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CASE REPORT

Cyclical Cushing's disease and its successful control under sodium valproate

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ABSTRACT. Several subgroups of Cushing's disease were recently described (anterior or intermediate lobe origin, hyper-or hypo-pulsatility of cortisol, presence or absence of response after GRH or TRH, cyclical Cushing's disease). We present here a detailed case report on a patient suffering from Cushing's disease whose endocrine functions were extensively investigated. Treatment with bromocriptine, as well as subsequent transsphenoidal surgery, were followed by rapid but transient reversal of symptoms. When clinical manifestations reoccurred, daily measurements of free urinary cortisol revealed a cyclic pattern of cortisol hyperexcretion. A study of ultradian rhythm revealed hyperpulsatility of cortisol secretion. More interestingly, a treatment with sodium valproate, a drug known to inhibit CRH production, was followed by a rapid and longstanding normalization of clinical and biological data for 2 years. Based on these data, and on information from the literature, the present case of Cushing's disease exhibits characteristics suggesting a possible hypothalamic origin.

INTRODUCTION

Cushing's disease may be due to various etiologies and can be expressed through different modes of steriod hypersecretion. Recently Lamberts et al. (1) described two distinct origins for ACTH secreting pituitary adenomas: those originating from the anterior lobe of the pituitary and those derived from cells of the intermediate lobe. The adenomas located in the anterior part of the pituitary can be easily removed by transsphenoidal surgery whereas those originating from the intermediate lobe, are not easily cured by selective adenomectomy because of the multiplicity of microadenomas or the presence of hyperplastic cell clusters. These two groups could be differentiated according to responses to various dynamic tests. Indeed, dopaminergic agonists induced suppression of ACTH and consequently cortisol in patients with "intermediate lobe Cushing's disease". This hypothesis was however not confirmed afterwards.

Studying cortisol pulsatility in Cushing's disease, Van Cauter and Refetoff (2) disclosed two subtypes of episodic cortisol secretion: a hyperpulsatile group, with peaks normal in number but of excessive height, and a hypopulsatile group with spikes of small amplitude. It appeared that surgical treatment was less successful in the hyperpulsatile group. These authors suggested that the hyperpulsatility of cortisol in certain cases of Cushing's disease may result from a hypothalamic origin.

On the other hand, cyclical Cushing's disease were recently described (3-5). The pattern varied from short-range fluctuations (a few days) to long range fluctuations (several months). The physiopathology of this entity remains unclear.

We describe here a patient with cyclical Cushing's disease. This case was extensively investigated and could be compared to the groups previously described (hyperpulsatility, transient improvement with bromocriptine, absence of surgical cure). Furthermore, treatment with sodium valproate (a drug known to inhibit CRH secretion) resulted in total

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remission persisting during two years of treatment. These data can suggest a hypothalamic origin for the present case of cyclical Cushing's disease.

CASE REPORT

A 17-year-old man was referred to our hospital with the diagnosis of Cushing's disease. He had been initially treated for psychiatric disturbances during three years without success. When purple striae appeared the diagnosis of Cushing's syndrome was proposed and confirmed by testing. At that time (age : 16 years) blood pressure was elevated (160/110 mm Hg) and body weight was in excess (85 kg for 180 cm). The obesity was mainly truncular and buffalo-neck was present. Treatment with bromocriptine at a dose of 5 mg daily (Parlodel^{R}, Sandoz) was prescribed. It was followed by a rapid reversal of some symptoms. After ten days, blood pressure normalized (120-80 mm Hg) and purple stries turned white. Furthermore the psychiatric status was improved. After 6 weeks, a relapse was observed. No adenoma could be demonstrated by sellar X-ray tomography, computerized tomoscan and nuclear magnetic resonance. A transsphenoidal approach of the pituitary was nevertheless decided, in order to resect a possible small microadenoma. At surgery, a white tissue tentatively identified as the adenoma was resected. In the early postoperative period, clinical data normalized. Psychiatric symptoms quickly improved. A transient substitutive treatment by cortisol was given. Five weeks after surgery, the clinical manifestations reoccurred discretely despite withdrawal of cortisol therapy. Control of plasma cortisol concentration and cortisol excretion realized on two separate days showed normal results. The persistence of cyclical psychiatric disturbances as well as the reappearence of purple striaes, led us to suspect an episodic variety of Cushing's disease.

