Hence, epilepsy, in turn, affects the gastrointestinal tract in different forms, such as abdominal aura, epilepsy with abdominal pain, and the adverse effects of medications on the gut and the gut microbiota.

Abdominal Aura:

An 'aura' is subjective warning feelings, experiences, movements, or events (e.g., specific memory, music, song, or swirling colors) some people with epilepsy may experience, usually before or at the onset of a tonic-clonic seizure. Auras occur in about 70% of patients with generalized epilepsy [58]. Auras arise due to the activation of a functional cortex by aberrant, unilateral, focal, and short neuronal discharge [59]. It is a form of an aware focal seizure that develops into another type of seizure. It usually occurs at the seizure onset before impairment or loss of consciousness and is usually memorized afterward. We should differentiate auras from the premonitory or prodromal sensations, which occur at least 30 minutes before the seizures [60]. There are different forms of auras depending on the epileptogenic zone. Auras could be visual, auditory, olfactory, gustatory, somatosensory, psychic, autonomic, or even sexual. Hence, auras serve as accurate anatomical markers of the epileptogenic zone [61]. However, auras could be multiple, as reported in 6% of patients with epilepsy. Multiple auras are associated with multifocal epilepsy or activation of a neural network that involves more than one functional region. The presence of aura has an essential role in diagnosing, localization, and classification of epilepsy. Epileptic aura could assist in differentiating partial from generalized seizures [62].

Gustatory auras or gustatory hallucination epilepsy are a type of simple partial seizures. They are characterized by taste sensations, including sweet, bitter, acidic, salty, or metallic tastes, as the first clinical manifestation of the seizure. It is one of the manifestations of parietal, temporal, or temporoparietal seizures and often evolves into complex partial seizures [59]. It occurs in the form of a sudden taste sensation of short duration, primarily seconds, that usually follow or is accompanied by the olfactory hallucination that resembles the perceived taste in the absence of an actual stimulus of the sensation. Both gustatory and olfactory auras are often linked together and are difficult to differentiate [63]. Gustatory auras arise from the mesial temporal region, particularly from the left side, and are a manifestation of mesial temporal sclerosis or tumors [64].

Epigastric aura (visceral aura) is a somatosensory (e.g., pain) aura that typically demonstrates an increasing epigastric sensation. It may appear as visceral sensations (e.g., abdominal discomfort), visceromotor symptoms (e.g., vomiting, borborygmi, or tachycardia), or vegetative symptoms (e.g., blushing or sweating). Epigastric aura occurs due to abnormal neuronal activation and discharges in the sensory cortex representing the abdominal viscera [65]. This type of aura is frequently seen in migraine or epilepsy. Epigastric auras are the most prevalent aura in medial temporal lobe epilepsy. It also may have an insular origin [66]. The presence, type, and severity of epigastric aura and other forms of autonomic manifestations depend on the seizure onset location and timing, propagation pathway, lateralization, and the persistence of interictal autonomic dysfunction. The presence of a severe autonomic aura can expect the occurrence of sudden death [67].

Abdominal skin temperature in focal epilepsy

Thermographic studies showed that the abdominal wall has colder spots and areas in patients with focal-onset epilepsy than in controls. It could be related to the visceral-somatic and the somatic-visceral neurological interactions [68]. We can use infrared thermography mapping and thermochromic/thermosensitive silicone (TTS) to locate the irritative epileptogenic areas in patients with focal epilepsy. Their accuracy and

safety are like electrocorticography. This thermographic localization of the epileptogenic activity can be used to locate the irritative zones in neurosurgery, particularly epilepsy surgery [69].

Epilepsy with Abdominal Pain (Abdominal Epilepsy)

Abdominal pain is one of the most frequent complaints, especially in pediatric age. It may result from a wide range of causes, both intra- and extra-abdominal. Systemic causes of abdominal pain may include hereditary, infectious, inflammatory, metabolic diseases, and neurologic disorders [70]. Many neurologic diseases can cause abdominal pain. For example, abdominal migraine, epilepsy, peripheral neuropathy, or even cerebral tumors can present with abdominal pain [71,72]. Occasionally the cause of the abdominal pain is ill-defined, making the diagnosis of abdominal pain without evident abdominal abnormality a puzzle for most physicians.

Epilepsy with abdominal pain is an uncommon condition of abdominal pain. It is a type of temporal lobe epilepsy that usually presents with abdominal auras and is characterized by recurrent episodic paroxysms of abdominal and periumbilical pain with various abdominal symptoms (e.g., nausea and vomiting) accompanied or followed by disturbed brain functions. Epilepsy with abdominal pain usually occurs in childhood, but it is also reported in adults [73]. The characteristic postictal manifestations (such as lethargy, drowsiness, headache, blindness, paraesthesia, or even convulsions) help to differentiate it from the abdominal migraine [74].

