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Catamenial Epilepsy: A Review

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Summary: This review of 126 reports on catamenial epilepsy describes seizure exacerbations associated with the menses. The importance of hormonal measurements, the influence of antiepileptic drugs and oral contraceptives, and the significance of hormonal changes on epilepsy are evaluated. The EEG changes during menses are discussed. Explanations for conflicting data are offered, and potential future investigations on catamenial epilepsy are suggested.

Catamenial exacerbations appear in a variety of neurologic disorders and symptoms. Exacerbations of headache from a meningioma (Ask-Upmark, 1955), increased engorgement and pulsation of an arterial-venous malformation (Ask-Upmark, 1955), and "essential" myoclonus (Shibasaki et al., 1973) have been reported during the menses. The premenstrual syndrome of headache, nausea, vertigo, depression, and irritability frequently troubles women (Greene and Dalton, 1953), and migraine headaches are more frequent during the menses. Among the most prominent of the disorders, however, are catamenial exacerbations of epileptic seizures.

Cyclical increases of epileptic attacks have been observed since antiquity. These changes were attributed to the moon, which was thought to influence both epilepsy and human behavior more generally (giving rise to the phrase "lunatic") (Aretaeus, 1856; Temkin, 1971). This theory predominated during the nineteenth century, and the noted neurologist Romberg (1853) thought that the phases of the new and full moons were especially influential on epilepsy. It was not refuted completely until Pastrňák (1967) documented that seizure frequency was not related to lunar or seasonal changes. The association of menses and epilepsy was first examined clinically by Gowers in 1885. Although several other investigators have addressed this problem since then, the relationship of seizure frequency to menses remains obscure. This review will attempt to clarify some of the problems which have been uncovered in previous research and will outline research possibilities for future investigators.

INCIDENCE

Several investigators have observed that seizure frequency sometimes increases with menstruation (Table 1), but many re-

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ports are limited by brief descriptions of the types of seizures and give only sketchy data about seizure frequency and antiepileptic treatment (Turner, 1907; Bailey, 1953; Zaichkina, 1963; Livingston, 1972). Enough inclusive reports exist, however, to suggest a specific relationship between menses and seizures (Gordon, 1909; Healey, 1928; Boeri, 1956; Logothetis et al., 1959; Sánchez Longo and González Saldaña, 1966; Zimmerman et al., 1973).

One study reported that catamenial exacerbations occurred in 63% of epileptic women (Ansell and Clarke, 1956*b*), but another found almost no evidence of such an increase (Bandler et al., 1957). This excessive variability has several explanations:

1. Documentation of the catamenial exacerbations is often inexact. For example, in the large study of 686 patients by Lennox and Lennox (1960), documentation consisted merely of a questionnaire.

2. The possibility of cyclical seizures unrelated to menses is often ignored. This factor was best shown by Bandler et al. (1957), who found monthly exacerbations of seizures in 16 women that did not correlate with a specific phase of the menstrual cycle.

3. Catamenial seizures have not been consistently defined. Either different days of the cycle are considered important or the catamenial phase is not described. Also, criteria for an exacerbation may vary.

4. Most studies do not adequately describe the types of seizures, medications, or seizure severity, all of which may be significant.

5. The length of follow-up of an individual patient is highly variable, from a minimum of 2 to 4 menses (Ansell and Clarke, 1956*b*) to almost 200 per patient (Laidlaw, 1956).

6. The possibility of anovulatory cycles is rarely mentioned.

Despite these inconsistencies, most authors agreed that the menses affect seizures in some women, at least in some months. In one of the studies with the longest evaluation and most specific criteria for exacerbation (Laidlaw, 1956), approximately 72% of women hospitalized for long-term antiepileptic therapy experienced at least a mild exacerbation of generalized tonic–clonic seizures in the premenstrual phase (defined as 2 days prior to menses) and during the menstrual phase itself. In certain patients, the effect can be quite prominent because seizures may occur only in cycles (Helmchen et al., 1964; Zimmerman et al., 1973).

SIGNIFICANCE OF SEIZURE TYPE

Few investigators have attempted to analyze catamenial seizures according to the type of seizure. Most reports did not mention the type of seizure analyzed (Gowers, 1885; Gordon, 1909; Healey, 1928; Dickerson, 1941; Thiry et al., 1954; Ansell and Clarke, 1956*b*; Bandler et al., 1957; Logothetis et al., 1959; Lennox and Lennox, 1960; Buntner and Rościszewska, 1975), and others were restricted to major seizures (Almquist, 1955; Laidlaw, 1956). Jeavons and Harding (1975) mentioned a pair of identical twins with photoconvulsive discharges on the EEG who had similar photosensitivity ranges early in the menstrual cycle but different sensitivity ranges at one time when the girls were at different phases of the menstrual cycle. Bäckström (1976) observed in 7 patients with mixed seizure types that the generalized seizures, but not the partial ones, appeared to be cyclical and were associated with changes in estrogen levels in the ovulatory patients. However, in the patient reported by Helmchen et al. (1964), the partial seizures, and not the generalized ones, were more cyclical. The patient of Sánchez Longo and Gónzalez Saldaña (1966) had cyclical patterns of both generalized tonic–clonic seizures and complex partial seizures. Thus, no specific type of seizure predominates in catamenial epilepsy.

SIGNIFICANCE OF SEIZURE SEVERITY

The significance of seizure frequency on cyclical patterns also has not been fully investigated. Most investigators did not mention the severity of the seizure disorders of their patients (Gowers, 1885; Gordon, 1909; Healey, 1928; Dickerson, 1941; Thiry et al., 1954; Ansell and Clarke, 1956*b*; Laidlaw, 1956; Logothetis et al., 1959; Lennox and Lennox, 1960; Buntner and Rościszewska, 1975). Bandler et al. (1957) mentioned only that each patient had experienced at least 5 seizures in observation periods of 6 to 39 months. In studies that did report seizure frequency (Helmchen et al., 1964; Sánchez Longo and González Saldaña, 1966; Zimmerman et al. 1973; Bäckström, 1976), seizures occurring as rarely as once every 2 to 3 months (Sánchez Longo and González Saldaña, 1966) and as frequently as 7 to 10 a day (Zimmerman et al., 1973) were associated with a cyclical frequency. Again, no pattern predominates.

