

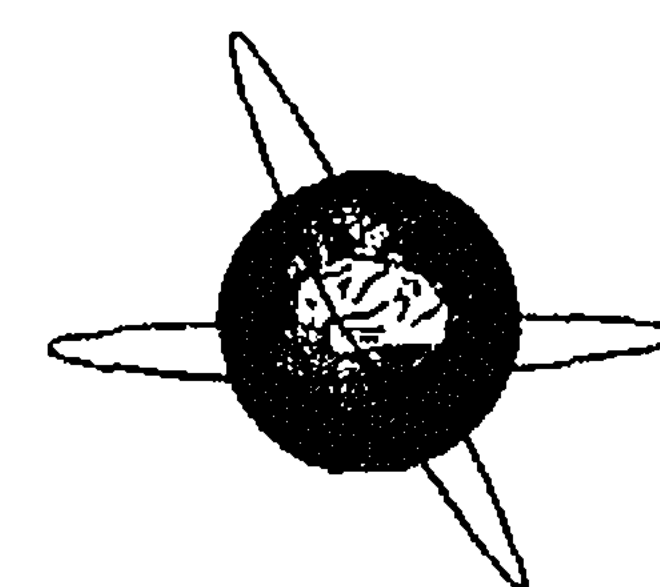
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Periodic fever associated with intermittent rhythmic delta activity: a syndrome of hypothalamic origin?

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Abstract

We report the case of a patient with a 16 year history of periodic (30 day cycle) fever attacks. The infradian cycle, associated clinical features, and the findings of electroencephalogram recorded during two fever attacks suggest a periodic hypothalamic syndrome. © 1997 Elsevier Science Ireland Ltd. All rights reserved

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1. Introduction

In the majority of patients with recurrent fever attacks a diagnostic work-up will usually reveal one of the more common causes such as infections, neoplasms and hypersensitivity diseases (Dinarello and Wolff, 1985; Stok et al., 1989). In some cases of recurrent fever extensive investigation reveals no cause. However, as the duration of recurrent fever increases, the likelihood of an infectious or neoplastic cause decreases. Reevaluation of such patients may ultimately reveal clues that lead to a diagnosis.

2. Case report

A 73 year old man was admitted on several occasions for evaluation of recurrent attacks of fever. His medical history included hemoptysis on two occasions related to a pulmonary arteriovenous malformation which was effectively embolised through a pulmonary artery catheterisation in 1984. Family history was negative for recurrent fever. Apart from slight obesity (body mass index, 28.7 kg/m²), the general physical examination was normal. There were no cushingoid features or cutaneous lesions. Neurological examination revealed an essential tremor of

both hands. Psychiatric consultation revealed a compulsive personality disorder. The attacks had been present for 16 years, recurred at irregular intervals of 30 days, and lasted 10–14 h. A typical episode always began on awakening with feeling cold, malaise, nausea, great fatigue, and logorrhoea. Rectal temperature rose early in each episode and usually reached 40°C around noon. At this stage frontal headache, thirst, and occasionally vomiting occurred. Fever episodes were associated with an elevated heart rate (120–140/min), normal state of consciousness and increase of the tremor. The temperature remained high until late in the afternoon when profuse sweating suddenly occurred, lasting approximately 2 h. With the onset of the sweating the temperature gradually decreased to a normal level. The next day the patient still felt tired and washed out. There were no precipitating factors that could trigger an attack.

3. Results

3.1. Laboratory findings

Repeated complete blood counts and urinalysis gave normal results. During the attacks a leucocytosis was observed, the highest count being $20.3 \times 10^9/l$ with 19% band forms. Multiple blood cultures were negative. During an attack CRP gradually increased from 16 mg/l to 105

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mg/l, and on serum immunoelectrophoresis immunoglobulin D was undetectable. Examination of the cerebrospinal fluid obtained during an attack showed a normal cell count and cytology.

3.2. Radiological studies

Magnetic resonance imaging of the brain showed a slight degree of diffuse atrophy. Computed tomographic scanning of the pituitary gland was normal. Computed tomographic scanning of the abdomen disclosed a tumor (size 3 cm) in the right adrenal. No signs of growth were found during 5 years of follow-up studies. X-rays of chest and sinuses were normal.

