Hypothalamo – pituitary dysfunction in patients with chronic subdural hematoma

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Short title:

Neuroendocrine dysfunction after chronic subdural hematoma

Summary.

Relatively frequent pituitary hormone deficiencies are observed after traumatic brain injury (TBI) and subarachnoid haemorrhage (SAH) and according to the published studies the neuroendocrine consequenses of traumatic brain injury are underdiagnosed. In a cohort of 59 patients (49 males, mean age 68.3 years, 36 – 88 years) after evacuation of subdural hematoma (SDH) were evaluated hypothalamo – pituitary functions one week after surgery, after three months and after one year. Hypogonadism was present in 26% of patients in an acute phase, but in the majority had a transient character. Less than half of patients was GH deficient (GHD) according to the GHRH+arginine test. We did not find any serious case of hypocortisolism, hypothyroidism, diabetes insipidus centralis nor syndrome of inappropriate secretion of ADH (SIADH). Transient partial hypocortisolism was present in two cases, but resolved. We did not find relation between extension of SDH or clinical severity and development of hypopituitarism.

Conclusion: in some patients with SDH growth hormone deficiency or hypogonadism was present. No serious hypocortisolism, hypothyroidism, diabetes insipidus nor SIADH was observed. The possibility of neuroendocrine dysfunction should be considered in patients with SDH, although the deficits are less frequent than in patients after TBI or SAH.

Key words: hypopituitarism, subdural hematoma, brain injury, growth hormone deficiency

Introduction.

Traumatic brain injuries (TBI) are a serious health problem with a frequency of 235/100 000 persons per year (Tagliaferri et al. 2006). The patients are endangered in an acute phase, but also due to chronic consequences. Among these belong orthopedic, neurologic, psychiatric and also endocrinological complications. The percentage of pituitary deficits after traumatic brain injury is quite high and it is estimated that this sequelae is underdiagnosed. In the metaanalysis of Schneider et al. was hypopituitarism observed in 15.4 - 50% in a chronic phase after TBI (hypocorticalism in 2.6 – 19.2%, hypothyroidism in 1-10%, hypogonadism in 1.9 - 20% and growth hormone deficiency (GHD) in 5.9 – 32.7%). After subarachnoid haemorrhage was the frequency of hypopituitarism even higher (37.5 – 55%)(Schneider et al. 2007).

Brain injury leads to brain oedema, increased intracranial pressure, haemorhages, microinfarctions, fibrosis in hypothalamus and pituitary (Harper et al. 1986, Salehi et al. 2007). In the late phase after TBI an autoimmune process in the pituitary is expected as the cause of some further hypopitutarisms (Tanriverdi et al. 2008). Similar conditions could be expected in patients with subdural haemorrhages, where preceding trauma, compression of the brain, shift of midline structures, possible compression of nutritive arteries and veins might compromise the structures of hypothalamo – pituitary endocrine unit. For these reasons we undertook this first study focused on neuroendocrine functions in patients operated for subdural hematomas (SDH).

Patients.

We examined in cooperation with Department of Neurosurgery 59 patients (49 males, mean age 68, 3 ±12,87 (SD) years, median age 72 years, range 36 - 88 years, BMI 26,5 kg/m^2, range 18-37,6) operated for SDH. Forty-nine consecutive patients (41 males, mean age 66,8 ±

13,0 years, median age 70,0 years, range 36 - 88 years, BMI 26,8 kg/m^2, range 18- 37,6)
were examined prospectively – first week after surgery, after three months and after 12
months. Ten patients (8 males, mean age 75,9 ± 7,6 years, median age 78 years, range 64 –
86 years, BMI 25,2 kg/m^2, range 22,4 – 30,5) were evaluated after one year after surgery for
SDH only.

In 13 patients in our group a trauma as clear cause of the subdural haematoma was
found. In those patients a mean interval between the trauma and diagnosis of the subdural
haematoma was 42, 3 days (range 4 - 110 days). Alcohol abuse was present in the history of
five patients.

Methods.

The neurological status and its dynamics was evaluated before and after surgery for SDH.
Midline structures shift and thickness of SDH was evaluated on CT scans.

In the mentioned intervals was evaluated basic biochemistry (minerals, renal functions,
AST, ALT, ALP, GGT, bilirubin, glycemia) and hypothalamo – pituitary endocrine functions
by measurement of basal values of hormones LH, FSH, testosterone/estradiol, freeT3, freeT4,
TSH, prolactin, ACTH, IGF-1, cortisol and by dynamic testing. ACTH (Synacthen 250 µg)
test, growth hormone releasing hormone (GHRH) + arginine test (1 µg GHRH/ kg of body
weight i.v. + 30 g of arginine hydrochloride in 30 minute infusion; blood samples in 0, 15, 30,
45, 60, 75, 90 min) and TRH tests (200 µg TRH i.v.; blood samples in 0, 20, 60 min) were
used.

