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A. G. Herzog
Harvard Neuroendocrine Unit, Beth Israel Deaconess Medical Center, Boston, USA

Disorders of reproduction in patients with epilepsy

Reproductive dysfunction is unusually common among women and men who have epilepsy [1–3]. It generally manifests as menstrual disorder, hirsutism, and infertility in women [2], and loss of libido, impotence, and infertility in men [3]. Reproductive dysfunction is often associated with and is the consequence of reproductive endocrine disorders [1–3]. Both epilepsy and antiepileptic drugs (AEDs) have been causally implicated [1–5]. Epilepsy and AEDs can target a number of substrates to have an impact on hormone levels. These include the limbic system, hypothalamus, pituitary, peripheral endocrine glands, liver, and adipose tissue [6, 7]. Reproductive endocrine disorders can lead not only to reproductive dysfunction, but also to the exacerbation of epilepsy [6, 7]. An understanding of these relationships and their underlying neurological and neuroendocrine mechanisms is important to the comprehensive management of women and men with epilepsy (MWE).

Reproductive dysfunction in women with epilepsy

Hospital- [2, 7, 8] and community-based [9] studies have shown that menstrual disorders are more common among women with epilepsy than in the general population. Menstrual disorders can be categorized in women with epilepsy as amenorrhea (no menses for 6 months), oligomenorrhea (cycle intervals > 32 days), polymenorrhea (cycle intervals < 26 days), abnormal variation in cycle intervals (> 4 days), and menometrorrhagia (heavy menses and bleeding between menses [10]). Cycle intervals between 26 and 32 days, rather than the currently popular broader range of 21–35 days, should be considered normal in women with epilepsy, because ovulatory rates drop substantially and statistically significantly, i. e., from > 75 to < 50 %, outside of the 26- to 32-day range [10]. Ovulation is considered to be an important criterion in this population because anovulatory cycles are associated with greater seizure frequency [11–13]. Menstrual disorders, using the above definition, are currently estimated to occur in one third of women with epilepsy compared with 12–14 % of women in the general population [6, 10]. More than one third of cycles in women with localization-related epilepsy are anovulatory, compared with 8–10 % in controls [10, 14, 15]. There is conflicting evidence as to whether anovulatory cycles are more common with localization-related epilepsy or primary generalized epilepsy [14, 15]. Women with idiopathic epilepsy are only 37 % as likely as unaffected female siblings to become pregnant [16]. This finding is not attributable to the marital rate or to seizure type, age at onset, or family history of epilepsy [16]. In comparison with the general female population, fertility is reduced to 69–85 % of the expected number of offspring among married women with epilepsy, primarily temporolimbic epilepsy (TLE) [17, 18].

Reproductive endocrine disorders in women with epilepsy

The most common reproductive endocrine disorder in women with epilepsy in addition to women in the general population is polycystic ovary syndrome (PCOS) [2, 19, 20]. PCOS occurs in 10 to 20 % of women with epilepsy compared with 5 % to 6 % of women in the general population [6, 7, 18, 20]. This increased rate of occurrence may be of considerable medical significance because PCOS is associated with a higher prevalence of migraine, emotional disorders, diabetes, cardiovascular disease, and female cancers in the general population [20].

Polycystic ovary syndrome is probably not a single nosological entity, but rather the common end point for a number of pathophysiological mechanisms, some of which may be attributable to epilepsy itself [2, 7, 19, 20] or to the use of AEDs, most notably valproate [5, 14, 15, 21]. PCOS represents the failure of the ovarian follicle to complete normal maturation during the menstrual cycle or a series of cycles, a failure that is perhaps related to the presence of inadequate levels of pituitary follicle-stimulating hormone (FSH), while levels of luteinizing hormone (LH) are normal or elevated [7, 20]. These conditions can produce two results. There is a failure of ovulation and the partially developed follicle is retained in the ovary in the form of a tiny cyst [7, 20]. This partially developed follicle is secretory, but deficient in aromatase, the enzyme that converts testosterone to estrogen, and, therefore has testosterone as its principal secretory product. Testosterone may increase the positive feedback of estrogen on pituitary LH secretion [21], resulting in increased ovarian steroid secretion, which, under these circumstances, may be predominantly testosterone and can result in hyperandrogenism. The testosterone is aromatized in peripheral adipose tissue, generally producing high–normal levels of estrogens, which is a major source of the estrogen feedback on the pituitary. The persistent occurrence of such cy-