The exact mechanism of epilepsy with abdominal pain is not fully understood but could be related to abnormal neuronal activation of the temporal lobe involving the amygdala. Amygdala then serves as a signal conductor to the gut through direct projections to the dorsal motor part of the vagus nerve nucleus. The vagus nerve then transmits the electrical activity to the target organs causing different gastrointestinal symptoms, especially abdominal pain (Figure 1) [75]. It is usually idiopathic; however, it may manifest temporal lobe lesions such as prematurity, febrile seizures, neuronal migration defects, cortical malformations, arterio-venous malformations, neuroendocrine dysfunction, mesial temporal lobe sclerosis, gliotic damage resulting

from encephalitis, or brain tumors such as dysembryoplastic neuroepithelial tumors, benign tumors, cerebral astrocytoma, or gliomas [76,77].

Epilepsy with abdominal pain has a characteristic tetrad [78]:

Paroxysmal gastrointestinal and autonomic complaints (abdominal pain, vomiting, nausea, flushing, palpitation, and stuttering) of unapparent cause.

Central nervous system disturbance symptoms (e.g., alteration of mental status, headache, dizziness, and convulsions).

Abnormal EEG findings characteristic of epileptic activity.

Improvement of the symptoms with antiseizure medications.

The diagnosis of epilepsy with abdominal pain is essentially clinical. To properly diagnose epilepsy with abdominal pain, we should rule out organic causes in the gastrointestinal tract and the nervous system. Other causes of recurrent abdominal pain should also be ruled out, such as porphyria, familial Mediterranean fever, abdominal migraine, and cyclic vomiting [79]. Describing the abdominal attacks by emphasizing the presence or absence of aura and postictal events may help reach the diagnosis. Complete physical, abdominal, and neurological examinations should be performed in suspected patients. Serum prolactin could increase within 20 minutes of the attack in epilepsy with abdominal pain. The sample should be taken within two hours. Presumably, the prolactin release is due to the propagation of epileptic activity from the temporal lobe spreading to the hypothalamic-pituitary axis. High serum prolactin could help to differentiate epilepsy with abdominal pain from psychogenic or functional causes of abdominal pain [80]. The presence of abnormal epileptogenic activity by EEG accompanying the pain paroxysm or between the attack confirms the diagnosis. Computerized tomography or magnetic resonance imaging of the brain may be needed to rule out neurologic diseases or tumors. Other laboratory tests to rule out the gastrointestinal causes of abdominal pain are tailored according to the clinical finding. Abdominal ultrasound could also help [77].

Epilepsy and migraine are frequent comorbid conditions and shared genetic susceptibility [81]. Abdominal migraine has many shared features with epilepsy with

abdominal pain: auras, abdominal pain, nausea, vomiting, and headache. So, when a patient with epilepsy with abdominal pain presents with a headache, it will be challenging to differentiate it from abdominal migraine (Table 1). The duration of the symptoms could help in diagnosis, as headache is usually prolonged in abdominal migraine rather than in abdominal epilepsy. Postictal manifestations, abnormal EEG, and high postictal serum prolactin could help confirm epilepsy with abdominal pain [79]. Treatment of epilepsy with abdominal pain with antiseizure medications is usually successful, with very few relapse rates. There are no current recommendations on the type of antiseizure medications, but many studies recommend using Oxcarbazepine [82].

Postictal Abdominal Manifestations:

Postictal states are transient brain conditions following seizures (most common complex partial and tonic-clonic seizures), manifested as neurological deficits (confusion, weakness, memory impairment, and headache) with/without psychiatric manifestations of variable severity and duration, frequently associated with EEG slowing or suppression, and persist for lasting minutes to days [83]. The duration of these symptoms usually corresponds to the intensity and duration of the ictal period. The mechanism of postictal states is related to robust cortical inhibitory mechanisms that try to inhibit and terminate the seizures, producing changes in membrane receptors and alteration of neurotransmitter release together with cerebrovascular changes, contributing to the development of these postictal events. Postictal event type depends on the type of epilepsy, the location of the epileptogenic activity, and the severity of the seizure [84,85]. Sometimes it is challenging to differentiate between ictal and postictal events, especially in nonconvulsive seizures [86]. The EEG and MRI brain changes usually relate to the postictal manifestations with characteristic slowing and temporary signal increases [87].

