Seizure 2000; **9**: 389–393
doi: 10.1053/seiz.2000.0434, available online at http://www.idealibrary.com on IDEAL

The impact of epilepsy surgery on sex hormones and the menstrual cycle in female patients

J. BAUER[†], B. STOFFEL-WAGNER[‡], D. FLÜGEL[†], M. KLUGE[†] & C. E. ELGER[†]

[†]*Department of Epileptology and;* [‡]*Department of Clinical Biochemistry, University of Bonn, Germany*

Correspondence to: Dr J. Bauer, Universitätsklinik für Epileptologie, Sigmund-Freud-str. 25, D-53105 Bonn, Germany. *E-mail*: Juergen.Bauer@meb.uni-bonn.de

We investigated the impact of temporal lobe epilepsy surgery on sex hormones and menstrual cycles. Sixteen female patients with temporal lobe epilepsy were investigated prior to surgery and 3, 6, and 12 months after surgery. The patients received carbamazepine (CBZ) as monotherapy (10 patients) or in combination with other antiepileptic drugs (six patients). Antiepileptic drugs were maintained after surgery. During the 1-year follow-up after surgery eight patients (50%) remained completely free of seizures. In another four patients (25%) only rare disabling seizures occurred. There were no significant differences between pre-surgical and post-surgical serum concentrations of testosterone, free testosterone, prolactin, dehydroepiandrosterone sulfate, growth hormone, cortisol and sex hormone binding globulin. There was, however, a significant increase in serum androstenedione concentration 6 months post-surgically ($P < 0.02$). Documentation of menstrual cycles in addition to laboratory parameters revealed individual post-surgical changes of the menstrual cycle in eight patients. Four patients had a change in menstrual periodicity: two patients with complete seizure control had regular cycles instead of oligomenorrhoea and two patients with incomplete seizure control had oligomenorrhoea instead of regular cycles. These data indicate that at least in some patients with temporal lobe epilepsy surgical treatment influences menstrual periodicity.

Key words: epilepsy; epilepsy surgery; menstrual cycle; reproductive hormones; antiepileptic drugs.

INTRODUCTION

Epileptic discharges from the temporal lobe may have an impact on the release of hormones from the hypothalamic–pituitary axis[1,2]. Not surprisingly, endocrine dysfunction is a common finding in female patients with temporal lobe epilepsy (TLE)[3]. Anovulatory cycles are detected in about one fourth to one third of women with TLE, whereas this is a less common finding in healthy controls (4–8%) and in patients with idiopathic generalized epilepsy (0%)[4–6].

Epilepsy surgery is a well established therapy of chronic focal epilepsy. In successfully treated patients total seizure control is achieved[7]. If epilepsy surgery has an impact on the epileptic disorder even beyond the manifestation of seizures one would expect that an endocrine dysfunction caused by epileptic discharges will normalize following successful surgical treatment. In order to prove this hypothesis we investigated female patients prior to surgery and 3, 6, and 12 months after surgery.

PATIENTS AND METHODS

Patients

All patients were women suffering from chronic focal epilepsy intractable to anticonvulsant drugs. Their age varied between 21 and 42 years (mean 31.6 years). They received carbamazepine (CBZ) as monotherapy or in combination with other anticonvulsants (Table 1). Anticonvulsant medication was maintained following surgery. Seizure type, type of surgery and outcome are listed in Table 1. Clinical as well as laboratory investigations and cranial magnetic resonance imaging excluded endocrine disorders in these patients. Informed consent was obtained from all patients before investigations were carried out.

Medical examination

All patients were medically examined prior to surgery and 3, 6, and 12 months post-surgically.

1059–1311/00/060389 + 05 $35.00/0

Table 1: Seizure type, antiepileptic drugs, type of surgery and outcome of patients.

Pat. No.	Age (y)	Seizure type	AED	Surgery	Outcome
1	42	SPS	CBZ	Left temporo-lateral	1
2	24	SPS, CPS	CBZ, VPA	Left temporo-basal	1
3	31	SPS, CPS	CBZ	Right SAHE	1
4	34	CPS	CBZ	Right 2/3 TL-ectomy	3
5	28	CPS	CBZ	Left temporo-polar	4
6	32	SPS, CPS, TCS	CBZ, LTG	Left SAHE	2
7	34	CPS	CBZ, TGB	Left SAHE	2
8	38	CPS	CBZ	Left SAHE	4
9	28	CPS	CBZ, PB	Right 2/3 TL-ectomy	2
10	35	CPS, TCS	CBZ	Left SAHE	1
11	25	CPS	CBZ	Right SAHE	1
12	35	CPS	CBZ	Right SAHE	1
13	33	CPS	CBZ	Right SAHE	1
14	34	SPS, CPS	CBZ, PB	Left 2/3 TL-ectomy	3
15	33	SPS, CPS	CBZ	Left SAHE	2
16	21	CPS	CBZ, PB	Left fronto-lateral	1

SPS = simple partial seizures; CPS = complex partial seizures; TCS = tonic–clonic seizures; CBZ = carbamazepine; TGB = tiagabine; LTG = lamotrigine; PB = phenobarbitone; VPA = valproate; SAHE = selective amygdalo-hippocampectomy; TL = temporal lobe.

