

## CLINICAL STUDY

# Hypothalamic–pituitary insufficiency following infectious diseases of the central nervous system

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## Abstract

**Objective:** Hypothalamic–pituitary insufficiency may have diverse causes. The aim of this study was to determine the incidence of hypothalamic–pituitary insufficiency in patients with previous infectious diseases of the central nervous system (CNS) of different etiologies and mild-to-moderate clinical course.

**Design:** Patient series. Basal and stimulated (insulin tolerance test) pituitary function testing was performed in 19 patients with previous neuroborreliosis, encephalitis, or meningitis following an interval of between 10 and 56 months (mean  $26.1 \pm 13.1$  months) after the acute event.

**Results:** Four patients (21%; two males, two females) showed an isolated corticotrophic insufficiency (peak cortisol  $< 181.25$   $\mu\text{g/l}$  during the insulin tolerance test). Two patients (11%, males) showed borderline gonadotropic insufficiency (basal testosterone between 2.4 and 3.0  $\mu\text{g/l}$ ). No patient had somatotrophic or thyrotrophic insufficiency or evidence for diabetes insipidus; all had prolactin concentrations within the reference range.

**Conclusions:** Hypothalamic–pituitary dysfunction and especially isolated corticotrophic insufficiency may develop in a relevant proportion of patients after infectious diseases of the CNS.

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## Introduction

Hypothalamic–pituitary insufficiency may have diverse causes: the most common ones being pituitary adenoma, craniopharyngeoma, Sheehan's syndrome, lymphocytic hypophysitis, irradiation, or surgery (1). Despite numerous case reports, the incidence of hypothalamic–pituitary dysfunction following traumatic brain injury (TBI) and subarachnoid hemorrhage (SAH) has been underestimated for decades. In 1986, Edwards & Clark reported 6 own and 47 reviewed cases of post-traumatic hypopituitarism (2). Furthermore, in the year 2000, Benveniste *et al.* reviewed 314 cases, including 15 own patients (3). The endocrine dysfunctions reached from panhypopituitarism to various partial deficiencies and were sometimes transient. Hyperprolactinemia was reported in the majority of cases; diabetes insipidus occurred in up to 50% of the patients. A delay in diagnosis of months to years was common (2, 3). Since then, several studies evaluating the rate and risk factors of hypothalamic–pituitary dysfunction after TBI and SAH have been conducted (4–10).

Infectious diseases of the central nervous system (CNS) may also affect the hypothalamus and/or the pituitary, although this has not been reported very often and not yet been studied systematically. In most of the

early case reports, the deficient hormone secretion has been caused by tuberculous meningitis (11–13). There are, however, reports to show that other infectious agents may also cause hypothalamic–pituitary dysfunction (14–19). Therefore, the aim of the present investigation was to determine the incidence of hypothalamic–pituitary insufficiency in patients with previous infectious diseases of the CNS of different etiologies and mild-to-moderate clinical course. To address this issue, patients underwent basal and stimulated (insulin tolerance test) pituitary function testing following an interval of at least 6 months after the acute event.

## Subjects and methods

### *Patients and study visits*

The study was conducted according to the Declaration of Helsinki, and the study protocol was reviewed and approved by the local ethics committee. Medical records of patients admitted to the Neurological Department of the University Hospital of Marburg/Germany during the last 5 years for in-hospital treatment of infectious diseases of the CNS (meningitis, meningoencephalitis, encephalitis, neuroborreliosis)

were screened. Patients of both sexes, aged 20–70 years, with an interval of at least 6 months between acute disease and medical record screening qualified for inclusion in this study. Exclusion criteria were any hormone intake, including oral contraceptives and topical/inhalative glucocorticoids; intake of neuroleptics; diabetes mellitus or other endocrine disorders; malignant disease; abuse of alcohol or drugs; or any other severe disease (especially coronary heart disease and a history of convulsion). Furthermore, severely disabled patients who were not able to give personal informed consent for participation in the study were excluded.

On the basis of 79 records screened, 5 had to be excluded, and another 8 patients could not be contacted any more because of unknown address. Of the remaining 66 patients, 38 refused to participate for personal reasons, and another 7 withdrew their consent after the first study visit before pituitary function testing.

