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Revisiting First-Line Therapeutics and the Exploration of Theoretical Novel Neurohormonal Modulation Strategies of Hypothalamic Hamartoma-Induced Gelastic Epilepsy

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ABSTRACT

Epilepsy, and the treatments associated, involvebio-hormonal disruption, altered endocrine physiology, and maladaptive reproductive influence. All of which may impact seizure susceptibility. Gelastic seizures (GS), are often linked to hypothalamic hamartomas (HH), which are uncommon congenital abnormalities characterized by the often-pathognomonic triad of GS, early puberty, and developmental delay. This systematic review aims to revisit first-line therapeutics associated with GS, as well as the theoretical surgical and non-surgical approaches targeting management of this disease process. A comprehensive literature review was conducted using the databases PubMed, ProQuest, and Science Direct. A diverse range of studies were chosen. The search included the keywords "First-Line Therapeutics for Gelastic Epilepsy" and "Novel Management Strategy for Gelastic Epilepsy". Out of 31 screened papers, 16 articles in total met the criteria for inclusion. One article explored contained inaccessible full-text records; therefore 15 articles were systematically reviewed. Research suggests GS are typically the initial seizure manifestation of hypothalamic hamartomas. Current and emerging pharmaceutical therapeutic strategies are currently being investigated; however, research indicates the surgicalanterior transcallosal interforniceal approachextremely effectivelywith othertreatment methods utilizing endoscopic and radio surgical ablative techniques a promising alternative.

Abbreviations: GS: Gelastic Seizures; HH: Hypothalamic Hamartomas; AEDs: Antiepileptic Drugs; ACTH: Adrenocorticotropic Hormone; VNS: Vagus Nerve Stimulation; DBS: Deep Brain Stimulation; EI-AEDs: Enzyme Inducer Antiepileptic Medications

Introduction & Background

Gowers (1881) and Trousseau (1877) were the first to describe gelastic seizures (GS), which are epileptic episodes marked by fits of laughter. Daly and Mulder first used the term "gelastic epilepsy" in 1957. Hypothalamic hamartomas (HH) are an extremely uncommon condition; in Israel, it affects 1 in 625,000 children and adolescents, and 1 in 200,000 in Sweden [1]. Research indicates GS, a type of seizure characterized by facial twitching and laughing vocalizations, are more common in men and often accompanied by autonomic symptoms like rapid heart rate and abnormal breathing [2]. Patients with epilepsy may experience a sudden, uncontrollable urge to laugh. These seizures may originate in the premotor and frontal opercula regions and travel through the cerebral cortex, pyramidal tract, and ventral brainstem. Generalized epileptic encephalopathy, characterized by cognitive decline and seizures, may also occur [3]. There has been a correlation linking generalized seizures with hepatic hepatitis and HH. More than one-third of HH patients experience GS during infancy, with some mild seizures and others intractable. GS and HH patients often have co-occurring mental health issues [4]. GS are challenging to manage, and surgery is the most likely treatment. Various surgical procedures have been attempted to control GS in HH patients [5].

Surgical resection of HH have been performed using both top-down and bottom-up accession technical surgical approaches. These approaches dissect delicate vascular and neuroendocrine structures with risk of post-surgical complications such as stroke or secondary tissue hyperplasia. Technical approaches for resecting sessile HH patients exist such as the transcallosal-interforniceal method used to reach the HH from above. This technique has shown better seizure control and improved cognitive function. However, it may cause short-term memory impairment [6]. Hypothalamotomy may or may not be indicated as a safer alternative to surgical resection of the HH. This procedure is typically reserved for specific, refractive, and severe cases. Often involving a multidisciplinary team of neurosurgeons, neurologists, and other specialists to assess the patient's condition and determine the most appropriate treatment approach. This method effectively blocks the intrinsic epileptogenic activity. Endoscopic disconnection, performed using depth electrodes, has shown the immediate disappearance of epileptic discharges [6]. Stereotactic radiofrequency thermocoagulation is a minimally invasive surgical approach for HH requiring a small burr-hole or twist-drill opening. A case report has shown this therapeutic intervention to provide total seizure control, with better control found in small lesions [7].