Outcome of surgery was classified in accordance to the proposal by Engel *et al.*[8]: class 1, free of disabling seizures; class 2, rare disabling seizures; class 3, worthwhile improvement; class 4, no worthwhile improvement.

Clinical endocrinological investigations were carried out to exclude the possibility of additional diseases that might affect the endocrine system. Cerebral magnetic resonance imaging (MRI) performed on all patients excluded morphological lesions in the pituitary.

Laboratory investigations

For laboratory investigations (pre-surgical and 3, 6 and 12 months after surgery), venous blood samples were withdrawn between 8 and 10 a.m. after an overnight fast. A heparin-lock venous cannula was placed in a forearm vein and, after a 30-minute rest, 20 ml of blood was withdrawn through the cannula. Serum samples were stored at $-20\,°C$ prior to the assays for circulating hormones and sex hormone binding globulin (SHBG). None of the patients had had a seizure within 12 hours before blood sampling.

Hormone measurement included luteinizing hormone (LH), follicle stimulating hormone (FSH), estradiol (E2), progesterone, testosterone (T), free testosterone (free T), androstenedione, prolactin (PRL), dehydroepiandrosterone sulfate (DHEAS), cortisol, human growth hormone (hGH), and sex hormone-binding globulin (SHBG).

Analyses and assays

Hormones and SHBG were measured by commercial enzyme immunoassays or radioimmunoassays. These methods including sensitivity and quality control data have been described in detail in a recent publication of our group[9].

Definition of the *phases* of the menstrual cycles

Follicular phase was defined as day 1–14 of the cycle with progesterone concentrations below 2.5 ng ml^{-1}. *Luteal phase* was defined as day $15 + x$ of the cycle with progesterone >2.5 ng ml^{-1}. *Anovulation* was defined as day $15 + x$ of the cycle and progesterone <2.5 ng ml^{-1}.

Definition of the *length* of the menstrual cycles: cycle length 26–30 days (regular cycle); cycle length >35 days (oligomenorrhoea).

Statistical methods

Data are expressed as mean $\pm$ standard of mean (SEM). Statistical comparisons were carried out by using the Mann–Whitney U Test. A P value less than 0.05 was considered significant.

RESULTS

During the 1-year follow-up after surgery eight patients (50%) remained completely free of seizures (outcome class 1, Table 1). In another four patients (25%) only rare disabling seizures occurred (outcome class 2, Table 1). Antiepileptic drugs (AEDs) were maintained following surgery. All patients received carbamazepine (CBZ), 10 patients as monotherapy, six patients in combination with other AEDs (Table 1). Prior to surgery the daily dosage of CBZ was 1200–2400 mg day^{-1} (mean 1623 mg day^{-1}) with CBZ

Table 2: Mean pre- and post-surgical serum concentrations (lower and upper range of 95% confidence intervals in brackets) of hormones and binding globulin.

		Testo. [nmol l^{-1}]	f. Testo. [pg ml^{-1}]	SHBG [nmol l^{-1}]	PRL [μg dl^{-1}]	DHEAS [μg dl^{-1}]	Androst. [μg l^{-1}]
Pre-surgical		27.35 (14.8–39.9) $N = 16$	1.38 (0.9–1.8) $N = 16$	94.87 (77.2–112.5) $N = 16$	10.64 (3.6–17.7) $N = 16$	1065.4 (609.5–1521.4) $N = 14$	1.64 (1.2–2.1) $N = 13$
Post-surgical	3 months	35.48 (24.8–46.2) $N = 13$	2.09 (0.6–3.5) $N = 13$	95 (77.7–112.3) $N = 12$	6.74 (0.1–13.4) $N = 13$	1063.5 (371.7–1755.3) $N = 13$	1.90 (1.5–2.3) $N = 12$
	6 months	41.05 (31.5–50.6) $N = 12$	1.44 (1.1–1.8) $N = 12$	99.5 (76.6–122.4) $N = 12$	3.25 (2.2–4.3) $N = 12$	984.6 (479.6–1489.7) $N = 11$	2.63* (2.0–3.3) $N = 12$
	12 months	29.47 (17.0–42.0) $N = 11$	1.24 (0.9–1.5) $N = 12$	99.16 (77.0–121.4) $N = 12$	3.68 (2.7–4.7) $N = 11$	896.54 (276.0–1517.1) $N = 11$	2.31 (1.8–2.8) $N = 11$