During the first study visit, written informed consent was obtained from each subject. A physical examination, a routine laboratory testing, and an analysis of body composition using a body composition analyser (Akren-RJL BIA 101/S) were performed.

After an overnight fast, basal concentrations of growth hormone (GH), insulin-like growth factor-I (IGF-I), adrenocorticotropin (ACTH), cortisol, luteinizing hormone (LH), follicle-stimulating hormone (FSH), testosterone (in males), estradiol and progesterone (in females), thyrotrophin (TSH), free tri-iodothyronine (fT<sub>3</sub>), free thyroxine (fT<sub>4</sub>), and prolactin (PRL) were determined and an insulin tolerance test (ITT) was performed (Table 1). All subjects received 0.10–0.15 IU/kg regular i.v. insulin (Insuman Rapid; Sanofi-Aventis, Deutschland GmbH, Frankfurt, Germany). Additional insulin was given if blood glucose concentrations below 40 mg/dl were not reached within 15 min. Samples for the determination of glucose, GH, ACTH, and cortisol were drawn. In addition, bedside determinations of glucose levels were done throughout the test.

No adverse events occurred during the ITT. Adequate hypoglycemia with clinical symptoms was achieved in all but two patients. One of these patients showed elevated basal glucose concentrations before the test because of formerly unknown diabetes mellitus. One patient showed normal basal glucose concentrations but did not reach adequate hypoglycemia. The ITT was

repeated on a second occasion with an increased insulin dose, but again no adequate hypoglycemia was achieved. Diabetes mellitus was suspected and an oral glucose tolerance test proposed, but the patient denied further investigations. These two patients were excluded from the analysis.

Eventually, data of 19 patients (13 males, 6 females) were included in the final analysis. They were 22–65 years old (mean  $38.7 \pm 11.7$  years). Time interval since diagnosis ranged from 10 to 56 months (mean  $26.1 \pm 13.1$  months). Diagnosis was proved by lumbar puncture. In all patients, an elevation of protein concentrations and pleocytosis of cerebrospinal fluid indicated a disturbance in the blood–brain barrier. A direct examination of bacteria and antibody determinations (herpes simplex, varicella, Epstein–Barr, neuroborreliosis, tick-borne encephalitis) in the cerebrospinal fluid and serum were performed. Of all these patients, 4 suffered from neuroborreliosis, 2 from encephalitis (2 tick-borne encephalitis), and 13 from meningitis (1 herpes simplex, 1 varicella, 1 enterovirus, 10 of unknown origin). Imaging (cranial computed tomography or magnetic resonance imaging) was performed in patient numbers 2, 4–8, 10, 14, 15, and 19. The degree of disease was mild (no neurological deficits) or moderate (neurological deficits, no impairment of consciousness or other severe complication, no treatment at an intensive care unit) in all cases. All patients were treated with acyclovir and different antibiotics, leading to improvement of symptoms. Patient characteristics are given in Table 2.

### Statistical analysis

Statistical analysis was performed using SPSS 12.0 for Windows. Groups were compared by one-factorial ANOVA, and correlations established according to Pearson.  $P < 0.05$  was considered significant. Data are given as mean  $\pm$  s.d.

### Assays and pituitary insufficiency

GH and IGF-I were determined using a solid-phase chemiluminescence immunometric assay (Immulate 2500; EURO/DPC, Llanberis, UK), and progesterone using a chemiluminescence assay (DXI 800; Beckmann

**Table 1** Insulin tolerance test: time of cortisol, growth hormone (GH), and adrenocorticotropin (ACTH) determinations.

Hormone	Regular insulin i.v. bolus (0.10–0.15 IU/kg body weight) given at 0 min						
	–30 min	0 min	15 min	30 min	60 min	90 min	120 min
Cortisol		X		X	X		
GH	X	X		X	X	X	X
ACTH		X	X	X			

**Table 2** Patient characteristics: age (years), sex (male, female), time from disease to testing (months), infectious disease, neurological deficits during acute CNS infection, and actual neurological and self-experienced deficits (corticotropin insufficient patients are marked in gray shades).