Anti-seizure drugs aim to eliminate seizures while minimizing side effects. Therapeutic intervention is considered after two documented cases, or one seizure seen in higher-risk populations. Factors like age, sex, comorbidities, seizure type, and tolerability influence treatment. Monotherapy is best, while polytherapy may increase risk [1]. Common pharmacologic therapeutics include: Carbatrol (carbamazepine), Keppra (levetiracetam), Lamictal (lamotrigine), Oxtellar XR (oxcarbazepine), Tegretol (carbamazepine), Topamax (topiramate), and Vimpat (lacosamide). There arenewer therapeutics being trialed or utilized such as: Brivaracetam, a newer version of levetiracetam that may have fewer side effects and better efficacy, Cannabidiol, a compound derived from cannabis that has anti-inflammatory and anti-seizure properties, Epidiolex, a purified form of cannabidiol that is approved by the FDA for the treatment of two rare and severe forms of epilepsy, Dravet syndrome and Lennox-Gastaut syndrome, and Fenfluramine, a drug that was previously used as an appetite suppressant, but was withdrawn from the market due to cardiovascular risks. It has been repurposed as an adjunctive therapy for Dravet syndrome. There is also Ganaxolone, a synthetic analog of allopregnanolone, a neurosteroid that modulates GABA receptors and has anticonvulsant effects, and Perampanel, a selective AMPA receptor antagonist that blocks glutamate-mediated excitatory neurotransmission [8].

Novel approaches, such as redefining abnormal neuronal circuitry utilizing stem cell therapy have also been shown to provide therapeutic and neuroprotective benefits to epileptic patients. Offering restorative and regenerative inhibitory GABA-ergic neurons, this therapy counteracts hyperexcitability, attenuates glutamate excitotoxicity, protects neurons, and promotes differentiation into astrocytes, thus regulating neuronal homeostasis and neuroinflammation [9]. Epilepsy is a long-term medical condition influenced by hormones that control seizures by altering neuron excitability, leading to issues with the neuroendocrine system. This can cause reproductive dysfunction, affecting both men and women [10]. This study examines such HHlesions and continues to focus on the neuroanatomy and potential role in epileptic seizure presentation.

Review Methods

For this systematic review, the methods for searching and analyzing the articles strictly adhered to the PRISMA guidelines presented by Liberati, et al. [11]. For the purpose of conducting this inquiry, the three databases that were used were PubMed, Science Direct, and ProQuest. For the purpose of narrowing down the search, the following keywords were utilized: "First-Line Therapeutics for Gelastic Epilepsy" and "Novel Management Strategy for Gelastic Epilepsy". For the purpose of this investigation, the electronic search was deemed to be potentially relevant. During the screening process, a point was made to rid any articles that were written in a language other than English or that were an exact duplication. The titles, abstracts, research styles, and accessibility of full texts of such papers studied were taken into consideration while evaluating them for the inquiry. A total of sixteen papers were finally selected from the thirty-one publications that were examined during the first search that was conducted across all three databases. One article chosen was removed due to inability of text access. A further reduction of evaluated articles is achieved via the use of specific keywords and the review of the abstracts. After applying the criteria for inclusion and exclusion, it was decided that fifteen articles were pertinent to the discussion.

Inclusion Criteria

The review included articles on human, English, first-line gelastic epilepsy treatment, peer-reviewed, full-text, meta-analyses, cohort studies, case-control, and observational studies. It specifically examined the neurohormonal modulation strategies of hypothalamic hamartoma-induced gelastic epilepsy, utilizing gray literature for new information.

Exclusion Criteria

We did not include systematic reviews in the study. Duplicate articles and those without complete text were also not included.