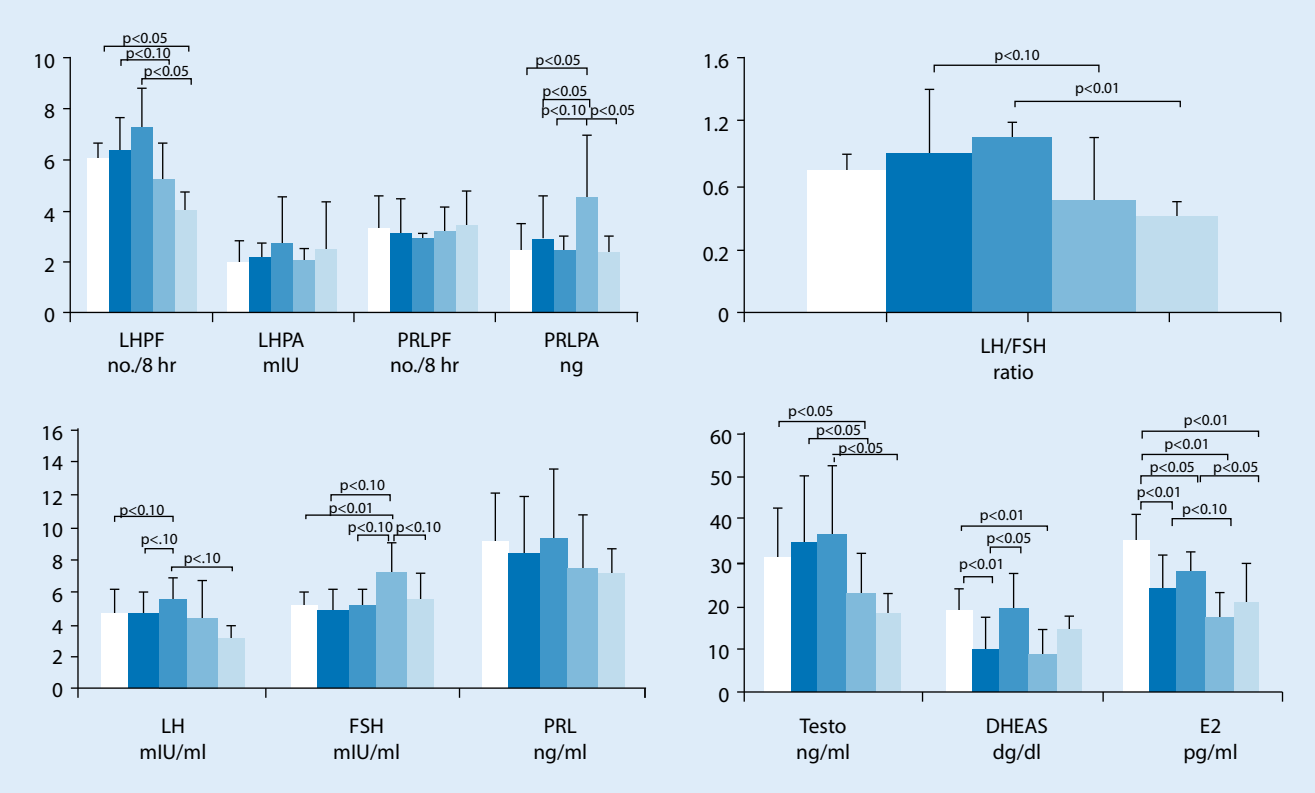

Fig. 1 ▲ Reproductive endocrine data in medicated and unmedicated women with left and right temporolimbic epilepsy (TLE)

cles results in hyperandrogenic chronic anovulation, which is currently the simplest and perhaps the most utilitarian definition of PCOS [20, 22].

Hypothalamic amenorrhea (HA – amenorrhea associated with low gonadotropin and estrogen levels and diminished LH response to gonadotropin-releasing hormone [GnRH] challenge), functional hyperprolactinemia (elevated prolactin levels without identifiable pituitary lesion) and premature menopause (cessation of ovarian function featuring amenorrhea and elevated gonadotropin levels) have also been found to be over-represented in women with epilepsy [2, 7, 18, 23, 24]. In an investigation of 50 consecutive women with clinical and electroencephalographic features of TLE, 28 (56 %) had amenorrhea, oligomenorrhea, or abnormally long or short menstrual cycle intervals [2]. Nineteen of the 28 women with epilepsy and menstrual disorders (68 %, 38 % overall) had readily identifiable reproductive endocrine disorders: PCOS in 10, hypothalamic amenorrhea in 6 (12 %), premature menopause, in this study before 30 years of age, in 2 (4 %), and functional hyperprolactinemia in 1 (2 %). The numbers of women with clinical and endocrine features of PCOS (20 %) and of HA (12 %) were significantly greater than the estimated frequencies (5 % for PCOS and 1.5 % for HA) in the general female population.

The data showed no significant relationship overall between the occurrence of menstrual disorders and the use of AEDs (53 % among users versus 60 % among non-users) and raised the possibility that epilepsy itself may be a factor [2]. PCOS was more common among the untreated (30 %) than the treated (13 %) women with epilepsy. Treatment AEDs were of the enzyme-inducing variety. The lower occurrence of PCOS among women treated with enzyme-inducing AEDs, such as carbamazepine, has also been demonstrated in an independent investigation by Hamed et al. [8]. This is in contradistinction to the notable relationship that has been demonstrated with the enzyme inhibiting AED, valproate [5].

The potential role of the epileptic substrate has been suggested by the finding that among women with unilateral epileptic foci, PCOS is associated with left temporal and right non-temporolimbic foci, whereas HA has been found to be more common with right TLE [25, 26] and by the finding that untreated women with primary generalized epilepsy have higher pulse frequency gonadotropin-releasing hormone secretion than normal controls [27]. Increased pulse frequency or amplitude of gonadotropin-releasing hormone secretion by the hypothalamus results in preferential LH versus FSH secretion by the pituitary [28, 29], which would promote the development of PCOS.

Pathophysiology of reproductive endocrine disorders in women with epilepsy

The brain controls reproductive function primarily through the hypothalamic regulation of pituitary secretion [29]. Regions of the hypothalamus that are involved in the regulation, production, and

secretion of gonadotropin-releasing hormone (GnRH) receive extensive direct connections from the cerebral hemispheres, especially from temporolimbic structures that are commonly involved in epilepsy, and most notably from the amygdala [1, 2]. Significant relationships have been uncovered through which epilepsy may influence the function of this complex neuroendocrine system.