Daily measurements of free urinary cortisol were consequently undertaken during 2 months. After demonstration of a cyclical pattern, the patient was treated with sodium valproate (Depakene^{R}), 1200 mg/day. This treatment was found efficient in the correction of both the clinical picture and the biological parameters. For the first time, the patient obtained very good school ratings. After two years, treatment was withdrawn for 20 days. Free urinary cortisol excretion increased while clinical signs reappeared. Blood pressure became elevated (170-110 mm Hg). The treatment was reinstored thereafter with quick normalization of all clinical signs including blood pressure as well as of all biological data.

METHODS

Endocrine studies

The endocrine functions under pituitary control were studied by determination of basal hormone concentrations as well as by following dynamic tests: LH and FSH but also ACTH and cortisol responses were measured after a 50 μg iv bolus of GRH; TSH, PRL, ACTH and cortisol were measured after a 200 μg iv bolus of TRH; GH response to insulin-induced hypoglycemia was studied after 0.1 U/kg iv; an oral glucose tolerance test (OGTT) was performed with sampling for glucose and insulin every 30 min for 6 h; a bromocriptine test (5 mg) was performed with sampling for PRL, ACTH and cortisol during 8 hours; ACTH and cortisol were measured during 120 min after a 50 μg iv bolus of CRH; the dexamethasone test was realized as follows: 0.5 mg was given orally every 6 h during 2 days, and on a third day, the dose was brought to 2 mg every 6 h. Cortisol blood level as well as 24-hour cortisol excretion were measured daily. Cortisol circadian rhythm was studied by sampling every 6 hours before operation. The pulsatile pattern of serum cortisol secretion was studied during sampling every 15 min for 12 h (and every 60 min during the night) under treatment with sodium valproate and 10 days after stopping the treatment. Study of infradian cortisol rhythm: the volume of all 24 h urine collections was measured and aliquots were stored at -20 C until measurements.

Venous catheterization of both inferior petrosal sinuses was accomplished through a percutaneous bilateral femoral approach. Blood was withdrawn simultaneously from both catheters and a peripheral vein for measurements of ACTH concentration in basal condition and after a 50 μg iv bolus dose of CRH.

Hormone assays

The concentrations of all hormones were measured by RIA using commercial kits. For pulsatile analysis and circadian rhythms of cortisol secretion, a specific and precise RIA was developed in our laboratory. The intraassay coefficient of variation was between 5.0 and 9.0% (80-20% B/Bo) corresponding to doses of 44.1 and 844.5 nmol/l, respectively. Serum CRH levels were kindly measured by Doctor K. von Werder (Munich) (6).

Plasma ACTH concentrations were measured using a RIA developed in our university by Dr. Demey: 200 µl of plasma sample were incubated overnight at 4 C with 100 µl of anti-ACTH antiserum (working dilution = 1: 120,000) from rabbit immunization with ACTH (1-24) coupled to BSA, and with ^{125}I-ACTH (10,000 cpm, ICN Biomedicals INC, Carson, USA). Nonspecific binding was applied for standard curve and for each plasma sample. Bound/free separation was achieved by double antibody method and a centrifugation at 3,000 x *g* for 20 min. The radioactivity of the pellets was determined. RIA characteristics are as follows: intraassay coefficient of variation = < 8% in the range of 20-80% B/Bo; interassay coefficient of variation = 12%; sentitivity = 2.7 pmol/l.

Analysis of data

Significant cortisol peaks were identified with the PULSAR program (7) in connection with MLAB system (8) running on Digital DEC-20 computer. This method has previously been described (9). Consecutive values of free urinary cortisol were studied using Fourier analysis.

Immunocytochemistry

The peroxidase-antiperoxidase immunocytochemical method was applied to pituitary tissue slices as previously described (10), using antisera specific to ACTH, LH, FSH, TSH, GH and PRL.