Standard biochemical tests were done on analyser Modular Analytics EVO (Hitachi,
Japan). LH, FSH, estradiol, testosterone, prolactin, TSH, freeT3 and freeT4 were assayed by

ADVIA Centaur (Siemens, Healthcare Diagnostics Inc, Tarrytown, NY, USA), with chemiluminometric detection. FSH, LH, prolactin and TSH were determined by sandwich immunoanalysis with direct chemiluminometric technology; for oestradiol, testosterone, free T3 and freeT4 competitive immunoanalysis, direct chemiluminometric technology was also used. Serum GH and IGF-I concentrations were measured by IRMA kits (IMMUNOTECH a.s., Prague, Czech Republic), following the manufacturer's instructions. Sensitivity for GH was 0.03 μg/l. Sensitivity for IGF-I was 12 μg/l. Serum cortisol levels were measured by commercial RIA kit ((IMMUNOTECH a.s., Prague, Czech Republic). Sensitivity was 10 nM. Plasma ACTH levels were measured by IRMA kits (Brahms Diagnostica, Hennigsdorf, Germany). Sensitivity was 1.2 pg/ml. The intra- and interassay variability of all kits was less than 5.0 % and 10.0 % respectively.

As an adequate response in ACTH test was considered maximal cortisol value of 550 nmol/l (Clark et al. 1998). In GHRH+ arginine test these cutoff levels for GHD were considered according to the patients´ body mass index (BMI): with BMI < 25 kg/m^2 a peak GH < 11 μg/l, with BMI 25- 30 kg/m^2 a peak GH < 8 μg/l and with BMI > 30 kg/m^2 a peak GH < 4 μg/l (Ho et al. 2007). The increase in TSH after TRH at least 6 mU/L in males and females younger than 40 years of age and 2 mU/L in older than 40 years was defined as normal. Evaluation of central hypothyroidism was based on complex evaluation of thyroid hormones and TSH values. Central hypogonadism was evaluated only in relevant situations (patients after menopause and males with peripheral hypogonadism were excluded). Reference testosterone values in our laboratory are 9.9-28 nmol/l for men of age below 50 years. The evaluation of hypogonadism in older age is not straightforward. Although the decline of mean testosterone values with age is known, there are no generally accepted lower limits of normal values for elderly males (Wang et al. 2008). However there is consensus of clinically important cutoff for total testosterone of 8 nmol/l, below which symptomatic males

usually benefit from testosterone replacement and we decided to use this limit for patients over 50 years in this evaluation (Wang et al. 2008).

Evaluation of DI and SIADH was also performed. In patients where concomitant medication could influence the results of hormonal tests, the influenced axis was not evaluated (i.e. thyroxin replacement for peripheral hypothyroidism etc.).

All the protocol was in accordance with the Declaration of Helsinki (2000) of the World Medical Association and was approved by the Ethics Committee of General Faculty Hospital in Prague.

Statistical analysis

Statistical analysis was performed using SAS 9.2 software (SAS Institute Inc., Cary, NC, USA). The statistical results on comparing different time-points were calculated using a Wilcoxon Signed Rank test due to non-gaussian distribution of many of analysed parameters. Analysis of the relationship between various continuous variables was done using Spearman rank correlation coefficient. P-values were considered statistically significant at the 0.05 level.

Results

Maximal thickness of SDH and shift of the midline structures was described and quantified on preoperative CT scans. The maximal thickness of SDH was 33 mm, minimal thickness was 9 mm, mean 20 ± 6 (SD) mm, median 20.5 mm. Bilateral SDH was found in 11 cases. Mean shift of the midline structures in our group was 8.3 ± 5.4 mm (range 0- 20 mm, median 8.8). Six patients had no shift of the midline structures – all of them had bilateral subdural hematomas.

In collaboration with neurosurgeons a neurological status was evaluated (Tab.1). Neurological status was evaluated before the operation and again soon after the operation in a prospectively followed group. The most common finding was mild mono or hemiparesis diagnosed in 16 patients. In 41 patients the operation led to complete restitution of the neurological deficit, in 8 patients was the reparation partial.

Individual evaluation of hormonal status (Table 2).

Evaluation of hormonal status immediately after surgery did not find any hypocortisolism, hypothyroidism nor diabetes insipidus. In 23 patients was the dynamic test in agreement with the diagnosis of GHD and in 9 cases central hypogonadism was present.