CYCLICAL EXACERBATION

Apart from the evaluation by Bandler et al. (1957) of 22 patients in which exacerbation of seizures was not prominent during the menstrual cycle, and a similar evaluation of 29 women by Almquist (1955), most studies found that seizure frequency increased near the time of ovulation and close to the time of menstrual flow (Table 1). Some reports described an increased incidence of seizures "at or near" the time of menstrual flow (Gowers, 1885; Turner, 1907; Logothetis et al., 1959; Sánchez Longo and González Saldaña, 1966; Livingston, 1972). In other, more exact investigations, premenstrual exacerbations within 2 days of the onset of menses were reported (Buntner and Rościszewska, 1975). Exacerbations primarily restricted to the time of menstrual flow were observed by Toulouse and Marchand (1913), Zimmerman et al. (1973), and Kramer (1977), and both premenstrual and menstrual exacerbations were noted by Ansell and Clark (1956*b*) in 63% of 42 patients, by Gordon (1909) in 23 patients, and by Laidlaw (1956) in 50 patients. In an extensive analysis of a single patient by Helmchen et al. (1964), seizure frequency increased slightly from the 14th to 16th days after the onset of menses, possibly correlating with ovulation. Reduced seizure activity in the luteal phase from the 4th to 13th days before menstruation were observed by Toulouse and Marchand (1913) and Laidlaw (1956). In the only study measuring plasma estrogen and progesterone concentrations, Bäckström (1976) studied the ovulatory and anovulatory cycles of 7 patients. In the ovulatory cycles, generalized tonic–clonic seizures increased during menstrual flow and during the preovulatory phases, corresponding with a higher concentration of estrogen than progesterone. During the anovulatory cycles, seizure exacerbations were correlated with estrogen concentrations, but not with menstrual phase.

TREATMENT

The effect of treatment on the menstrual exacerbation of seizures has not been fully examined. Bromide was first used successfully as an antiepileptic agent in the control of catamenial and hysterical epilepsy (Locock, 1857), but it has not been used generally as the drug of choice for treatment of catamenial epilepsy. Hormonal therapy, primarily through the administration of oral contraceptives, has occasionally been successful (see below), but the reports are usually anecdotal. The reduction of endogenous estrogen has also been beneficial, as shown by patients who experienced seizure control with menopause or ovarectomy (Gordon, 1909; Bandler et al., 1957). Nevertheless, Lennox and Cobb (1928), in an early review, noted that many women have been castrated without improvement of their seizures, and castration is not an accepted procedure.

TABLE 1. *Seizure patterns in patients with catamenial epilepsy*

Reference	No. of patients	Age (yr)	No. of menses per patient	Seizure type	Patients with monthly seizure increases		Patients with exacerbation during a specific menstrual phase						
					Unrelated to menses	Related to menses	Premenstrual	Menstrual	Postmenstrual	Preovulatory	Ovulatory	Postovulatory	Not mentioned
Almquist, 1955	84	18–63	8	Generalized tonic–clonic	27	2		2					
Ansell and Clarke, 1956b	42	—	2–4	—		26		26[a]					
Bäckström, 1976	7	13–45	1–2	Generalized tonic–clonic complex partial				*b*		*b*			
Bandler et al., 1957	22	—	6–39	—	6	16	2[c]	5		4		4	
Buntner and Rościszewska, 1975	11	—	3	—		11	11						
Dickerson, 1941	269	10–49	1–14	—		27		27					
Gordon, 1909	23	—	—	—		23	14	7	2				
Gowers, 1885	82	—	—	—	10	46	17	15	4				
Healey, 1928	73	—	—	—		45							45
Helmchen et al., 1964	1	18	48	Generalized tonic–clonic, complex partial							1[d]		
Kramer, 1977	1	16	45	Complex partial		1	1						
Laidlaw, 1956	50	—	186 (avg)	Generalized tonic–clonic		36	*b*	*b*	*b*		*e*		
Lennox and Lennox, 1960	686	—	—	—		333							333
Logothetis et al., 1959	10	16–45	13.5 (avg)	—		10	*b,f*	*b*					
Sánchez Longo and González Saldaña, 1966	1	12	—	Generalized tonic–clonic, complex partial			1[c]						
Rebattu et al., 1922	100	—	—	—		35							35
Thiry et al., 1954	58	—	—	—		37							37
Toulouse and Marchand, 1913	10	—	23 (avg)	"Essential"		4		*b*				*e*	
Zimmerman et al., 1973	1	8	14	"Generalized"				1					

[a] includes day prior to flow of menses
[b] seizures for entire group increased
[c] length of phase uncertain
[d] phase extends from days 14-16 of cycle
[e] seizures for entire group decreased
[f] phase extends to 4 days prior to menses

Premenstrual, includes the 2 days before menstrual flow; postmenstrual, includes the 2 days after menstrual flow; preovulatory, includes all days from postmenstrual phase to ovulation; postovulatory, includes all days from postmenstrual to premenstrual phase.

Although acetazolamide has been suggested for the treatment of catamenial seizures (Ansell and Clarke, 1956*a*; Livingston, 1972), its efficacy has not been firmly demonstrated. In 3 patients of Ansell and Clarke (1956*a*) with catamenial exacerbations of generalized tonic–clonic or absence seizures, only increasingly higher doses of the drug could maintain seizure control for a maximum follow-up of 4 months after the last period. The authors also described improvement for 3 months in 2 patients given acetazolamide only on the day before and the day of onset of menstrual flow, but a prolonged follow-up study was not performed. An efficacious treatment of catamenial seizures, then, has not been conclusively shown, although many therapies have been successful in selected patients.

