INT. J. BIOL. BIOTECH., 21 (4): 445-463, 2024.

CATAMENIAL EPILEPSY: HISTORY, EPIDEMIOLOGY, DIAGNOSIS, PATHOPHYSIOLOGY AND MANAGEMENT

Zahir Hussain*

Department of Physiology, Faculty of Medicine, Umm Al-Qura University, Makkah-21955, Saudi Arabia
E-mail: zahirhussa@gmail.com, zhakbar@uqu.edu.sa

ABSTRACT

Epilepsy is a disease resulting from the disorders in neuronal excitability. There are impressive views that explain the mechanism of the occurrence of epileptic seizures. The present clinical review on the history, epidemiology, diagnosis, pathophysiology, and management of catamenial epilepsy uncovers various aspects that are either needed to be further confirmed or otherwise are needed to be conducted for newer information at cellular and molecular level. The history of epilepsy summarized in the present article provides the diagnostic and therapeutic approaches to understand the catamenial seizures and carry out further studies for better understanding and applications. The variation in steroid, gonadotropic and other hormones/ systemic changes/ comorbidity associated changes has enormous involvement in the development/ exacerbation/ inhibition of seizures/ seizure disorders/ catamenial seizures in women with epilepsy during any of the involved cycle phase/ segment. There is an urgent requirement of incorporating multidisciplinary approach for clinicophysiological, and physicomathematical applications for better understanding and innovative management of medical disorders. Such and other therapeutic approaches in medicine could revolutionize the methodologies for pathophysiological understandings especially employing the biophysical and mathematical medicine for the management of seizures/ catamenial seizures and other medical disorders. Further studies would hopefully explore the intricate impact of hormones and other factors/ changes in the pathophysiology and diagnostic and therapeutic aspects of catamenial epilepsy.

Keywords: Catamenial epilepsy, steroid hormones and gonadotropins, history, epidemiology, diagnosis, pathophysiology, management

INTRODUCTION

Epilepsy is a disease resulting from the disorders in neuronal excitability. In general, about 65 million people world-over suffer from epileptic disorders (Ngugi *et al*., 2010). The International League Against Epilepsy (ILAE) provides the criteria for epilepsy/epilepsy syndromes to establish a diagnostic uniformity (Kansal *et al*., 2024). In this regard, some of the factors causing alteration in excitability are electrolytes, glucose, blood gases, hormones etc. that may cause the development of seizures. It has been documented that no specific variation occurs by gender (Burneo *et al*., 2005). However, the endocrine and neuroendocrine variations occurring during menstrual cycle influences the epilepsy and severity of seizures/ epileptic disorders (Roeder and Leira, 2021; Octaviana *et al*., 2022; Sazgar *et al*., 2023; Rider *et al*., 2024). Furthermore, it is also known that the seizure dispersion could be affected by the pattern of seizure occurrence, and hence it seems necessary to evaluate more thoroughly the dispersion of seizures and with/ without medication (Kariyawasam *et al*., 2009; Voinescu and Pennell, 2017; Octaviana *et al*., 2022).

There are impressive views that explain the mechanism of the occurrence of epileptic seizures (Delgado-Escueta *et al*., 1986; Hussain *et al*. 1987; Aziz and Hussain, 1994a, b; Kariyawasam *et al*., 2009; Leppik and Birnbaum, 2010; Frank and Tyson, 2020; Roeder and Leira, 2021). The involved factors in the pathophysiology of epilepsy were presented (Haglund and Schwartzkroin, 1990; Hussain, 1991; Pitkänen *et al*., 2007; Kariyawasam *et al*., 2009; Frank and Tyson, 2020; Roeder and Leira, 2021; Kansal *et al*., 2024). It was evident that epilepsy patients present various hormonal disturbances (Hussain *et al*., 2006; Qureshi *et al*.,1988; Pennell, 2009; Herzog and Frye, 2014; Frank and Tyson, 2020; Octaviana *et al*., 2022; Sazgar *et al*., 2023; Rider *et al*., 2024). Important reports in perimenstrual seizures (Rosciszewska, 1987; Herzog *et al*., 1997; Herzog and Frye, 2014; Roeder and Leira, 2021) provided firm evidence that seizure frequently occurs in association with menstruation/ menstruation related cycle phases.

There are different views about cause of the occurrence/ dispersion of catamenial seizures (El-Khayat *et al*., 2008; Kariyawasam *et al*., 2009; Herzog and Frye, 2014; Frank and Tyson, 2020), e.g., water retention (McQuarrie, 1932), primary role of progesterone and estrogen (Laidlaw, 1956; Backstrom, 1976) decrease of progesterone in luteal phase but not in the follicular phase (Rosciszewska *et al*., 1985; Herzog and Frye, 2014), and psychic and emotional disturbances/complications (Stieglitz and Kimble, 1949) denied by Ansell and Clarke (1956b). Epileptic

*Extracted from author's presentations

seizures during the menstrual cycle and the role of steroid hormones (mainly estrogen and progesterone) in catamenial epilepsy were studied thoroughly (Backstrom, *et al*., 1985; Hussain *et al*., 1987; Qureshi *et al*., 1988; Hussain, 1991; Tuveri *et al*., 2008; Kariyawasam *et al*., 2009; Herzog and Frye, 2014; Frank and Tyson, 2020; Octaviana *et al*., 2022; Sazgar *et al*., 2023; Rider *et al*., 2024).

Several studies emphasize the relationship of various factors with epilepsy e.g., temperature and sleep-wake cycle (Hussain, 1991), calcium (Hussain, 1991; Hamed *et al*., 2004), epileptic seizures and the cortical excitability and gonadotrophic hormones (Luef, 2010), prolactin (Hussain, 1991; Luef, 2010), cortisol (Hussain, 1991; Marek *et al*., 2010), electrolytes and water metabolism (Hussain, 1991; Castilla-Guerra *et al*., 2006; Reynolds *et al*., 2007), and antiseizure medication (Hussain *et al*., 1987, 2007a; Qureshi *et al*., 1988; Hamed *et al*., 2004).

The feedback mechanism (Rebar and Yen, 1979) explains the control of hypothalamo-pituitary axis (HHPA). Electrolytes and seizure occurrence were found associated (Jacono and Robertson, 1987). The occurrence of seizures in women with epilepsy with/ without medication was studied thoroughly (Kariyawasam *et al*., 2009; Voinescu and Pennell, 2017; Herzog and Frye, 2014; Frank and Tyson, 2020; Roeder and Leira, 2021). However, the present review emphasizes the need of further studies for dispersion pattern of epileptic seizures in women with catamenial and noncatamenial seizures, and their association with the variation in hormones for diagnostic, pathophysiological and management purpose.

EPILEPSY- CLASSIFICATION/ TYPES

Epilepsy and its classification have been presented considering various views (Marsden and Reynolds, 1982; Kansal *et al*., 2024). Based on various approaches, just a seizure cannot be considered as epilepsy since epilepsy is a neuronal disorder originating from brain neurons (Weiner and Levitt, 1989). If clinical processes or events detectable by a subject or the observer in response to neuronal paroxysmal discharge, then such discharge is termed as the epileptic seizure (Hopkins, 1987). Epilepsy is a consequence of various causes expressing finally as the recurrent seizures (Gastaut,1973). Epilepsy is a condition characterized by recurrent two or more seizures and is quite oldest condition in the human history, (WHO, 2001a) and further techniques have helped diagnosing the people with epilepsy (WHO, 2001b). Various criteria were established for classifying epilepsy/ epileptic seizures (International Classification of Functioning and Disability, 1999; Kansal *et al*., 2024).

The earlier classification that was well organized later (Hill, 1958) constituted cortical, primary/secondary subcortical and that originating from cortical/ subcortical areas. Later the term epilepsies were found more appropriate than just epilepsy due to complex forms of symptoms (Porter, 1984). Reoccurring seizures chronically with no specific precipitants constitutes epilepsy (Giblin and Blumenfeld, 2010), and about 8-10/ 1000 individuals in most of the areas was the prevalence of epilepsy (Forsgren and colleagues, 2005). The International League Against Epilepsy (ILAE) provides the details for diagnostic features/criteria for epilepsy syndromes that establishes a uniformity for diagnosing epilepsy/ epilepsy syndromes in various conditions. (Kansal *et al*., 2024). Taylor (1931) suggested occasional excessive and a quite disorderly neuronal discharges were aligned with seizures. Such seizures or fits and their manifestations occur in response to excessive neuronal activity, but epilepsy was found more than were these seizures (Marsden and Reynolds, 1982).

Epilepsy syndromes were included in epilepsy classification (Dreifuss, 1987; Kansal *et al*., 2024). The concept of dichotomies while classifying epilepsies was challenged (Engel, 2006), and the concept of systems in the ictal phenomenon/ event in generalized seizures was introduced (Polack *et al*., 2007). Five important criteria (type of seizures and EEG analysis, causes/ etiology, extent/ magnitude of seizure severity, level of chronicity and predominantly involved body part) (Merlis, 1972) helped classifying epilepsy as generalized (primary or secondary) and partial. It was noted that as suggested previously (Penfield and Erickson, 1941) for epilepsy being only the reoccurrence of fits or seizures, and only the "paroxysmal cerebral dysrhythmia" (Gibbs *et al*., 1937) could not be understood clearly. It was redefined by Penfield physiologically as a tendency to periodic involuntary neuronal discharges /explosions (Kiloh *et al*., 1981).

HISTORY AND EPIDEMIOLOGY OF CATAMENIAL EPILEPSY

The menstrual cycle is regulated by the endocrine and neuroendocrine hormones/ factors and other mechanisms mainly under the control of hypothalamo-hypophyseal-ovarian axis (HHO), and the cycle lasts for around 28 days (24-35) with day 14 as the ovulatory day, while around day around -14 is considered as ovulation day in longer cycles (Herzog *et al*., 1997; Foldvary-Schaefer and Falcone 2003). Catamenial epilepsy precisely is a type of epilepsy characterized by the increase in the frequency of seizure occurrence mainly during the perimenstrual and periovulatory phases and seizure exacerbation may occur during/ around ovulation or any other phase/ phases. (Hussain *et al*., 1987, 2006, 2007a; Hussain, 1991, 2010; Kariyawasam *et al*., 2009; Pennell, 2009; Herzog and Frye, 2014; Frank and Tyson, 2020; Roeder and Leira, 2021). The name catamenial epilepsy was used to indicate the

cyclical increase/ exacerbation of epileptic seizures during a specific phase/ phases/ periods in menstrual cycle (Herzog 2008).

There are reports for 10-78% prevalence of catamenial pattern (Schelp and Speciali, 1983; Taubøll *et al*., 1991). The terms precatamenial and premenstrual epilepsy are sometimes used synonymously to explain the premenstrual seizure exacerbations mainly or exclusively during few or several days before the start of menstruation. Prevalence of catamenial seizure pattern was documented as the highest where a rough estimation of the dispersion of seizures was found quite high in perimenstrual phases (Taubøll *et al*., 1991). Herzog *et al*. (1997) defined catamenial epilepsy a type of epilepsy showing greater than average seizure frequency during perimenstrual or periovulatory periods in normal ovulatory cycles and during the luteal phase in anovulatory cycles. The term pericatamenial was used for those conditions where seizures exacerbation occurs during the menstruation related cycle phases (premenstruation, menstruation and postmenstruation) (Hussain *et al*., 2006, 2007a). Another term semi-pericatamenial or partial pericatamenial was used to describe the conditions where partial dominance of seizure occurrence is found during perimenstrual or menstrual related cycle phases/menstruation related cycle segment (Hussain *et al*., 2006, 2007a, b).

Some of the women with epilepsy may have certain menstrual abnormality (Bosak *et al*., 2018) including the absence of ovulation. Tuveri *et al*., (2008) used a fractional change method to calculate the catamenial change in seizure frequency, but due to wide variability, this method of assessing the catamenial influence is not considered as a proper procedure to be employed for catamenial epilepsy. Decreased levels of progesterone permit gonadotropin-releasing hormone to be increased for generating a new cycle (Foldvary-Schaefer and Falcone 2003; Reddy 2009). Progesterone deficiency and inappropriate luteal phase occur when the cycle is anovulatory (Herzog *et al*., 1997).