Animal experimental studies have shown that the amygdala can be parceled into cytoarchitectonically distinct functional divisions that exert opposing modulatory influences on pituitary hormone secretion [30, 31], reproductive function [30, 31], and the resting membrane potentials of individual ventromedial hypothalamic neurons [32]. Following amygdaloid seizures, fos, a protein marker for neuronal activation, is increased in the sexually dimorphic regions of the hypothalamus that are involved in reproductive endocrine secretion and reproductive function, i. e., the medial preoptic, ventromedial, and ventral premammillary nuclei, but much less so in other hypothalamic nuclei [33]. Seizures also decrease GnRH fiber staining in the ventromedial hypothalamus [34, 35]. Both of these responses to unilaterally provoked amygdaloid seizures occur in a laterally asymmetric fashion with significantly and substantially greater involvement ipsilaterally than contralaterally to the seizure focus [33, 35]. Preferential ipsilateral involvement is potentially important because there are lateralized biochemical and physiological differences between the left and right sides of the limbic system and also of the hypothalamus. Specifically, anovulatory cycles are more common with right than with left unilateral amygdalectomies [36]. GnRH content in the ventromedial hypothalamus of the female rat has been reported to be 50–100 % greater in the right ventromedial hypothalamus than in the left ventromedial hypothalamus [37, 38]. The left and right vagus nerves exert different modulatory influences on ovarian structure and function [37, 38]. The experimental findings in the female rat are consistent with the notion that disruption of the normal temporolimbic modulation of hypothalamopituitary function may interfere with ovarian hormonal secretion and promote the development of reproductive endocrine disorders [39]. The findings suggest, moreover, that the reproductive neuroendocrine system, like many other brain systems, shows a lateralized asymmetry that may, by virtue of ipsilaterally predominating effects, contribute to the development of distinct reproductive endocrine disorders in association with unilateral left- and right-sided epileptic foci [40].

There are also important clinical findings that indicate that reproductive endocrine function differs between women with epilepsy and normal controls and that the laterality and focality of epilepsy may be important determinants of re-

Abstract · Zusammenfassung

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Disorders of reproduction in patients with epilepsy

Abstract

Disorders of reproduction are unusually common among people with epilepsy. They are generally associated with and may be the consequence of reproductive endocrine disorders. Epilepsy itself and epileptic seizures have been implicated in their pathophysiology.

This review focuses on how temporolimbic dysfunction in epilepsy might disrupt normal neuroendocrine regulation and promote the development of reproductive endocrine disorders. The particular nature of the dysregulation may relate to the laterality and focality of the epilepsy and some hormonal changes may develop in close temporal relation to the occurrence of epileptiform discharges. In women, reproductive endocrine disorders include polycystic ovary syndrome, hypothalamic amenorrhea, functional hyperprolactinemia, and premature menopause. In men, hypogonadism may be hypogonadotropic, hypergonadotropic or related to hyperprolactinemia. The significance of these reproductive endocrine disorders is that they may contribute not only to sexual dysfunction and infertility, but may also have an adverse impact on seizure control.

This review also includes sections on special considerations in the treatment of reproductive endocrine disorders for women and men with epilepsy.

Keywords

Endocrine · Polycystic ovary syndrome · Epilepsy · Reproduction · Hormones

Reproduktionsstörungen bei Patienten mit Epilepsie

Zusammenfassung

Reproduktionsstörungen sind unter Menschen mit Epilepsie ungewöhnlich weit verbreitet. Sie sind allgemein mit reproduktiven endokrinen Störungen verbunden und können auch deren Resultat sein. In ihrer Pathophysiologie spielen die Epilepsie selbst sowie epileptische Anfälle eine Rolle.

Dieser Überblick befasst sich mit der Frage, wie temporolimbische Dysfunktion bei Epilepsie die normale neuroendokrine Regulation stören und die Entwicklung von reproduktiven endokrinen Störungen fördern kann. Die besondere Natur der Dysregulation mag mit der Lateralität und Fokalität der Epilepsie zusammenhängen und manche hormonelle Veränderungen können sich im engen zeitlichen Zusammenhang zum Auftreten von epileptiformen Entladungen entwickeln. Bei Frauen umfassen reproduktive endokrine Störungen das polyzystische Ovar-Syndrom, die hypothalamische Amenorrhoe, die funktionelle Hyperprolaktinämie und die vorzeitige Menopause. Bei Männern kann der Hypogonadismus hypogonadotrop, hypergonadotrop oder durch Hyperprolaktinämie verursacht sein. Die Bedeutung dieser reproduktiven Erkrankungen ist, dass sie nicht nur zu sexueller Dysfunktion und Unfruchtbarkeit führen, sondern auch ungünstige Auswirkungen auf die Anfallsbehandlung haben können.

Der Überblick enthält auch Abschnitte zu speziellen Überlegungen in der Behandlung von reproduktiven endokrinen Störungen bei Frauen und Männern mit Epilepsie.