	Age	Sex	Time	Infectious disease	Neurological deficits	Actual symptoms
1	63	M	16	Neuroborreliosis	Vertigo	Fatigue, paraesthesia (legs)
2	37	M	49	Meningitis, unknown etiology	No	Cephalgia
3	42	M	18	Meningitis, unknown etiology	No	Fatigue
4	29	F	19	Meningitis, unknown etiology	Hemihypesthesia and hemiparesis	No
5	36	M	12	Herpes simplex meningitis	No	Lack of concentration
6	34	F	45	Neuroborreliosis	Cramps, generalized paresis	Myalgia, cramps, generalized paresis, cold intolerance, lack of concentration, reduced vision
7	42	M	56	Tick-borne encephalitis	No	No
8	35	M	19	Varicella meningitis	No	Cephalgia
9	24	M	43	Neuroborreliosis	Paraparesis (legs)	No
10	36	M	30	Meningitis, unknown etiology	No	No
11	24	M	17	Tick-borne encephalitis	Reduced vision	No
12	65	M	31	Neuroborreliosis	Dysbasia	Fatigue, dysbasia, RLS, paraesthesia, sleep disturbance
13	22	F	16	Enterovirus meningitis	No	Fatigue
14	50	F	22	Meningitis, unknown etiology	No	Fatigue
15	38	M	22	Meningitis, unknown etiology	No	Fatigue, forgetfulness
16	43	F	20	Meningitis, unknown etiology	No	Mood disturbance
17	38	M	28	Meningitis, unknown etiology	No	No
18	30	F	22	Meningitis, unknown etiology	No	Fatigue
19	48	M	10	Meningitis, unknown etiology	No	Cephalgia

Coulter, Krefeld, Germany). All other endocrine parameters were determined using the ADVIA Centaur System (Bayer HealthCare); cortisol, estradiol, testosterone,  $fT_3$ , and  $fT_4$  using a competitive immunoassay; and LH, FSH, PRL and TSH using a sandwich immunoassay (direct chemiluminescence technology). Due to technical reasons, the method of ACTH determination had to be changed during the study. ACTH was determined using an immunoluminometric assay (LUMitest ACTH; Brahms, Hennigsdorf, Germany) in patient numbers 1, 3, 4, 6, 8, 11, 12, 16, and 18, and a solid-phase chemiluminescence immunometric assay (IMMULITE 2500; EURO/DPC) in patient numbers 2, 5, 7, 9, 10, 13, 14, 15, 17, and 19.

Corticotropin insufficiency was defined as peak cortisol concentration during the ITT  $<181.25 \mu\text{g/l}$  ( $500 \text{ nmol/l}$ ) (10). Severe somatotropin deficiency was defined as peak GH concentration during the ITT  $<3 \text{ ng/ml}$  ( $0.14 \text{ pmol/l}$ ), and partial deficiency as peak GH concentration between 3 and 5 ng/ml ( $0.23 \text{ pmol/l}$ ) (20). Gonadotropin deficiency was defined as testosterone concentration  $<2.4 \mu\text{g/l}$  ( $8.4 \text{ nmol/l}$ ) without LH elevation ( $>9.2 \text{ U/l}$ ) in males, referring to the reference range given by the manufacturer of the assay, and the presence of menstrual disturbances in females. As a higher cut-off for males has also been proposed (21), a borderline gonadotropin deficiency was defined as testosterone concentration between 2.4 and 3.0  $\mu\text{g/l}$  ( $10.5 \text{ nmol/l}$ ) in males. Thyrotropin deficiency was defined as  $fT_3$  concentration  $<3.1 \text{ pmol/l}$  ( $2.0 \text{ pg/ml}$ ) and/or  $fT_4$  concentration  $<7.5 \text{ pmol/l}$

( $0.59 \text{ ng/dl}$ ) without TSH elevation ( $>5.6 \text{ mU/l}$ ). PRL concentrations were considered normal between 2.1 and 17.7  $\mu\text{g/l}$  (93.2 and 785.9 pmol/l) in men and between 2.8 and 25.0  $\mu\text{g/l}$  (124.3 and 1109.8 pmol/l) in women. Posterior pituitary insufficiency was considered in case of reported polydipsia and polyuria and electrolyte disturbances.

## Results

### Corticotropin axis

Four patients (21%; two males, two females) showed a peak of cortisol  $<181.25 \mu\text{g/l}$  during the ITT. In the patients with a corticotropin deficiency, peak cortisol ranged from 115 to 172  $\mu\text{g/l}$  (mean  $141.0 \pm 28.3 \mu\text{g/l}$ ), and in the non-deficient patients from 183 to 240  $\mu\text{g/l}$  (mean  $210.5 \pm 19.7 \mu\text{g/l}$ ), the difference being highly significant ( $P=0.000$ ). The corticotropin insufficiencies were not combined with any further pituitary deficiency (Table 3).