RESULTS

Preoperative data

No pituitary insufficiency was recognized (Table 1). It should be noted that a paradoxical release of ACTH and cortisol was observed with GnRH but not with TRH. Repeated measurements of free urinary cortisol showed values ranging between 483 and 1035 nmol/24 h.

Surgical cure and immunohistochemical analysis

The transsphenoidal approach revealed no typical adenoma. A tissue with a white aspect, 6 mm in diameter, tentatively identified as abnormal was removed.

Unfortunately, very few tissue was available for microscopic analysis. Islets of ACTH-positive cells were recognized by immunohistochemistry among other cell types of the anterior pituitary.

Postoperative study

Two months after surgery serum cortisol levels measured at 08:00 and 20:00 h were normal.

Table 1 - *Preoperative data.*

Daily rhythm	08:00	12:00	16:00	20:00	02:00	Clock time
ACTH (pmol/l)	28.0	4.7	13.3	9.5	25.0	
Cortisol (nmol/l)	824	523	451	439	602	
Bromocriptine	0	2	4	6	8	h
ACTH (pmol/l)	39.7	20.2	15.7	8.4	13.8	
Cortisol (nmol/l)	462	467	289	205	252	
LHRH	0	15	30	45	90	minutes
ACTH (pmol/l)	-	83.3	-	15.8	-	
Cortisol (nmol/l)	615	903	977	971	723	
OGTT	0	30	60	120	180	minutes
Glycemia (g/l)	0.93	1.67	1.52	1.34	1.26	
Insulin (µU/ml)	32	298	224	216	138	
CRH	0	30	60	90	120	minutes
ACTH (pmol/l)	24.2	34.0	42.4	13.1	11.7	
Cortisol (nmol/l)	222	784	677	559	500	
Dexamethasone		0.5 mg x 4 (2 days)		2 mg x 4 (1 day)		
ACTH (pmol/l)				14.0		
Cortisol (nmol/l)		32		36		

Daily measurements of free urinary cortisol (Fig. 1a) revealed a cyclic pattern of cortisol excretion, characterized by a first rhythm (1 peak/± 6 days) of hyperexcretion superimposed on long trends of cortisol excretion ranging from normal to highly pathological values.

Additionally Fourier analysis revealed cycles with period lasting 2.4, 5.8, 8 and 9 days. The peaks had a greater amplitude (190%) than the mean amplitude of background. Under sodium valproate, a rapid fall to within normal values was observed but with persistence of rhythmic excretion (Fig. 1 b). Indeed all the periods between 2.4 and 9 days disappeared but a significant period of 30 days emerged with a peak amplitude at 350% from the mean background amplitude.

After two years of treatment, withdrawal of sodium valproate resulted in a rapid elevation of cortisol excretion which normalized after reinstoration of the treatment (Fig. 1c).

The study of cortisol pulsatility without treatment revealed 10 peaks (amplitude 246.7 ± 129.7 nmol/l) (Fig. 2a). Under sodium valproate, 8 peaks (amplitude 184.9 ± 138.0 nmol/l) were recorded (Fig. 2b). Peripheral CRH levels (34 pg/ml) were within the normal limits (< 50 pg/ml). Bilateral simultaneous catheterization and sampling of the inferior petrosal sinus did not cause any complication. In basal condition, ACTH levels were similar at both sides, but a clear asymmetry was evidenced after CRH injection (Table 2).

DISCUSSION

Classically, Cushing's disease was considered to originate from the anterior pituitary lobe. However, with the support of recent studies, the existence of several subgroups of Cushing's disease became more obvious (see Introduction). The physiopathological signifcance of these observations remains nevertheless unclear. Indeed, the studies were only based on a few characteristics of Cushing's disease and the parameters chosen by the authors most often varied.