Penfield and Jasper (1954) concluded that epileptic seizures in females often begin around the menarche that shows some relationship of seizures with the menstrual cycle. It was in accordance with the views for menstrual epilepsy (Wilson 1940) that seizures occur mainly before the onset or during menstruation and rarely after the end of menstruation. When the proper definition or specified criteria were strictly followed, the prevalence of catamenial seizure patterns were found low (Kariyawasam *et al*., 2009). The term menstrual or catamenial epilepsy was used to describe the seizure occurrence in relation with the menstrual cycle (Laidlaw (1956; Gastaut, 1973). Another study showed 12.5% of prevalence when around 75 % seizures occurred 10 day perimenstrually in three consecutive menstrual cycles (Duncan *et al*., 1993).

Wilson (1940) used the term menstrual epilepsy in those women who had majority of their seizures during or after menstruation, and the details were provided later by Penfield & Jasper (1954). The association of seizures in women with sex, menstruation and menstrual cycle were supported (Lennox, 1955; Bandler *et al*., 1957; Temkin, 1971). It was found that catamenial or menstrual epilepsy occurs around menstruation (Bouchet and Cazauveilh, 1826; Penfiled and Jasper, 1954; Lennox, 1955; Ansell and Clarke, 1956b; Logothetis *et al*., 1959; Backstrom, 1976; Newmark and Penry, 1980; Laidlaw and Richens, 1982; Hussain *et al*., 1987; Rosciszewska, 1987; Qureshi *et al*., 1988; Reddy, 2004a; Pennell, 2009; Herzog and Frye, 2014; Frank and Tyson, 2020; Roeder and Leira, 2021). However, most of the previous studies did not provide the detailed information about the type of epileptic seizures and antiseizure medication (Livingston, 1972).

Two-fold or greater increase in seizures in certain specific phase in at least two consecutive cycles is currently emphasized for better understanding of the catamenial patterns (Reddy, 2009; Herzog 2015; Frank and Tyson, 2020). Gastaut (1973) named pubertal epilepsy and catamenial epilepsy respectively while seizures occurring during puberty and perimenstrual periods, and defined catamenial epilepsy as: "A type of epilepsy characterized mainly or exclusively by catamenial epileptic seizures". Rosciszewska (1987) studied epilepsy in women in their puberty, pre/post-menopause, and pregnancy. Further, the catamenial seizure was defined by Gastaut (1973) as "An epileptic seizure that occurs either during menstruation or several days preceding or following it and that is caused by a lowering of the convulsive threshold secondary to endocrine and cellular changes brought about by menstruation". It was suggested that following / accepting different definitions has influence on how we find the prevalence in the same population (Herzog *et al*., 1997), and while when considering/ including the data of a greater number of cycles (Herzog *et al*., 2012). The definition of catamenial epilepsy proposed by Gastaut (1973) is generally accepted (Hussain *et al*., 1987; Qureshi *et al*., 1988; Herzog *et al*. 2004; Hussain *et al*., 2006, 2007a; Reddy, 2009).

Analysis of seizure dispersion pattern classifies the menstrual cycle into segments/ phases (Hussain *et al*., 1987; Hussain, 1991, 2010). The other important segment of the menstrual cycle is ovulation related (periovulatory) cycle segment. Catamenial seizures (either perimenstrual or periovulatory) are observed during ovulatory and anovulatory cycles (El-Khayat *et al*., 2008). The terms like semi/partial precatamenial, semi/partial catamenial, semi/partial postcatamenial can also be used considering the seizure dispersion pattern (Hussain *et al*., 1987; Hussain, 1991, 2010). However, it has also been viewed that a two-fold or greater increase in seizure frequency during a particular phase of the menstrual cycle could generally be considered as catamenial epilepsy (Reddy, 2009).

DIAGNOSIS OF CATAMENIAL EPILEPSY

Seizure occurrence and plasma hormone levels during the cycle phases of premenstruation (last four days of the cycle, D: -1, D: -2, D: -3 and D: -4), menstruation (D:1, D:2, D:3, D:4 and D:5, depending on phase duration) and postmenstruation (D:+1, D:+2, D:+3, and D:+4 were studied (Hussain *et al*., 1987, Qureshi *et al*., 1988; Hussain, 1991; 2010). Though the seizures appearing at or around the time of menstrual bleeding were termed as catamenial seizures (Rosciszewska, 1987), different criteria were emphasized by various researchers, and cyclical seizures unrelated to menses were ignored (Bandler *et al*., 1957). Hence, the proper diagnosis is highly essential, as described in detail (Frank and Tyson, 2020; Kansal *et al*., 2024). The catamenial epilepsy is an intractable type of epilepsy depending on the resistance in cycle phases/ or certain timings in cycle phases (El-Khayat *et al*., 2008; Pennell, 2009; Reddy, 2009; Herzog and Frye, 2014; Frank and Tyson, 2020; Roeder and Leira, 2021). Patients with both simple partial complex partial and generalized tonic-clonic seizures show association of epilepsy with the menstrual cycle (Rosciszewska, 1980; Backstrom *et al*., 1984).

To explore the specific phase/ phases involved in catamenial epilepsy, it was revealed that seizure occurrence increased frequently at or around the time of menstrual flow (Logothetis *et al*., 1959; Frank and Tyson, 2020), only during the time of menses (Kramer, 1977), during almost 2 days after the start of menses (Bunter & Rosciszewska, 1975), in both premenstrual and menstrual phases (Ansell and Clarke, 1956b; Laidlaw, 1956) and during all three perimenstrual phases (premenstrual, menstrual and postmenstrual) though mostly during the last part of premenstrual phase (Hussain *et al*., 1987, Qureshi *et al*., 1988; Hussain, 1991; 2010). Backstrom (1976) studied both ovulatory and anovulatory cycles and reported that generalized tonic-clonic seizures increased during menstrual flow and during preovulation phases. Rosciszewska (1987) showed that only 4 of 226 women with epilepsy had seizures regularly with every menstruation and a further six had occasional seizures during some menstruations only (Rosciszewska, 1974). It was noted that seizure frequency increased for days 14-16 after the start of menses (Helmchen *et al*., 1964) and decreased during luteal phase from days 4-15 days before menstruation (Laidlaw, 1956). Furthermore, the perimenstrual or periovulatory catamenial seizures were observed to appear in ovulatory as well as anovulatory cycles (El-Khayat *et al*., 2008). Grudzinska and Rosciszewska (1980) noted that most of their patients had tonic-clonic seizures on day 6 and day 22 of menstrual cycle.

It was found that rapid increase in seizures with concomitant fast drop in progesterone occurred during specific phases of the menstrual cycle, especially during the last part of premenstrual phase (Qureshi *et al*., 1988; Hussain, 1991; Hussain, 2010). Women patients with catamenial epilepsy showed increase in estradiol during premenstrual days (Qureshi *et al*., 1988; Hussain, 1991; Hussain, 2010). Another report showed drop in estrogen (Herzog *et al*., 1997) during specific periods of menstrual cycle. Periovulatory pattern of seizure occurrence showed rapid increase in estrogen but no association with increase in progesterone (Navis and Harden, 2016; Frank and Tyson, 2020). There are studies showing seizure exacerbations during and around menses as 10-63% (Ansell & Clarke, 1956b; 72%: Laidlaw, 1956), exacerbation of seizures as 31–60% (Herzog *et al*., 2004; El-Khayat *et al*., 2008) and exacerbation of two third of women (Rosciszewska, 1980). These studies confirmed the previously suggested association of seizures during various cycle phases, though no apparent relationship of seizures with various cycle phases were documented (Bandler *et al*., 1957). Such seizures unrelated to menstrual cycle or any specific cycle phases were considered as noncatamenial seizures (Hussain *et al*., 1987).

Frequency of seizures is doubled in cycles in the second half of luteal phase with inadequate luteal phase where deficiency of progesterone and elevated estradiol/progesterone ratio occur (Navis and Harden, 2016; Frank and Tyson, 2020). The variation of seizure occurrence in ovulatory and anovulatory cycles can be described with the neuroactive properties of estrogen and progesterone, and serum levels of these steroid hormones in ovulatory compared to anovulatory cycles (Herzog and Fowler, 2008; Herzog and Frye, 2014; Frank and Tyson, 2020). It is necessary to record the seizures occurring in various phases in the menstrual cycle to verify that the patients are fulfilling the diagnostic criteria to be considered as having the catamenial seizure pattern owing to association with endocrine/ neuroendocrine changes (Kariyawasam *et al*., 2009; Pennell, 2009; Herzog and Frye, 2014; Frank and Tyson, 2020; Roeder and Leira, 2021).

Tonic-clonic seizures were more cyclical in patients with more than one type of epileptic seizures (Rosciszewska, 1987). Frequency for partial seizures increases during menstruation and just before ovulation but decreases during luteal phase (Backstrom *et al*., 1984). Collecting the precise records of seizure parameters as well as menstrual cycle provide the major information for the proper diagnosis of catamenial/ menstrual epilepsy (Hussain, 1991; Herzog, 2006; Herzog and Frye, 2014; Frank and Tyson, 2020; Kansal *et al*., 2024). Three main patterns of catamenial exacerbations noted during perimenstrual phases are: premenstrual (C1), periovulatory (C2), and luteal (C3) (Herzog *et al*., 1997; Kariyawasam *et al*., 2009; Pennell, 2009; Herzog and Frye, 2014; Frank and Tyson, 2020; Roeder and Leira, 2021). First day of the menstrual bleeding was recorded as first day of menstrual cycle (Reddy, 2009). Reddy (2009) divided the menstrual cycle into four phases: menstrual phase (days −3 to +3),

follicular phase (days +4 to +9), ovulatory phase (+10 to +16) and luteal phase (days +17 to −4). However, a little different procedure for evaluating the seizure dispersion pattern in the menstrual cycle was described earlier (Hussain *et al*., 1987) and the data of non-catamenial epileptics and catamenial epileptics were evaluated (Hussain *et al*., 1987; Qureshi *et al*., 1988; Hussain, 1991, 2010).

Though the endocrine factors were considered unimportant, various studies related to the occurrence/ dispersion of seizures and the analysis and anticonvulsant treatment during menstrual cycle (Hussain *et al*., 1987; Jacono and Robertson, 1987; Rosciszewska, 1987; Qureshi *et al*., 1988; Hussain, 1991; Hussain *et al*., 2006, 2007a,b; El-Khayat *et al*., 2008; Kariyawasam *et al*., 2009; Pennell, 2009; Reddy, 2009; Hussain, 2010; Herzog and Frye, 2014; Frank and Tyson, 2020; Roeder and Leira, 2021) indicate an important involvement of hormones in the pathophysiology of catamenial epilepsy.

Controversial results were found for the type of seizures showing catamenial pattern (El-Khayat *et al*., 2008; Kariyawasam *et al*., 2009; Pennell, 2009; Reddy, 2009; Herzog and Frye, 2014; Frank and Tyson, 2020; Roeder and Leira, 2021). Both the focal and generalized epilepsy patients present catamenial epilepsy (El-Khayat *et al*., 2008), and epilepsy syndrome and temporal lobe epilepsy patients have prominent catamenial pattern (Morrel, 1999). But unfortunately, most of the previous reports did not describe such information (Ansell and Clarke, 1956b; Bandler *et al*., 1957) or otherwise included the patients with generalized seizures (Laidlaw, 1956). One report showed generalized but not the partial seizures as cyclical and associated with the menstrual cycle with concomitant variation of estrogen in ovulatory subjects (Backstorm, 1976), whereas partial seizures and not the generalized seizures as cyclical or catamenial (Helmchen *et al*., 1964) or both generalized tonic-clonic seizures and complex partial seizures were found with catamenial pattern (Sanchez-Longo and Gonzales-Saldana, 1966), However, association of catamenial epilepsy more in partial epilepsy specially related to temporal lobe epilepsy than in the generalized epilepsy was found later (Foldvary-Schaefer and Falcone, 2003).