Schlüsselwörter

Endokrin · Polyzystisches Ovar-Syndrom · Epilepsie · Reproduktion · Hormone

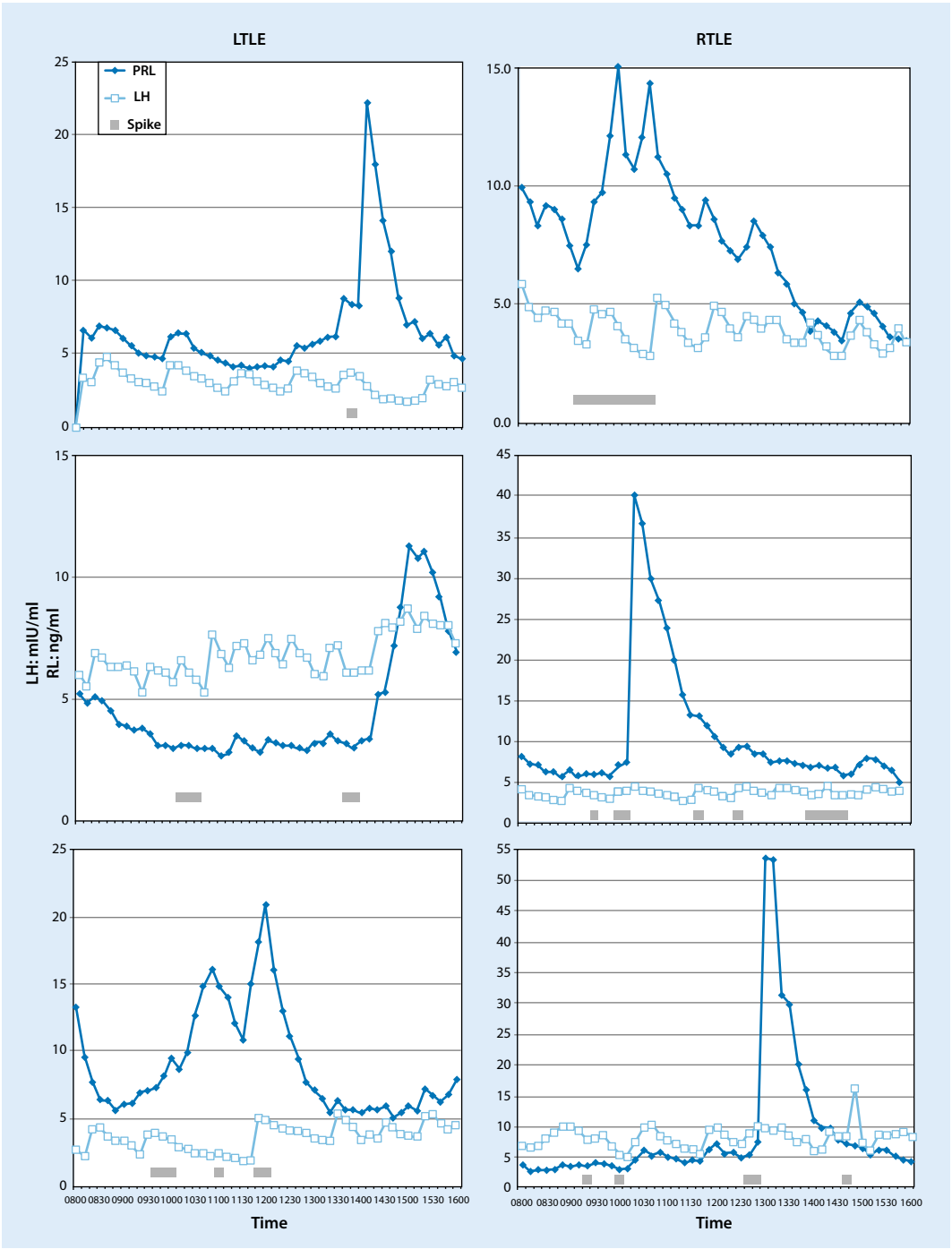

Fig. 2 ◀ Interictal paroxysmal EEG discharges and closely related reproductive endocrine changes in gonadotropin and prolactin secretion in women with left- and right-sided unilateral TLE. Left temporal discharges were often accompanied by abnormal suppression (> 104.3 min without a pulse peak) of LH pulsatility and subsequent abnormal > 27 % elevation in mean baseline LH levels. Right temporal discharges were often followed by abnormally high prolactin pulse peak values and continuation of LH pulsatility

productive endocrine function [7]. Unilateral temporolimbic discharges are associated with laterally differing, consistent, predictable, stochastic directional changes in hormonal secretion at all levels of the reproductive neuroendocrine axis, i. e., hypothalamus, pituitary, and ovary (**Fig. 1**; [7]).

Hypothalamic parameters. Luteinizing hormone pulse frequency (LHPF) was significantly more variable among women with TLE than among controls (6.0 ± 0.7 vs 5.8 ± 1.7; $p < 0.01$). Women with left TLE had higher LHPF than women with right TLE (6.5 ± 1.5 vs 4.9 ± 1.7; $p < 0.01$), regardless of medication use (untreated: 7.2 ± 1.6 vs 4.0 ± 0.8; $p < 0.01$). Luteinizing hormone pulse amplitude (LHPA) was significantly higher among untreated women with TLE than among treated women (3.0 ± 1.4 vs 2.3 ± 0.7; $p = 0.05$) and controls (2.1 ± 0.6; $p < 0.05$) without any significant laterality effect.

Prolactin pulse frequency (PRLPF) showed no significant findings in relation to epilepsy, epilepsy laterality or medication use. Prolactin pulse amplitude

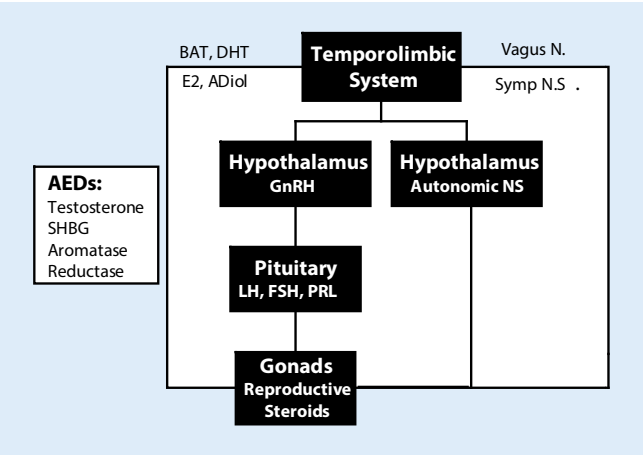

Fig. 3 ▲ Gonadal steroid secretion is regulated by pituitary gonadotropins, luteinizing hormone (LH), and follicle-stimulating hormone (FSH), that are, in turn, regulated by the pulsatile secretion of gonadotropin-releasing hormone (GnRH) by sexually dimorphic reproductive endocrine nuclei in the hypothalamus. The amygdala can be parceled into two cytoarchitectonically distinct functional divisions, corticomedial and basolateral, that exert opposing modulatory influences on the hypothalamic regulation of pituitary secretion. The amygdala also regulates the autonomic (sympathetic – Symp N.S. – and parasympathetic – Vagus) innervation of the testes that likely plays a trophic and an endocrine regulatory function, and receives vagal afferents (dotted line) that have an impact on amygdaloid excitability. Anti-epileptic drugs differentially affect gonadal testosterone biosynthesis, hepatic sex hormone binding globulin (SHBG) production, and aromatization and reduction of testosterone to potent glutamatergic neuroexcitatory (estradiol – E2) and GABAergic neuroinhibitory (androstanediol – ADiol) metabolites that may feed back (dashed line) to modulate temporolimbic neuroexcitability and seizures