Testo. = testosterone; f. Testo. = free testosterone; SHBG = sexual hormone binding globulin; PRL = prolactin; DHEAS = dehydroepiandrosterone sulfate; Androst. = androstenedione; * = $P < 0.02$.

serum concentrations between 5.8–13.8 μg ml^{-1} (mean 9.4 μg ml^{-1}). One year after surgery daily CBZ dosage was between 800–2400 mg day^{-1} (mean 1656 mg day^{-1}) with CBZ serum concentrations between 5.7–14.3 μg ml^{-1} (mean 10μg ml^{-1}).

Post-surgical hormone serum concentrations of T, free T, PRL, DHEAS, hGH, cortisol and SHBG did *not* demonstrate significant differences to pre-surgical concentrations (Table 2). However, androstenedione demonstrated a *significant increase* 6 months after surgery ($P < 0.02$) (Table 2).

A subanalysis of the above listed hormones and of SHBG in only those eight patients who achieved total seizure control (outcome class 1) also did not demonstrate significant differences between post-surgical and pre-surgical hormone concentrations.

Based on the measurement of serum levels of LH, FSH, progesterone and E2 as well as the documentation of cycle length menstrual periodicity was analysed. These data allowed the analysis of post-surgical changes of the menstrual cycles in only eight patients (Table 3). Four of these patients showed a change in menstrual periodicity: in the two patients in whom complete seizure control was achieved (patient numbers 3 and 10, Table 3), regular cycles occurred instead of oligomenorrhoea. In another two patients (numbers 6 and 9, Table 3) where incomplete seizure control had been achieved, oligomenorrhoea occurred instead of regular cycles.

DISCUSSION

Epileptic discharges from the temporal lobes may contribute to endocrine disturbances in female patients with focal epilepsy[3]. An increased rate of anovulatory cycles has been demonstrated in patients with TLE[5,6]. Furthermore, the fertility rate is known to be reduced in women suffering from epilepsy when compared to the general population[10].

The analysis of serum concentrations of sex hormones as well as SHBG prior to surgery and during a 1-year follow-up did not show significant changes in the 16 patients investigated. This finding was independent of the success of epilepsy surgery. There was one exception: serum androstenedione concentrations were significantly increased 6 months after surgery. This was a transient finding no longer existent 12 months after surgery. It is unlikely that the increase of serum androstenedione (a precursor of testosterone) was responsible for the alteration of menstrual cycle regularity[11]. Only an increase of serum testosterone concentrations (which was not the case in our study) might have influenced menstrual cycles[12,13]. An explanation for the increase of serum androstenedione can hardly be given. A stress-related increase of serum androstenedione concentrations has been described 2 hours following surgery[14]. However, this finding is not comparable to an increase 6 months after surgery.

Many changes in serum concentrations of sex hormones and the binding globulin observed in patients with epilepsy have to be attributed to the treatment with enzyme-inducing AEDs. In a previous study[9] on 22 female patients with chronically treated focal epilepsy we studied the possible influence of AED treatment: TSH, DHEAS, follicular LH and luteal phase E2 were significantly lower and PRL and SHBG were significantly higher than in healthy controls. We found increased SHBG levels, decreased LH levels during the follicular phase and decreased E2 levels during the luteal phase[9]. Serum concentrations of T

Table 3: Pre- and post-surgical length of the menstrual cycles and phase of the cycles at the time of investigation.

Pat No.	Pre-surgical		Post-surgical					
			3 months		6 months		12 months	
	mc-phase	mc-length	mc-phase	mc-length	mc-phase	mc-length	mc-phase	mc-length
1	FP	RC	OV	–	FP	–	FP	–
2	LP	RC	FP	–	–	–	–	–
3	Anov	OLM	FP	OLM	FP	RC	FP	–
4	LP	RC	FP	RC	–	–	–	–
5	Anov	OLM	Anov	OLM	Anov	OLM	FP	OLM
6	LP	RC	Anov	OLM	Anov	OLM	Anov	–
7	–	–	Anov	OLM	–	–	–	–
8	FP	RC	FP	RC	FP	RC	FP	RC
9	FP	RC	–	–	–	–	LP	OLM
10	LP	OLM	FP	OLM	FP	RC	FP	RC
11	FP	RC	–	–	FP	–	–	–
12	LP	–	FP	–	–	–	–	–
13	LP	–	LP	–	LP	–	LP	–
14	FP	RC	LP	RC	FP	RC	LP	RC
15	LP	RC	FP	RC	FP	RC	FP	–
16	LP	–	LP	–	LP	–	LP	–