Quality Assessment

The PRISMA checklist and flowchart (Figure 1) was included in the systematic review to ensure thorough, honest, and equitable reporting. To evaluate the quality of the study, researchers utilized either the Quantitative Studies Critical Evaluation Form (Law, et al. 1998), the Critical Review Form for Qualitative Studies (Letts, et al. 2007), developed by McMaster University, or the Critical Appraisal Skills Programme (Singh, 2013) for systematic reviews. The rigor, research design, and bias risk of the included studies were assessed using these quality criteria.

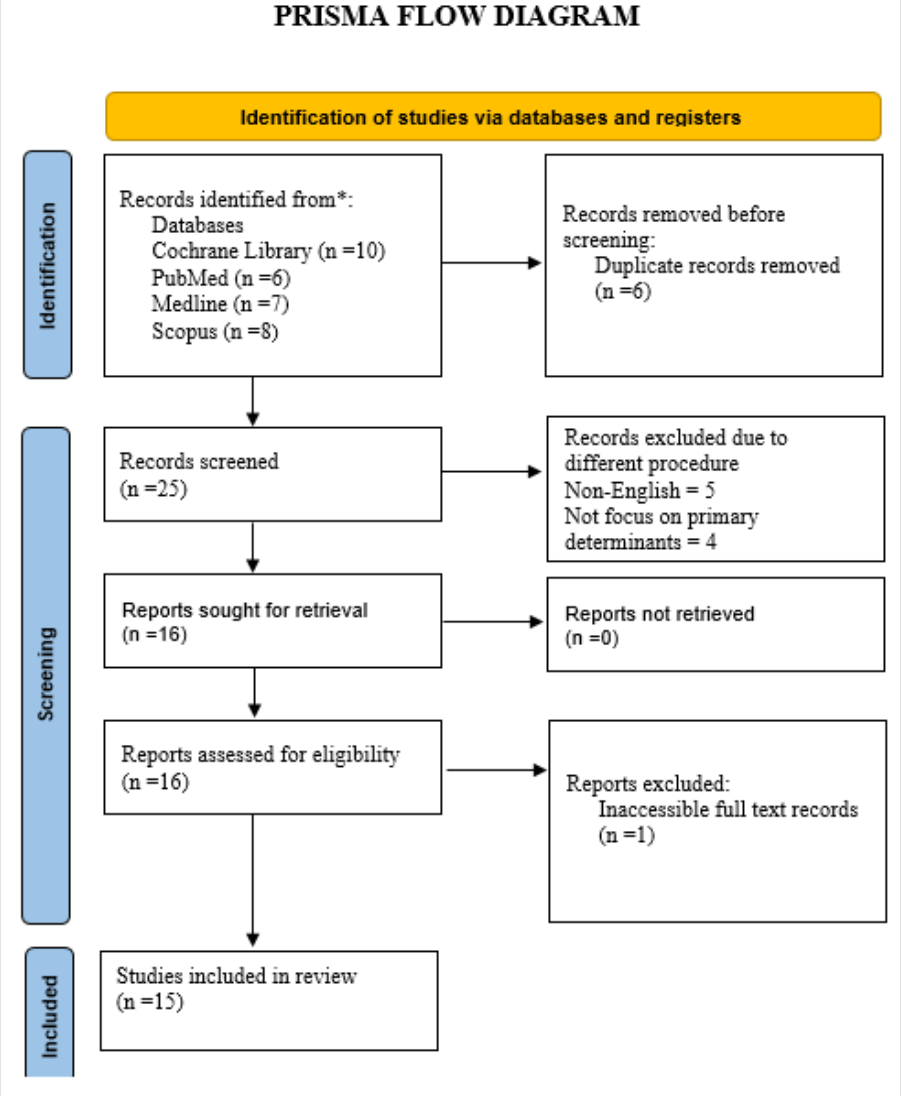

Figure 1: Flow Chart of Data Inclusion Strategy for Systematic Review.