In the patients with corticotropin deficiency, basal cortisol ranged from 81 to 144  $\mu\text{g/l}$  (mean  $103.3 \pm 29.3 \mu\text{g/l}$ ), basal ACTH from 7.5 to 14.1 pg/ml (mean  $11.0 \pm 3.5 \text{ pg/ml}$ ), and peak ACTH during the ITT from 14.1 to 72.8 pg/ml (mean  $35.3 \pm 25.9 \text{ pg/ml}$ ). In the non-deficient patients, basal cortisol ranged from 53 to 186  $\mu\text{g/l}$  (mean  $121.6 \pm 36.5 \mu\text{g/l}$ ), basal ACTH from 4.6 to 40.5 pg/ml (mean  $15.7 \pm 10.3 \text{ pg/ml}$ ), and peak ACTH during the ITT from 4.6 to 245.9 pg/ml (mean  $70.0 \pm 74.7 \text{ pg/ml}$ ). The differences between both

**Table 3** Hormone concentrations: basal and stimulated cortisol ( $\mu\text{g/l}$ ), growth hormone (GH; ng/ml), adrenocorticotropin (ACTH; pg/ml), basal thyrotrophin (TSH; mU/l), free tri-iodothyronine ( $\text{fT}_3$ ) and free thyroxine ( $\text{fT}_4$ ; pmol/l), luteinizing hormone (LH) and follicle-stimulating hormone (FSH; U/l), testosterone ( $\mu\text{g/l}$ ), estradiol (ng/l), progesterone ( $\mu\text{g/l}$ ), prolactin (PRL;  $\mu\text{g/l}$ ), and insulin-like growth factor-I (IGF-I; ng/ml).

	Cortisol	Cortisol peak	GH	GH peak	ACTH	ACTH peak	TSH	$\text{fT}_3$	$\text{fT}_4$	LH	FSH	Testo.	Estr.	Prog.	PRL	IGF-I
1	139	186	1.2	5.6	22.5	22.5	1.7	3.9	10	1.7	4.7	4.7	—	—	6.2	133
2	53	219	<0.05	18.1	7.8	38.7	0.56	6.1	10	2.6	1.8	4.7	—	—	5.4	136
3	144	158	0.1	36.5	14.1	14.1	0.5	4.6	12	4.1	11	5.5	—	—	5.9	121
4	97	221	0.08	17.3	9.8	127	1.2	4.7	11	13	7.3	—	135	1	9.4	179
5	104	188	1.96	19.5	10.0	10.0	1.3	4.6	12	3.7	2.1	3.0	—	—	4.8	155
6	159	185	7.17	14.2	13.2	13.2	1.9	4.4	11	46	13	—	185	1.7	16.7	170
7	119	221	0.081	18.5	14.3	14.3	0.94	4.5	12	3.1	3.1	4.0	—	—	7.2	192
8	179	212	<0.05	9.57	29.8	90.7	0.49	5.2	11	2.7	5	3.1	—	—	5.0	143
9	142	240	2.19	36.9	16.9	135	2.1	5.1	13	4.3	7.8	4.9	—	—	9.3	177
10	136	228	<0.05	8.92	8.9	166	0.86	4.5	13	2.3	7.1	3.6	—	—	5.0	130
11	122	214	0.33	11.9	40.5	245.9	0.95	4.4	12	2.5	3.6	3.0	—	—	8.1	165
12	105	183	1.03	8.81	4.6	4.6	1.2	3.8	9.8	2.6	4.3	2.9	—	—	7.8	100
13	81	115	9.59	9.59	8.6	72.8	0.68	5.1	10	5.9	5.9	—	51	0.55	7.2	209
14	86	225	0.366	9.72	6.3	15.1	0.84	4.6	9.3	7.1	32	—	<20	0.75	6.9	147
15	83	172	0.125	31.7	7.5	30.2	0.23	4.3	13	2.3	2.9	5.9	—	—	2.4	211
16	81	210	0.26	16.4	5.5	13.5	1.1	5.2	12	2.3	8.5	—	49	2.1	8.7	86.3
17	186	237	17.9	33.1	25.3	133	0.8	4.5	10	4.1	2.5	3.6	—	—	5.4	113
18	105	119	4.3	8.9	13.9	24.1	3.4	5.1	12	3.6	2.7	—	83	6.2	6.9	170
19	116	188	3.26	14.3	19.9	19.9	0.79	4.9	12	3	5.1	2.7	—	—	6.7	124