(PRLPA) was significantly more variable among women with TLE than among controls (4.6 ± 6.1 vs 3.0 ± 1.5; p < 0.001). Variability was significantly greater among women with right TLE than among women with left TLE (6.7 ± 8.6 vs 3.0 ± 1.8; p < 0.001). PRLPA values were significantly greater for treated women with right TLE (8.1 ± 9.6) than for untreated women with right TLE (2.4 ± 0.7; p < 0.05), in addition to women with LTLE (treated: 2.9 ± 1.7; p < 0.05; untreated: 3.5 ± 2.3; p < 0.10) and controls (3.0 ± 1.5; p < 0.05). LH/FSH was significantly greater for women with left TLE than for women with right TLE (1.1 p ± 0.5 vs 0.65 ± 0.35; p < 0.01), regardless of medication use (untreated: 1.4 ± 0.6 vs 0.58 ± 0.10; p < 0.01).

Pituitary parameters. Luteinizing hormone was more variable among women with TLE than among controls (4.9 ± 2.5 vs 4.7 ± 1.5; p = 0.05). The mean value was higher among untreated women with left TLE (7.1 ± 3.7) than among treated women with LTLE (5.0 ± 1.9; p < 0.10) and controls (4.7 ± 1.5; p < 0.10), and more than twofold greater than the mean value for untreated women with right TLE (3.1 ± 0.9; p = NS). FSH was more variable among women with TLE than among controls (5.9 ± 2.0 vs 5.2 ± 0.9; p = 0.01). FSH was significantly higher for women with right TLE (6.7 ± 2.0) than for women with left TLE (5.3 ± 1.8; p < 0.05). This lateralized difference among women with TLE was statistically significant only among treated women (7.1 ± 2.0 vs 5.4 ± 2.0; p < 0.05). PRL did not show any significant finding in relation to epilepsy, epilepsy laterality or medication use.

Peripheral gland parameters. Testosterone levels were significantly greater for left TLE than for right TLE (35 ± 16 vs 22 ± 9; p < 0.01) as they were for controls (32 ± 11 vs 22 ± 9; p < 0.01). There was no significant finding in relation to medication use. Estradiol levels were significantly greater among controls than women with epilepsy (35 ± 6 vs 22 ± 8; p < 0.001) regardless of medication use (untreated: 25 ± 7; p < 0.01; treated: 21 ± 7; p < 0.01). E2 levels were significantly greater for left TLE than for right TLE (25 ± 7 vs 18 ± 6; p < 0.01) and each was significantly less than controls (35 ± 6; p < 0.01). Lower E2 values with medication use were attributable to the use of enzyme-inducing drugs (E2 for barbiturate, carbamazepine, phenytoin users versus controls = 14.5 + 4.5 vs 35.4 + 6.2; p < 0.001) as opposed to non-enzyme-inducing drugs (E2 for gabapentin, lamotrigine, valproate users versus controls = 28.3 + 9.4 vs 35.4 + 6.2; p = N.S.). Untreated women with TLE had substantially lower E2 levels (24.9 + 7.6) than controls (35.4 + 6.2), albeit without statistical significance (p < 0.20). Dehydroepiandrosterone sulfate (DHEAS) values were significantly greater for controls than for women with TLE (189.2 ± 51.1 vs 110.4 ± 72.7; p < 0.001). DHEAS values were significantly greater for controls (189.2 ± 51.1;p < 0.01) and untreated women with TLE (160.1 ± 65.3; p < 0.01) than for treated women with TLE (93.8 ± 68.2). Lower DHEAS values with medication use were attributable to the use of enzyme-inducing drugs (DHEAS for barbiturate, carbamazepine, phenytoin users versus controls: 49.2 + 37.2 vs 189.2 + 51.1; t test p < 0.001) as opposed to non-enzyme-inducing drugs (DHEAS for gabapentin, lamotrigine, valproate users = 108.5 + 50.7 vs 189.2 + 51.1; t test p = N.S.). Values for enzyme-inducing drug users were significantly lower than for non-enzyme-inducing drug users (49.2 + 37.2 vs 108.5 + 50.7; p < 0.001).

These directional changes are consistent with the finding that different reproductive disorders may develop in relation to left- and right-sided temporolimbic epilepsy. Specifically, left TLE is associated with significantly higher pulse frequencies of GnRH secretion [7]. Higher GnRH pulse frequency, in turn, is associated with higher LH/FSH ratios and higher serum testosterone levels. This combination of neuroendocrine changes

characterizes PCOS and is consistent with the previously suggested association between left unilateral TLE and PCOS. Ten percent to 20 % of women with TLE have been found to have PCOS, in comparison with about 5–6 % in the general population [20]. Right unilateral TLE is associated with lower GnRH pulse frequency, which is in turn associated with decreased LH and estradiol levels [2, 7]. These features are characteristic of HA [2, 7, 18, 25, 26]. Some hormonal changes can show close a temporal relationship with the occurrence of interictal epileptiform discharges and these vary in relation to the laterality of the discharges (**Fig. 2**; [7]). Specifically, the occurrence of abnormal prolactin pulse amplitudes predominantly after right temporolimbic discharges, and the suppression of LH pulsatility with subsequent elevation of LH baseline values after left temporolimbic discharges, raise the possibility that paroxysmal interictal discharges may acutely disrupt normal hypothalamopituitary endocrine function. Menstrual disorders have been found to be significantly more common among women with interictal discharges as well with associated abnormal neuroendocrine regulation [7].

Antiepileptic drugs have substantial and differential effects on reproductive hormone levels [7]. There are notable differences between enzyme-inducing and -non-inducing drugs, with the former being associated with lower serum levels of some ovarian and adrenal steroids: estradiol, testosterone and dehydroepiandrosterone sulfate [7]. There is also considerable evidence to suggest that menstrual disorders, anovulatory cycles, polycystic ovaries and PCOS might be more common among women who take valproate and particularly so when started early during the reproductive years [15, 41]. These findings implicate valproate in the pathophysiology of PCOS.