The treatment of our patient with bromocriptine resulted in a total but transient remission of clinical and of biological signs. The partial hypophysectomy also resulted in an apparent transient recovery of clinical and biological signs, suggesting that some ACTH cells were resected but also that the underlying pathological mechanisms remained basically unchanged. According to these data, the patient could be compared to the group qualified by Lamberts et al. (1) as originating from the intermediate lobe but with a better response to dexamethasone

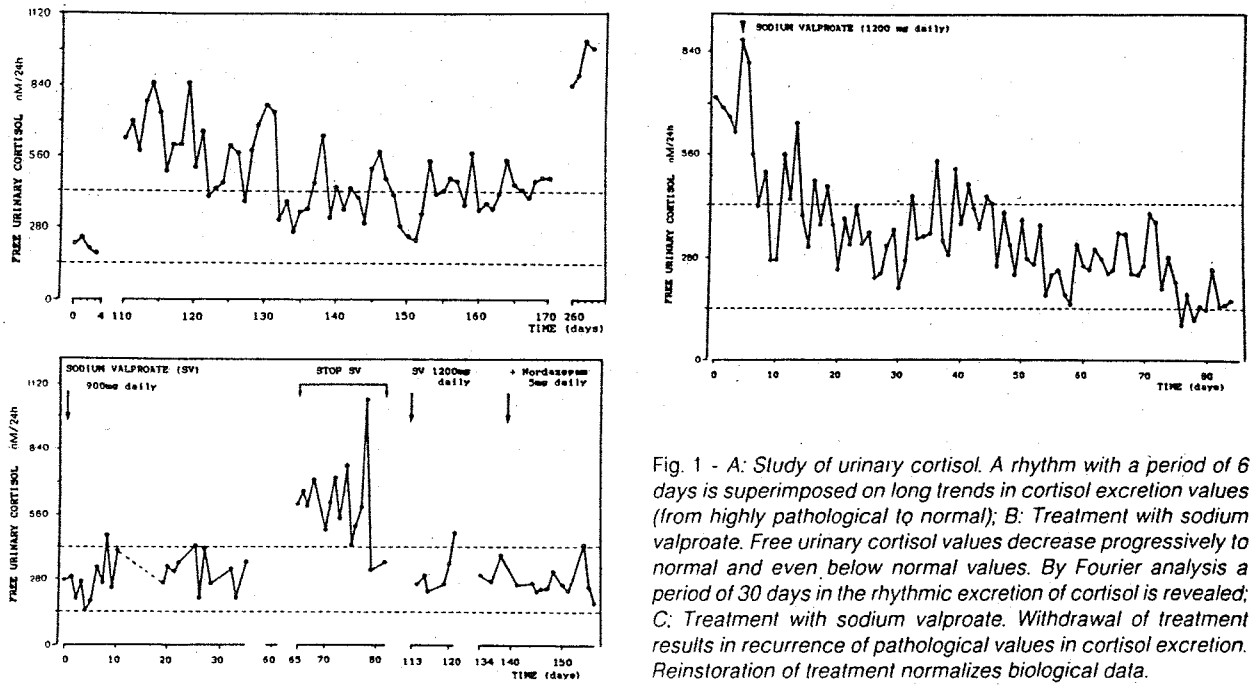

Fig. 1 - *A: Study of urinary cortisol. A rhythm with a period of 6 days is superimposed on long trends in cortisol excretion values (from highly pathological to normal); B: Treatment with sodium valproate. Free urinary cortisol values decrease progressively to normal and even below normal values. By Fourier analysis a period of 30 days in the rhythmic excretion of cortisol is revealed; C: Treatment with sodium valproate. Withdrawal of treatment results in recurrence of pathological values in cortisol excretion. Reinstoration of treatment normalizes biological data.*

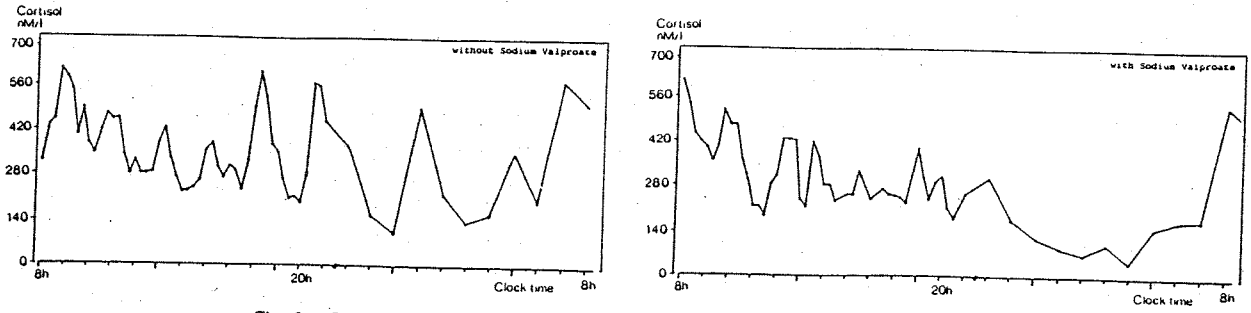

Fig. 2 - *Cortisol pulsatility without (A) and with (B) sodium valproate treatment.*