PATHOPHYSIOLOGY OF CATAMENIAL EPILEPSY

WATER METABOLISM:

Change in serum sodium in patients having catamenial epilepsy with and without anticonvulsant therapy (Hussain 1991, 2010; Shah *et al*., 2001; Frank and Tyson, 2020) revealed that water metabolism was found related to the occurrence of catamenial pattern of seizures. Furthermore, the precatamenial (or premenstrual catamenial) epilepsy women showed weight gain in premenstruation and weight loss during menstrual phase (Hussain 1991, 2010), though the extracellular water storage was not primarily found responsible for exacerbation of seizures (Ansell and Clarke, 1956b). Most of the data determined for uncovering the etiology of catamenial epilepsy have been the hormonal (mainly steroid hormones) evaluations (Frank and Tyson, 2020; Roeder and Leira, 2021). It is suggested to carry out further studies to verify the role of water metabolism in the pathobiology of catamenial epilepsy. Acetazolamide showed efficacy in catamenial epilepsy (Lim *et al*., 2001), whereas valproate, electrolyte disturbances (Castilla-Guerra *et al*., 2006), combined anticonvulsant therapy (Jallon and Picard, 2001), increased levels of serum sodium in response to long-term anticonvulsant medication (Hamed *et al*., 2004) increase body weight and metabolic effects and may cause insulin sensitivity (Reynolds *et al*., 2007), whereas lamotrigine is not related with weight gain in women with menstruation related epilepsy (Morrell *et al*., 2003).

A significant linear correlation of body weight with menstrual disturbances was obtained in women with generalized epilepsy without any linear correlation of weight change with reproductive hormones/ menstrual disorders (Prabhakar *et al*. 2007). However, change in the levels of gonadosteroids, adrenosteroid hormones, antiepileptic drug (AED) levels and water and electrolyte metabolism in epilepsy women with catamenial pattern was documented (Ansell and Clarke, 1956b; Backstrom, 1976; Tuveri *et al*., 2008). Decreased levels of ionized calcium may cause seizures (Glasser and Levy, 1960); and overhydration may also lead to generalized tonic-clonic seizure treatable by increase in osmolality (Saly and Andrew, 1993).

GONADOSTEROID HORMONES:

The effect of estrogen on pre-existing epileptic foci in response was suggested since the estrogen administration as a therapy was performed in some of the epilepsy patients, and the response was even aggravation of seizures (Logothetis *et al*., 1959). It has been documented that urinary excretion of estradiol, estriol and pregnanediol decrease in patients with menstrual epilepsy, whereas excretion of pregnanetriol decrease in epilepsy women with non-catamenial seizures only (Buntner & Rosciszewska, 1975). However, other reports show inconsistent excretions of estrogen or pregnanediol in patients with catamenial pattern of seizures, and excretion of estrogen in patients having both catamenial and non-catamenial pattern of seizures (Thirty *et al*., 1954; Zaichkina, 1963), but no specific pattern of hormonal excretion could be investigated.

Estrogen facilitates convulsions in kindling model (discovered by Graham Goddard, 1967), hippocampal excitability and audiogenic seizures in animal studies, and hence it is considered as having proconvulsant/ anticonvulsant properties (Logothetis *et al*., 1959; Wooley and Timiras, 1962a; Backstrom, *et al*., 1985; Hussain *et al*., 1987, 2006; Qureshi *et al*., 1988; Hussain, 1991, 2010). The ovariectomized female rats showed that estrogen changes the acquisition of seizures kindled by pentylenetetrazole (PTZ) or repeated stimulation of amygdala (Hom and Buterbaugh, 1986). The estradiol levels associated negatively with the ionized calcium (Jacono and Robertson, 1987). Despite the animal models showed convulsant effects of estrogen and anticonvulsant effects of progesterone (Logothetis *et al*., 1959; Backstrom, *et al*., 1985), later studies could not find the convulsant effects of estrogen (Rosciszewska *et al*., 1986; Rosciszewska 1987). It was further investigated that low dose of estradiol has neuroprotective action (Veliskova and Velisek, 2007; Velísek and Velísková, 2008).

Regarding the role of progesterone in epilepsy, it is pertinent to mention that progesterone in serum and brain correlates since progesterone crosses blood-brain barrier (BBB) quickly (Stoffel-Wagner 2001) and it helps in inhibiting the development and occurrence of seizures (Holmes and, Weber 1984). Progesterone acts a: via converting allopregnanolone and other neurosteroids and hence influencing the brain receptors (Kapur and Joshi, 2021), b: by slow and long lasting post-transcriptional mechanisms (Joshi *et al*., 2018; Shiono *et al*., 2021), c: the gamma aminobutyric acid receptor A ($GABA_A$) receptors that cause effects of allopregnanolone (Joshi and Kapur, 2019), d: by forming 5α-dihydroprogesterone that inhibits the neuronal activity (Wu and Burnham, 2018), e: as the sulfated progesterone metabolites that decrease the GABAergic neurotransmission, and hence increase in excitability occurs (Joshi and Kapur, 2018; Kapur and Joshi, 2021), f: leading to occurrence of perimenstrual seizures by the activation of progesterone receptors in the last part of luteal phase that elevates the glutamatergic action related to excitatory transmission (Joshi *et al*., 2018; Kapur and Joshi, 2021), g: by its direct action on brain progesterone receptors and increasing neural excitability, h: by the effect of allopregnanolone to increase the inhibitory effects of $GABA_A$ (Reddy 2004 a), h: as the concentration of progesterone and allopregnanolone are reduced in the last part of luteal phase that increases the excitability (Reddy *et al*., 2001), and i: as progesterone and allopregnanolone concentration in the mid-luteal phase is maximum, and hence, progesterone has protective effect and maximum inhibition against epileptic seizures (Reddy 2022).

It is known that estrogen causes hyperexcitability (Herzog, 2015), increases the glutamatergic related excitatory transmission through NMDA N-methyl-D-aspartate (NMDA) receptors (glutamate receptors) via mediation of kainite (that activate glutamate receptors) (Smejkalova and Woolley, 2010). Cytochrome aromatase enzymes synthesize estradiol in the hippocampus, and hence the level of estradiol is increased in hippocampus than that in the serum (Hojo *et al*., 2009). Increase in the frequency of seizures during the pre-ovulatory phase associates with the increased level of estrogen, and similarly increase in estrogen/progesterone ratio during the inadequate luteal phase also associates with increase in the frequency of epileptic seizures (Reddy, 2009).

There are studies that indicate that very high and very low doses of estrogen may increase the epileptic activity, whereas low levels of estrogen decrease the epileptiform activity (Zhang *et al*., 2005). There is much controversy for the action of estrogen. A U-shaped excitability and dose-dependance style was obtained (Zhang *et al*., 2015). Estrogen shows a protective effect (Velísková *et al*., 2010). It was also found that estrogen delayed the time of the onset/ occurrence of seizures induced by kainite (Velísková *et al*., 2000). Negative correlation of progesterone levels and number of seizures, and positive correlation of estrogen/progesterone ratio with the number of seizures was revealed (Backstrom, 1976; Rosciszewska, 1987). The luteinizing hormone (LH) levels verified the decreased levels of progesterone in luteal but not in follicular phase (Rosciszewska *et al*., 1985; Qureshi *et al*., 1988; Hussain, 1991, 2010; Hussain *et al*., 2006). Significant reduction was recorded in spike frequency after intravenous administration of progesterone in some of the patients (Backstrom, 1984), and it was verified that menstrual cycle and steroid hormones are influenced by seizures and AEDs (Morrell and Montouris, 2004; Kariyawasam *et al*., 2009; Voinescu and Pennell, 2017; Frank and Tyson, 2020).

The incidence of overweight/obesity especially related to estradiol levels in women of reproductive age is associated with infertility and related disorders and may lead to other disorders attributed both to epilepsy and use of AEDs (Isojärvi *et al*., 2005; Rehman *et al*., 2012a, b, 2013a, b, c, d, 2016). The experimental and clinical studies (Abbas *et al*., 1995; Inam *et al*., 1995; Khan *et al*., 1995; Masood *et al*., 1995; Isojärvi *et al*., 2005) confirmed the metabolic influences of estradiol.

On the other hand, progesterone was found having anticonvulsant/antiepileptic activity in animal models and human studies (Logothetis *et al*., 1959; Backtrom *et al*., 1984, 1985; El-Khayat *et al*., 2008; Tuveri *et al*., 2008). The anticonvulsant activity of progesterone was found clearer than the effects of estrogen, e.g., reduction of mid luteal seizures in the presence of increased progesterone levels (Laidlaw, 1956; Backstrom, 1976), and increased seizure occurrence near menstrual period owing to decreasing levels of progesterone (Laidlaw, 1956). Furthermore, the data

from ovulatory cycles in women with generalized as well as partial seizures revealed increased estrogen-progesterone ratio associating with increased seizure occurrence (Backstrom, 1976).

Besides other functions of transient receptor potential (TRP) channels related to common molecular mechanisms for polycystic kidney disease of different genotypes (Wu *et al*., 2006), a TRP channel activated by heat and endogenous neuro-steroid pregnenolone sulfate have been suggested to be involved in epilepsy and other related disorders (Matsubara *et al*., 2021; Zhao and Rohacs, 2021). The use of depot medroxyprogesterone acetate, Depo-Provera or DMPA as a contraceptive has demonstrated reduced sperm penetration, show estrogen-associated complications/ disorders, reduced seizure frequency in epilepsy, reduced pre-menstrual symptoms/complications, decreased menstrual flow, and prevention of iron deficiency/ iron deficiency anemia. However, one main drawback/disadvantage of using it is that weight gain occurs (Khoiny *et al*., 1996; Rehman *et al*., 2014, 2015).

Applications of the density functional theory (DFT) for understanding the epimeric and anomeric structural complexities (Ahmadi *et al*., 2017) and studies related to DFT of the reproductive hormones (progesterone and estrone) help understanding the pathophysiological involvement of cyclic variations (Liang *et al*., 2024), and pathophysiology of epilepsy (Singh and Pathak, 2024). The literature shows that the ion channel and non-ion channel mutations due to gene mutations are the main involvements in epilepsies e.g., sodium channel mutations in epilepsy (Meisler and Kearney, 2005). The role of hydrogen bonding in sodium and other ion channels in epilepsy have revolutionized the area of epileptology, epileptoelectrophysiology and epileptopharmacology (Ahsan, 2013; Hussain 2022 a, 2024 a).

GONADOTROPINS AND OTHER HORMONES:

Serum/ plasma levels of LH and follicle stimulating hormone (FSH) were determined in women with epilepsy and controversy about the gender-based variation in FSH and LH was noticed (Kuba *et al*., 2006). Various studies showed: post-puberty increased LH in patients taking carbamazepine and valproic acid, and increased LH in untreated patients compared to controls and decreased LH after carbamazepine therapy for initial year (Isojarvi, 1990) and decreased LH-RH (luteinizing hormone-releasing hormone) levels after two months' therapy of carbamazepine; correlation of seizure occurrence with LH levels and abnormal release of LH in women with epilepsy (Morrell, 1999); change in the LH pulse frequency (Bauer, 2001); increased LH concentration in women with epilepsy (Rosciszewska *et al*., 1985); and significant increase in LH in women with catamenial epilepsy (Hussain, 1991, 2010).

LH was found increased after electroshock convulsions and in the women with generalized epilepsy having increased BMI and menstrual disorders (Prabhakar *et al*., 2007). Postictal increases in LH, and FSH was found in patients with generalized tonic-clonic as well as partial seizures (Luef, 2010). Abnormalities in LH and FSH were found in women with epilepsy having reproductive disorders (Hamed *et al*., 2004). Furthermore, a recent study reveals that hypothalamo-pituitary-ovarian (HPO) axis is influenced by neuroendocrine mechanisms after the occurrence of epilepsy and hence, secretions of gonadotropins are disturbed (Sazgar *et al*., 2023). Valproate and lamotrigine therapy associated with variation in FSH and estradiol levels, whereas polytherapy including clobazam caused irregular cycles. (Octaviana *et al*., 2022).

Levels of serum/ plasma prolactin in women with epilepsy in spontaneous seizures were determined. Some of the significant investigations are: increased plasma prolactin in women with catamenial epilepsy (Hussain, 1991, 2010; Bauer, 2001; Hamed *et al*., 2004), higher serum concentration of prolactin than normal healthy subjects, positive correlation of prolactin with plasma levels of phenytoin and primidone and elevated levels in after puberty patients undergoing anticonvulsant therapy of valproate and carbamazepine and postictal increased prolactin in epileptic seizures compared to psychogenic attacks, slight correlation of prolactin with seizure duration, no change in prolactin during one year of carbamazepine therapy but decrease after one year therapy, direct correlation with seizure frequency, association of prolactin with the reproductive disorders in women with epilepsy, postictal increase in prolactin in patients with partial seizures and tonic-clonic generalized seizures, and increased levels of serum prolactin after repetitive seizures in women having epilepsy (Isojarvi, 1990; Hamed *et al*., 2004); Luef, 2010). The lower levels of prolactin and estradiol in women with epilepsy associated with higher seizure frequency (Octaviana *et al*., 2022).