3.3. Neurophysiological studies

The EEG recorded during one of the patient's attacks is shown in Fig. 1. Rectal temperature at the time of registration was 39.5°C. The EEG showed intermittent rhythmic delta activity with predominantly frontal localisation and generalised slowing. Reactivity of the alpha rhythm to eye opening was decreased. The response to photic stimulation was decreased in comparison with later EEGs. The next day during a period of normal temperatures, another EEG was recorded, in which no abnormalities were present (Fig. 1). A third EEG was recorded during another less severe fever attack when a rectal temperature of 38.0°C was

noted. This EEG (not illustrated) showed mild generalised slowing, less pronounced than in the first EEG, and no intermittent rhythmic delta activity. Investigation of cardiovascular reflexes showed no abnormalities.

3.4. Endocrinological studies

Basal plasma hormone levels are shown in Table 1. Circulating thyroid hormone levels were well within the normal range. The basal TSH level was 0.71 m μ /l and increased to 4.57 m μ /l after an i.v. injection of 200 μ g TRH (normal incremental level for males >4 m μ g/l). After stimulation with 100 μ g/l LHRH the basal plasma concentration of LH 9.1 μ g/l increased to 18.5 μ g/l (normal incremental level >100%), and the basal level of FSH of 4.7 μ g/l increased to 6.1 μ g/l (normal increase \geq 50%). Testosterone levels were slightly depressed, but a repeated study in 1990 revealed a normal level of 20.1 nmol/l. Plasma prolactin concentration was slightly increased at the 1985 examination, but in 1990 it was normal (4.7 μ g/l). As shown in Table 2 the diurnal plasma cortisol concentrations were abnormal, with definite elevated levels at 2300 h, and an insufficient suppression after orally administered dexamethason (1 mg). However, the diurnal rhythm seemed to be intact during the studies of 1990. Because of the abnormal earlier results of plasma cortisol, further studies of the pituitary-adrenal axis were performed. Administration of metyrapone (6 \times 750 mg