At 3 months´ evaluation we found a subnormal response of cortisol in ACTH test (maximal cortisol value was slightly below 500 nmol/l) in 2 patients, but control tests one month later showed a normal response. Central hypogonadism was present in two patients. Response of GH in GHRH+ arginine test was insufficient in 16 cases.

At 12 months (analysed both groups – prospective and retrospective) was no hypocortisolism nor hypothyroidism diagnosed, 3 patients were hypogonadal and 15 had GHD. There was no case of DI nor SIADH in any phase of the study.

Both hypogonadism and GHD was present in 7 patients in an acute phase, 1 after 3 months (the second hypogonadal patient refused GHRH+arginine test) and in 2 patients after a year.

Head trauma as a clear cause of subdural hematoma was present in the history of 13 patients. In two of these patients was GHD present permanently and in four other was GHD and/or hypogonadism present transiently.

There was a problematic compliance during the study period in some patients and it increased with time. Although we contacted all the patients, only part of them agreed with repeated examination. Some non-compliant SDH patients did not feel health problems and others suffered from some other concomitant disease and refused further examination after 3 and 12 months.

Analysis of the hormonal status of the whole group (Table 3).

Statistical analysis of the maximal response of GH in GHRH+arginine test showed different behavior for values in prospective individual assessment and for results of group analysis and this disabled statistical evaluation.

Analysing the relationship between various variables and the clinical status, we found significant correlation between basal TSH value and maximal TSH value in TRH test ($r=0.82$, $p < 0.001$). There was no correlation between midline structures shift, which could represent the severity of trauma of midline structures, and the hormonal values nor any other analyzed parameters.

Discussion.

The majority of clinical studies have demonstrated that TBI and SAH frequently cause neuroendocrine dysfunction in adults and also in children and adolescents (Schneider et al. 2007, Čáp 2006, Zapletalová et al. 2010, Krahulik et al. 2010, Aleksijevič et al. 2010, Kosák

and Hána 2011). In accordance with this observation is also the recently published analysis of large German and Austrian registry (Schneider et al. 2011). The structures of hypothalamus and pituitary appear to be very sensitive to trauma and vascular insult in the acute phase (Benvenga et al. 2000, Salehi et al. 2007) and the participation of autoimmune process in the chronic phase is assumed (Tanriverdi et al. 2010a). Relationship between severity of trauma and hormonal dysfunction have been observed by some (Bondanelli et al. 2004, Klose et al. 2007) but not by others (Agha et al. 2004, Aimaretti et al. 2005, Schneider et al. 2006). It has been clearly demonstrated that even mild TBI can cause neuroendocrine dysfunction (Tanriverdi et al. 2010b). Hypothalamo-pituitary dysfunction was described even in association with brain operation of distant structures (DeMarinis et al. 2006).

This is the first study focused on patients with chronic subdural hematoma in which we prospectively evaluated neuroendocrine functions during one year after evacuation of SDH. We did not observe in our cohort during the whole study any serious dysfunction of adrenocortical nor thyroid axes and no diabetes insipidus nor SIADH, except of two cases of subnormal cortisol response in ACTH test in 3 months´ testing. These two patients had maximal stimulated cortisol slightly below 500 nmol/l, but in a control test one month later was the response again normal.

Slight, but significant increase of mean basal cortisol first week after surgery could be simply a marker of stress.

Similarly to TBI studies we observed quite frequently dysfunction in gonadotrophic axis and growth hormone secretion, especially in an acute phase. Growth hormone deficiency according to GHRH+arginine test was the most frequent in our group. Recovery of gonadotrophin secretion after the acute phase appeared in the majority of patients. The time course of central hypogonadism was recently exactly described in an acute phase after brain trauma. Study of Wagner et al. revealed that within 10 days of complicated mild, moderate,

and severe TBI, testosterone suppression occured in all men and estrogen suppression occured in over 40% of women (Wagner et al. 2010).

Chronic subdural hematoma most frequently occurs in older males (Kanat et al. 2010). We are aware that evaluation of gonadotrophin axis and especially of GH secretion, in our cohort with a mean age of 68 years is rather complicated. The activity of both axes declines with age and is influenced by non-endocrine factors like for instance comorbidities, obesity etc. It is likely that function of gonadotrophic axis is a marker of general health (Araujo et al. 2011). Establishing in this group of patients with various comorbidities the diagnosis of GHD and hypogonadism caused strictly by SDH is sometimes impossible. Replacement therapy of these axes in older people is for the mentioned reasons also limited. Nevertheless not all patients were of advanced age. Evaluating patients younger than 60 years of age there was GHD in an acute phase in 4/14 (GHD/evaluated patients under 60), after 3 months 3/10 and after 12 months in 2/8 patients. In one 36 years old patient with confirmed severe GHD was GH replacement commenced.