Results

The search yielded a cumulative total of 31 articles, including 10 sourced from the Cochrane Library, 6 from PubMed, 7 from Medline, and 8 from Scopus. Out of the exclusions, 6 articles were duplicates, 5 were in a language other than English, and 4 did not primarily concentrate on the main factors. As a consequence, 15 articles were eliminated during the automated screening process, leaving 16 items for human screening. Papers were meticulously evaluated by considering the abstract, title, research type, and availability of the full text. As a result, 18 papers were examined to determine their suitability. In the end, a total of 15 papers were selected for the final analysis.

Neurohormonal Modulation Strategies

Neurohormonal modulation refer to approaches aimed at altering the activity of certain neurotransmitters and hormones in the brain to reduce seizure frequency and severity. A new understanding of the connection between hormonotherapy, and epilepsyis currently taking place [12]. Neurohormonal modulation strategies may involve the following: Pharmacotherapy, to target specific neurotransmitter systems or hormone receptors involved in seizure generation or propagation. These medications may include the antiepileptic drugs (AEDs) previously discussed, or hormone-modulating drugs that affect hormonal levels. Hormone therapy, the manipulation of hormone levels through therapeutics reduce seizure activity. Hormones such as cortisol and

adrenocorticotropic hormone (ACTH) may be involved in modulating seizure activity, and hormone therapy may aim to stabilize their levels. Neurostimulation, Using devices such as vagus nerve stimulation (VNS) or deep brain stimulation (DBS) to modulate neural activity and hormonal release, reduce seizure frequency and severity. Surgical intervention as previously discussed to help alleviate seizure activity by removing the source of abnormal neural firing and hormonal dysregulation. Lastly, lifestyle modifications: Certain lifestyle factors such as stress, sleep deprivation, and hormonal fluctuations can influence seizure activity.

Therefore, implementing strategies to manage stress, improve sleep quality, and stabilize hormonal levels may complement other treatment approaches in reducing seizure frequency. Overall, neurohormonal modulation strategies aim to target the underlying mechanisms contributing to gelastic seizures and epilepsy, with the goal of reducing seizure frequency and improving overall quality of life for individuals affected by these conditions. It is also important to note the hypothalamic-pituitary axis regulates the production and metabolism of endogenous steroids. Medications used to treat seizures may also affect hormonal physiology, which in turn inhibits fertility. As a result, both men and women may have decreased fertility and dysfunctional sexual functions as a result of this. Women may encounter irregular periods, excess weight, hyperandrogenism, infertility, polycystic ovaries, sperm abnormalities, as well as, slowed sexual maturation that can be seen in males [13].

The Effect of Hormones on Epilepsy

Estrogens

Among the three physiologically active estrogens, estriol is the most important during pregnancy, whereas estradiol is the primary estrogen in fertile women. Both ERα and ERβ are intracellular receptors that estrogens use to influence the brain; the latter is particularly crucial for the non-reproductive actions of estrogens. While estradiol does not influence GABA-ergic processes, it does improve glutamate responsiveness in cerebellar neurons. Estradiol inhibits glutamate decarboxylase activity in the amygdala and substantia nigra, which in turn reduces GABA production and suppresses GABA-ergic inhibition of hippocampus neurons with prolonged exposure. Furthermore, estradiol alters the brain structure by influencing the connections between synapses in the hippocampus and increasing the density of dendritic spines. Extensive research has shown that the effects of estradiol on brain excitability vary by territory [14].

Progesterone

Metabolites of progesterone affect brain excitability in both conventional and non-classical ways; the latter is by far the more significant. The brain is filled with progesterone receptors, and by converting them to 3α-5α-THP, an anticonvulsant neurosteroid, and the effects on postsynaptic GABA-ergic neurons are amplified. By acting at the NMDA receptor and reducing glutamate responsiveness, progesterone, and its metabolites may influence excitatory pathways that influence brain excitability and sexual behavior. Neurosteroidscan influence all GABA-A receptor isoforms, which warrants further investigative research as a novel therapeutic strategy for the treatment of catamenial epilepsy in women [15].