groups were not significant ( $P=0.369$ ,  $0.391$ , and  $0.382$ ). Peak cortisol concentrations were not correlated with basal cortisol, basal ACTH, or peak ACTH concentrations ( $P=0.315$ ,  $0.412$ , and  $0.080$ ).

In patients reporting self-experienced fatigue, peak cortisol concentrations were lower than those in patients not reporting fatigue ( $165.4 \pm 38.9$  vs  $213.6 \pm 18.4$   $\mu\text{g/l}$ ;  $P=0.002$ ).

### Somatotropic axis

No patient showed a peak GH  $< 5.0$  ng/ml during the ITT. Only one patient showed a response close to a partial somatotrophic insufficiency (peak GH  $5.6$   $\mu\text{g/l}$ ). This particular patient showed a sufficient cortisol response during the ITT and normal IGF-I concentrations.

Basal GH ranged from  $0.05$  to  $17.9$  ng/ml (mean  $2.63 \pm 4.55$  ng/ml), peak GH from  $5.6$  to  $36.9$  ng/ml (mean  $17.34 \pm 9.98$  ng/ml), and basal IGF-I from  $86.3$  to  $211$  ng/ml (mean  $150.6 \pm 34.9$  ng/ml). Fifteen patients had IGF-I concentrations within the age-related reference range, three patients between  $-2$  and  $-1$  s.d., and one patient below  $-2$  s.d. (22).

### Thyrotrophic axis

No patient showed  $\text{fT}_3$  or  $\text{fT}_4$  concentrations below the reference range. Basal  $\text{fT}_3$  ranged from  $3.8$  to  $6.1$  pmol/l (mean  $4.7 \pm 0.52$  pmol/l), basal  $\text{fT}_4$  from  $9.3$  to  $13.0$  pmol/l (mean  $11.3 \pm 1.2$  pmol/l), and basal TSH from  $0.23$  to  $3.4$  mU/l (mean  $1.13 \pm 0.73$  mU/l).

### Gonadotrophic axis

No male patient showed testosterone concentrations below  $2.4$   $\mu\text{g/l}$ ; all women had a regular menstrual cycle. Two male patients showed a borderline gonadotrophic insufficiency with testosterone concentrations between  $2.4$  and  $3.0$   $\mu\text{g/l}$  and low LH concentrations. One of these patients reported loss of erection and libido, and the other did not show any clinical evidence for a gonadotrophic insufficiency.

Basal testosterone ranged from  $2.7$  to  $5.9$   $\mu\text{g/l}$  (mean  $4.0 \pm 1.1$   $\mu\text{g/l}$ ), basal estradiol from  $20.0$  to  $185.0$  ng/l (mean  $87.2 \pm 61.9$  ng/l), basal progesterone from  $0.55$  to  $6.20$   $\mu\text{g/l}$  (mean  $2.1 \pm 2.1$   $\mu\text{g/l}$ ), basal sex hormone binding globulin (SHBG) from  $13.0$  to  $87.0$  nmol/l (mean  $37.1 \pm 19.5$  nmol/l), basal LH from  $1.7$  to  $46.0$  U/l (mean  $6.2 \pm 10.0$  U/l), and basal FSH from  $1.8$  to  $32.0$  U/l (mean  $6.9 \pm 6.8$  U/l).

### Lactotrophic axis

All patients showed PRL concentrations within the reference range. Basal PRL ranged from  $2.4$  to  $16.7$   $\mu\text{g/l}$  (mean  $7.1 \pm 2.9$   $\mu\text{g/l}$ ).

### Posterior pituitary insufficiency

No patient showed evidence for diabetes insipidus.