General studies about the pathophysiological role of cortisol were related to serum/ plasma levels of cortisol after the occurrence of spontaneous epileptic seizures (Hussain, 1991, 2010; Marek *et al*., 2010; Rider *et al*., 2024), and influence of antiseizure medication. Cortisol is considered as the differential marker for the diagnosis of epileptic seizures (Ess) and psychogenic non-epileptic seizures (PNESs) (Rider *et al*., 2024). Some of the pertinent investigations were elevated levels of cortisol (Marek *et al*., 2010); decreased level of DHEAS/cortisol ratio in catamenial epileptics during perimenstrual phases (Tuveri *et al*., 2008); and non-significant variation of cortisol (Isojarvi, 1990).

SYSTEMIC AND COMORBIDITY ASSOCIATED CHANGES:

Several changes occur during the seizure occurrence. e.g., it was documented that alteration in sleep-wake cycle (Ogihara *et al*., 2010) and increase in basal body temperature (Hussain, 1991; Ogihara *et al*., 2010) may facilitate the occurrence of seizures. Low levels of dopamine in neostriatum and nucleus accumbens septi in epileptic mice showing improvement after intraventricular supply of calcium chloride. Systemic effects of seizures and AEDs in epilepsy was documented (Shah *et al*., 2001; Hamed *et al*., 2004). It was demonstrated that anesthetized rats presented extracellular potassium and extracellular calcium response patterns, and calcium influx during the paroxysmal depolarization shift (PDF) after pentylenetetrazol (PTZ) administration (Luecke and Speckmann,1990). It was further found that the ketamine may block spontaneous epileptiform activity recorded in low calcium, but when there is still some synaptic transmission present.

Changes in sodium and calcium induced by quisiqualate, excitatory synaptic contacts, accumulation of extracellular potassium in penicillin-induced epileptogenesis, epileptic bursting activity and inactivation of potassium conductance causing potassium channel inactivity and generating epileptic activity (Swann *et al*., 2000). It shows the possibility of potassium-channel activators as novel therapeutic intervention in epilepsy disorders. Association of serum calcium with the occurrence of seizures (Hamed *et al*., 2004), and negative correlation of estrogen and ionized calcium was investigated in healthy women and women with epilepsy having catamenial pattern (Jacono and Robertson, 1987).

Epilepsy as a risk factor in patients with ischemic stroke, and effect of menstrual cycle on stroke and other neurological complications (Hussain *et al*., 1987; Hussain, 1991; Khan *et al*., 2009; Naz *et al*., 2009; Hussain, 2010; Roeder and Leira, 2021) reveal the involvement of catamenial seizure pattern. There is an important role of alpha-actinin in menstrual cycle and epileptogenesis and its enhancing property for transient receptor potential channel-3 (Li *et al*., 2007; Sbai *et al*., 2020). Sexual problems and endocrine changes in progesterone and testosterone in men and women with epilepsy and other disorders (Smith *et al*., 2007; Hussain *et al*., 2017; Demirkhanyan *et al*., 2018; Mohandass *et al*., 2020) leading to abnormal functions of TRP channels (Mohandass *et al*., 2020) and variations in endogenous steroids e.g., progesterone metabolites via GABA(A) receptor (GABAR) mediation result in premenstrual disorders and catamenial epilepsy (Smith *et al*., 2007).

Epilepsy and catamenial epilepsy were found influenced by sex hormones with the complications of infertility, ischemic disorders, diabetes mellitus and other disorders (Lemley and Voinescu, 2023). These complications were studied in various perspectives (Khan and Hussain, 2008; Sohail and Hussain, 2008, 2009, 2013; Yasmeen *et al*., 2008, 2009; Sohail *et al*., 2013, 2019; Lemley and Voinescu, 2023). Oxidative stress and lipid profile under the effect of black seed oil showed evidence in experimental hypercholesterolemia and patients with intractable epilepsy (Fatima *et al*., 2007; Shawki *et al*., 2013).

The clinical, diagnostic, and therapeutic aspects of common cold and effect of common cold on development of epileptic seizures has been revealed (Jallon *et al*., 1986; Anjum and Hussain, 1998 a, b; 1999 a, b,c,d,e; Mahmood and Hussain, 1998, 1999; Munir and Hussain, 1999; Takahashi *et al*., 2003; Fujita *et al*., 2011; Hussain and Hussain, 2020; Neshige *et al*., 2023). A 25-year-old woman with non-herpetic acute limbic encephalitis (NHALE) suffered from generalized seizures following common cold that improved after high dose of methylprednisolone, but the symptomatic epileptic seizures could not be managed probably due to the involvement of host immune system in NHALE (Takahashi *et al*., 2003). The diagnostic and therapeutic aspects of pneumonia (Ahmed *et al*., 1994) reveal pneumonia accompanied with epilepsy and acute respiratory distress syndrome (Saito *et al*., 2013). There are several etiological factors in hypertension (Siddiqui *et al*., 1994). One of those factors is the use of low doses of combined estrogen-progestin-containing oral contraceptives (OCs) that decrease the risks of hypertension and other related disorders and have favorable effects in menstrual or catamenial epilepsy (Presl, 1991).

Women with epilepsy associated to menstrual cycle suffer from several sex-specific disturbances including seizure exacerbation, viral and bacterial infections of skin and cosmetic problems influencing skin/ hair with the use of AEDs (Inam *et al*., 1994; Røste and Taubøll, 2007). Erythrocyte osmotic fragility was significantly increased in erythrocyte malondialdehyde release in the epileptic compared to control subjects. Hence, it was viewed that the usage of antioxidants in addition to AEDs provide beneficial effects (Zafar *et al*., 1990; Yalçin *et al*., 1994). Low level of kisspeptin (Kp) was found associated with infertility, and intracerebroventricular administration of prolactin-releasing peptide (PrRP), and Kp was noted as causing decrease in cortical excitability while searching for anticonvulsants for intractable epilepsy (Buffel *et al*., 2015; Mumtaz *et al*., 2016). A variety of immunological, biochemical, and physiological factors/ markers were found associated with anemia, immune disorders, epilepsy, and cerebrovascular disorders (Hussain and Hassan, 1982; Breckwoldt *et al*., 1990; Hussain, 2022 a, b, 2024 a, b).

THEAPEUTIC APPROACHES

Systematic studies were conducted to evaluate and investigate the role of estrogen and progesterone in women with epilepsy with and without antiseizure treatment in various cycle phases (Rosciszewska *et al*., 1986; Hussain *et al*., 1987, 2006, 2007; Frank and Tyson, 2020). Conventional drugs that are hormonal and non-hormonal are optimized for the patients with catamenial epilepsy. No specific treatment could yet be approved for patients showing catamenial pattern (Patel and Foldvary-Schaefer, 2014), though various therapies have been proposed. Non-hormonal treatment comprises cyclic (e.g., clobazam) and non-cyclic (e.g., acetazolamide, lamotrigine) products that are used for the treatment for the patients with catamenial epilepsy. The mechanism of action for the clobazam relates to $GABA_A$ receptor modulator, whereas the mode of action for lamotrigine is sodium channel blocker and for accetazolamide is the carbonic anhydrase inhibitor (Lim *et al*., 2001; Gilad *et al*., 2008). There are various side effects of the mentioned products.

Gilad *et al*. (2008) investigated the role of EEG in assessing the efficacy of lamotrigine in decreasing the seizure occurrence in patients with catamenial epilepsy. While understanding the pathophysiology of catamenial pattern, it was found that cortical excitability during various cycle phases in women with catamenial epilepsy was involved that manifested a reduced inhibition owing to GABA-ergic neurotransmission in luteal phase and menstruation phase in women having catamenial epilepsy. The exacerbation of catamenial seizures is due to fall though non-significant in plasma phenytoin level in menses despite a rapid drop of plasma phenytoin in menstruation as compared to that in ovulation and around ovulation. Some important features are: increased concentration of after- puberty estrogen in monotherapy either of valproate or carbamazepine, and the appearance of beneficial effects of clomiphene on seizure occurrence/ frequency in women with complex partial seizures and reproductive/endocrine disorders, (Herzog, 1988).

The therapies of cyclic hormone products and suppressive hormone products (Maguire and Nevitt, 2021) are two main approaches for the hormonal treatment of catamenial epilepsy. Cyclic hormonal product/ therapy is progesterone (for reducing the seizure frequency) given during luteal phase but indicated for those patients who present regular cycles. It is supplemented specially for perimenstrual seizure exacerbation (Herzog *et al*., 2012). However, a later study found a negative association for perimenstrual seizure frequency and the serum level of progesterone (Herzog and Frye, 2014). Besides progesterone, anti-estrogen agents have also been used for the treatment of catamenial patterns of seizures. No clear evidence could be obtained (Herzog, 1988), though it was suggested that anti-estrogen product could decrease the premenstrual seizure frequency (Hussain, 1987; Qureshi *et al*., 1988; Hussain, 1991, 2010). Efficacy of gonadotropic releasing hormone was found in women with intractable/ drug resistant seizures in perimenstrual phase days (Bauer *et al*., 1992).

It is known that both antiepileptic drugs and gonadosteroidal hormones that are metabolized by cytochrome P450 liver enzyme have two-way influence, and hence the blood concentration of antiepileptic drugs remains fluctuating that may cause toxicity or decreased level of anticonvulsant efficacy (Patel and Foldvary-Schaefer, 2014). The women with perimenstrual seizures showed lower levels of phenytoin, and it was found that decreased phenytoin levels correlated with the perimenstrual seizure frequency (Rościszewska *et al*., 1986). An interesting investigation (Isojarvi *et al*, 2005) showed the increased metabolism of steroid hormones by enzyme-inducing AEDs that may affect contraception and other serious disorders contrary to the non-enzyme-inducing AEDs that usually do not cause such consequences. Furthermore, a previous study found change in the levels of steroid hormones under carbamazepine treatment in epileptics (Isojarvi, 1990). It was investigated that some of the AEDs may decrease the efficacy of oral contraceptives (Harden and Leppik, 2006; Velísková, 2007) and may cause the reproductive/endocrine disorders related to gonadosteroids. However, further studies are required to be conducted to understand the complex interaction among AEDs, gonadosteroids, and contraceptives.

There are reports of ochratoxin contamination in various commercial feeds used for broilers (Zafar *et al*., 2001) and high levels of ochratoxin causing nodding syndrome (NS)-a special type of epilepsy manifesting repeated head-nodding convulsions (Echodu *et al*., 2018). The efficacy of cannabidiol was verified for the treatment of epileptic seizures by clinical drug-drug interaction (DDI) studies simulated for itraconazole, and other products employing physiologically based pharmacokinetic models (Eh *et al*., 2021) and liposomal models (Matias *et al*., 2017; Eh *et al*., 2021; Yeung *et al*., 2023). The seizure control in women with epilepsy was studied employing monotherapy of first-line antiepileptic drugs, and it was found that interaction of estrogen could have altered (Grover *et al*., 2012) that was viewed as a possibility in epilepsy and a variety of other membrane related disorders Matias *et al*., 2017).

A famous American physician (Internal Medicine, Psychiatry & Physiology) Edmund Jacobson (April 22, 1888 – January 7, 1983) founded Progressive Relaxation (PR) or Progressive Muscle Relaxation (PMR) & of Biofeedback (Jacobson 1927, 1929, 1938). Several medical disorders including epilepsy were treated successfully employing the techniques, therapy, or training of PR (Canter *et al*., 1975; Rousseau *et al*., 1985). Later, a Modified Progressive Relaxation (MPR) was founded (Hussain 1982, 1984, 1994, 2001) that demonstrated the combined

effects. It was found that effect of stimulation frequency on muscle fatigue associates with the progressive relaxation exercises (Hussain, 1983; Akgün Şahin and Dayapoğlu, 2015). Such and other therapeutic approaches in medicine may revolutionize the methodologies for pathophysiological understandings especially employing the biophysical and mathematical medicine for the management of seizures/ catamenial seizures and other medical disorders.