Androgens

Sex hormones known as androgens have dual actions as anticonvulsants and antiepileptics. The estrogens may be converted into 17β-estradiol, an excitatory hormone, whereas androstanedioland dihydrotestosterone have strong antiepileptic properties. The proconvulsant action of flutamide demonstrates the standard method by which androgens function, but there are other, non-classical ways as well. Androgens have antiseizure effects in wild-type animals, but feminized mice lack these effects because of abnormalities in the intracellular androgen receptor. Androgens also influence receptors that are not part of the conventional membrane. As an example, a study in mice has shown that androstanediolmay reduce seizures and increase GABA-activated currents in the hippocampus. Application of testosterone to gonadectomized male rats increases spine synapses in the hippocampus and contributes to plastic changes throughout the menstrual cycle, demonstrating that androgens also impact neuronal structure and function [16].

Testosterone

A hormone may increase the frequency of seizures because of its by-products. As a proconvulsive, estradiol (E2) is a by-product of physiologically active testosterone. Both partial and generalized epilepsy are associated with low testosterone levels in males. An androgen shortage and an increase in seizure recurrence may occur in patients using liver enzyme inducer antiepileptic medications (EI-AEDs). Enhancing ionotropic glutamate receptors in region CA1 and expanding dendritic spines, E2 has a detrimental impact on the hippocampus. Additionally, it dampens the slow post-hyperpolarization caused by Ca-dependent potassium (K) currents and inhibits GAB-Aergic transmission. Changes in seizure activity may be caused in part by the binding of intracellular estrogen receptors by other testosterone metabolites such as 5'-androstane-3' and 17-diol (3'-diol). Mice protected against GABAA receptor antagonist-induced seizures were given 3'-androstanediol to reduce brain excitability via allosteric regulation of GABAA receptors [17].

Glucocorticoids

Epileptogenesis has been associated with pituitary-adrenal hormones, particularly neurosteroids and corticosteroids. In response to acute stress, animals' seizure thresholds are raised, and epilepsy patients with persistent stress are at increased risk for seizures. The levels of neurosteroids and corticosteroids, such as cortisol and DOC, are elevated in the brain and plasma when stress is present. Because

corticosterone and other stress hormones increase hippocampus activity and may induce neuronal damage, chronic stress may increase susceptibility to epileptogenesis. In addition to mineralocorticoid and antiseizure characteristics, the adrenal zona fasciculate also produces deoxycorticosterone. Evidence suggests that 11-deoxycortisol, a precursor of cortisol, may cause persistent seizures. Some research suggests that regular exercise may help prevent or postpone the onset of epilepsy. Endogenous neurosteroids may be part of the exercise therapy that lowers brain vulnerability. Additionally, stress may influence seizure regulation of seizures; whereas short-term stress may have anticonvulsant-like effects, long-term stress can induce epileptic seizures. Under stressful conditions, the ratio of proconvulsant to anticonvulsant components may change, leading to seizures that are triggered by the stress itself [3].

Neurosteroids

One possible mechanism by which neurosteroids influence epilepsy is by controlling the excitability that occurs during epileptogenicity by modulating the activation of extrasynaptic GABA-A receptors. Research has shown that reducing synaptic inhibition in the brains of epileptics preserves tonic conductance. To modulate epileptogenesis and improve phasic and tonic inhibition, endogenous neurosteroids could be useful. Dysregulation of neurosteroid production may aid in the development of epilepsy (Table 1). The capacity of therapeutic programs to prevent epilepsy is hindered by a lack of knowledge about epileptogenesis, even if scientific understanding has improved [18].

Table 1: A summary of the studies is presented in the following table.