Postictal hypersalivation is rare but occurs entirely in seizures of mesial origin in temporal lobe epilepsy, mainly from the left side [88]. Hypersalivation reflects a purposeful response to hypersecretion following regaining consciousness after a complex partial seizure. It is prevalent in patients with temporal lobe epilepsy,

especially mesial temporal lobe epilepsy [89]. This postictal event is more common in females than males supporting the gender differences in epilepsy [90]. ***Postictal hyperphagia and compulsive water drinking*** were reported in a few cases-reports in patients with secondary epilepsy due to temporal lobe lesion. It showed a dramatic response to carbamazepine [91]. It was also reported in secondary epilepsy due to frontal lobe lesions [92]. Remick *et al* described three patients who experienced postictal hyperphagia [93].

Effects of Antiseizures Medications on the Gastrointestinal Tract:

antiseizure medications generally have a narrow therapeutic window with many adverse effects, especially on the gastrointestinal tract. According to the reporting method, the prevalence of the antiseizure side effects ranges between 10-90% of the patients [94]. Over the last one and half centuries, the adverse effects of antiseizure medications remain the primary cause of treatment failure. About 10-30% of the patients with epilepsy did not tolerate these side effects and stopped the drugs, especially with polytherapy [95]. Gastrointestinal side effects were observed in many antiseizure medications. Table 2 summarizes the common gastrointestinal side effects observed with the commonly used antiseizure medications.

On the other side, some antiseizure medications can improve some gastrointestinal manifestations. For example, gabapentin can improve functional dyspepsia, which is resistant to the other conventional therapies [104]. Gabapentin also decreases the rectal mechanosensitivity and enhances the rectal compliance in patients suffering from diarrhea-predominant-irritable bowel syndrome [105]. Another interesting finding by Liu *et al* is the ability of valproate to prevent peritoneal adhesion following abdominal injury through chymase inhibition [106]. Valproate was also able to decrease intestinal inflammation in inflammatory bowel disease [107].

Meanwhile, Patel *et al* showed that Sodium valproate could experimentally inhibit the proliferation of carcinogenic cells in colon cancer associated with diabetes mellitus [108]. As valproate is a GABA agonist, it can modulate gastrointestinal motility and the anal sphincter. Valproate can normalize the activity of the human lower esophageal

sphincter and reduces the number of reflux episodes in health and gastroesophageal reflux disease [109]. Phenobarbital is effective and safe for preventing prenatal and treating postnatal hyperbilirubinemia through its effects on the hepatic enzymatic elimination of bilirubin [110,111].

III- ABDOMINAL MANIPULATIONS TO MANAGE EPILEPSY:

As the gut-brain axis has a bidirectional effect on both gut and brain, modulation of the gut microbiota could positively impact the management of diverse types of epilepsy. The gut microbiota may influence the brain functions in several ways, including the CNS, the hypothalamic-pituitary-adrenal axis, immune and inflammation modulation, and neuromodulators. Therefore, gut microbiota modulation could exert a beneficial role in epilepsy management. Prebiotics, probiotics, synbiotics, postbiotics, a ketogenic diet, and fecal microbiota transplantation are probable methods to treat epilepsy *via* modulation of the microbiota-gut-brain axis [112]. Probiotics are living organisms able to provide the host with health benefits when supplied in an appropriate dose. At the same time, prebiotics is selective nutritious substrates for specific types of host microorganisms to confer health benefits to the host. Synbiotics are a mixture of both pre-and probiotics. Postbiotics are the metabolic end products of the probiotic organisms that can confer health benefits to the host [113].

Gómez-Eguílaz *et al* found a reduction in seizure frequency by 50% in about 28.9% of patients with drug-resistant epilepsy when supplied with a probiotic mixture as adjuvant therapy for four months. This effect persisted for another four months after probiotic discontinuation in 78.9% of those who showed improvement [114]. The gut microbiota can modulate brain activity by the peripheral production of GABA, metabolizing the precursors of serotonin, and modulating brain-derived neurotrophic factors that correlate with epilepsy severity. The bacterial production of short-chain fatty acids, which have anti-inflammatory effects, is another factor explaining the probiotic effects in the treatment of epilepsy. Gut microbiota also modulates the endocannabinoid system with its inflammatory suppressor effects on the seizure events

[115]. At the same time, some strains of the gut microbiota can metabolize some anticonvulsants affecting their antiseizure effect. For example, the gut microbiota can metabolize the antiseizure Zonisamide into pharmacologically inactive 2-sulfamoyl-acetyl-phenol [116]. Fecal microbiota transplantation (FMT) is a promising approach to reconstructing the gut microbiota. It is successfully used to treat various diseases, including neurological disorders. He Z *et al* successfully treated a girl with long-term Crohn's disease and epilepsy for 17 years with FMT, which could prevent seizure relapse during 20 mo of follow-up [117]. However, we need more time to have a valuable experience with the efficacy of FMT in treating epilepsy.