CONCLUSIONS

The present clinical review on the history, epidemiology, diagnosis, pathophysiology, and management of catamenial epilepsy uncovers various aspects that are either needed to be further confirmed or otherwise are needed to be conducted for newer information at cellular and molecular level. The history of epilepsy summarized in the present article provides the diagnostic and therapeutic approaches to understand the catamenial seizures and carry out further studies for better understanding and applications. The variation in steroid, gonadotropic and other hormones/ systemic changes/ comorbidity associated changes has enormous involvement in the development/ exacerbation/ inhibition of seizures/ seizure disorders/ catamenial seizures in women with epilepsy during any of the involved cycle phase/ segment. There is an urgent requirement of incorporating multidisciplinary approach for clinicophysiological, and physicomathematical applications for better understanding and innovative management of medical disorders. Further studies would hopefully explore the intricate impact of hormones and other factors/ changes in the pathophysiology and diagnostic and therapeutic aspects of catamenial epilepsy.

DEDICATION

The author dedicates this article to the loving memory of his highly intellectual mentor and the Ph.D. research guide - the Late Prof Khawaja Zaki Hasan (Zaki Hasan or K. Zaki Hasan) MB, FRCP (Edin) (1927, Panipat, District Karnal, British India – December 15, 2007, Karachi, Pakistan). Prof Zaki Hasan was a famous physician, neuropsychiatrist, behavioral scientist, former Head Department of Neuropsychiatry (presently the departments of Neurology & Psychiatry), JPMC, Karachi, and formerly the chairman of UNICEF. He was particularly focused on the health, social aspects of children, and human rights of the working class and other segments of the society. Dr. Zaki Hasan got his initial education in Hyderabad Deccan and got MBBS from the Usmania University Medical College, Hyderabad before migrating to Pakistan. He initially joined the Dow Medical College (DMC), Karachi in the early 50's, and later served in various positions at JPMC and other institutions. He had a collaborative research lab with Late Prof. Atta-ur-Rehman (Professor of Biochemistry & Director Basic Medical Sciences Institute (BMSI), JPMC).

Prof. Dr. K. Zaki Hasan, MB, FRCP (Edin)

The author of this article had a great facility to carry out much of his research work in this research laboratory for his pre-PhD, PhD, and later studies. Dr Zaki Hasan was quite involved in the foundation of Baqai Medical University and Jinnah Medical and Dental College (JMDC), Karachi, and served as Vice Chancellor and Dean in the mentioned institutions, respectively. Prof. Zaki Hasan was famous in medicine, neuropsychiatry, and behavioral sciences as Prof Salimuzzaman Siddiqui (the Late Professor of Chemistry at the University of Karachi) in science and technology. Dr Zaki Hasan supervised a number of clinical and research programs in Europe, North America, and other regions. The Late Prof. Khawaja Zaki Hasan has an enormous contribution in shaping the health-related studies/ plans/ programs in Pakistan, and supervising/ advising for various innovative medical science programs world over.

REFERENCES

Abbas, K., N. Khan, S. Inam, S. Masood and Z. Hussain (1995). Influence of estradiol valerate on plasma phospholipids in Uromastix hardwickii. *First National Conference on Pharmacology and Therapeutics*. Faculty of Pharmacy, University of Karachi, P: 43.

Ahmed, N., Z. Hussain, S. Inam and S. Masood S (1994). Recent advances in clinical diagnosis and treatment of pneumonia. *Advances in Clinical Medicine*, p: 5-7.

Ahmadi, S., V.M. Achari, Z. Hussain and R. Hashim (2017). Epimeric and anomeric relationship of octyl- α -D-gluco/galactosides: insight from density functional theory and atom in molecules studies. *Computational and Theoretical Chemistry* (Amsterdam: Elsevier), 1108: 93–102.

Ahsan, M.J. (2013). Semicarbazone analogs as anticonvulsant agents: a review. *Cent Nerv Syst Agents Med Chem*., 13(2):148-58.

Akgün Şahin, Z and N. Dayapoğlu (2015). Effect of progressive relaxation exercises on fatigue and sleep quality in patients with chronic obstructive lung disease (COPD). *Complement Ther Clin Pract*., 21(4):277-81.

Anjum, S. and Z. Hussain (1999 a). Common cold-upper respiratory infection. *The Medicine International*, 2 (1), 5-7

Anjum, S. and Z. Hussain (1999 b). Diagnostic features in common colds. *The Medicine International*, 2 (2), 10-12

Anjum, S. and Z. Hussain (1999 c). Rhinovirus and common colds. *The Medicine International*, 2 (4), 8-10

Anjum, S. and Z. Hussain (1999 d). Age of children and common colds. *The Medicine International*, 2 (11), 6-8

Anjum, S. and Z. Hussain (1999 e). Complications in common colds. *The Medicine International*, 2 (12), 5-7

Anjum, S. and Z. Hussain (1998 a). How do common colds spread? *The Medicine International*, 1 (2), 9-12.

Anjum, S. and Z. Hussain (1998 b). Cellular and molecular pathophysiology of common colds. *The Medicine International*, 1 (6), 2-4

Ansell, B. and E. Clarke (1956b). Acetazolamide in treatment of epilepsy. *Br Med J*., 1(4968): 650-654.

Aziz, H. and Z. Hussain (1994a). Neonatal seizures- Diagnosis and treatment. In: *Biological Foundations of Medicine*. PAASK, Karachi, p:5-9.

Aziz, H. and Z. Hussain (1994b). Recent advances and future perspectives in epilepsy-A Review. In: *Advances in Clinical Medicine*, PAASK Karachi, p:8-14.

Backatrom, T. (1976). Epileptic seizures in women related to plasma estrogen and progesterone during the menstrual cycle. *Acta Neurol Scand*., 54(4):321-347.

Backstrom, T., M. Bixo and S. Hammarback (1985). Ovarian steroid hormones. Effects on mood, behaviour and brain excitability. *Acta Obstet Gynecol Scand Suppl*., 130:19-24.

Backstom, T., B. Zetterlund, S. Blom and N. Romano (1984). Effects of intravenous progesterone infusions on the epileptic discharge frequency in women with partial epilepsy. *Acta Neurol Scand*., 69 (4): 240-248.

Bandler, B., I.C. Kaufman, J.W. Dykens, M. Schleifer and L.N. Shapiro (1957). Seizures and the menstrual cycle *Am J Psychiat.*, 113(8): 704-708.

Bauer, J. (2001). Interactions between hormones and epilepsy in female patients. *Epilepsia*, 42Suppl 3: 20.

Bauer, J., L. Wildt, D. Flügel and H. Stefan (1992). The effect of a synthetic GnRH analogue on catamenial epilepsy: a study in ten patients. *J Neurol*,, 1992 May;239(5): 284-6.

Bosak, M., A. Słowik, and W. Turaj (2018). Menstrual disorders and their determinants among women with epilepsy. *Neuropsychiatr Dis Treat*., 14: 2657-64.

Bouchet, C. A. and A. Cazauveilh (1826). Recherches sur la nature et la sieze de ces deux maladies. *Archives Generales de Medicine*, 1826; 10: 5.

Breckwoldt, M., P. Wieacker and F. Geisthövel F (1990). Oral contraception in disease states. *Am J Obstet Gynecol*., 163(6 Pt 2): 2213-2216.

Buffel, I., A. Meurs, J. Portelli, R. Raedt, V. De Herdt, L. Sioncke, W. Wadman, F. Bihel, M. Schmitt, K. Vonck, J.I. Bourguignon, F. Simonin, I. Smolders and P. Boon (2015). Neuropeptide FF and prolactin-releasing peptide decrease cortical excitability through activation of NPFF receptors. *Epilepsia*, 56(3): 489-98.

Buntner, B. and D. Rosciszewska (1975). Uninary excretion of estrogen fractions, alpha and beta pregnanediol and pregnanetriol in women with epileptic seizures during the premenstrual period. *Neurol Neurochir Pol*., 9(3): 311-317.

Burneo, J.G., J. Tellez-Zenteno and S. Wiebe (2005). Understanding the burden of epilepsy in Latin America: a systematic review of its prevalence and incidence. *Epilepsy Res*., 66(1-3): 63-74.

Canter, A., C.Y. Kondo and J.R. Knott (1975). A comparison of EMG feedback and progressive muscle relaxation training in anxiety neurosis. *Br J Psychiatry*, 127: 470-477.

Castilla-Guerra, L., M. del Carmen Fernández-Moreno, J.M. López-Chozas and R. Fernández-Bolaños (2006). Electrolytes disturbances and seizures. *Epilepsia*, 47(12): 1990-1998.

Delgado-Escueta, A.V., A.A. Ward, D.M. Woodbury and R.J. Porter (1986). *Basic mechanisms of the epilepsies*. 1986; Raven Press, New York

Demirkhanyan, L., V. Krishnan, S. Asuthkar, B. Alexander, Z. Hussain, P. Baskaran, Y. Nersesyan, A. Cohen, E. Pavlov, B. Thyagarajan and E. Zakharian (2018). TRPM8 regulates sexual desire and satiety. *Biophysical Journal*, 114 (3), Supplement 1, p643a.

Driefuss, F.E. (1987). The different types of epileptic seizures and the international classification of epileptic seizures and of the epilepsies. In: *Epilepsy* (Ed. Hopkins A, Chapman and Hall, London, p. 98.

Duncan, S., C.L. Read and M.J. Brodie (1993). How common is catamenial epilepsy? *Epilepsia*, 34(5): 827-31.

Echodu, R., H. Edema, G.M. Malinga, A. Hendy, R. Colebunders, J. Moriku Kaducu, E. Ovuga and G. Haesaert (2018). Is nodding syndrome in northern Uganda linked to consumption of mycotoxin contaminated food grains? *BMC Res Notes*, 11(1): 678.

Eh Suk VR, A. Marlina, Z. Hussain and M. Misran (2021). N-Stearoyl Chitosan as a Coating Material for Liposomes Encapsulating Itraconazole. *Arabian Journal for Science and Engineering*, 46 (6): 5645-5653.

El-Khayat, H.A., N.A. Soliman, H.Y. Tomoum, M.A. Omran, A.S. El-Wakad and R.H. Shatla (2008). Reproductive hormonal changes and catamenial pattern in adolescent females with epilepsy. *Epilepsia*, 49: 1619-1626.

Engel, J. Jr. (2006) Report of the classification core group. *Epilepsia,* 47: 1558-1568.

Fatima, S., N.I. Khan, G. Yasmeen, B. Hajir and Z. Hussain (2007). Antiatherogenic effects of Nigella Sativa (Kalonji) in rabbits with experimentally induced hypercholesterolemia. *Int J Biol Biotech*., 4(4): 437-441.

Foldvary-Schaefer, N. and T. Falcone (2003). Catamenial epilepsy: pathophysiology, diagnosis, and management. *Neurology*, 61(6 Suppl 2): S2-15.

Forsgren, L., E. Beghi, A. Oun and M. Sillanpaa (2005). The epidemiology of epilepsy in Europe: a systematic review. *Eur J Neurol*., 12: 245-253.

Frank, S. and N.A. Tyson (2020). A Clinical Approach to Catamenial Epilepsy: A Review. *Perm J*, 24: 1-3.

Fujita, Y., Y. Imai, W. Ishii, A. Endo, C. Arakawa, R. Kohira, T. Fuchigami, O. Okubo and H. Mugishima (2011). Improvement of intractable childhood epilepsy following acute viral infection. *Brain Dev*., 33(1): 62-8.

Gastaut, H. (1973). *Dictionary of epilepsy, Part I: Definitions*. WHO, Geneva.

Gibbs, F.A., E.L. Gibbs and W.G. Lennox (1937). Epilepsy: A paroxysmal cerebral dysrhythmia. *Brain*, 60 (4): 377-388.

Giblin, K.A. and H. Blumenfeld (2010). Is epilepsy a preventable disorder? New evidence from animal models. *Neuroscientist*, 16(3): 253-275.

Gilad, R., M. Sadeh, A. Rapoport, R. Dabby and Y. Lampl (2008). Lamotrigine and catamenial epilepsy. *Seizure*, 17(6): 531-534.

Glaser, G.H. and L.L. Levy (1990). Seizures and idiopathic hypoparathyroidism, *Epilepsia* (Amsterdam), 1: 454-465.

Goddard, G.V. (1967). Development of epileptic seizures through brain stimulation at low intensity. *Nature*, 214(5092): 1020.

Grover, S., M. Gourie-Devi, K. Bala, S. Sharma and R. Kukreti (2012). Genetic association analysis of transporters identifies ABCC2 loci for seizure control in women with epilepsy on first-line antiepileptic drugs. *Pharmacogenet Genomics*, 22(6): 447-465.

Grudzinska, B. and D. Rosciszewska (1980). Dynamics of EEG changes during the menstrual cycle in epileptic women. In: *Abstracts of XI Meeting of the Polish Neurological Association. Bydgoszcz*, P. 61.