Author year	Objective	Type of Study	Outcome measures	Results
(Shim, et al. [25])	Endoscopic Treatment of Hypothalamic Hamartomas	Original article	Seizure	In conclusion, endoscopic disconnection is a highly favorable option for treating hypothalamic hamartomas. The article discusses various aspects of the procedure, including presurgical evaluation and patient care.
(Rekate, et al. [26])	The objective of this research is to share our own experiences with the endoscopic extraction of hamartomas.	prospective review	Seizure control and improvement in behavior.	Sessile hypothalamic hamartomas may be surgically excised or detached, followed by a comprehensive one-year assessment to evaluate seizure management, behavioural enhancement, and emotional functioning.
(Chulabhorn, [27])	Surgical removal of a hypothalamic hamartoma, which caused uncontrollable episodes of laughter, was successfully performed using a method that included accessing the brain via the corpus callosum and the subchoroidal region.	Case Reports	Seizures.	Surgical removal of a hypothalamic hamartoma, which caused uncontrollable episodes of laughter, was successfully performed using a method that included accessing the brain via the corpus callosum and the subchoroidal region.
(Eguchi, et al. [28])	In hypothalamic hamartoma, the mamilla-thalamic tract is selectively disconnected surgically, resulting leads to the complete disappearance of gelastic seizures.	Original article	seizures	The study reveals that disconnection between hypothalamic hamartomas and mammillary bodies may reduce hypothalamic damage and potentially control intractable gelastic seizures with fewer complications
(Homma, et al. [29])	The use of stereotactic thermocoagulation for treating hypothalamic hamartoma with intractable gelastic epilepsy since 1997 has been controversial, but this review aims to clarify its usefulness.	Original article	seizures	Patients with ictal onset were treated with stereotactic thermocoagulation of hypothalamic hamartoma, resulting in reduced seizure frequency and seizure-free outcomes.
(Shirozu, et al. [30])	The study evaluates the feasibility of repeat stereotactic radiofrequency thermocoagulation (re-SRT) for hypothalamic hamartoma patients, focusing on clinical and surgical factors affecting seizure outcomes.	Original article	seizures	Repeated stereotactic radiofrequency thermocoagulation offers the potential for recurrent Gelastic-Seizures, butincreases complications. Early surgical indications for non-Gelastic Seizures and intellectual disability should be avoided.
(Alayli, et al. [31])	Stem cell therapy offers an alternative treatment for epilepsy, reducing seizure frequency and neurological deficits.	Original article	seizures	Research has shown that stem cell transplantation effectively decreases the frequency, severity, and neurological impairments associated with seizures in individuals with epilepsy.

(Striano, et al. [32])	To outline the signs and symptoms of hypothalamic hamartoma (hypothalamic hamartomas)-related epilepsy with gelastic seizures and how these seizures often progress over time.	Cross-sectional study	Six individuals (two females and four males)	the severity of epilepsy and its progression over time
(Velíšková, [33])	The function of oestrogens in seizures and epilepsy: Are they harmful or good?	Review article	neuronal excitability	The influence of oestrogens on seizures is complicated, and their usage in individuals with seizure disorders should be evaluated individually. The loss of oestrogens during menopause may raise the risk of neurological disorders.
(Reddy, [34])	Hormones and neurosteroids: their function in the development of epilepsy	Review article	neuronal excitability	A shortage of medications authorised by the FDA addresses the issue of epilepsy, a brain illness that may be caused by damage. Epigenetic neuronal excitability may be mediated by steroid hormones, including corticosteroids, estrogen, and progesterone.
(Taubøll, et al. [35])	The role of hormones in epilepsy	Review article	neuronal excitability	There is a reciprocal relationship between sex steroid hormones and epilepsy; the former may influence the latter, and vice versa, which in turn can disturb the reproductive endocrine system. Hormones from both sexes affect excitability in the brain; progesterone is anticonvulsant while oestrogen is proconvulsant. Epileptic activity impacts reproductive function and causes asymmetric hypothalamic activation; seizures and epileptic discharges also impact hormones.
(Cutia, et al. [36])	The identification of elastic seizures in the study of epilepsy involves investigating the processes that link neurological disorders with reproductive endocrine dysfunction.	Review article		The specific mechanisms that explain the connection between epilepsy and hormones in the hypothalamic-pituitary-gonadal (HPG) axis have not been discovered yet. However, it is understood that seizures that occur in brain regions such as the hippocampus and amygdala, which are involved in emotions and memory, may disrupt the functioning of the HPG axis without being influenced by the actions of antiseizure medications (ASMs).
(Kapur, et al. [37])	Progesterone modulates neuronal excitability bidirectionally	Review article	progesterone receptors, PRs	Progesterone's metabolite THP has anticonvulsant effects, suppressing seizures or status epilepticus. However, prolonged exposure may cause tolerance due to altered GABAAR subunit expression.
(Reddy, [38])	The therapeutic possibilities and endogenous function of neurosteroids in the human brain	Review article	neuronal excitability	Sulfatedneurosteroids enhance memory and may be therapeutic for anxiety, epilepsy, and other brain disorders due to their improved bioavailability and efficacy.
(Taubøll, et al. [39])	The interactions between reproductive hormones and epilepsy	Review article	endocrine dysfunction	Hormones, epilepsy, and antiepileptic drugelastic seizuresinteract, affecting hormone levels in both sexes. Epileptic activity affects hormones in both genders, leading to reproductive endocrine dysfunction. AEDs can alter hormone metabolism and synthesis.