### Body impedance analysis

Body mass index (BMI) ranged from 16.6 to 34.7 kg/m<sup>2</sup> (mean 25.5 ± 5.1 kg/m<sup>2</sup>), fat mass from 5.7 to 42.2 kg (mean 17.4 ± 9.9 kg), fat-free mass from 34.0 to 84.0 kg (mean 63.3 ± 12.8 kg), and body water from 24.9 to 61.5 kg (mean 46.3 ± 9.4 kg).

BMI and body composition were not different between patients with a corticotrophic insufficiency and non-deficient patients (23.8 ± 5.3 vs 25.9 ± 5.2 kg/m<sup>2</sup>, 13.7 ± 8.1 vs 18.3 ± 10.4 kg, 58.8 ± 12.8 vs 64.5 ± 13.0 kg and 43.1 ± 9.3 vs 47.2 ± 9.5 kg; *P* = 0.473, 0.417, 0.445, and 0.448).

## Discussion

Infectious diseases of the CNS may cause hypothalamic and/or pituitary dysfunction. The aim of this study was to determine the incidence of hypothalamic-pituitary insufficiency in patients with previous infectious diseases of the CNS of different etiologies and mild-to-moderate clinical course.

In most previous case reports, isolated posterior pituitary insufficiency following infectious diseases of the CNS has been described in children: in a retrospective analysis, severe CNS infection was seen in 8 out of 73 children with central diabetes insipidus. The infectious agents were group B streptococcus, *Haemophilus*

*influenzae*, *Streptococcus pneumoniae*, and unknown virus (23). Central diabetes insipidus developed in five infants with congenital cytomegalovirus infection (24) and in a 5-year-old boy with encephalitis caused by Coxsackie virus B1 after resuscitation (25). Only few cases of isolated posterior pituitary insufficiency in adults following CNS infections have been reported, mainly affecting immunocompromised patients. Infectious agents were herpes simplex (26), *S. pneumoniae* (27), and cryptococci (28) in patients with AIDS, and herpes simplex in one female with ectopic ACTH-dependent Cushing's syndrome due to metastatic carcinoid. Autopsy revealed involvement of the hypothalamus with a viral destruction of vasopressin-producing neurons in this particular patient (29). Finally, an otherwise healthy woman developed diabetes insipidus 3 weeks after acute herpes simplex encephalitis (30).

Basal anterior pituitary hormone levels were normal (26, 30) or were not determined (23, 25, 27, 28) in these patients, and stimulation tests have been performed in only few (24). Reports of anterior pituitary dysfunction following infectious diseases of the CNS are rare, and the incidence has not yet been studied systematically. In almost all reported cases, the anterior pituitary insufficiency was caused by viruses (14–18), and only one bacterial meningoencephalitis associated with diabetes insipidus and suspected corticotrophic insufficiency has been reported. A CT of the head revealed a contrast-enhanced suprasellar lesion in this particular patient (19). The endocrine deficiencies reached from complete panhypopituitarism including diabetes insipidus (14–16, 18) to various partial defects (14, 15, 17). Data of these patients are given in Table 4.

**Table 4** Reported cases of anterior pituitary insufficiency after infectious diseases of the CNS: age (years), sex (male, female), time from disease to diagnosis (years), infectious agent, neurological and endocrine deficits.

	Age	Sex	Time	Infectious agent	Neurological deficits	Endocrine deficits	Reference
1	43	F	0	Unknown virus	Retrobulbar neuritis	Gonadotropic, thyrotropic and somatotropic insufficiency, diabetes insipidus	Hagg <i>et al.</i> (14)
2	53	M	0	Coxsackie B5	Paresis of the sixth nerve on both sides	Gonadotropic, thyrotropic and somatotropic insufficiency	Kupari <i>et al.</i> (15)
3	23	M	3	Influenza A	No	Somatotropic and corticotrophic insufficiency	
4	39	F	0	Unknown virus	Paresis of the right arm, face and third nerve, retrobulbar neuritis	Panhypopituitarism, diabetes insipidus	Lichenstein <i>et al.</i> (18)
5	54	F	0	Herpes simplex	Convulsions and unresponsiveness	Corticotrophic and somatotropic insufficiency, hypoprolactinemia	
6	41	M	0	Unknown virus	Somnolence and disorientation	Panhypopituitarism, hyperprolactinemia, diabetes insipidus	
7	53	F	0	Unknown bacteria	Tremor, lethargy, loss of cognitive functions and visual hallucinations	Corticotrophic insufficiency, diabetes insipidus	Jew <i>et al.</i> (19)
8	76	F	0	Herpes simplex	Akinetic parkinsonian syndrome	Corticotrophic, thyrotropic and gonadotropic insufficiency, hyperprolactinemia, diabetes insipidus	Lickenstein <i>et al.</i> (16)
9	49	M	27	Herpes simplex	Expressive aphasia	Thyrotropic and gonadotropic insufficiency	Vesely <i>et al.</i> (17)