An alternative and possibly unifying consideration is that PCOS may develop as an interactional effect between AED use and epilepsy [20, 42]. Specifically, there is the possibility that epilepsy may promote PCOS development and that enzyme-inducing AEDs treat not only the epilepsy, but also the PCOS by enzyme induction that increases the synthesis of sex hormone binding globulin and the metabolism of testosterone resulting in lower levels of bioavailable testosterone [20, 42]. In contrast, enzyme-inhibiting drugs, most notably valproate, may retard the aromatization of testosterone to estrogen and potentiate the development of epilepsy-related hyperandrogenism and hence PCOS [20, 42]. Antiseizure medications other than valproate, therefore, may treat hyperandrogenism and thus PCOS, whereas valproate therapy may not. This mechanism, thereby, could contribute to a higher occurrence of PCOS in valproate-treated women with epilepsy. If this were an extant mechanism, then valproate would not be the primary cause of PCOS, yet its selection as treatment may be an important factor.

Special considerations in the treatment of reproductive endocrine disorders in women with epilepsy

The standard treatment for PCOS in the general population is with the use of oral contraceptive pills. The use of contraceptive hormones, however, requires special precautions in women with epilepsy because the results of the Epilepsy Birth Control Registry, a large-scale, community-based survey of more than 1,000 women with epilepsy thus far, finds that the use of hormonal contraception is associated with more reports of seizure increase and decrease than the use of non-hormonal contraception. Overall, in comparison with non-hormonal methods, hormonal contraception had a significantly greater relative risk of both seizure increase (21.0 % vs 3.9 %; RR = 5.39 [95 % CI = 3.77–7.73, $p < 0.0001$]) and seizure decrease (10.3 % vs 5.6 %; RR = 1.85 [95 % CI = 1.30–2.62, $p = 0.0006$]), with seizure increase being substantially higher (RR = 5.39 vs 1.85) [43]. Since insulin resistance is a common feature of PCOS, metformin is another common endocrine treatment of PCOS. This too requires caution because hypoglycemia can trigger seizures.

Reproductive dysfunction in men with epilepsy

Diminished libido or potency occurs in approximately 20 % of MWE as determined by standardized questionnaire survey [4]. Older studies, using mostly structured or unstructured interviews, found higher frequencies ranging from 38 to 71 % [3, 4, 6, 44–49]. Abnormal semen analysis, including decreased sperm count, abnormal morphology or impaired motility, have been reported in upwards of 90 % of MWE [41, 44, 46]. Men with idiopathic epilepsy are only 36 % as likely as male unaffected siblings to ever father a pregnancy [16]. This reduction is associated with localization-related epilepsy, onset of seizures before 20 years of age, and absence of a family history of epilepsy [16]. The effect is mitigated by reduced marital rates. Among married MWE, reproductive disadvantage was confined to those with onset before 10 years of age [16].

Reproductive endocrine dysfunction in men with epilepsy

Hypogonadism refers to diminished gonadal function as determined by low serum testosterone level and/or decreased or abnormal sperm production [6]. It can manifest as diminished sexual interest, potency, fertility, energy, mood, competitive drive, bone and muscle mass, and secondary sexual characteristics. Physical signs include a loss of male escutcheon, gynecomastia, and testicular atrophy. The clinical impression of hypogonadism can be verified by laboratory testing. Testosterone exists in three major forms: tightly bound to sex hormone binding globulin (SHBG, 45–50 %), loosely bound to albumin (50–55 %), and unbound (1–2 %) [6]. The albumin-bound and free portions are available to tissues and, therefore, constitute the clinically important bioavailable portion. Measures of bioavailable testosterone (BAT) suggest that hypogonadism may occur in one third of men with TLE [4]. BAT shows a substantially earlier and greater age-related decline in MWE than in controls [4]. In a sample of men

with localization-related epilepsy, we found that BAT fell below normal control levels in 11 % of men between 20 and 30 years, 27 % between 30 and 40 years, and 89 % between 40 and 50 years of age [4]. Several [4, 47, 49], but not all [50], investigations have found significant relationships between reduced serum BAT measures and sexual dysfunction. MWE may show evidence of sexual dysfunction in the setting of low to normal BAT levels at which men in the general population may not show clinical manifestations [3, 4, 6]. This may constitute an argument against the importance of the BAT level. Alternatively, higher BAT levels may be required for normal sexual function in the setting of the altered brain substrate of TLE.

Pathophysiology of reproductive endocrine disorders in men with epilepsy

The etiology of hypogonadism in addition to reproductive and sexual dysfunction in MWE has been attributed to a number of possible causes. These include psychosocial stress, AEDs, and epilepsy itself [6].

Psychosocial stress associated with epilepsy may play an important role in hypogonadism [51–56]. From a neuroendocrine perspective, stress response involves the activation of the hypothalamo-pituitary-adrenal (HPA) axis [6, 52–56]. Cortisol levels are higher in individuals with epilepsy than in controls, not unlike individuals with depression [53]. Unlike depression, however, diurnal variation is often lost in epilepsy [53]. Factors that increase the activity of the HPA axis interfere with reproductive endocrine secretion and reproductive function [6, 52–56], and may contribute to seizure exacerbation [6]. Stress increases the release of proopiomelanocortin (POMC), the precursor protein that is cleaved to form adrenocorticotropic hormone (ACTH) and endorphin [54, 56], both of which inhibit gonadotropin secretion and reproductive function [52, 56]. ACTH increases cortisol secretion; endorphins increase dehydroepiandrosterone production. Both of these steroids have GABA-negative allosteric modulatory properties that can lower seizure thresholds and increase anxiety [6, 57].

