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Fatigue after aneurysmal subarachnoid hemorrhage evaluated by pituitary function and 3D-CBF

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Objective – The reason for longstanding fatigue following aneurysmal subarachnoidal hemorrhage (SAH) is still not clarified. The bleed from supratentorial aneurysms is often in the vicinity of the hypothalamus and pituitary gland making an endocrine dysfunction plausible. *Methods* – Ten patients with post-SAH fatigue were investigated with 3D-CBF (SPECT) and underwent an evaluation of the pituitary function. *Results* – Five had normal pituitary function. Disturbances in the gonadotropin function was detected in three patients and suspected in two. The mean insulin-like growth factor I (IGF-I) value of the patients was in the lower part of the reference range. In the patients with endocrine dysfunction, the 3D-CBF was pathologic in the central structures of the basal region. *Conclusions* – The present results indicate that an aneurysmal SAH may result in partially impaired pituitary capacity. This deficit may contribute to fatigue after aneurysmal SAH, but cannot solely explain this disorder. SPECT identified regional tissue damage in the patients with pituitary dysfunction after SAH.

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Key words: aneurysmal subarachnoid hemorrhage; cerebral blood flow; single photone computeraided tomography; pituitary function; hypothalamic insufficiency; growth hormone; pituitary insufficiency

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Modern neurosurgical care of patients with a subarachnoidal hemorrhage (SAH) because of ruptured cerebral aneurysm, including aggressive anti-ischemic treatment, has improved neurologic outcome (1, 2). However, neuropsychological follow-up of the seemingly well-doing patients reveals a great number of individuals complaining of general exhaustion, lack of initiative and increased sleep demand (3–10) i.e. "post-aneurysmal SAH fatigue". In many of these patients it would be reasonable to designate the outcome as unfavorable despite lack of gross neurological deficits (7). The cause of these symptoms has never been elucidated. From a theoretical point of view a hypothalamic and/or pituitary endocrine dysfunction as a consequence of the bleed into basal cerebral structures, could be one explanation (11). Another could be a direct influence of the blood per se on the function of adjoining brain structures or sequela because of cerebral ischemia.

In the present study, we tried to further penetrate the reason for post-aneurysmal SAH fatigue by evaluating the pituitary function in 10 patients with these complaints at long-term follow-up. Furthermore, in order to estimate the functional integrity of central subcortical structures in the brain a 3D-cerebral blood flow (CBF) was measured at the time of endocrine assessement.

Material and methods

After local ethical approval, 10 consecutive individuals with fatigue after aneurysmal SAH and no history of premorbid endocrine dysfunction at follow-up, were investigated. All 10 patients had noticeable complaints of general exhaustion, lack of initiative and increased sleep demand, problems that they had not experienced before the bleed. They were preoperatively in Hunt & Hess (12) score I–III, Fisher grade II–IV and had underwent early surgery (within 72 h after the bleed) for a ruptured supratentorial aneurysm. Surgery had been performed through a standard pterional approach. Induced hypotension was not used. As soon as the

Table 1 Showing the case number, age, gender, H & H Score: Hunt & Hess Score and Fisher Grade

Case number	Age (years)	Gender	H & H score	Fisher grade	Aneurysm localization	Retractor time	Time bleed to surgery	Additional information
1	42	M	2	3	ACoA-R	120	36	Art Hypert
2	49	M	3	3	ACoA-R	180	61	Art Hypert
3	42	F	2	2	ACoA-L	75	25	
4	50	M	2	2	ACoA-R	80	72	
5	45	F	1	2	ACoA-R	50	26	Art Hypert
6	59	M	3	3	ACoA-L	130	39	DM
7	47	M	3	3	ACoA-R	85	18	Art Hypert
8	52	F	3	3	BA-R	120	50	
9	47	M	2	3	ACoA-R	140	26	
10	41	F	3	4	MCA-R	150	22	Art Hypert

The aneurysm location was ACoA: anterior communicating artery, BA: basilar artery and MCA: middle cerebral artery. The suffix R and L refers to right and left. The retractor time in minutes and the time from the bleed to the surgery are in hours. Additional information refers to the patients other diagnosis where Art Hyper is Arterial Hypertension and DM is Diabetes Mellitus.

diagnosis aneurysmal SAH was confirmed, the patients were given nimodipine intravenously, continued for an average of 1 week. Glucocorticosteroid treatment was not given to any patient. Eight patients were at following-up classified as having made a good neurologic recovery, while two ended up with moderate neurologic deficits.