Mc-length = length of menstrual cycle; mc-phase = phase of the menstrual cycle; FP = follicular phase; LP = luteal phase; Anov = anovulation; RC = regular cycle; OLM = oligomenorrhoea.

and free T remained unchanged[9]. Most of these findings were related to AED treatment, especially the decrease in DHEAS and the increase in SHBG, as has also been reported by other investigators[15–18]. Since AED treatment was maintained during the post-surgical follow-up, it is not surprising that serum concentrations of sex hormones and SHBG did not show a significant change during the 12-month follow-ups in the patients reported here.

If epilepsy surgery influences endocrine gonadotrophic dysfunction in female patients, menstrual disorders should normalize following successful surgery. The possible impact of epileptic discharges from the temporal lobes on these endocrine functions has been demonstrated in various studies[1, 6, 19, 20]. The impact of epilepsy which is reported in humans is supplemented by findings in animal models of epilepsy[21, 22]. In experiments on female rats, Edwards *et al.*[22] tested the hypothesis that limbic seizures directly contribute to reproductive dysfunction. Seizures arrested ovarian cyclicity in all amygdala-kindled animals. In our study, documentation of menstrual cycles in addition to hormone measurements allowed the analysis of post-surgical changes of the menstrual cycle in eight patients. Four patients had a change in menstrual periodicity: two patients with complete seizure control had regular cycles instead of oligomenorrhoea and two other patients with incomplete seizure control had oligomenorrhoea instead of regular cycles. One might hypothesize that following successful surgery, interictal epileptic activity will no longer be able to disturb the functioning of the hypothalamic–pituitary axis[23, 24]. Consequently, regular cycles may develop in patients with oligomenorrhoea prior to surgery.

In a *retrospective* analysis of menstrual cycles in 10 patients with temporal lobe surgery by Sosa *et al.*[25], seven patients reported a change in menstrual cycles, i.e. a decrease in duration of menses (one patient), bleeding between periods (one patient) and irregular periods (five patients). The follow-up of these complaints was at least 5 months.

The results of our study in 16 patients indicate that at least in some patients with temporal lobe epilepsy surgical treatment influences menstrual periodicity.

ACKNOWLEDGEMENTS

The authors would like to thank those colleagues from the Department of Neurosurgery, University of Bonn, who did the surgical treatment of epilepsy in the investigated patients. We would also like to thank Professor F. Bidlingmaier, Department of Clinical Biochemistry, University of Bonn, who kindly reviewed the final draft of the manuscript.

REFERENCES

1. Herzog, A. G., Seibel, M. M., Schomer, D. L., Vaitukaitis, J. L. and Geschwind, N. Reproductive disorders in women with partial seizures of temporal lobe origin. *Archives of Neurology* 1986; **43**: 341–346.
2. Bauer, J. Epilepsy and prolactin in adults: a clinical review. *Epilepsy Research* 1996; **24**: 1–7.
3. Herzog, A. G. Disorders of reproduction and fertility. In: *Epilepsy: A Comprehensive Textbook* (Eds J. Engel Jr. and T. A. Pedley). Philadelphia, Lippincott-Raven, 1997: pp. 2013–2019.