OTHER TYPES OF CYCLICAL EPILEPSY

Complicating the above findings is the observation that seizures may occur in monthly cycles in men and prepubescent girls, who obviously are not subject to the hormonal changes that adult women undergo (Table 2). In one study, 10 girls had recurrent monthly attacks from the age of 5 until menarche, when the attacks turned into catamenial epilepsy (Livingston, 1972). Cyclical seizures were reported in 1 man with complex partial, absence, and generalized tonic–clonic seizures (Denys, 1963); in 3 men with generalized tonic–clonic seizures (Griffith and Fox, 1938; and in 2 men with generalized tonic–clonic attacks and complex partial seizures (Helmchen et al., 1964). The most careful study of cyclical seizure activity was performed by Almquist (1955) in 84 women and girls and 62 men who had a mixture of seizure disorders. Only generalized tonic–clonic seizures were counted, as "minor motor seizures" were not thought to be adequately measurable. Eighteen men and 29 women and girls had rhythmical increases of seizure frequency, with a periodicity varying between 8 and 46 days. Two of the 29 female patients were girls, and 5 women had irregular menses that did not correlate with the seizure exacerbations. Among the women with a sufficient number of menses to correlate with the seizure exacerbations, only 2 had exacerbations related to the menstrual flow, a percentage which was considered statistically insignificant.

ELECTROENCEPHALOGRAPHIC CHANGES

Several investigators have described minor EEG fluctuations in nonepileptic

TABLE 2. *Periodic seizure frequency in men and prepubescent girls*

Reference	No. of patients	Sex	Age (yr)	Seizure type	Intervals between seizure exacerbation
Almquist, 1955	18	M	19–54	Generalized tonic–clonic	8–46 days
	2	F	6–8	Generalized tonic–clonic	14–22 days
Denys, 1963	1	M	59	Generalized tonic–clonic, complex partial	Monthly
Griffiths and Fox, 1938	3	M	11–40	—	26–35 days
Helmchen et al., 1964	2	M	16–54	Generalized tonic–clonic, complex partial	22–25 days
Livingston, 1972	10	F	5–puberty	—	4 weeks

women during the menstrual cycle. Using a three-channel electroencephalograph, Dusser de Barenne and Gibbs (1942) discovered cyclical background slowing during two menstrual phases: the time of menstrual flow and the midmenstrual day, which was thought to be close to the ovulatory phase. The slowing during ovulation was not confirmed by others (Lamb et al., 1953), but Jeavons (personal communication, 1978) noted that a previously normal EEG may become abnormally slow during menstruation. In addition to the rate changes, the amplitude of the EEG may drop during the premenstrual and menstrual phases (Margerison et al., 1964; Sugerman et al., 1970).

EEG changes also have been correlated with gonadotropin titers, basal metabolic rates, and vaginal smears. According to Pitot and Gastaut (1954), alpha and beta activity increased during preovulatory and premenstrual phases and decreased during postovulatory and menstrual phases as theta activity increased. These findings were not entirely corroborated in a nonepileptic patient in whom theta activity was prominent on preovulatory days but decreased after ovulation (Gautray et al., 1970*a*,*b*). Alpha activity was low just prior to ovulation but rising by the time of ovulation. Creutzfeldt et al. (1976), measuring blood levels of hormones and recording EEGs on alternate days, discovered a consistent, small increase of occipital alpha of 0.3 Hz from the luteal phase to the onset of menstruation. In addition, minor cyclical changes of occipital and temporal theta activity were also seen. Correlation of the EEG changes with reaction times revealed a mild decrease in reaction time during periods of relatively increased alpha frequency. Reduced photic driving was associated with increased estrogen in ovulatory women (Vogel et al., 1971). In conclusion, the EEG changes in nonepileptic individuals are usually minimal, but in certain patients, slowing or reduced amplitude may appear during the menstrual cycle, usually during menstrual flow.

Only two studies of cyclic EEG changes have been performed on epileptic women during the menstrual cycle. In a woman with absence and generalized tonic–clonic seizures, the number of generalized spike and wave discharges increased significantly during menstrual days compared with nonmenstrual days (Lin et al., 1952). The inclusion of absence seizures in this study is particularly important, since they are often avoided because of the difficulty of obtaining accurate counts. In 44 women with mixed seizure types, an increase in the number of paroxysmal discharges was found during the menses, in the days preceding the menses, and in midcycle (Rościszewska, personal communication, 1979). Thus, the EEG data parallel the clinical findings, with epileptiform activity increased during the menses.

LABORATORY EVALUATIONS

The cause of catamenial epilepsy has been investigated from two major aspects: water metabolism and endocrine changes. It has been well known since the work of Thorn et al. (1938) that women gain weight during the premenstrual phase and lose weight during the menses. The significance of weight gain was suggested by McQuarrie's (1932) report of a patient with generalized tonic–clonic seizures who experienced an increased seizure frequency within 3 days after the appearance of positive water balance. Blyth (1943), in fact, used pitressin-induced water retention to diagnose doubtful cases of epilepsy. Ansell and Clarke (1956*b*), however, performed body water measurements in 7 seizure patients, 3 of whom had increased seizure frequency with menstruation, and compared their water metabolism with that of 5 normal individuals. The ^{22}Na half-lives and percentage of body weight of total body

water were the same in patients with noncatamenial and catamenial epilepsy and normal subjects, and a disturbance of extracellular water storage did not appear to be primarily responsible for exacerbation of the seizures. Although these water changes, which occur normally in women, are not primarily responsible, they may further exacerbate an underlying catamenial seizure disorder.