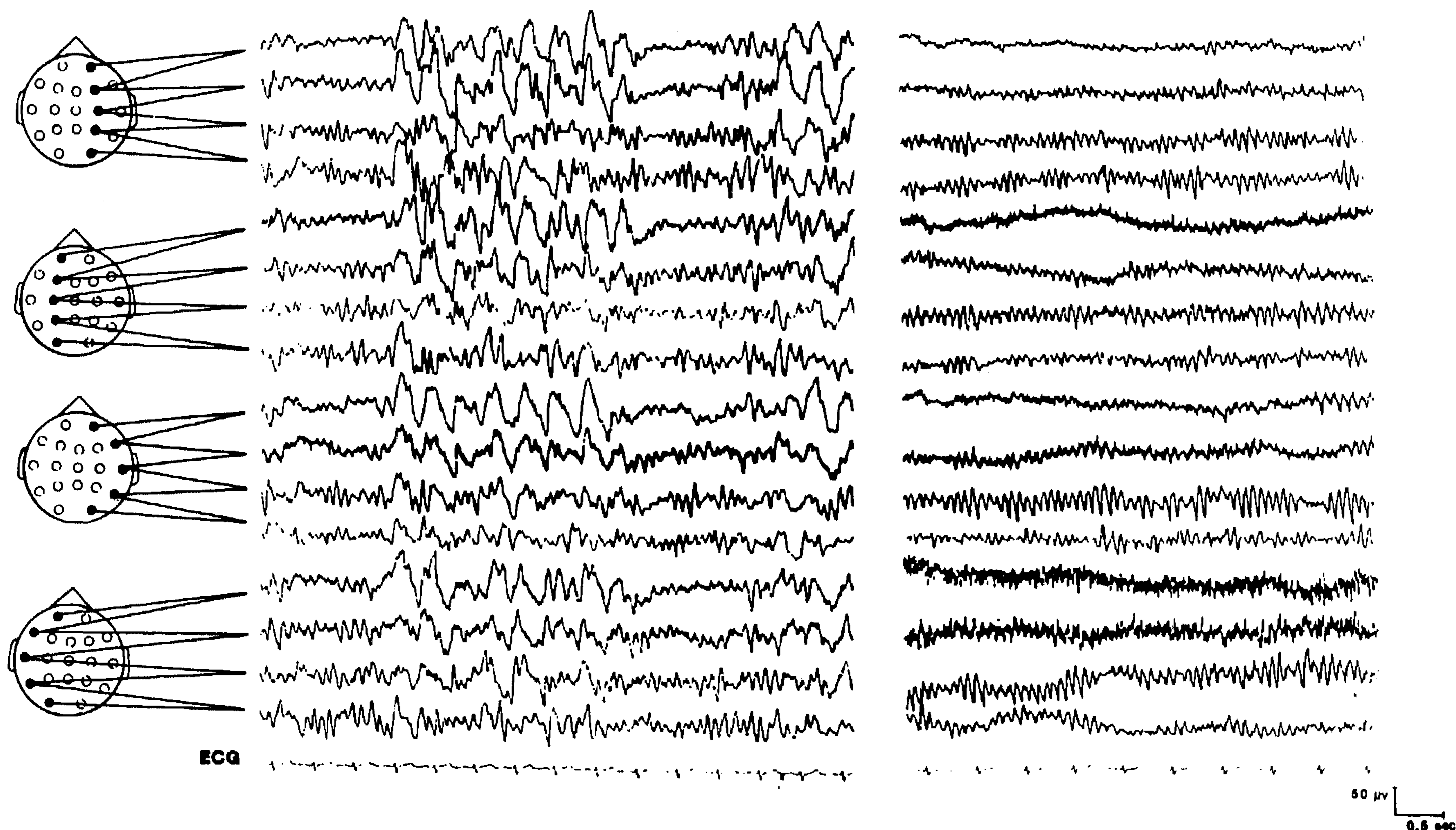


Fig. 1. EEGs recorded during a fever attack (rectal temperature 39.5°C) showing rhythmic delta activity with predominantly frontal localisation, and generalised slowing (left side). No abnormalities on the next day, when the fever had subsided (right side).

Table 1

Plasma hormone levels

Hormone	Plasma concentration	Reference value
Thyroxine (nmol/l)	121	70–160
T3 resin uptake (%)	29.5	25–35
T3 (nmol/l)	2.0	1.1–3.1
IGF-I (nmol/l)	8.3	7.6–17.3
Prolactin (μ g/l)	16.5	2–12
Testosterone (nmol/l)	12.3	12.5–35

orally) resulted in a normal increase of 17 ketogenic steroids from 57.6 μ mol/24 h to 132 μ mol/24 h. A 8 h ACTH infusion (250 μ g cortrosyn) increased cortisol levels from 0.67 μ mol/l to a maximum level of 2.08 Tmol/l. During a 5 day dexamethason suppression test (3 mg/day in 3 divided doses) the urinary excretion of 17 ketogenic steroid decreased from 50 μ mol/24 h to 16.8 μ mol/24 h (normal suppressed level of <18 μ mol). During hospitalisation in 1990 an i.v. hCRF test (100 μ g) increased the plasma cortisol concentration from 0.59 μ mol/l to 0.94 μ mol/l (normal increase >0.20 μ mol/l). In the same period a Liddle test was performed. The urinary cortisol excretion decreased from 357 nmol/24 h to 47 nmol/24 h after 2 days with 2 mg oral dexamethason administration, and to 48 nmol/24 h after another 2 days with 8 mg dexamethason (normal suppressed values <20 nmol/24 h). It must be noted that during the first day of dexamethason administration the patient experienced a major attack of fever. The cortisol excretion during this 24 h period was 381 μ mol (normal levels 70–220 nmol/l) In 1985, during hospitalisation, the excretion of the 17 ketogenic steroids measured during 20 days, revealed a mean daily excretion of 60.8 μ mol/24 h (range 45–81 μ mol/24 h). During this period one minor fever attack occurred (maximum temperature 38.0°C), and the excretory level increased to 104.5 μ mol/24 h. During hospitalised period in 1987 the cortisol excretion varied from 168 to 406 nmol/24 h (mean level of 240 nmol/24 h). A major fever attack (maximum temperature 39.5°C) increased the excretory level to 549 nmol/24 h. The urinary excretion of vanillyl mandelic acid, dopamine, nonadrenaline, adrenaline, and 5 hydroxy-indolacetoacid were normal in seven 24 h urinary specimens.

3.5. Drug studies

Numerous drug trials including colchicine, ketoconazole, domperidone, chlorpromazine, metoclopramide, and haloperidol had no effect on frequency or severity of the fever episodes. During a treatment with carbamazepine (4 months) the frequency of fever attacks increased. The patient had a negative noradrenalin provocation test. During the fever episodes paracetamol had no effect on the fever.