Haglund, M.M. and P.A. Schwartzkroin (1990). Role of Na-K pump potassium regulation and IPSPs in seizures and spreading depression in immature rabbit hippocampal slices. *J Neurophysiol*., 63(2): 225-239.

Hamed, S.A., M.M. Abdellah and N. El-Melegy (2004). Blood levels of trace elements, electrolytes, and oxidative stress/antioxidant systems in epileptic patients. *J Pharmacol Sci*., 2004; 96(4):465.

Harden, C.L. and I. Leppik (2006). Optimizing therapy of seizures in women who use oral contraceptives. *Neurology*, 67(Suppl 4): S56-58.

Helmchen, H., H. Kunkel and H. Selbach (1964). Periodic influences on the individual frequency of epileptic seizures. *Arch Psychiatr Nervenkr*, 206: 293-308.

Herzog, A.G. (1988). Clomiphene therapy in epileptic women with menstrual disorders. *Neurology*, 38(3): 432-4.

Herzog, A.G. (2015). Catamenial epilepsy: current concepts of definition, prevalence, pathophysiology and treatment. *Zeitschrift fur Epileptol*, 2015; 28: 295-303.

Herzog, A. G. and C.A. Frye (2014). Progesterone Trial Study Group. Allopregnanolone levels and seizure frequency in progesterone-treated women with epilepsy. *Neurology*, 83(4): 345-8.

Herzog, A.G., K.M. Fowler, S.D. Smithson, L.A. Kalayjian, C.N. Heck, M.R. Sperling, J.D. Liporace, C.L. Harden, B.A. Dworetzky, P.B. Pennell and J.M. Massaro (2012). Progesterone Trial Study Group. Progesterone vs placebo therapy for women with epilepsy: A randomized clinical trial. *Neurology*, 78(24): 1959-1966.

Herzog, A.G. and K.M. Fowler (2008). NIH Progesterone Trial Study Group. Sensitivity and specificity of the association between catamenial seizure patterns and ovulation. *Neurology*, 70(6): 486-487.

Herzog, A.G., P. Klein and B.J. Ransil (1997). Three patterns of catamenial epilepsy. *Epilepsia*, 38(10): 1082-8.

Herzog, A.G., C.L. Harden, J. Liporace, P. Pennell, D.L. Schomer, M. Sperling, K. Fowler, B. Nikolov, S. Shuman and M. Newman (2004). Frequency of catamenial seizure exacerbation in women with localization-related epilepsy. *Ann Neurol*., 56(3): 431-434.

Herzog, A.G. (2006). Menstrual disorders in women with epilepsy. *Neurology*, 66(6 Suppl 3): S23-28.

Herzog, A.G. (2008). Catamenial epilepsy: definition, prevalence pathophysiology and treatment. *Seizure*, 17(2): 151-59.

Hill, D. (1958). Value of the EEG in diagnosis of epilepsy. *Brit Med J*., 1(5072): 663-666.

Hojo, Y., S. Higo, H. Ishii, Y. Ooishi, H. Mukai, G. Murakami, T. Kominami, T. Kimoto, S. Honma, D. Poirier and S. Kawato (2009). Comparison between hippocampus-synthesized and circulation-derived sex steroids in the hippocampus. *Endocrinology*, 150(11): 5106-5112.

Holmes, G.L. and D.A. Weber (1984). The effect of progesterone on kindling: a developmental study. *Brain Res*., 318(1): 45-53.

Hom, A.C. and G.G. Buterbaugh (1986). Estrogen alters the acquisition of seizures kindled by repeated arnygdala stimulation or pentylenetatrazole administration to ovariectomized female rats. *Epilepsia*, 27(2): 103-108.

Hopkins, A. (1987). *Epilepsy*. Chapman and Hall. London, p. 1.

Hussain, M.H. and Z. Hussain (2020). Common cold in children-diagnostic considerations. *International Journal of Biology and Biotechnology*, 17 (3): 455-458.

Hussain, Z. (2024 b). Investigating the role of serum hepcidin and interleukin-6 in non-anemic women with acute ischemic stroke. *International Journal of Biomedicine*, 14(2): 260-264.

Hussain, Z. (2024 a). Sodium channel hydrogen bonding in epilepsy: molecular physiology and biophysics. *International Journal of Biology and Biotechnology*, 21 (1): 45-52

Hussain, Z. (2022 b). Serum C-reactive protein as inflammatory marker in men with epilepsy. Int J Biol Biotech., 19 (4): 605-610.

Hussain, Z. (2022 a). Electrophysiology of membrane potentials: mathematical physiology and mathematical medicine perspectives. *Int. J. Biol. Biotech*., 19 (2): 161-170

Hussain, Z., L. Demirkhanyan, S. Asuthkar and E. Zakharian (2017). Testosterone is a Highly Potent and Specific Agonist of TRPM8. *Biophysical Journal*, 110 (3): Supplement 1, p613a.

Hussain, Z. (2010). *Menstrual Cycle and Epilepsy: Premenstrual Reproductive Study*. Germany (Printed in USA & UK). German National Library-Thomson Reuters-ISI Copyright Library. Pages:239.

Hussain, Z., K.Z. Hasan, H. Aziz and M.A. Qureshi (2007a). Clinical and neurological study of women with precatamenial epilepsy. *J Coll Physicians Surg Pak*., 17(4): 211-214.

Hussain, Z., S. Sohail and A. Ashraf (2007b). Blood cholesterol concentration in smoking and non-smoking patients with diabetes mellitus. *Hum Health*, 3 (7&8): 5-8.

Hussain, Z., M.A. Qureshi, K.Z. Hasan and H. Aziz (2006). Influence of steroid hormones in women with mild catamenial epilepsy. *Journal of Ayub Medical College Abbottabad*,18(3): 17-20.

Hussain, Z. (2001). Modified progressive relaxation- Psychophysiological foundations of medicine. *The Med Intern*., 4: 5-7.

Hussain, Z. (1994). Modified progressive relaxation therapy-discovery of a new horizon in psychobiology. *Med Rev.*, 6 (1): 3-5.

Hussain, Z. (1991). *Clinical, electroencephalographic and hormonal study in menstruation related seizures* (Ph.D. thesis). Department of Physiology, University of Karachi

Hussain, Z. (Azeemi, Z.H.), M.A. Qureshi, K.Z. Hasan and H. Aziz (1987). Effect of anticonvulsants on seizure occurrence in women with epilepsy. *Annals of JPMC*., 4 (1): 13-18

Hussain, Z. (1984). *Steroids, neurosteroids, PMS, catamenial epilepsy and MPR therapy*. Monograph, Dept of Neuropsychiatry, JPMC, Karachi.

Hussain, Z. (1983). *Effect of stimulation frequency on fatigue occurrence in skeletal muscles* (M.Sc. thesis), Department of Physiology, University of Karachi, Karachi, Pakistan.

Hussain, Z. (1982). *MPR therapy and Jacobson's progressive relaxation therapy*. Monograph, Dept of Neuropsychiatry, JPMC, Karachi

Hussain, Z. and K.Z. Hassan (1982). *Anemia of inflammation and autoimmune anemia*. Monograph. Department of Neuro-Psychiatry, Faculty of Medicine, Jinnah Postgraduate Medical Centre (JPMC), Karachi.

Inam, S., S. Masood, K. Abbas, N. Khan and Z. Hussain (1995). Changes in plasma calcium under influence of estradiol valerate. *First National Conference on Pharmacology and Therapeutics.* Faculty of Pharmacy, University of Karachi. P: 45.

Inam, S., S. Masood, M.A. Siddiqui and Z. Hussain (1994). *Skin infections caused by virus*. Biological Foundations of Medicine, p: 11-12.

International Classification of Functioning and Disability (1999). *Beta-2 Draft, Full Version*. Geneva: World Health Organization,

Isojarvi, J.I. (1990). Serum steroid hormones and pituitary function in female epileptic patients during carbamazepine therapy. *Epilepsia*, 31(4): 438-445.

Isojarvi, J.I., E. Taubøll and A.G. Herzog (2005). Effect of antiepileptic drugs on reproductive endocrine function in individuals with epilepsy. *CNS Drugs*, 19(3): 207-223.

Jacobson, E. (1938). *Progressive relaxation*. Chicago: University of Chicago Press.

Jacobson, E. (1929). *Progressive relaxation*. Chicago: University of Chicago Press.

Jacobson E. (1927). Action currents from muscular contractions during conscious processes. *Science*, 66(1713): 403.

Jacono, J.J. and J.M. Robertson (1987). The effects of estrogen, progesterone, and ionized calcium on seizures during the menstrual cycle of epileptic women. *Epilepsia*, 28: 571-577.

Jallon, P. and F. Picard (2001). Bodyweight gain and anticonvulsants: a comparative review. *Drug Saf*., 2001;24(13): 969-978.

Jallon, P., P. Louiset and P. Loiseau (1986). Epileptics, beware of colds! Danger of drugs containing phenylpropanolamine. *Presse Med*., 15(37): 1877-78.

Joshi, S. and J. Kapur (2019). Neurosteroid regulation of $GABA_A$ receptors: A role in catamenial epilepsy. *Brain Res*., 1703: 31-40.

Joshi, S., H. Sun, K. Rajasekaran, J. Williamson, E. Perez-Reyes and J. Kapur (2018). A novel therapeutic approach for treatment of catamenial epilepsy. *Neurobiol Dis*., 111: 127-137.

Kansal, B., A. Anand, D. Garg, A. Gupta, A. Kumar and S. Sharma (2022). Applicability of the International League Against Epilepsy (ILAE) 2022 diagnostic criteria for epilepsy syndromes in children: A retrospective review of 1550 children with epilepsy. *Seizure*, 117: 288-292.

Kapur, J. and S. Joshi (2021). Progesterone modulates neuronal excitability bidirectionally. Neurosci Lett, 744:135619.

Kariyawasam, S.H., U. Mannapperuma, W.J. Jayasuriya, J. Weerathunga and K. Munasinghe (2009). Occurrence of menstrual cycle related seizure patterns among epileptic women attending the tertiary neurology clinics of the National Hospital of Sri Lanka. *Epilepsy Res*., 84: 257-62.

Khan, N.I., L. Naz, S. Mushtaq, L. Rukh, S. Ali and Z. Hussain (2009). Ischemic stroke: prevalence of modifiable risk factors in male and female patients in Pakistan. *Pak J Pharm Sci*, 22(1): 62-67.

Khan, N.I. and Z. Hussain (2008). Pathophysiology of ischemic disorders: 1- LDL cholesterol and Ischemic stroke. *Int J Biol Biotech*., 5 (1-2): 1-16.

Khan, N., K. Abbas, S. Masood, S. Inam and Z. Hussain (1995). Effect of estradiol valerate on plasma cholesterol in Uromastix hardwickii. *First National Conference on Pharmacology and Therapeutics*. Faculty of Pharmacy, University of Karachi. P: 43.

Khoiny, F.E. (1996) Use of depo-provera in teens. *J Pediatr Health Care*, 10(5): 195-201.

Kiloh, L.G., A. J. McComas, J.W. Osselton, and A.R.M. Upton (1981). *Clinical electroencephalography*. 1981; Butterworth and Company, London, p. 88.

Kramer, M.S. (1977). Menstrual epileptoid psychosis in an adolescent girl. *Am J Dis Child*., 131(3): 316-17.

Kuba, R., M. Pohanka, J. Zákopcan, I. Novotná and I. Rektor (2006). Sexual dysfunctions and blood hormonal profile in men with focal epilepsy. *Epilepsia*, 47(12): 2135-2140

Laidlaw, J. (1956). Catamenial epilepsy. *Lancet*, 271(6955): 1235-1237.

Laidlaw, J. and A. Richens (1982). *A textbook of epilepsy*. Churchill Livingstone, Edinburgh.

Lemley, R.J. and P.E. Voinescu (2023). Assisted reproductive technology outcomes and management considerations for people with epilepsy. *Curr Opin Endocrinol Diabetes Obes*., 30(6): 280-284.

Lennox, W.G. (1955). The rign of the uterus, *Epilepsia*, 4: 91-98.

Leppik, I.E. and A.K. Birnbaum (2010). Epilepsy in the elderly. *Ann N Y Acad Sci*., 1184: 208-24.

Li, Q., X.Q. Dai, P.Y. Shen, Y. Wu, W. Long, C.X. Chen, Z. Hussain, S. Wang and X.Z. Chen (2007). Direct binding of alpha-actinin enhances TRPP3 channel activity. *J Neurochem*., 103(6): 2391-400.