Major efforts to determine the etiology of catamenial seizures have been directed toward hormonal evaluations, but the data from such studies are inconsistent. One explanation of the inconsistencies is a possible interaction of antiepileptic medication with hormonal metabolism. As Buchanan and Sholiton (1972) noted, the metabolism and hydroxylation of phenytoin, phenobarbital, and many endogenous steroids depend on the same metabolic enzymes. Both increased and decreased metabolism of antiepileptic medications have been observed to be secondary to hormonal therapy. Reduced phenytoin metabolism was noted by Kutt and McDowell (1968) in a patient who experienced phenytoin intoxication after estrogen treatment, and by Fernandez-Pol and Zaninovich (1975), who found an increased half-life of phenytoin. The latter authors postulated that the increased phenytoin half-life was secondary to an increased binding capacity for phenytoin of thyroxine-binding globulin, which decreased hepatic availability of phenytoin. A direct hepatic effect was not ruled out, however. Sherwin et al. (1974) found reduced plasma phenytoin levels in young women compared with men of the same age who were given the same dose (in mg/kg), a finding which was not corroborated by others (Travers et al., 1972; Eadie et al., 1973; Houghton et al., 1975). Rościszewska (personal communication, 1979) noted that blood drug levels fluctuated significantly during the menstrual cycle and that phenytoin and phenobarbital levels dropped during ovulatory and postovulatory phases in 44 women. The evidence is therefore somewhat contradictory on the interaction of antiepileptic medication and the menses, and the phenomenon will not be defined until changes in blood levels of these drugs are analyzed in relation to changes in estrogen and progesterone during the menstrual cycle.

Several hormonal excretion measurements have been performed in catamenial patients, but a specific, consistent abnormality has not been identified. Buntner and Rościszewska (1975) found reduced urinary estradiol, estriol, and pregnanediol excretion in all seizure patients, and reduced pregnanetriol excretion in all noncatamenial seizure patients only. On the other hand, Zaichkina (1963) did not find consistently abnormal excretion of estrogen or pregnanediol in 60 catamenial patients, and Thiry et al. (1954) similarly found an inconsistent excretion of estrogen in both catamenial and noncatamenial seizure patients. Thiry et al. (1954) and Rościszewska and Buntner (1975) found 17-ketosteroids to be normal or low in most catamenial and noncatamenial patients, and Rościszewska and Buntner (1975) found reduced levels of 17-hydroxycorticosteroids in the urine of women with catamenial and noncatamenial seizures. Although hormonal excretion is frequently abnormal in women with catamenial epilepsy, a specific pattern has not emerged.

An important correlation between plasma estrogen and progesterone levels and seizure activity has been suggested. Bäckström (1976) measured plasma levels of estrogen and progesterone in women with both partial and generalized tonic–clonic seizures. During the ovulatory cycles, an increased estrogen–progesterone ratio correlated with a higher incidence of generalized tonic–clonic seizures, whereas reduced seizure activity appeared with increased plasma progesterone levels. A less prominent but similar correlation with changes in estrogen and progesterone

was present with partial seizures. In anovulatory cycles, elevated estrogen levels correlated with seizure frequencies of both the partial and generalized tonic–clonic seizures. This well-performed study was limited by the relatively few menstrual cycles measured and the unknown effects of the seizures themselves on the estrogen measurements. Although published studies of the effects of seizure activity on estrogen and progesterone are lacking, the effects of electroshock convulsions on gonadotropins have been measured in two studies. Ryan et al. (1970) found significant increases in serum follicle-stimulating hormone (FSH) and luteinizing hormone (LH) in some men, and no significant effect in postmenopausal women. Another study by Vigas et al. (1975) demonstrated a significant increase of LH only after the first electroshock convulsion in female psychiatric patients. FSH was not affected. Prolactin, another hormone affected by hypothalamic stimulation, may increase significantly after generalized tonic–clonic seizures or unilateral electroconvulsive therapy (Trimble, 1978). Whether this change in prolactin concentration affects seizure sensitivity is unknown.

HORMONAL TREATMENT

Several investigators have examined the effects of various sex hormones on epilepsy, but most studies have been small and usually limited by a lack of data on the blood levels of antiepileptic drugs and an incomplete description of the seizures. Perhaps the best results have been found with catamenial seizures. Although Sánchez Longo and González Saldaña (1966) described a patient with catamenial seizures who suffered a severe exacerbation after the addition of an oral contraceptive, another patient in the same paper gained complete control of a combination of seizure types upon the addition of an oral contraceptive. Zimmerman et al. (1973) described a girl with precocious puberty and "generalized seizures" associated with the menses. When medroxyprogesterone was added to her regimen, both catamenial and noncatamenial seizures were sharply reduced. The report stated only that significant changes in the blood levels of antiepileptic drugs did not occur. Groff (1962) reported complete seizure control in a patient with previously refractory catamenial seizures after the addition of a norethynodrel–mestranol combination, and Hall (1977) described a woman whose generalized tonic–clonic seizures were controlled for 7 months after she had been given a progesterone oral contraceptive. Livingston (1972) reported successful use of norethynodrel–mestranol in 5 patients with catamenial epilepsy, but he did not describe the type of seizure affected. Also, despite successful seizure control, all patients eventually had to be withdrawn from the contraceptives because of untoward effects of the compounds. Logothetis et al. (1959) mentioned that 3 of 5 patients with catamenial exacerbations improved after treatment with progesterone. In 15 patients with catamenial seizures, intravenous injection of conjugated estrogen increased paroxysmal epileptogenic activity in the EEGs of 11 patients and precipitated frank seizures in 4 patients. In this paper, the types of seizures were not mentioned, nor was previous antiepileptic treatment carefully delineated. These reports suggest that the addition of an estrogen–progesterone combination or progesterone alone may reduce the frequency of seizures in patients with catamenial epilepsy, but definite conclusions cannot be reached without controlled investigations of the efficacy of these compounds.