3.6. Chronobiological studies

During a 7 year period our patient registered his fever attacks in a diary. This enabled us to perform a Fourier analysis of the periodic fever interval data. The results of this analysis on data over a period of 2540 days, with 121 attacks of fever, have been published previously, and clearly disclosed a 30 day rhythm (Stok et al., 1989). At our request he kept daily records of his hours of sleep combined with, as frequently as possible, self-measurements of subjective sleep quality and alertness, mood and oral temperature during 1 month. Results showed normal circadian rhythmicity of these variables.

4. Discussion

Chronic recurrent fever of central nervous system (CNS) origin is extremely rare, and only a small number of these patients show cyclic fever attacks (Dinarello). In a review on periodic diseases, periodic fever was delineated as a specific entity (Reinmann, 1951). In view of current knowledge on the heterogeneous spectrum of causes of periodic fever, this approach seems questionable. Recurrent and periodic febrile syndromes have been described under various names, e.g. Reimann's syndrome, Wolff syndrome, hypothalamic attacks and autonomic (diencephalic) epilepsy (Engel and Aring, 1945; Lennox, 1960; Plum and Van Uitert, 1978). In many of these cases information on modern examinations in the evaluation of recurrent fever is lacking.

Fever is defined as a controlled elevation of body temperature resulting from a shift of the hypothalamic temperature setpoint; it is the result of a normally functioning thermoregulatory mechanism (Dinarello et al., 1988). In our patient, the behavioral and physiological responses associated with the rise and defervescence of body temperature suggest that the elevation of body temperature should be classified as fever and not hyperthermia. Fundamental in the pathogenesis of fever is that pyrogens raise the thermoregulatory setpoint by increasing the production of hypothalamic arachidonate metabolites (Dinarello et al., 1988). In our patient no involvement of systemic or CSF cytokine responses could be demonstrated. Additionally,

Table 2

Plasma cortisol levels (μ mol/l) during daytime and after dexamethason administration

Date	Time of day			
	0800 h	1700 h	2300 h	0800 h
May 1985	0.36	0.54	0.34	0.11
June 1985	0.59	0.50	0.35	0.19
July 1986	0.37	0.22	0.17	0.10
June 1987	0.30	0.22	0.15	–
May 1990	0.37	0.10	0.09	–

One mg dexamethason was given orally at 2300 h.

antipyretics had no effect on the fever attacks. A role of hypothalamic arachidonate metabolism in the altered set-point regulation during the fever attacks is therefore unlikely. We postulate that our patient's hypothalamic thermostat is periodically reset at a higher level by an unexplained central mechanism. The start of symptoms on awakening, and the infradian 30 day cycle of fever also suggest involvement of the hypothalamus or cortico-hypothalamic connections (Engel and Aring, 1945; Muller and Wohlfahrt, 1950; Van Hilten et al., 1993).

Interestingly, recurrent fever attacks associated with CNS disorders frequently occur at night or in the early morning (Wolf and Wolf, 1942; Wolff et al., 1964; Van Hilten et al., 1993). Furthermore, the attacks were associated with incessant talking which is a feature of a manic syndrome, but which has also been described in right frontal and temporal lobe and hypothalamic lesions (Alpers, 1937; Kolb, 1981; Bakchine et al., 1989). However, the EEG changes during both attacks were generalised and argue against a localised right hemispheric lesion. The role of previous personality structure in the etiology of recurrent fever attacks appears unsolved. In one case report the presence of obsessive compulsive neurosis was emphasised, and in several patients the episodes of fever occurred in a setting of unusual tension and anxiety (Wolf and Wolf, 1942; Reinmann, 1947; Wolff et al., 1964).

The main EEG abnormality, intermittent rhythmic delta activity, is not specific for any localisation or etiology (Sharbrough, 1987). Its rapid disappearance as the fever subsided and the recurrence of mild abnormalities on a second fever attack of less severity proved a linkage to the fever attacks. Also, EEGs recorded during fever in patients without neurologic or systemic disease capable of involving the CNS, showed no rapidly reversible characteristic EEG findings (Lifshitz et al., 1987). Therefore, it is unlikely that the EEG abnormalities in our patient are a consequence of the high temperature. Some of the cases with thermal epilepsy described by Lennox show a remarkable resemblance to the fever episodes reported in our and other patients (Lennox, 1960). Such attacks recurred regularly at intervals varying between 2 and 4 weeks, lasted on average 2 or 3 days, and were associated with paroxysmal slowing (high voltage 4–5/s waves) in one patient (Lennox, 1960).