4. Pettersson, F., Fries, H. and Nillius, S. J. Epidemiology of secondary amenorrhea. Incidence and prevalence rates. *American Journal of Obstetrics and Gynaecology* 1973; **117**: 80–86.
5. Cummings, L. N., Giudice, L. and Morrell, M. J. Ovulatory function in epilepsy. *Epilepsia* 1995; **36**: 355–359.
6. Bauer, J., Burr, W. and Elger, C. E. Seizure occurrence during ovulatory and anovulatory cycles in patients with temporal lobe epilepsy: a prospective study. *European Journal of Neurology* 1998; **5**: 83–88.
7. Zentner, J., Hufnagel, A., Wolf, H. K. *et al.* Surgical treatment of temporal lobe epilepsy: clinical, radiological, and histopathological findings in 178 patients. *Journal of Neurology, Neurosurgery and Psychiatry* 1995; **58**: 666–673.
8. Engel, J. Jr., Van Ness, P. C., Rasmussen, T. B. and Ojemann, L. M. Outcome with respect to epileptic seizures. In: *Surgical Treatment of the Epilepsies.* 2nd Edition. (Ed. J. Engel Jr.). New York, Raven Press, 1993: pp. 609–621.
9. Stoffel-Wagner, B., Bauer, J., Flügel, D., Brennemann, W., Klingmüller, D. and Elger, C. E. Serum sex hormones are altered in patients with chronic temporal lobe epilepsy receiving anticonvulsant medication. *Epilepsia* 1998; **39**: 1164–1173.
10. Wallace, H., Shorvon, S. and Tallis, R. Age-specific incidence and prevalence rates of treated epilepsy in an unselected population of 2 052 922 and age-specific fertility rates of women with epilepsy. *Lancet* 1998; **352**: 1970–1973.
11. Orth, D. N., Kovacs, W. J. and DeBold, C. R. The adrenal cortex. In: *Williams Textbook of Endocrinology.* 8th Edition. (Eds J. D. Wilson and D. W. Foster). Philadelphia, W.B. Saunders, 1992: pp. 489–619.
12. Carr, B. R. Disorders of the ovary and female reproductive tract. In: *Williams Textbook of Endocrinology.* 8th Edition. (Eds J. D. Wilson and D. W. Foster). Philadelphia, W.B. Saunders, 1992: pp. 733–798.
13. Van Hooff, M. H., Voorhorst, F. J., Kaptein, M. B., Hirasing, R. A., Koppenaal, C. and Schoemaker, J. Insulin, androgen, and gonadotropin concentrations, body mass index, and waist to hip ratio in the first years after menarche in girls with regular menstrual cycles, irregular menstrual cycles, or oligomenorrhea. *Journal of Clinical Endocrinology and Metabolism* 2000; **85**: 1394–1400.
14. Batrinos, M. L., Panitsa-Faflia, C., Koutsoumanis, C., Vourlioti, T. and Koutsilieris, M. Surgical stress induces a marked and sustained increase of adrenal androgen secretion in postmenopausal women. *In Vivo* 1999; **13**: 147–150.
15. Brodie, M. J., Boobis, A. R., Gill, M. and Mashiter, K. Does rifampicin increase serum levels of testosterone and oestradiol by inducing sex hormone binding globulin? *British Journal of Clinical Pharmacology* 1981; **12**: 431–432.
16. Toone, B., Wheeler, M., Nanjee, M., Fenwick, P. and Grant, R. Sex hormones, sexual activity and plasma anticonvulsant levels in male patients. *Journal of Neurology, Neurosurgery and Psychiatry* 1983; **46**: 824–826.
17. Duncan, S., Blacklaw, J., Beastall, G. H. and Brodie, M. J. Sexual function in women with epilepsy. *Epilepsia* 1997; **38**: 1074–1081.
18. Murialdo, G., Galimberti, C. A., Gianelli, M. V. *et al.* Effects of valproate, phenobarbital, and carbamazepine on sex steroid setup in women with epilepsy. *Clinical Neuropharmacology* 1998; **21**: 52–58.
19. Carrillo, A. J. Stimulation of the hippocampus and ovulation in the rat: specific or nonspecific effects. *Neuroendocrinology* 1981; **33**: 223–229.
20. Meo, R., Bilo, L., Nappi, C. *et al.* Derangement of the hypothalamic GnRH pulse generator in women with epilepsy. *Seizure* 1993; **2**: 241–252.
21. Mellanby, J., Dwyer, J., Hawkins, C. A. and Hitchen, C. Effect of experimental limbic epilepsy on the estrous cycle and reproductive success in rats. *Epilepsia* 1993; **34**: 220–227.
22. Edwards, H. E., Burnham, W. M., Ng, M. M., Asa, S. and MacLusky, N. J. Limbic seizures alter reproductive function in the female rat. *Epilepsia* 1999; **40**: 1370–1377.
23. Herzog, A. G. A hypothesis to integrate partial seizures of temporal lobe origin and reproductive endocrine disorders. *Epilepsy Research* 1989; **3**: 151–159.
24. Bauer, J., Stefan, H., Schrell, U. *et al.* Serum prolactin concentrations and epilepsy. A study which compares healthy subjects with a group of patients in pre-surgical evaluation and circadian variations with those related to seizures. *European Archives of Psychiatry and Clinical Neuroscience* 1992; **241**: 365–371.
25. Sosa, V. N., Foldvary, N., Morris, H. and Gidwani, G. Menstrual changes in women with epilepsy after temporal lobe surgery: a retrospective questionnaire (abstract). *Epilepsia* 1997; **38** (Suppl. 8): 231.