In contrast to the improved control of catamenial seizures, hormonal treatment of noncatamenial seizures has not been as efficacious. Three reports have examined the effect of estrogen or oral contraceptives on seizure frequency in epileptic patients who did not necessarily have catamenial exacerbations. Whitehead and McNiel

(1952) used trihydroxyestrone to treat 18 patients who had absence or generalized tonic–clonic seizures and observed significant improvement in 8 patients and partial improvement in 6 during observation periods of 2 to 21 months. Two patients with absence seizures suffered more attacks, but effective antiabsence agents were not available at the time of the study. Bickerstaff (1975) reported that 6 patients with either complex partial or generalized tonic–clonic seizures had more attacks with the addition of oral contraceptives. Their seizure frequency returned to pretreatment rates when the agents were withdrawn. This report did not mention blood levels of antiepileptic drugs, which might change with hormonal therapy. In 11 patients with complex partial or generalized tonic–clonic seizures, Toivakka (1967) examined the effects of high doses (4 times the needed contraceptive dose) of a lynestranol–mestranol combination. The 1 patient who suffered more seizures had decreased the prescribed amount of antiepileptic medication shortly before the trial. After the dosage was increased, seizure frequency returned to the usual pattern. Thus, the effects of hormonal therapy on noncatamenial seizures cannot be predicted; in most patients they are probably minimal, but an occasional patient may be either helped or hurt by oral contraceptives.

EEGs have also been obtained from epileptic patients after the addition of oral contraceptives. Graudenz and Fichtner (1966) noted markedly increased paroxysmal activity after the addition of oral contraceptives in 5 of 33 patients, with return to the previous level of activity on discontinuation of the agents. Logothetis et al. (1959) found that increased paroxysmal activity occurred 30 sec to 21 min after the intravenous injection of conjugated estrogen. Different results of chronic therapy with oral contraceptives were found by Toivakka (1967), who obtained three EEGs from each of 11 patients 4 days after onset of the menses. In 17 of 33 menstrual cycles, seizure frequencies were unchanged; they improved in 12 and were worse in 4. Except for a patient whose medication dose had been reduced before the study, no patient showed persistent deterioration. This series, which most closely approximates clinical conditions, demonstrated a minor effect of oral contraceptives on seizures.

Minor changes have been noted in the EEGs of nonepileptic patients after oral contraceptive use or other hormonal therapy. Ferroni et al. (1969), in 36 patients on an undisclosed oral contraceptive; Cress and Greenblatt (1945), in 3 patients given progesterone or stilbestrol; and Toivakka (1967), in 10 patients on higher than usual doses of lynestranol-mestranol, did not notice any consistent changes, whereas West and West (1966) found abnormalities in 30 of 34 women with headache or other vague neurologic symptoms and in 5 of 14 women free of all neurologic symptoms. They did not define the nature of the abnormalities, however. In psychiatric patients who used oral contraceptives, Struve et al. (1976) detected increased "paroxysmal activity," but they likewise used a nonspecific definition for "paroxysmal activity." Ansari et al. (1970) found mild borderline abnormalities in 75% of 88 patients on oral contraceptives, consisting of minor changes, usually with a normal background, and did not include epileptiform activity. After withdrawal of the oral contraceptives, 6 of 14 patients improved. Similar nonspecific abnormalities were present in 60% of the women tested by Elwan et al. (1973).

Among specific findings, slowing of background activity is perhaps the most common change in nonepileptic patients after oral contraceptive use. Creutzfeldt et al. (1976) found peak alpha rhythm on the EEG to be 0.5 Hz slower in 16 patients on oral contraceptives than in control patients. Malyshenko (1969) found that estradiol dipropionate produced synchronization and

TABLE 3. *Effect of pregnancy on seizure frequency*

Reference	No. of patients	Age (yr)	Seizure type	Patients affected (*n* or %)				
				Increased	Decreased	No change	Seizure onset	Status epilepticus
Baptisti, 1938	37	—	—	4	5	21	4	
Burnett, 1946	16 (19 pregnancies)	22–42	—	42%	5.5%	52.5%		1
Cvetko, 1970	24 (32 pregnancies)	—	Partial seizure, "centrencephalic," diffuse, undetermined	12.5%	53.1%	34.4%		
Huhmar and Jarvinen, 1961	96	—	"Centrencephalic," partial seizure	70%[a]		20%[a]		3
				40%[b]		40%[b]	28%	
				17%[c]		57%		
Knight and Rhind, 1975	59 (153 pregnancies)	—	—	45%	5%		14	2
				95–100%[d]				
				50–60%[e]				
				25%[f]				
Lennox and Lennox, 1960	73	—	—	44%	29%	27%		
Loiseau et al., 1974	25 (60 pregnancies)	—	—	1	1	23		

Maroni and Markoff, 1969	32 (37 pregnancies)	—	—	~25%		~75%		
Mauranges, 1966	260	—	—	11		249		
McClure, 1955	20 (28 pregnancies)	—	Generalized tonic–clonic	11	4	5		1
Rościszewska and Grudzińska, 1970	29	—	—	7	14	8		
Sabin and Oxorn, 1956	27	—	Generalized tonic–clonic, absence, complex partial, elementary partial	9	4	14		
Suter and Klingman, 1957	132	—	Generalized tonic–clonic, complex partial	43	7	43	30	
Turner, 1907	21	—	—	14	6	1	2	

Prepregnancy seizure frequency:
[a] "serious"
[b] "mild"
[c] "slight"
[d] >1 per mo.
[e] 1 per 1-4 mo.
[f] <1 per 4 mo.

hypersynchronization of the background, and progesterone produced decreased amplitude and mild slowing. Matsumoto et al. (1966) examined the sleep tracings of 6 patients taking oral contraceptives and found slow sleep spindles of 8 to 10 Hz, which were absent in control patients. Photic driving is reduced after estrogen therapy in nonovulatory women according to Vogel et al. (1971), who speculated that the effect may have been due to changes in adrenergic central nervous system function.

MENARCHE AND MENOPAUSE

Few investigators have studied the effect of menarche or menopause on the incidence of seizures. Lennox and Lennox (1960) observed in 385 patients that seizure disorders began within 1 year of menarche, but did not report the type of seizure that occurred. Certain EEG patterns closely associated with a specific seizure type reach their peak in childhood and early adolescence and then decrease during early to midadulthood. The photoconvulsive responses (Doose and Gerken, 1973) and generalized spike and wave discharges (Metrakos and Metrakos, 1961) both have maximal prevalence between the ages of 5 and 16 years, with a considerable decline during the adult years. Although the prevalence of abnormal EEGs is similar in both sexes in the spike-wave group, photoconvulsive abnormalities peak in girls between 14 and 16 years of age. It is doubtful that these EEG changes are entirely secondary to estrogen changes, because similar, although less prominent, changes are also common in men. A combination of hormonal and maturational factors is more likely.