It is possible that the adenoma secreted androgenic steroids since the urinary excretion of 11-hydroxy-androsterone was slightly elevated and could not sufficiently be

suppressed by dexamethason administration. It must be stressed that on no occasion our patient had clinical symptoms of elevated levels of plasma cortisol. A causal relationship with the occurrence of the fever attacks seems, therefore, unlikely, and in this respect, our patient differs from a case described previously (Wolff et al., 1964).

References

- Alpers, B.J. Relation of the hypothalamus to disorders of personality. *Arch. Neurol.*, 1937, 38: 291–303.
- Bakchine, S., Lacomblez, L., Benoit, N., Parisot, F., Chaine, F. and Lhermitte, F. Maniclike state after bilateral orbitofrontal and right temporoparietal injury: efficacy of clonidine. *Neurology*, 1989, 39: 777–781.
- Dinareello, C.A. and Wolff, S.M. Fever of unknown origin. In: G.L. Mandell, R.G. Douglas and J.E. Bennet (Eds.), *Principles and Practice of Infectious Diseases*, 2nd edn. Wiley, New York, 1985, pp. 339–347.
- Dinareello, C.A., Cannon, J.G. and Wolff, S.M. New concepts of the pathogenesis of fever. *Rev. Infect. Dis.*, 1988, 10: 168–190.
- Engel, G.L. and Aring, C.D. Hypothalamic attacks with thalamic lesion. I. Physiologic and psychologic considerations. *Arch. Neurol.*, 1945, 54: 37–50.
- Kolb, B. Affective behavior in patients with local cortical excisions: role of lesion site and side. *Science*, 1981; 214: 89–91.
- Lennox, W.G. Thermal epilepsy. In: W.G. Lennox (Ed.), *Epilepsy and Related Disorders*. Little Brown, Boston, 1960, p. 332.
- Lifshitz, A., Lopez, M., Florelli, S., Medina, E., Osuna, G. and Halabe, J. The Electroencephalogram in adult patients with fever. *Clin. Electroencephalogr.*, 1987, 18: 85–88.
- Muller, R. and Wohlfahrt, G. Craniopharyngiomas. *Acta Med. Scand.*, 1950, 138: 121–138.
- Plum, F. and Van Uitert, R. Neuroendocrine diseases and disorders of the hypothalamus. In: S. Reichlin, R.J. Baldessarini and J.B. Martin (Eds.), *The Hypothalamus*. Raven Press, New York, 1978, pp. 434–437.
- Reinmann, H.A. Regularly periodic fever of eleven years duration. *Acta Med. Scand. (Hilding Besglund Suppl.)*, 1947, 196: 666–673.
- Reinmann, H.A. Periodic disease. *Medicine*, 1951, 30: 219–245.
- Sharbrough, F.W. Nonspecific abnormal EEG patterns. In: E. Niedermeyer and F.H. Lopes da Silva (Eds.), *Electroencephalography*. Urban and Schwarzenberg, Baltimore, 1987, pp. 163–181.
- Stok, C.J., Van der Meer, J.W.M. and Nieuwenhuijzen Kruseman, A.C. Computer analysis of fever interval data. *Eur. J. Clin. Invest.*, 1989, 19(2): 154–158.
- Van Hilten, J.J., de Bakker, H.M., de Beer, F.C. and Roos, R.A.C. Periodic fever: an unusual manifestation of a recurrent Rathke's cleft cyst. *J. Neurol. Neurosurg. Psychiatry*, 1993, 53: 533.
- Wolf, S. and Wolf, H.G. Intermittent fever of unknown origin: recurrent fever and benign outcome in a patient with migraine and notes of 'neurogenic fever'. *Arch. Intern. Med.*, 1942, 70: 293–302.
- Wolff, S.M., Adler, R.C., Buskirk, E.R. and Thompson, R.H. A syndrome periodic hypothalamic discharge. *Am. J. Med.*, 1964, 36: 956–967.