We also analysed the relationship between extension of SDH or clinical severity and development of hypopituitarism, but we did not find any association. From our results it is not possible to select patients more susceptible to hypopituitarism after SDH on the basis of clinical status nor CT scan.

Comparing results in our cohort with TBI or SAH studies is complicated by substantially higher age and more confounding comorbidities in our group. Nevertheless it is obvious that we observed less severe neuroendocrine dysfunction after SDH than it was published after TBI. In a prospective study after TBI had subnormal cortisol response 16% of patients in an acute phase and 18% after 6 and 12 months and hypothyroidism was present in 2% (Agha et al. 2005). We observed no serious deficiency in corticotrophic axis. We also did not observe disturbance in thyrotrophic axis, nor diabetes insipidus nor SIADH. Comparing

the gonadotrohic axis and GH secretion is impossible for the above mentioned reasons of different groups of patients.

How to explain less pituitary dysfunction in SDH patients in relation to TBI and SAH? We propose, that there could be several reasons. As the chronic SDH is typical for older persons, some brain atrophy diminishes the pressure of SDH on brain structures. The other reason could be in a slowly developing SDH (most frequently for at least several weeks) providing time for adaptation of possible vascular mechanisms, which could cause the injury of hypothalamic and pituitary structures. We must also admit, that not all published studies prove a high frequency of hypopituitarism after brain insult. Klose et al. did not find any chronic hypopituitarism in 62 patients after subarachnoid haemorrhage (Klose et al. 2010) and recently published study evaluating neuroendocrine functions in children after structural TBI in early childhood did not find any permanent hypopituitarism in almost 200 children (Heather et al. 2011).

We think that patients with SDH, especially those with head trauma in the history, should be managed like patients with mild TBI (Tanriverdi et al. 2010b). Despite we did not find any hypocortisolism in our cohort, we are aware of limited cohort of our patients and we believe that an evaluation of ACTH axis should be done in an acute phase on clinical basis and measurement of basal cortisol. Measurement of free thyroid hormones should be done in this phase also. In the chronic phase all the pituitary hormones and hormones of regulated glands should be measured and in clinical context using of appropriate dynamic tests should be considered.

In conclusion, results of our study showed no serious hypocortisolism, hypothyroidism, diabetes insipidus nor SIADH in patients operated for chronic subdural hematoma. Severe GHD was present in less than half of patients. Central hypogonadism was

diagnosed in a quarter of patients in an acute phase, but recovered in the majority of them during the follow up. The possibility of neuroendocrine dysfunction should be considered in patients with SDH, although the deficits are less frequent than in patients after TBI or SAH.

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Table 1. The frequency of each type of neurological finding before operation

Clinical presentation	Frequency (No. of patients) n= 49
Mild paresis (mono or hemi)	16
Moderate paresis (mono or hemi)	4
Severe paresis (mono or hemi)	1
Hemiplegia	0
Speech disorder	5
Alteration of the mental status +	10
Other neurological symptom ++	14

+ Alteration of the mental status – confusion, bradypsychia.

++ Other neurological symptom **-** headache, worse memory, dyscoordination, instability,

falls, reduced unilateral sensitivity

Table 2. Evaluation of hormonal status– number of deficiencies

	Number of deficiencies		
	first week after surgery (n=49)	3 months (n=37)	12 months (n=32)
Hypocortisolism	0	2 (mild, transient)	0
Hypothyroidism	0	0	0
Central hypogonadism	9 (n=35)	2 (n=28)	3 (n=25)
Growth hormone deficiency	23	16	15
Hypogonadism + growth hormone def.	7	1	2
Diabetes insipidus centralis/SIADH	0	0	0

n – number of assessable patients

Table 3. Hormonal values of the whole group (x±SD)

	first week after surgery (n=49)	3 months (n=37)	12 months (n=32)
basal cortisol (nmol/l)	517 ± 130	445 ± 142 §	431 ± 121 §
maximal cortisol in ACTH test (nmol/l)	981 ± 209	917 ± 217	903 ± 184
free T4 (pmol/l)	15.1 ± 2.4	14.0 ±2.4	15.1± 1.7
testosterone (nmol/l)	12.0 ± 5.1	15.7 ± 5.7	13.4 ± 5.6
maximal TSH in TRH test	8.1 ± 5.2	9.8 ± 5.8 §§§	11.1 ± 7.0 §§§

§   P<0.01   - against day 0

§§§   P<0.05%   - against day 0