Several investigators have observed catamenial seizures first appearing with menarche. Helmchen et al. (1964), Sánchez Longo and González Saldaña (1966), and Zimmerman et al. (1973) reported the appearance of catamenial seizures, consisting of complex partial or generalized tonic–clonic seizures, at puberty, and Bandler et al. (1957) noted that 4 of 29 women with catamenial seizures had seizure onset within the menarche. Logothetis et al. (1959) noted that the onset of seizures occurred within 3 years of menarche in 16 of 25 patients with catamenial exacerbations. Lin et al. (1952) observed a patient in whom the reduction in absence seizure frequency at menarche was accompanied by the onset of generalized tonic–clonic seizures. Rościszewska (1975), in the only study devoted primarily to the effect of menarche on seizures, studied 62 patients with generalized tonic–clonic, complex partial, or elementary partial seizures. The frequency of the seizures was unchanged in 19 patients, more frequent in 20, and less frequent in 20. Five of the 7 patients with complex partial seizures had an increased seizure frequency at time of menarche. Patients whose seizures began earlier or who had abnormal neurologic signs tended to have increased seizures at puberty. The effects of previous seizure frequency on the changes induced by menarche were not studied, but patients with the most profound neurologic deficits were more affected by pubertal changes.

The effects of menopause on seizure disorders have not been adequately studied. Turner (1907) mentioned that in his experience menopause had no effect on seizure frequency, and Lennox and Cobb (1928) noted that several women had been castrated in unsuccessful attempts to control seizures.

PREGNANCY

The findings of several large studies on the effects of pregnancy on seizure disorders have varied greatly. The incidence of exacerbation during pregnancy has ranged from a low of 2 to 4% in some studies (Mauranges, 1966; Loiseau et al., 1974) to a high of 41 to 45% in others (Burnett, 1946; Suter and Klingman, 1957; Lennox and Lennox, 1960; Knight and Rhind, 1975). This wide range of findings is probably secondary to different patient populations and

different methods of measuring seizure frequency. Although changes in blood levels of medications and the prepregnancy type and severity of seizures may affect seizure susceptibility in pregnancy, they are rarely mentioned in these reports. Status epilepticus is a rare but significant event in pregnancy, occurring in 1 to 3% of women with seizures (McClure, 1955; Huhmar and Jarvinen, 1961; Knight and Rhind, 1975). The danger of status epilepticus is probably greatest in the third trimester (Guzman and Matute, 1968), when the decline in blood levels of antiepileptic medications, particularly phenytoin, is greatest (Ramsay et al., 1978). Hormonal or water changes are a less likely etiology of this third-trimester seizure risk.

Seizure exacerbation during pregnancy may be affected by hormonal changes, fluid imbalance, changes in the metabolism of antiepileptic drugs, or disorders caused by the pregnancy. Besides the obvious hormonal changes, Suter and Klingman (1957) noted that weight gain may be significant in pregnant epileptic patients and presented an example of a woman with a 49-pound weight gain who did not return to her baseline seizure frequency until the weight was lost. Increased phenytoin clearance during pregnancy is another major factor, and patients with the greatest increase in seizures often have the greatest change in phenytoin clearance (Mygind et al., 1976). Daily phenytoin requirements may increase in the majority of women taking the drug (Lander et al., 1977) and will occasionally reach extraordinary proportions. A woman who suffered status epilepticus in midtrimester had a marked reduction in intestinal absorption of phenytoin, which increased the therapeutic oral requirement to 1,200 mg/day (Ramsay et al., 1978). Phenobarbital metabolism changes secondary to pregnancy have not been as common, with some women unaffected (Mygind et al., 1976) and others requiring higher doses to maintain equivalent blood levels (Lander et al., 1977). Additionally, the pregnancy itself may cause diseases which either aggravate the existing epilepsy or cause a new seizure disorder. Boshes and McBeath (1954) reported 8 pregnant patients with new seizure disorders, 4 of whom continued to have seizures after the pregnancy ended. One patient had suffered a cerebral embolism, another had a venous thrombosis, and a third had seizures secondary to the growth of a meningioma.

The severity of the prepregnancy seizure disorder may be significant for predicting an exacerbation during pregnancy. Although Rościszewska and Grudzińska (1970) did not find a relationship between seizure severity and exacerbation during pregnancy in 29 patients, most investigators have found a correlation. Baptisti (1938) noted that in 37 patients those who averaged a seizure every 2 weeks were the most likely to have exacerbations. In 96 patients, Huhmar and Jarvinen (1961) found that seizure frequency increased during pregnancy in 70% of those severely affected, but in only 17% of those mildly affected. Knight and Rhind (1975) reported that exacerbations occurred in 45% of 153 pregnancies of 59 patients. If the seizure frequency was greater than 1 per month, almost all patients suffered from an increase in seizures, but if seizures occurred less than once every 4 months, only 25% had an increase. Only two studies have investigated the type of seizure most likely to be affected by pregnancy. Huhmar and Jarvinen (1961) found more exacerbations in generalized seizure disorders than in partial ones, but Rościszewska and Grudzińska (1970) found no correlation between exacerbation and seizure type.