The ketogenic diet is an old modality used to treat drug-resistant epilepsy and metabolic diseases since 1920. Though the precise mode of action is not well known, its activity could be related to modifying the gut microbiota composition and function. The gut microbiota modification causes alteration of beta-hydroxybutyrate levels and elevates the hippocampal GABA compared to the glutamate content [118]. In addition, the ketogenic diet modification of the gut microbiota reduces the alpha-diversity and increases the proposed beneficial bacteria like *Akkermansia muciniphila* and *Parabacteroides* spp. This microbiota modulation changes the colonic luminal metabolome, with a decrease in gamma-glutamyl amino acids and an increase in the brain GABA/glutamate content by reducing the blood gamma-glutamyl amino acids [119]. A ketogenic diet also alters neuronal metabolism by reducing CSF glucose levels, increasing ketone bodies, and reducing cortical hyperexcitability with a reduction in seizure frequency [120]. Ketone bodies such as acetoacetate exerted a broad-spectrum anticonvulsant effect through modulation of neurotransmitter release and modification of ATP-sensitive potassium channels [121]. Additionally, ketone bodies have a direct inhibitory influence on the vesicular glutamate transport [122].

Vagus nerve stimulation was approved by the Food and Drug Administration (FDA) as adjuvant treatment in patients with multi-drug resistant epilepsy who are not fit for epilepsy surgery since 1997. The vagus nerve is a vital brain-gut axis component and plays an essential role in inflammation modulation, intestinal homeostasis maintenance,

food intake, satiety regulation, and energy homeostasis [123]. Vagus nerve stimulation leads to electrical energy discharge into a wide brain area, disturbing the unusual brain activity that produces seizures [124]. At the same time, vagal stimulation has anti-inflammatory properties affecting the gastrointestinal tract through hypothalamic-pituitary-adrenal axis activation and vasovagal reflex-induced cortisol release, which has an anti-tumor necrosis factor effect [125]. Consequently, vagus nerve stimulation can be used to treat multi-drug resistant epilepsy and, at the same time, can treat gut inflammatory disorders such as IBD, which at the same time is a risk factor to increase the incidence of epilepsy [126].

Omentum is a large double peritoneal flat sheet of fatty tissue that hangs from the greater and the lesser gastric curvature to float on the intraperitoneal organs, including large and small intestines. It has many functions, including fat storage, immune regulation, neovascularization, tissue regeneration, and healing. Omental transposition or graft was used in various surgeries, including abdominal, cardiac, thoracic, orthopedic, plastic, vascular, orthopedic, urogenital, gynecological, and neurosurgeries [127]. ***Omental transposition*** on the brain surface enhances neoangiogenesis with the generation of plentiful new vessel connections between the omentum and the brain which induces healing of neural injury by increasing the cerebral blood flow and the available oxygen to the neural tissues, releasing omental neurotransmitters such as acetylcholine, and dopamine, noradrenaline. It also releases neurotrophic factors such as gangliosides and nerve growth factors that help to restore neurologic functions [128]. Rafael *et al* used omental transplantation to treat two patients with uncontrolled temporal lobe epilepsy. They transplanted the omental tissues directly upon the epileptic focus on the left temporal lobe and the anterior perforated space. One patient showed complete recovery, while the other showed about 85% improvement in seizure frequency and severity [129]. However, there are few reported cases, and there is a need for long-term follow-up to have a better experience with omental transplantation to treat epilepsy.

CONCLUSION

There is a strong interaction between the gut and the brain. This interaction forms the typical gut-brain axis. Consequently, gastrointestinal dysfunction can be seen in neurological disorders, and neurological dysfunction can be seen in gastrointestinal disorders. There is an increase in epilepsy incidence in various gastrointestinal diseases. On the other hand, epilepsy, in turn, affects the gastrointestinal tract in different forms, such as abdominal aura, epilepsy with abdominal pain, and the adverse effects of antiseizure medications on the gut and the gut microbiota. Various gut manipulations could help manage epilepsy, such as gut microbiota modification, fecal microbiota transplantation, ketogenic diet, vagus nerve stimulation, and omentum transplant. Understanding the strong relation between epilepsy and the gut could help to alleviate both epileptic and gastrointestinal disorders.

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