Liang, S., J. Zhao, W. Zhao, N. Jia, Z. Zhang, B. Li (2024). Qualitative and Quantitative Detection of Typical Reproductive Hormones in Dairy Cows Based on Terahertz Spectroscopy and Metamaterial Technology. *Molecules*, 29(10): 2366.

Lim, L.L, N. Foldvary, E. Mascha and J. Lee (2001). Acetazolamide in women with catamenial epilepsy. *Epilepsia*, 42(6): 746-9.

Livingston, S. (1972). *Comprehensive management of epilepsy in infancy, childhood and adolescence*. CC Thomas, Springfield, Ill.

Logothetis, J., R. Haner, F. Morrell and F. Torres (1959). The role of estrogen in catamenial exacerbation of epilepsy, *Neurology*, 9: 352-360.

Luef, G.(2010). Hormonal alterations following seizures. *Epilepsy Behav*., 19(2): 131-3.

Maguire, M.J. and S.J. Nevitt (2021). Treatments for seizures in catamenial (menstrual-related) epilepsy. *Cochrane Database Syst Rev*., 9(9): CD013225.

Mahmood, A. and Z. Hussain (1999). Common colds- prevention and general measures. *The Medicine International*, 2 (2): 7-9.

Mahmood, A. and Z. Hussain (1998). Clinical and epidemiological aspects of common colds. *The Medicine International*, 1 (5): 3-5.

Marek, B., D. Kajdaniuk, B. Kos-Kudła, J. Kapustecki, E. Swietochowska, Z. Ostrowska, L. Siemińska, M. Nowak, J. Głogowska-Szelag, H. Borgiel-Marek, N. Ciesielska-Kopacz, W. Foltyn, K. Pierzchała, R. Krysiak and R. Bienek (2010). Mean daily plasma concentrations of beta-endorphin, leu-enkephalin, ACTH, cortisol, and DHEAS in epileptic patients with complex partial seizures evolving to generalized tonic-clonic seizures. *Endokrynol Pol*., 61(1): 103-110.

Marsden, C.D and E.H. Reynolds (1982). *Neurology-Part I in: A Textbook of Epilepsy*. (Ed. Laidlaw J and Richens A), Churchill Livingstone, New York, P. 97.

Masood, S., S. Inam, K. Abbas, N. Khan and Z. Hussain (1995). Fluctuation in plasma sodium in response to estradiol valerate *First National Conference on Pharmacology and Therapeutics.* Faculty of Pharmacy, University of Karachi. P: 46.

Matias, C., M.H. Hussain and Z. Hussain (2017). Lipid membrane-estrogen interaction: molecular and biophysical perspective: A mini overview. *International Journal of Biology Research*, 5 (2): 35-42.

Matsubara, Y., S. Akamine, P.F. Chong, S. Kawakami, K. Maehara, Y. Kaku, M. Kurokawa, N. Morisada, K. Iijima and R. Kira (2021). Infantile spasms and early-onset progressive polycystic renal lesions associated with TSC2/PKD1 contiguous gene deletion syndrome. *Seizure*, 86: 82-84.

McQuarrie, I. (1932). Some recent observations regarding the nature of epilepsy, *Ann Intern Med*., 6(4) : 497-505.

Meisler, M.H. and J.A. Kearney (2005). Sodium channel mutations in epilepsy and other neurological disorders. *J Clin Invest*., 115(8): 2010-2017.

Merlis, J.K. (1972). Treatment in relation to classification of the epilepsies. *Acta Neurologica Latinoamericana*, 18(1): 42-51.

Mohandass, A., V. Krishnan, E.D. Gribkova, S. Asuthkar, P. Baskaran, Y. Nersesyan, Z. Hussain, L.M. Wise, R.E. George, N. Stokes, B.M. Alexander, A.M. Cohen, E.V. Pavlov, D.A. Llano, M.X. Zhu, B. Thyagarajan and E. Zakharian (2020). TRPM8 as the rapid testosterone signaling receptor: Implications in the regulation of dimorphic sexual and social behaviors. *FASEB J*., 34(8): 10887-10906.

Morrell, M.J. (1999). Epilepsy in women: the science of why it is special. *Neurology*, 53(4 Suppl 1): S42-48.

Morrell, M.J., J. Isojärvi, A.E. Taylor, M. Dam, R. Ayala, G. Gomez, F. O'Neill, P. Tennis and J. Messenheimer (2003). Higher androgens and weight gain with valproate compared with lamotrigine for epilepsy. *Epilepsy Res*., 54(2-3): 189-199.

Morrell, M.J. and G.D. Montouris (2004). Reproductive disturbances in patients with epilepsy. *Cleve Clin J Med*., 71(Suppl 2): S19-24.

Munir, R and Z. Hussain (1999). Epidemiology of common colds. *The Medicine International*, 2 (3): 3-5

Mumtaz, A., A. Khalid, Z. Hussain, F. Alam and R. Rehman R (2016). Kisspeptin and unexplained infertility. *2nd Annual conference of Ziauddin University & European Society of Translational Medicine*.

Navis, A. and C. Harden (2016). A Treatment Approach to Catamenial Epilepsy. *Curr Treat Options Neurol*., 18(7): 30.

Naz, L., Z. Hussain and T. Husain (2009). Risk factors and biochemical variations in patients with ischemic stroke (2009. *Int J Biol Biotech*., 6 (1-2): 83-87.

Neshige, S., S. Aoki, T. Nezu, M. Nakamori, Y. Yamazaki, T. Ohshita and H. Maruyama (2023). Are patients with Parkinson's disease at a lower risk of catching the common cold? Propensity score matching. *Parkinsonism Relat Disord*., 106: 105227.

Newmark, M.E. and J.K. Penry (1980). Catamenial opilepsy: A review. *Epilepsia* 21: 281-300.

Ngugi, A.K., C. Bottomley, I. Kleinschmidt, J.W. Sander and C.R. Newton (2010). Estimation of the burden of active and life-time epilepsy: a meta-analytic approach. *Epilepsia*, 51(5): 883-90.

Octaviana, F., K. Sumapraja, W. Wiratman, L.A. Indrawati and A. Budikayanti (2022). Characteristics of menstrual disorders and reproductive hormones in women with epilepsy at an Indonesian national referral hospital. *Front Neurol*, 13: 964761.

Ogihara, M, S. Shirakawa, T. Miyajima, K. Takekuma and A. Hoshika (2010). Diurnal variation in febrile convulsions. *Pediatr Neurol*., 42(6): 409-412.

Patel, S.I. and N. Foldvary-Schaefer (2014). Catamenial epilepsy. In: (Bui B, Klein A. eds) *Women with epilepsy: a practical management handbook*. Cambridge: Cambridge University Press; p. 101-112.

Penfield, W. and T.C. Erickson (1941). Epilepsy and cerebral localization. Bailliere, Tindal and Cox, London, p. 12

Penfield, W. and H. Jasper (1954). Epilepsy and the functional anatomy of the human brain. Little Brown, Boston

Pennell, P.B. (2009). Hormonal aspects of epilepsy. *Neurol Clin*., 2009; 27(4):941-965.

Pitkänen, A., I. Kharatishvili, H. Karhunen, K. Lukasiuk, R. Immonen, J. Nairismägi, O. Gröhn and J. Nissinen (2007). Epileptogenesis in experimental models. *Epilepsia*, 48 Suppl 2: 13-20.

Polack, P.O., I. Guillemain, E. Hu, C. Deransart, A. Depaulis and S. Charpier (2007). Deep layer somatosensory cortical neurons initiate spike- and-wave discharges in a genetic model of absence seizures. *J Neurosci.*, **27**: 6590-6599.

Porter, R.J. (1984). *Epilepsy: 100 elementary principles*. WB Saunders Company, London. p. 14

Prabhakar, S., P. Sahota, P.S. Kharbanda, R. Siali, V. Jain, V. Lal and D. Khurana (2007). Sodium valproate, hyperandrogenism and altered ovarian function in Indian women with epilepsy: a prospective study. *Epilepsia*, 48(7): 1371-1377.

Presl, J. (1991). Favorable effects of oral estrogen-progestin contraception. *Cesk Gynekol.*, 56(5-6): 350-352.

Qureshi, M.A., Z. Hussain (Z.H. Azeemi), H. Aziz and K.Z., Hasan (1988). Changes in estrogen and progesterone, seizure occurrence and effect of anticonvulsant medication in catamenial epileptics. *FASEB (Fed Amer Soc Exp Biol) J.*, 2 (5): 4500.

Rebar, R.W. and S.S.C. Yen (1979). Endocrine rhythms in gonadotrophins and ovarian steroids with reference to reproductive process. In: *Endocrine Rhythms* (Ed. Krieger, DT). Raven Press, New York, p. 259.

Redd,y D.S. (2022). Neurosteroid replacement therapy for catamenial epilepsy, postpartum depression and neuroendocrine disorders in women. *J Neuroendocrinol.*, 34(2): e13028.

Reddy, D.S. (2004). Role of neurosteroids in catamenial epilepsy. *Epilepsy Res*., 62(2-3): 99-118.

Reddy, D.S., H.Y. Kim and M.A. Rogawski (2001). Neurosteroid withdrawal model of perimenstrual catamenial epilepsy. *Epilepsia*, 42(3): 328-36.

Reddy, D.S. (2009). The role of neurosteroids in the pathophysiology and treatment of catamenial epilepsy. *Epilepsy Res.*, 85(1): 1-30.

Rehman, R., Z. Hussain, S.S. Fatima, F. Alam and H. Gul (2016). *Impact of obesity on infertility Research Day*, Department of Medicine, Aga Khan University, Karachi. P: 10.6

Rehman, R., Z. Hussain, S.S. Fatima, F. Alam and H. Gul (2015). Effect of body mass index on implantation after intracytoplasmic sperm injection. *6th Annual Research Day*, Feb 2015, Conference, (Dow University of Health Sciences) DUHS, Karachi

Rehman, R., Z. Hussain, H. Zahir and R. Khan (2014). Impact of peak/mid luteal estradiol on pregnancy outcome after intracytoplasmic sperm injection. *J Pak Med Assoc*., 64(7): 780-784.

Rehman, R., Z. Hussain, S. Jawaid, H. Gul and R. Khan (2013d). *Effect of estradiol on ovarian cycle*. JSMU (Jinnah Sindh Medical University), Karachi.

Rehman, R., Z. Hussain and S.S. Fatima (2013c). Effect of weight status on pregnancy outcome in intra cytoplasmic sperm injection. *Iran J Reprod Med.*, 11(9): 717-724.

Rehman, R., Z. Hussain and N.A. Zuberi (2013b). Prediction of success in intracytoplasmic sperm injection (ICSI) by estimation of serum estradiol/progesterone ratio on the day of embryo transfer. *J Pak Med Assoc*., 63(5): 609-613.

Rehman, R., Z. Hussain and N. Faraz (2013 a). Effect of body mass index on reproductive outcome after intra cytoplasmic sperm injection. *3rd BUMDC (Bahria University Medical & Dental College) symposium*. Karachi.

Rehman, R., Z. Hussain and A.A. Siddiq (2012a). Role of Progesterone in Human Embryo Implantation. *Rawal Medical Journal*, 37(2): 194-198.

Rehman, R., Z. Hussain and N. Faraz (2012b). Effect of estradiol levels on pregnancy outcome in obese women. *J Ayub Med Coll Abbottabad*, 24(3-4): 3-5.

Reynolds, M.F., E.C. Sisk and N.L. Rasgon (2007). Valproate and neuroendocrine changes in relation to women treated for epilepsy and bipolar disorder: a review. *Curr Med Chem*., 14(26): 2799-2812.

Rider, F, A. Turchinets, T. Druzhkova, G. Kustov, A. Guekht and N. Gulyaeva (2024). Dissimilar Changes in Serum Cortisol after Epileptic and Psychogenic Non-Epileptic Seizures: A Promising Biomarker in the Differential Diagnosis of Paroxysmal Events? *Int J Mol Sci*., 25(13): 7387.

Roeder. H.J. and E.C. Leira (2021). Effects of the Menstrual Cycle on Neurological Disorders. *Curr Neurol Neurosci Rep*., 21(7): 34.

Rosciszewska, D. (1974). *Clinical course of epilepsy during puberty, maturity and climacterium.* Dissertation, Katowice, p.25.