In our study, we found no evidence for posterior pituitary deficiencies; however, no dynamic testing (i.e., water deprivation test) has been performed and partial posterior pituitary insufficiencies might have been missed. On the contrary, there were a substantial number of isolated corticotropic deficiencies. With these findings, we are in concordance with Kreitschmann-Andermahr *et al.* (10), who found a high incidence of isolated corticotropic deficiencies in patients with previous SAH. Contrary to their data, in our present study, other anterior pituitary deficits despite two borderline gonadotropic deficiencies were not seen, especially no somatotropic deficiencies and no differences in body composition.

It is reasonable to assume that the incidence and pattern of hormonal deficiencies after an acute infectious (meningo-) encephalitis may vary with the type of causative agent, the localization of brain lesion, as well as with the severity of disease. The hormonal deficiencies may be transient (15, 19) or permanent (15–17, 23, 30).

Endocrine deficiencies have been reported following infectious diseases of the CNS of different etiologies. Three of the patients with corticotropic insufficiency in our study had suffered from meningitis of unknown origin; in one patient meningitis caused by enterovirus had been diagnosed. It has been suggested that focal neurological symptoms from the basal regions of the brain might be suggestive of an increased risk of hypothalamic–pituitary damage (14, 15), but heterogeneous neurological deficits have been reported in affected patients. Few patients (15) and also all patients with corticotropic deficiency in our study had presented with symptoms of general illness (cephalgia, myalgia, fever), but no neurological deficits at all. In only one patient (15), imaging of the head had been performed during acute illness, revealing no abnormalities of the pituitary gland or hypothalamus. In earlier case reports, endocrine investigations and elevated basal PRL levels (probably due to the loss of tonic inhibition of the pituitary lactotrophs by the hypothalamus) were suggestive of a hypothalamic rather than a pituitary lesion (14, 16, 18). On the contrary, in other patients, the pituitary gland seemed directly affected (15, 17). In our investigation, PRL concentrations were within the normal ranges in all patients. However, the presence of an isolated corticotropic deficiency has been taken as a hint for a hypothalamic rather than a pituitary damage (10). The site of the endocrine dysfunction and the reason for the predominance of isolated corticotropic insufficiency remain speculative.

Especially, self-reported persisting fatigue following an infectious CNS disease might be suggestive of the presence of a hypothalamic–pituitary damage. Of the seven patients reporting fatigue, four proved to have an isolated corticotropic insufficiency in our study. A hydrocortisone substitution therapy was started. One patient (no. 18) experienced massive subjective

improvement of well-being and vitality. Two patients (numbers 3 and 15) seemed not to benefit from the hormone substitution. Both had a moderately diminished peak cortisol during the ITT. Another patient (no. 13) declined a substitution therapy. Although these early results do not allow any final conclusions, they point toward a possible use and necessity of hormone substitution therapy in some patients following infectious diseases of the CNS.

Finally, it has to be mentioned that our data might be biased for the following two reasons: during recruitment many patients denied to take part in our study as they felt completely healthy and favoring the inclusion of patients with self-experienced deficits might lead to an overestimation of the incidence of hypothalamic–pituitary insufficiencies. On the other hand, the acute disease of most patients in the published case reports were more severe than that in our patients, resulting in neurological deficits and even death. Only slightly or moderately ill patients with a good neurological outcome were included in our study, and the incidence of pituitary insufficiencies might be higher in patients with severe persistent neurological deficits.

In summary, it may be that hypothalamic–pituitary dysfunction and especially isolated corticotropic insufficiency may develop in a relevant proportion of patients after mild and moderate infectious diseases of the CNS, and that the clinical picture of some patients with endocrine insufficiency might be misinterpreted as an ordinary post-encephalitic syndrome. Furthermore, prospective studies investigating patients during and after infectious diseases of the CNS and the effects of hormone replacement therapy are warranted.

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