ANIMAL MODELS

Estrogen

Electroshock and Audiogenic Seizure Models

A direct hormonal etiology for catamenial seizures is suggested by experiments that have shown an epileptogenic effect in

several species. The minimal electroshock seizure threshold is lowest during estrus in the mature rat, a phase of increased circulating estrogen (Woolley and Timiras, 1962*a*). Exogenous estrogen has also increased the extent and severity of seizures in animals subjected to maximal electroshock and has decreased the minimal electroshock seizure threshold in mice (Blackhan and Spencer, 1970), in rats (Woolley et al., 1960; Werboff and Corcoran, 1961; Woolley and Timiras, 1962*b*; Werboff et al., 1963; Heim, 1966; Vernadakis and Timiras, 1966; Stitt and Kinnard, 1968; Terasawa and Timiras, 1968), in rabbits (Logothetis and Harner, 1960), and in cats (Marcus et al., 1966). Specifically, Blackhan and Spencer (1970) showed that mestranol (1 mg/kg/day) for 4 days increased the intensity and duration of fits caused by maximal electroshock in mice. Woolley and Timiras (1962*b*) demonstrated that long-term administration of estradiol produced a significant decrease in the minimal electroshock seizure threshold and increased tonic extension to maximal electroshock in normal adult male rats, ovarectomized females, hypophysectomized females, and normal females. Since hypophysectomized animals also responded to estrogen, the estrogen effect was apparently independent of a pituitary factor. The electroshock seizure threshold was also decreased in rats by the combinations of estradiol and medroxyprogesterone, or norethynodrel and mestranol in ratios of 66:1 and 25:1 (Stitt and Kinnard, 1968). Similar results were found in developing rats given estradiol, which caused an earlier, more adult pattern of tonic–clonic seizures than that usually seen with maximal electroshock (Vernadakis and Timiras, 1966), and in newborn rats, in which the increased tonic extension and decreased tonic flexion existed for at least 6 months after treatment with estrogen (Heim, 1966). The findings thus consistently demonstrate increased seizure sensitivity to estrogen in a wide variety of models. In addition to the electroshock model, Werboff and Corcoran (1961) and Werboff et al. (1963) found an increased duration and frequency of audiogenic-induced seizures in seizure-sensitive rats after the administration of estradiol alone or in combination with progesterone.

Focal Electrical Stimulation

Terasawa and Timiras (1968) showed that local seizure thresholds in rats may be affected during the estrous phase and after estradiol dipropionate. They found a decreased seizure threshold in the dorsal hippocampus and medial amgydala during the proestrus and estrus phases of mature rats, whereas the lateral amygdala developed an increased threshold during the same periods. Ovariectomized animals did not demonstrate this pattern, but estradiol dipropionate returned the pattern to the previous one.

Focal Cortical Lesions

Under specific conditions, focal cortical lesions are also affected by estrogen. Logothetis and Harner (1960) examined the effect of conjugated estrogen (10–20 mg, i.v.) on rabbits with cortical lesions produced by ethyl chloride. Epileptiform discharges were activated in 5 of the 7 animals tested; 2 animals died after the induction of seizures. Marcus et al. (1966) attempted to define the conditions necessary for increased epileptiform activity after estrogen. They examined adult cats under four experimental conditions: (1) animals without local lesions (intact blood–brain barrier without a seizure focus), (2) animals with focal cortical lesions produced by conjugated estrogen or strychnine (seizure focus with an apparently intact blood–brain barrier), (3) animals with focal lesions produced by chloroform–methanol solution (impaired blood–brain barrier without a seizure focus), and (4) animals with lesions caused by a combination of ethyl chloride and estrogen or strychnine (seizure focus with an impaired blood–brain barrier).

They found that only massive doses of intravenous conjugated estrogen could activate seizure discharges in animals with an intact blood–brain barrier, even with a previous seizure focus, but relatively small doses could activate seizure discharges in animals with both a focal lesion and impaired blood–brain barrier. High doses of estrogen were required to activate epileptiform discharges in animals that had an impaired blood–brain barrier without a seizure focus.

Estrogen has also been used as a potent local irritant for induction of seizures in cats (Logothetis and Harner, 1960; Marcus et al., 1966; Marcus and Watson, 1966; Hardy, 1970; Angeleri et al., 1972; Julien et al., 1975; Lange and Julien, 1978) and in monkeys (Marcus et al., 1968; Marcus and Jacobson, 1969; Mirsky et al., 1973). Local application to the cortex of both hemispheres produced a bilaterally synchronous spike and wave pattern of 2 to 4 Hz, which depended on intracortical and transcallosal mechanisms rather than mesencephalic and diencephalic mechanisms (Marcus and Watson, 1966). In studies on the cat, corpus callosal sectioning disrupted the interhemispheric synchrony, but blocks of cortex separated from the deeper structures of the hypothalamus, rostral mesencephalon, and thalamus demonstrated synchronous discharges if the corpus callosum remained intact (Marcus and Watson, 1966).

Progesterone

The effects of progesterone on seizure discharges are not as striking as those of estrogen. One of the most impressive findings has been that intramuscular injection of progesterone before the initiation of an agenized zein diet, which produced seizures in all control animals, protected one-half of the dogs against a convulsion (Costa and Bonnycastle, 1952). The amount of progesterone administered was not mentioned, and only 6 dogs were tested. In studies on the cat, progesterone in a dose that gave blood concentrations of 40 ng/ml depressed the spontaneous interictal spikes produced by the application of penicillin to the cerebral cortex (Landgren et al., 1978). Other investigations have shown little effect of progesterone on seizures, including studies on audiogenic seizure-sensitive and seizure-resistant rats (Werboff et al., 1963) and on rats subjected to electroshock (Spiegel and Wycis, 1945; Woolley et al., 1960; Woolley and Timiras, 1962*b*; Stitt and Kinnard, 1968). Craig (1966) found that 300 mg/kg of progesterone protected mice against seizures produced by pentylenetetrazol, but not those produced by maximal electroshock. In the testing of progesterone-related compounds of various antiepileptic and hormonal potencies, the most effective of these, which was devoid of hormonal effect, was insufficiently potent to warrant further testing (Craig, 1966). The effect of progesterone on the nonepileptic brain is inconclusive, as shown by Beyer et al. (1967), who found EEG cortical spindling and decreased diencephalic background activity in association with elevated blood pressure. The EEG changes may have been due to the primary action of the drug or secondary to the hypertension. Thus, progesterone has significantly less effect on seizures than estrogen.