Discussion

The occurrence of seizures in people with gelastic epilepsyis attributed to abnormalities in the hypothalamic and hippocampal regions of the cerebral cortex induced by the mass effect of the hypothalamic hamartoma. The origin of these seizures has been substantiated using stereo-EEG recordings of GS, which capture the electrical activity from the hypothalamic lesion. Additionally, the HH have been stimulated using depth electrodes, providing further evidence of this phenomena. Ictal spectral hyperperfusion has been seen during these convulsions. Radiofrequency coagulation, surgical and gamma-knife ablation, and localized resections have all been beneficial in managing seizures caused by HH. However, GS have not been successfully treated using these approaches [19]. Previously, it was believed that diencephalic-hypothalamic regions were responsible for the release of affective and emotional responses. The tight anatomical connections between HH's and these tissues explain the hormonal alterations and autonomic symptoms seen in GS. Surface electroencephalograms (EEG) taken during episodes of laughing fits typically show a lack of coordination in the background brain activity, with few or no signs of sudden abnormal activity. Dacrystic seizures, characterized by involuntary bouts of crying, have a similar EEG pattern, sometimes presenting in the first phases of gelastic epilepsy [20].

As the manifestation of this condition advances, more types of seizures often occur consecutively. Empirical data from clinical observations and electroencephalographic studies indicate that partial seizures are mostly associated with temporal or frontal lobe impairment. These seizures may manifest as either simple or, more often, complex. However, gelastic seizures are not influenced by localized cortical resections, and MRI spectroscopy did not identify any harm to the patient's temporal lobe neurons [21]. Secondary generalized epilepsy evolves into generalized spike-wave discharge seizures, which often mimic Lennox-Gastaut syndrome and have features of catastrophic epileptic encephalopathy. The hypothalamus's structural and functional connections to the thalamus and cortex have been used to elucidate this kind of evolutionary process. In cases of secondary generalized epilepsy, the hypothalamic discharges do not coincide with the interictal generalized spike-wave discharges. Secondary epileptogenesis is the probable cause of both localized and broad seizures, which seem to be events occurring beyond the affected area [22]. Individuals afflicted with this condition exhibit a broad range of symptoms, ranging from the least severe form known as "pressure to laugh" (Gelastic Seizures) to more extreme variations manifesting the global mass effect induced by the HH which is linked to early onset generalized epilepsy and premature puberty.

The severity and staging of the disease process may be determined by factors such as the size of the HH, their location (tuber cinereum vs. mammillary bodies), the kind of attachment (pedunculate vs. sessile), and the degree of hypothalamic displacement [23]. Pedunculate hypothalamic hamartomas are rare in patients with gelastic epilepsy and may be linked to endocrinologic disorders or visual impairment; nonetheless, sessile hamartomas are more prevalent. No correlation exists between less severe occurrences and cognitive deficits or behavioral disorders. Within the intermediate range, some individuals suffer from severe epilepsy and have different cognitive deficits; however, they do not display indications of secondary generalized epilepsy. Precocious puberty is not always a consistent or prevalent symptom seen in GS [24-39]. In summary, HH are uncommon tumors that are linked to a combination of developmental delay, early onset of puberty, and gelastic epilepsy. The overwhelming majority of individuals diagnosed with HH's have intractable epilepsy, a condition that is often detected in neonates. While GS are the predominant seizure type in these people, they often have a range of other seizures, including complex partial seizures, generalized tonic-clonic seizures, drop attacks, and infantile spasms.