Enzyme-inducing AEDs can directly suppress gonadal testosterone synthesis, increase testosterone binding by the induction of sex hormone binding globulin (SHBG) synthesis, and increase serum estradiol levels in absolute or relative terms [4, 58]. Although constituting only 1 % of the total reproductive steroid, estradiol exerts one half of the negative feedback on the hypothalamopituitary axis [6]. Therefore, a small increase in the estradiol level, presumably as a result of an AED-induced increase in aromatase activity, could have a disproportionately large negative feedback effect on gonadotropin production, thereby contributing to hypogonadism. In a comparison of sexual/reproductive function and reproductive hormone levels among 85 MWE who took various AEDs (25 on carbamazepine [CBZ], 25 on phenytoin [PHT], 25 on lamotrigine [LTG], and 10 untreated for at least 6 months (No AED)] and 25 controls, Herzog et al. [4] found that sexual function scores (S-scores), hormone levels (bioactive testosterone, estradiol), hormone ratios (bioactive testosterone/bioactive estradiol), and gonadal efficiency (bioactive testosterone/luteinizing hormone) were significantly greater in the control and LTG-treated groups than in the CBZ- and PHT-treated groups. Sex hormone binding globulin was significantly higher in the CBZ and PHT groups than in all other groups. Among the significant findings were the following. S-scores were below the control range in 20 % of the MWE, including 32 % on CBZ, 24 % on PHT, 20 % on no AEDs, and 4 % on LTG. Bioactive testosterone was below the control range in 28.2 %, including 48 % on CBZ, 28 % on PHT, 20 % on no AEDs, and 12 % on LTG. Among MWE who had low S-scores, 70.6 % had bioactive testosterone levels below the control range compared with 17.6 % among men with normal S-scores. Among MWE who had abnormally low bioactive testosterone, 50.0 % had low S-scores; among men with normal bioactive testosterone, 8.2 % had low S-scores. Bioactive testosterone decline with age was greater among MWE than among controls and notably greater in the CBZ and PHT groups than in the LTG and untreated groups. Overall, sexual function, bioavailable testosterone levels, and gonadal efficiency in MWE who took LTG were comparable with control and untreated values and significantly greater than with carbamazepine or phenytoin treatment.

The temporolimbic system is one of the most common sites of origin or involvement in adult epilepsy. It also plays an integral role in reproductive endocrine regulation and feedback, and in sexual and reproductive function [1, 3, 6]. Consequently, the development of epileptiform discharges in medial temporal lobe structures may disrupt the hypothalamic regulation of pituitary secretion and hence alter gonadal function and reproductive function (**Fig. 3**; [1, 3, 6]). Animal experimental investigations have shown that focal limbic seizures, in addition to generalized seizures, disrupt the normal gonadal structure, physiology, and serum androgen levels in the male rat [59], and that the induction of seizures in the amygdala, but not in the motor cortex, produces hyposexuality in the male cat [60]. Clinical studies suggest that TLE might be associated with altered gonadotropin response to GnRH infusion regardless of AED use [61]. Mean baseline LH and LH pulse frequency are significantly more variable among MWE than among controls and may show bidirectional changes that relate to EEG laterality [62]. Epileptiform discharges in men are accompanied by acute elevations in prolactin levels [63] and may also be accompanied by acute changes in patterns of LH secretion [6]. Quigg et al. [63] have found that interictally, LH pulse frequency and mean concentration are lower and pulse amplitudes are higher than in controls. Postictally, they found no change in mean pulse frequency, but did detect a significant change in the regularity of pulse occurrence. Clinically, there may be a greater occurrence of sexual dysfunction in men with right, rather than left, lateralized TLE [3, 65, 66]. There is also animal

experimental evidence to suggest that the left and right sides of the hypothalamus might exert different effects on sexual function [67]. Testosterone levels may be lower in men with temporal foci than in those with extratemporal foci [68]. Successful temporal lobectomy in hypogonadal men with intractable seizures has been associated with the normalization of testosterone levels [69] and improvement in sexual interest and function [70]. A remarkably high frequency of abnormal findings in semen analysis has been reported to occur among untreated and among treated MWE [4, 71].

Changes in reproductive steroid concentrations may have an impact on seizure tendency and reproductive function. While estrogen is proconvulsant and progesterone is anticonvulsant in most adult animal models of LRE, the effect of testosterone on experimental seizures appears to be mixed. This may be related to its ready metabolism by aromatase to estradiol, which has neuroexcitatory effects [72], while it can also be metabolized by reductase to dihydrotestosterone and further to androstanediol, a potent GABAergic steroid with antiseizure properties [6, 73].

Special considerations in the treatment of reproductive endocrine disorders in men with epilepsy

Treatment of hypogonadism may involve a transition from potent enzyme-inducing to non- or less-inducing AEDs. A report of 4 cases suggests that switching AED treatment from carbamazepine to oxcarbazepine in MWE might reduce the erectile dysfunction side effects observed with carbamazepine [74].

Testosterone replacement has proven only moderately effective in restoring sexual function, possibly because of its ready metabolism to estrogen, especially in the setting of enzyme-inducing AEDs, one pilot study has reported superior results using combined treatment with testosterone and an aromatase inhibitor that blocked the transformation of testosterone to estradiol [75]. Combined therapy was associated with seizure reduction as well [75].

A prospective, randomized, double-blind trial compared the effects of depotestosterone + another aromatase inhibitor anastrozole (T-A) versus depotestosterone + placebo (T-P) on sexual function, hormone levels, mood, and seizure frequency. Forty men with focal epilepsy, hyposexuality, and hypogonadism were randomized 1:1 to one of two groups (T-A or T-P) for a 3-month treatment trial of depo-testosterone + either anastrozole or matching placebo [76]. Outcomes included both efficacy and safety measures. Normalization of sexual function (S-score) occurred with greater frequency in the T-A (72.2 %) than in the T-P (47.4 %) group, but the difference was not statistically significant. T-A resulted in significantly lower E2 levels and sexual function scores correlated inversely with E2 levels at baseline and during treatment. Beck's Depression Inventory (BDI II) scores improved significantly in both groups and changes in sexual function scores correlated inversely with changes in BDI II score. Changes in seizure frequency correlated with changes in BDI II score. Seizure frequency decreased with both treatments and showed significant correlations with E2 levels. Triglyceride levels increased with T-P and decreased with T-A. The difference in TG changes between the two treatments was significant and correlated with changes in E2 levels. Significant correlations between E2 levels and sexual function scores, in addition to seizure outcomes and triglyceride levels, suggest that further study might be necessary regarding the potential role of anastrozole in the treatment of MWE who have hyposexuality and hypogonadism. By way of important adverse effect considerations, anastrozole is an inhibitor of P450 enzymes and thereby can increase the effective dose of some medications taken concomitantly. It can also result in hepatic dysfunction and increase liver enzymes.