Rosciszewska, D. (1980). Analysis of seizure dispersion during menstrual cycle in women with epilepsy. *Monog Neural Sci*., 5: 280-284.

Rosciszewska, D. (1987). Epilepsy and menstruation. In: *Epilepsy* (Ed. Hopkins, A.), Chapman and Hall, London, p. 373.

Rościszewska, D., B. Buntner, I. Guz and L. Zawisza (1986). Ovarian hormones, anticonvulsant drugs, and seizures during the menstrual cycle in women with epilepsy. *J Neurol Neurosurg Psychiatry*, 49(1): 47-51.

Rosciszewska, D., J. Dutkiewicz and A. Blecharz (1985). Luteinizing hormone (LH) serum level during the menstrual cycle in female epileptic patients. *Neurol Neurochirurg Pol*., 29: 205-210.

Røste, L.S. and E. Taubøll (2007). Women and epilepsy: review and practical recommendations. *Expert Rev Neurother*., 7(3): 289-300.

Rousseau, A., B. Hermann and S. Whitman (1985). Effects of progressive relaxation on epilepsy: analysis of a series of cases. *Psychol Rep*., 57(3 Pt 2): 1203-1212.

Saito, N., K. Shimizu, Y. Yoshii, J. Kojima, T. Ishikawa, K. Saito and K. Kuwano (2013). A case of Legionella pneumophila pneumonia accompanied by acute respiratory distress syndrome and epilepsy. *Kansenshogaku Zasshi*, 87(3): 389-392.

Saly, V. and R.D. Andrew (1993). CA3 neuron excitation and epileptiform discharge are sensitive to osmolality. *J Neurophysiol*., 69(6): 2200

Sanchez Longo, L.P. and L.E. Gonzalez Saldana (1966). Hormones and their influence in epilepsy. *Acta Neurol Lat Am*., 12(1): 29-47.

Sazgar, M., L. Mnatsakanyan, A.M. Pack and C.L. Harden (2023). Epilepsy and Anti-Seizure Medications: Secret Agents for Endocrine Disruption. *Epilepsy Curr*., 24(2): 79-83.

Sbai, O., R. Soussi, A. Bole, M. Khrestchatisky, M. Esclapez and L. Ferhat (2020). The actin binding protein α-actinin-2 expression is associated with dendritic spine plasticity and migrating granule cells in the rat dentate gyrus following pilocarpine-induced seizures. *Exp Neurol*., 335: 113512.

Schelp, A.O. and J.G. Speciali (1983). Clinical study of catamenial epilepsy: clinical types of epileptic crises. *Arq Neuropsiquiatr*., 41(2): 152-157.

Shah, Q.A., A.A. Jamil, V.P. Gupta, M.M. Kabiraj and A.H. Shah (2001)). Changes in serum electrolytes in childhood epilepsy: A hospital based prospective. *Greenwich J Sci Technol*., 2: 18.

Shawki, M., L. El Wakeel, R. Shatla, G. El-Saeed, S. Ibrahim and O. Badary (2013). The clinical outcome of adjuvant therapy with black seed oil on intractable paediatric seizures: a pilot study. *Epileptic Disord*., 15(3): 295-301.

Shiono, S., H. Sun, T. Batabyal, A. Labuz, J. Williamson, J. Kapur and S. Joshi (2021). Limbic progesterone receptor activity enhances neuronal excitability and seizures. *Epilepsia*, 62(8): 1946-1959.

Siddiqui, M.A., S. Inam, S. Masood and Z. Hussain (1994). Etiological factors in hypertension. *Medical Review*, 6 (6): 1-2.

Singh, H. and D. Pathak (2024). Unveiling the Anti-convulsant Potential of Novel Series of 1,2,4-Triazine- 6H-Indolo[2,3-b]quinoline Derivatives: *In Silico* Molecular Docking, ADMET, DFT, and Molecular Dynamics Exploration. *Curr Comput Aided Drug Des*., 20(6): 822-834.

Smejkalova, T. and C.S. Woolley (2010). Estradiol acutely potentiates hippocampal excitatory synaptic transmission through a presynaptic mechanism. *J Neurosci.*, 30(48): 16137-16148.

Smith, S.S., H. Shen, Q.H. Gong and X. Zhou (2007). Neurosteroid regulation of GABA(A) receptors: Focus on the alpha4 and delta subunits. *Pharmacol Ther*., 116(1): 58-76.

Sohail, S., A. Javaid, T.A. Khan, H. Zahir and Z. Hussain (2019) Diabetes mellitus, obesity and adipocytokines pathophysiological perspectives *Int J Biol Biotechnol*., 16 (2): 325-339.

Sohail, S. and Z. Hussain (2013). Pathophysiology of ischemic disorders- Ischemia, adipocytokines and diabetes mellitus. *Int J Biol Biotech*., 10 (2): 155-166.

Sohail, S., Z. Hussain, Quratul ain, S.J. Ashraf (2013). Blood cholesterol and leptin levels in male smoking and non-smoking patients with diabetes mellitus. *International Journal of Biology Research*, 1(1): 15-18.

Sohail, S. and Z. Hussain (2009). Influence of diet and physical activity in pre-diabetes. *46th Annual Symposium, JPMC.* Karachi, Pakistan

Sohail, S. and Z. Hussain (2008). Electrolyte and cholesterol variations in patients with diabetes mellitus. *35th All Pak Sc Conf, Genomics for Health and Prosperity*. University of Karachi

Stieqlitz, E.J. and S.T. Kimble (1949). Premenstrual intoxication. *Am J M Sc*., 218: 616-623.

Stoffel-Wagner, B. (2001). Neurosteroid metabolism in the human brain. *Eur J Endocrinol*.. 145(6): 669-679.

Swann, J.W. and J.J. Hablitz, (2000). Cellular abnormalities and synaptic plasticity in seizure disorders of the immature nervous system. *Ment Retard Dev Disabil Res Rev*., 6: 258-267.

Takahashi ,T., S. Kamei, K. Miki, K. Ogawa and T. Mizutani (2003). The analysis of cytokines in cerebrospinal fluid (CSF) in two cases of non-herpetic acute limbic encephalitis (NHALE). *Rinsho Shinkeigaku*. 43(4): 162-69.

Taubøll, E., A. Lundervold and L. Gjerstad (1991). Temporal distribution of seizures in epilepsy. *Epilepsy Res*., 8(2): 153-165.

Taylor, J. (1931). *Selected writings of John Hughlings Jackson, Vol. 1: On Epilepsy and Eiileptiform convulsions*. Hodder od Stoughton, London.

Temkin, O. (1971). *The falling sickness.* The John Hopkins Press, Baltimore, p. 467.

Thirty, A., C. Heusgem and P. Legentil (1954). Study of the urinary exeretion of estrogens, 17 Ketosteroids and reducing steroids in epilepsy, particularly the so called catamenial epilepsy. *Rev Med Liege*, 9. 238-246.

Tuveri A, A. M. Paoletti, M. Orrù, G.B. Melis, M.F. Marotto, P. Zedda, F. Marrosu, C. Sogliano, C. Marra, G. Biggio and A. Concas (2008). Reduced serum level of THDOC, an anticonvulsant steroid, in women with perimenstrual catamenial epilepsy. *Epilepsia*. 49(7): 1221-9. doi: 10.1111/j.1528-1167.2008.01555.x. PMID: 18325018.

Tuveri, A., A.M. Paoletti, M. Orrù, G.B. Melis, M.F. Marotto, P. Zedda, F. Marrosu, C. Sogliano, C. Marra, G. Biggio and A. Concas (2008). Reduced serum level of THDOC, an anticonvulsant steroid, in women with perimenstrual catamenial epilepsy. *Epilepsia*, 49: 1221-1229.

Velísek, L. and J. Velísková (2008). New avenue of research: antiepileptic drug and estradiol neuroprotection in epilepsy. *Recent Patents CNS Drug Discov*, 3:128-137.

Velísková, J., G. De Jesus, R. Kaur and L. Velísek (2010). Females, their estrogens, and seizures. *Epilepsia*, 51 (Suppl 3): 141-144.

Velíšková, J. (2007). Estrogens and Epilepsy: Why are we so excited? *Neuroscientist*, 13: 77-88.

Velísková, J. and L. Velísek (2007). Beta-estradiol increases dentate gyrus inhibition in female rats via augmentation of hilar neuropeptide-Y. *J Neurosci*., 27: 6054-6063.

Velísková, J., L. Velísek, A.S. Galanopoulou and E.F. Sperber (2000). Neuroprotective effects of estrogens on hippocampal cells in adult female rats after status epilepticus. *Epilepsia*, 41 Suppl 6: S30-35.

Voinescu, P.E. and P.B. Pennell (2017). Delivery of a Personalized Treatment Approach to Women with Epilepsy. *Semin Neurol*., 37(6): 611-623.

Weiner, H.L. and L.P. Levitt 1989). *Neurology for the house officer*, (Ed. Fisher MG.), Williams and Wilkins, Maryland. p. 73.

W.H.O. (2001a). *Epilepsy: aetiology, epidemiology and prognosis* (Vol. Fact Sheet N 165).

W.H.O. (2001b). World Health Organization: epilepsy: epidemiology, aetiology and prognosis. WHO Factsheet.

Wilson, S.A.K. (1940). *Neurology*, 2 volumes, Williams and Wilkins, Baltimore.

Woolley, D.E. and P.S. Timiras (1962a). The gonad-brain relationship: effects of female sex hormones on electroshock convulsions in the rat. *Endocrinology*, 70: 196-209.

Wu, Y.V. and W.M. Burnham (2018). Progesterone, 5a-dihydropogesterone and allopregnanolone's effects on seizures: A review of animal and clinical studies. *Seizure*, 63: 26-36.

Wu, Y., X.Q. Dai, Q. Li, C.X. Chen, W. Mai, Z. Hussain, W. Long, N. Montalbetti, G. Li, R. Glynne, S. Wang, H.F. Cantiello, G. Wu and X.Z. Chen (2006). Kinesin-2 mediates physical and functional interactions between polycystin-2 and fibrocystin. *Hum Mol Genet.*, 15(22): 3280-3292.

Yalçin, A.D., I. Onaran I. and A.S. Yalçin (1994). Effect of antiepileptic drugs on erythrocyte osmotic fragility and lipid peroxidation. *Epilepsy Res.*, 19(3): 249-52.

Yasmeen, G., Z. Hussain and M.L. Bharwani (2009). Gender variations in blood picture of the patients with ischemic acute renal failure. *29th Pakistan Congress of Zoology (International Congress)*. Zoology Society of Pakistan, At: University of Sindh, Jamshoro. P: 150.

Yasmeen, G., Z. Hussain and M.L. Bharwani (2008). Gender differences in the progression of acute renal failure. *Int J Biol Biotech*., 5 (3-4): 215-218.

Yeung, C.H.T., J.L. Beers, K.D. Jackson and A.N. Edginton (2023). Verifying in vitro-determined enzyme contributions to cannabidiol clearance for exposure predictions in human through physiologically-based pharmacokinetic modeling. *CPT Pharmacometrics Syst Pharmacol.*, 12(3): 320-332.

Zafar, F., N. Yasmeen, I. Hussain and Z. Hussain (2001). Effects of ochratoxin incidence in different commercial feeds fed to broilers of Karachi region. *The 21st Pakistan Congress of Zoology*. University of Agriculture, Faisalabad, Zoological Society of Pakistan, Cell Biology, Biochemistry, Genetics and Physiology (CBGP).

Zafar, F., R. Arshad, Z. Hussain (Z.H. Azeemi) and H.A. Shaikh (1990). A comparative study on the osmotic fragility of erythrocytes in reptile, bird and mammal. *Karachi University Journal of Science*, 18 (1 & 2): 107-117.

Zaichkina, T.S. (1963). Pathogeresis of so-called menstrual epilepsy. *Zh Nevropatol Psikhiatr*., 63: 1716-1724.

Zhang, Y., Y. Huang, X. Liu, G. Wang, X. Wang and Y. Wang (2015). Estrogen suppresses epileptiform activity by enhancing Kv4.2-mediated transient outward potassium currents in primary hippocampal neurons. *Int J Mol Med*., 36(3): 865-872.

Zhao, S. and T. Rohacs. (2021). The newest TRP channelopathy: Gain of function TRPM3 mutations cause epilepsy and intellectual disability. *Channels* (Austin), 15(1):386-397.

(*Accepted for publication October 2024*)