in our case. After GnRH, an ACTH and cortisol response was observed like in the group with a lower cure rate at surgery described by Pieters et al. (11).

After the operation, it was necessary to repeat measurements of free urinary cortisol to establish biologically the reoccurrence of the disease. It revealed the cyclical patterns of cortisol excretion. This has seldom been described.

Indeed, very few case reports of cyclical Cushing's disease had been published (4, 12-17) until Atkinson et al. (5) described a series of five such cases out of 14 consecutive patients suffering from Cushing's disease.

That study would signify that provided appropriate investigations are conducted, a cyclical pattern of cortisol (and ACTH) secretion would be more frequently diagnosed. The physiological significance of that mode of secretion has to be confirmed. Indeed, Halberg (18) has shown cycles of steroid production in normal individuals, so that the cycles observed in some Cushing's disease could be a pathological exaggeration of cyclical variations found in the normal population. The cycles observed in our case could be compared to those observed by Atkinson et al. with nadirs within normal range.

This explains the difficulties encountered in establishing the diagnosis. Cortisol pulsatility pattern could be compared to the one described by Van Cauter and Refetoff for the "hyperpulsatile" group of Cushing's disease (2). The central (hypothalamic or pituitary) origin in our case was ascertained by the results of the catheterism (which proved the pituitary origin of ACTH) and by measurements of peripheral CRH levels (which excluded the possibility of a pituitary stimulation by paraneoplastic tissue secreting CRH).

A strong argument for the hypothalamic origin of Cushing's disease in the present case is, in our view, the spectacular and sustained response to sodium valproate treatment. This was previously demonstrated in cases of Nelson's syndrome (19, 20) but to our knowledge, such a response has been described in only three cases of Cushing's disease (21-24), two of them being attributed to an ACTH-producing tumor of the intermediate lobe (21, 22). This medication used for therapy of epilepsy is known to provoke an increase in gamma-amino-butyric-acid (GABA) level which in turn inhibits CRH secretion (25).

Interestingly, in contrast to other drugs such as bromocriptine and cyproheptadine, sodium valpro-

Table 2 - *Selective catheterization of the inferior petrosal sinus for determination of plasma ACTH concentration during CRH test.*

Time (min)	0	10	20	30	40
ACTH (pmol/l)					
a	8.7	118.0	52.8	52.4	69.0
b	6.7	53.9	30.2	16.4	27.6
c	7.5	5.6	6.4	7.3	9.1

a: Right inferior petrosal sinus.

b: Left inferior petrosal sinus.

c: Right forearm.

ate do not inhibit the ACTH secretion of pituitary cells in culture (19, 26). Nevertheless, it has been shown that sodium valproate inhibits the mitotic indices of neuroblastoma and glioma cells *in vitro* (27). Nussey et al. (28) also suggested that valproate may be a useful medication in the treatment of some patients with Cushing's disease as it may have an action both upon the hypothalamus and the periphery. An antimitotic effect of sodium valproate on pituitary corticotropic cells has not been demonstrated but cannot be ruled out, although the rapidity of relapse after interruption of the therapy, as well as the effect on the pulsatility, are not consistent with that hypothesis. In our case, the efficiency of that medication cannot be denied since, after two years of successful treatment, withdrawal of the drug for one month induced a rapid relapse in biological and clinical symptomatology.

In conclusion, our data bring new arguments for a hypothalamic disturbancy in the etiology of some cases of Cushing's disease, and insist on methodological aspects necessary for their diagnosis. Furthermore, our success in using sodium valproate to control the disease brings hope for a medical management of such cases.

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