As the treatment of androgen deficiency may generally be more effective for loss of libido than potency, the use of phosphodiesterase inhibitor and prostaglandin warrant consideration in the treatment of MWE who have erectile dysfunction. There are no clinical investigations, however, that specifically address their safety and efficacy in this population. Animal investigations have shown mixed effects in different models, perhaps reflecting the modulatory effects of nitric oxide and cGMP on both excitatory and inhibitory pathways [77, 78]. Of some concern, however, are the reports of a few healthy men who had seizures within a few hours of the use of sildenafil [79] or vardenafil [80] and a 4 % rate of seizure occurrence with alprostadil [81].

The neuromodulatory role of reproductive steroids suggests that a greater understanding of neuroendocrine regulation in MWE might be important, not only for reproductive function, but also for the optimal management of seizure disorders.

Corresponding address

A. G. Herzog, M.D.
Harvard Neuroendocrine Unit, Beth Israel Deaconess Medical Center
330 Brookline Avenue, 02215 Boston, MA, USA
aherzog@bidmc.harvard.edu

Compliance with ethical guidelines

Conflict of interest. A.G. Herzog states that there are no conflicts of interest.

This article does not contain any studies with human participants or animals performed by any of the authors.

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Buchbesprechung

H.G. Loos

Herzberge

Die Geschichte des psychiatrischen Krankenhauses Berlin-Herzberge von 1893 bis 1993

Berlin-Brandenburg: bebra wissenschaft 2014, 256 S., (ISBN 978-3-95410-021-7), geb., 30.00 EUR

In den letzten Jahren beschäftigt sich die Psychiatriehistoriographie zunehmend mit lokalen Aspekten. Diesem Trend folgt auch das Buch von Herbert G. Loos, das die Geschichte des psychiatrischen Krankenhauses Berlin-Herzberge von seiner Gründung im Jahre 1893 bis zur Fusion mit dem heutigen Königin Elisabeth-Krankenhaus Herzberge beleuchtet. Es reiht sich in die Arbeiten von Sabine Hanrath und Wolfgang Rose über die staatliche Anstaltspsychiatrie in Brandenburg nach dem Zweiten Weltkrieg ein. Damit wird das Bemühen deutlich, die Institutionsgeschichte einzelner Krankenhäuser fortzuschreiben, um gleichzeitig nach den Folgen der gesundheitspolitischen Entwicklungen für die Anstaltspsychiatrie zu fragen.

Herbert Loos, der sich schon frühzeitig um die historische Aufarbeitung der Psychiatrie in der DDR verdient gemacht hat, bringt sowohl die fachspezifische als auch medizinhistorische Kompetenz mit. Als Facharzt für Neurologie und Psychiatrie war er fast 30 Jahre an dieser Klinik tätig. Zudem arbeitet er seit über 30 Jahren über medizinhistorische Themen.

Loos hat einen reichhaltigen Quellenfundus aus Primär- und Sekundärquellen zusammengetragen. Die detaillierte Darstellung und die Verwendung zahlreicher Abbildungen aus allen Zeitperioden sprechen den Leser an. Leider verzichtet der Autor auf ein Namens- und Ortsregister sowie auf ein Stichwortverzeichnis. Dies hätte die gezielte Suche erleichtert und Querverweise ermöglicht. Auch ein Literaturverzeichnis fehlt am Ende des Buches.

Loos gliedert sein Buch in fünf Abschnitte. Der Leser erfährt zu Beginn etwas über die Herausbildung von Irrenanstalten, dann über die Entwicklung in Berlin bis zur Eröffnung der Städtischen Irrenanstalt Herzberge. In den folgenden Abschnitten wird die wechselvolle Geschichte des Krankenhauses während der Zeit des Ersten Weltkriegs, der Weimarer Republik bis zur Zeit des Nationalsozialismus dargelegt und mit konkreten Beispielen aus dem Klinikalltag und dem Schicksal einzelner Protagonisten, auch Patienten verknüpft. Damit wird Geschichte lebendig vermittelt. Das letzte und umfangreichste Kapitel beschäftigt sich mit dem Aufbau des Fachkrankenhauses für Neurologie und Psychiatrie nach Kriegsende. Hier kann Loos auf eigene Erfahrungen zurückgreifen. Neben seiner langjährigen Tätigkeit in der Klinik war er auch Vorsitzender einer Kommission, die sich 1990 mit der Frage nach dem Missbrauch in der Ostberliner Psychiatrie beschäftigt hatte. Er blickt kritisch auf das Verhältnis von Psychiatrie und Ministerium für Staatssicherheit im damaligen Ostberliner Fachkrankenhaus. Loos geht zudem auf die Gesamtsituation der Psychiatrie in der DDR und einige Entwicklungen wie die sozialpsychiatrische ein. Eine Berücksichtigung der gerade in den letzten Jahren dazu publizierten Erkenntnisse fehlt weitgehend und hätte geholfen, den einen oder anderen Aspekt treffender einordnen zu können.

Fazit: Das Buch kann allen in der Psychiatrie Tätigen und an der Geschichte des Fachgebietes Interessierten sehr empfohlen werden.

E. Kumbier (Rostock)