There is enough evidence to support significant mental comorbidities often accompany the progression of cognitive decline. Adults may have fewer seizures and show improved neurophysiological results, indicating a more favorable prognosis for the condition. A significant number of these patients will have cerebral testing before surgery due to the challenging nature of their treatment. GSare often refractive to pharmacological intervention, as such, the transcallosal operation has shown superior efficacy among surgical treatments for seizures. However, non-surgical methods like radiosurgery and ablative techniques are becoming more popular due to their promising outcomes.

Conclusion

Empirical research indicates that individuals diagnosed with epilepsy have a higher susceptibility to seizure episodes as a result of hormonal fluctuations, which affect their endocrine system. The impact of reproductive hormones on neuronal excitability, seizures, and the resulting damage is intricate owing to their diverse mechanisms of action. There is a widely held assumption that estrogen has the ability to promote seizures, whereas progesterone has the ability to prevent seizures. This perspective has led to using specific analyses to study these effects. Further research using stringent treatment protocols is necessary to comprehend the biphasic dose-dependent effect of sex hormones. Estradiol and progesterone/allopregnanolone have potential therapeutic benefits for individuals with epilepsy. Progesterone may attenuate seizure activity, but it does not have substantiated neuroprotective effects against seizure-induced damage. Estradiol has reduced efficacy as an anticonvulsant drug, but it demonstrates the ability to safeguard hippocampus neurons from damage caused by seizures. Customized therapeutic approaches, which include modifying medication dosages, are essential for enhancing seizure management and the well-being of individuals with epilepsy. If the seizures are unresponsive to medications, surgery at an early stage of the treatment plan for hypothalamic hamartoma with epilepsy is advisable.

These findings indicate that the severity and lasting consequences of brain injury may increase in correlation with the length of unregulated seizures. The systematic review conducted in this study sheds light on the complexities surrounding the treatment of gelastic seizures (GS) associated with hypothalamic hamartomas (HH). Despite advancements in understanding the pathophysiology and therapeutic options, challenges persist in effectively managing this condition. The review highlights the significance of early recognition and intervention, as GS often serve as the initial manifestation of HH-related epilepsy. Current therapeutic strategies primarily focus on surgical interventions, with the anterior transcallosal interforniceal approach demonstrating promising efficacy. However, it's noteworthy that this approach may entail risks such as short-term memory impairment. Non-surgical methods like endoscopic and radio surgical ablative techniques are emerging as viable alternatives, offering potential benefits in terms of seizure control and cognitive outcomes. The exploration of novel pharmacological treatments presents a promising avenue for future therapeutic developments. Emerging drugs such as brivaracetam, cannabidiol derivatives, and neurosteroids show potential in modulating neurotransmitter systems and hormonal pathways implicated in seizure generation and propagation.

Additionally, stem cell therapy emerges as a novel approach offering neuroprotective and regenerative effects, presenting new avenues

for therapeutic exploration. Despite these advancements, further research is warranted to elucidate the underlying mechanisms driving GS associated with HH and to optimize therapeutic interventions. Specifically, there is a need for comprehensive studies evaluating the long-term efficacy and safety of both surgical and non-surgical approaches. Moreover, investigations into the neuroendocrine modulation strategies and their impact on seizure control and reproductive function are essential for addressing the multifaceted nature of HH-related epilepsy. In conclusion, this review underscores the imperative for continued research efforts aimed at advancing our understanding of GS associated with HH and refining therapeutic strategies to improve outcomes and quality of life for affected individuals.

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