Testosterone

Testosterone, similar to progesterone, has minimal efficacy against seizures. Testosterone reduced seizure sensitivity in female rats subjected to audiogenic stimulation alone or in combination with a subconvulsive dose of pentylenetetrazol (Werboff and Corcoran, 1961) and in seizure-sensitive castrated male rats (Werboff et al., 1963). However, in intact male rats (Woolley et al., 1960) and in female rats (Spiegel, 1943), testosterone afforded little protection against electroshock and had no effect on agene-induced convulsions in dogs (Costa and Bonnycastle, 1952).

Gonadotropins

Brain dysfunction in seizure activity has been shown to alter gonadotropin levels

and hormonal function. Temporal lobectomies produced irregular menstrual cycles in monkeys (Wada and Erikson, 1962) and convulsions in the rabbit (Pawlaczyk et al., 1973), and audiogenic seizures in the rat (Popovichenko, 1971) produced pathologic changes in the hypothalamus. After electrical stimulation of the amygdala of the rat (Ellendorff et al., 1973) and the amygdala medial preoptic area and hippocampus (Kawakami and Terasawa, 1972), serum and/or pituitary gonadotropin levels were significantly altered. Despite this effect of seizure activity on hormonal activity, however, the converse has not been shown; that is, whether gonadotropin changes may alter seizure activity.

CONCLUSION

Cyclical variations in seizure frequency and severity have frequently been observed in women and less commonly in men and children. The rarely reported cyclical fluctuations in men and children have usually been only superficially described, and their cause is unclear. Possible etiologies may be broadly categorized as follows: (1) endogenous cyclical factors that may affect brain activity (i.e., hormonal or fluid changes), and (2) exogenous factors (i.e., changes in blood levels of antiepileptic drugs, environmental changes, and stress). The relative contributions of these factors to noncatamenial cyclical seizure exacerbations have not been determined.

Cyclical seizure exacerbations in women have been correlated with the menstrual cycle, because increased seizure activity often occurs at the time of menses and ovulation. These peaks of activity were associated with a high plasma estrogen/progesterone ratio in one study, but this association has not been corroborated by independent observers. The relationship of catamenial seizures to clinical factors has not been defined; the importance of seizure type, severity, and etiology of the seizure disorder is unknown, and should be determined in future studies.

Estrogen and progesterone changes may also be responsible for the change in seizure sensitivity at menarche and menopause, but the changes in seizure activity at these times have been only superficially investigated. Although initial findings suggest that menarche has little effect on the seizure disorder, specific types of seizures, such as photic-induced attacks, which may be more sensitive to hormonal influences, have not been investigated. Since photic-induced seizures commonly occur near the age of puberty, an important role for estrogen is reasonable.

Seizure exacerbations during pregnancy are likely to be the result of decreased blood levels of antiepileptic medication, possibly through reduced gastrointestinal absorption. Whether the hormonal changes of pregnancy may also directly affect seizure disorders is unclear. Since most seizure exacerbations have responded to increased doses of antiepileptic medication, evidence for a direct effect is not impressive.

The effect of estrogen and the menstrual cycle on the EEG is usually minimal, but it is possible that there exists a subset of individuals who may be affected by estrogen. Patients who have photoconvulsive responses, for example, may be partially subject to catamenial exacerbations. The spike and wave pattern, which has a less striking sex influence, may be similarly affected.

The findings concerning the effects of hormonal therapy on seizure disorders are also inconclusive, and they may differ between noncatamenial and catamenial seizure disorders. Most seizure patients are not adversely affected by hormonal therapy (usually oral contraceptives), although some occasionally experience increased seizures. Among catamenial seizure patients, specifically, anecdotal reports have suggested that selected patients may be helped. The most effective therapy—estrogen, progesterone, or a combination of both—has not been determined, and a

comparison of hormonal therapy with antiepileptic medication is still lacking. Other therapies used for catamenial seizures, usually diuretics, are not generally effective.

Animal experiments have almost uniformly demonstrated an epileptogenic effect of estrogen and a minimal effect of progesterone. Experiments have not been performed, however, on the baboon, an animal with a menstrual cycle. Since the baboon *Papio papio* is also a model for spontaneous and photosensitive epilepsies, the effects of hormones on seizure frequency and EEG abnormalities may easily be measured and may be a source of future understanding.

Although several trends exist in the current findings about catamenial epilepsy, much remains to be evaluated. Before research can be initiated, a consistent definition of catamenial epilepsy is required. Although catamenial epilepsy may be narrowly defined to include patients with seizures only during menses, this restrictive definition eliminates most epileptic patients with catamenial exacerbations.

A broader definition might include patients with exacerbations of seizures during a consistent phase of the menstrual cycle, not exceeding 7 days, and not necessarily restricted to the phase of menstrual flow. Under this definition, the effects of changes in the blood levels of antiepileptic medication, plasma levels of estrogen and progesterone, and body weight (an indirect measure of body water) could be analyzed against changes in seizure frequency, seizure type, and EEG patterns. After these basic observations, a more accurate description of the changes induced by menses could be obtained, and the extent and etiology of these changes would be suggested.

Once patients with catamenial seizures are identified, controlled clinical trials are needed to determine the most effective therapy, evaluating antiepileptic drugs, hormones, and diuretics. The complex interaction of heredity, photosensitivity, and hormones requires investigation. The effects of hormonal changes on the EEGs of relatives of photosensitive probands are not known. A definition of the relationship of these factors could improve understanding not only of photosensitivity, but also of many facets of generalized seizure mechanisms.

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RESUMEN

Esta revisión de 126 casos de "epilepsía catamenial" describe la exacerbación de las crisis durante los periodos menstruales. La importancia de las mediciones hormonales, de la influencia entre anticomiciales y contraceptivos orales y la significación de los cambios hormonales en la epilepsía son tratadas en este estudio. Se dan explicaciones para los datos contradictorios existentes y se sugieren vias de investigación potencial sobre la "epilepsía catamenial".

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