Mean time elapse from haemorrhage to the endocrine and 3D-CBF or single photone computeraided tomography (SPECT) evaluation was 1 year.

Relevant patient data are given in Table 1.

Evaluation of pituitary function

Pituitary function was evaluated by routine laboratory investigations analyzed by the local Clinical Chemical Department. The protocol included measurement of serum levels of:

(1) follicle cell-stimulating hormone (FSH);
(2) luteinizing hormone (LH) before and after luteinizing hormone-releasing hormone (LH-RH)-stimulation (100 μg synthetic analogue, LH-RH, i.v.; Ferring, Limhamn, Sweden);
(3) thyroid stimulating hormone (TSH) before and after TSH-releasing hormone (TRH) stimulation (200 μg Thyrefact, i.v.; Hoechst, Frankfurt am Main, Germany);
(4) prolactin;
(5) on another day corticotropin (ACTH) and growth hormone (GH) were measured before and after insulin-induced hypoglycemia (0.1 units/kg BW of Actrapid, i.v.; Novo Nordisk, Copenhagen, Denmark).

Furthermore, the serum basal levels of testosterone/estradiol were analyzed in men/women as well as well as the free thyroxine (FT4) concentration.

The plasma level of insulin-like growth factor I (IGF-I) was analyzed with a kit from Nichols Institute at the Medscand Diagnostics Laboratory, Stockholm, Sweden.

Hypoglycemia was not induced in the patients with a history of epileptic seizures and in the patient with neurologic sequelae.

SPECT measurements

Each patient had an injection of 500 MBq (10 mCi) of ^{99m}Tc-HMPAO. Five minutes after the injection, the patient was positioned in a SPECT camera (Tomomatic 564, Medimatic AS, Copenhagen, Danmark). Two measurements with a sample time of 5 min each were performed resulting in 10 transaxial images parallel to the orbito-meatal line with a separation of 1 cm and an intraslice resolution of about 1 cm. The images were reconstructed using filtered back-projection and a linear attenuation correction. The images were scanned using a moving crossection profile in posterior-anterior direction covering the whole picture on the computer screen. Side to side asymmetries exceeding 10% were considered pathologic. The areas of blood flow disturbance were then recognized.

Results

Patient data with their pathology is given in Table 1 and the results from the endocrine evaluation in Table 2. Representative pictures from the SPECT scannings are given in Fig. 1. The endocrine interpretation and SPECT results of the different patients are given below.

Patient number 1: A *S*-testosteron level in the lower part of the reference range without increased basal levels of gonadotropins might indicate impairment of gonadotropin function. Insulin-induced

Table 2 The endocrine results in the 10 patients. SAH-Invest is the time in month from the bleeding to the investigation. The bolded headline represent the type of stimulation

Patient number (unit)	SAH–Invest (month)	Insulin ⇒ Hypoglycemia				TRH			LH-RH		IGF-I	T/E
		Glu (mmol/l)	GH (μg/l)	ACTH (ng/l)	C (mmol/l)	TSH (mlU/l)	ProL (μg/l)	FT4 (pmol/l)	FSH (μg/l)	LH (μg/l)	(μg/l)	(nmol/l)
1	11	3.8	2	12	469	9	22	12	1.7	4.3	210	8/
2	7	2.2	1	8	495	18	20	15	0.7	3.3		
3	16	1.6	22	23	656	12	22	16	1.7	4.2	223	
4	9	1.7	10	21	690	7	15	16	0.8	2.4	224	17/
5	16	1.3	86	14	788	74	38	13	13	15	149	
6	16	DM	DM	DM	DM	4	12	19	13	19	221	10/
7	14	1.5	4	20	757	6	10	16	6.8	8.5	109	12/
8	4		4.8*	2.4*	567*	74	31	12	8.9	8.4	114	/111
9	13		0.8*	5.0*	531*	7	14	17	5.3	14	187	25/
10	15				209*	0.7*	5*	12	7.4*	6.7*	73	

Glu: Glucose (mmol/l), is the lowest value during the insulin tolerance test. GH: growth hormone (μg/l), ACTH: adrenocorticotropin (ng/l) and C: cortisol (nmol/l) after insulin induced hypoglycemia. TSH and Prl: maximum levels of thyrotropin (mlU/l) and prolactin (μg/l) after TRH-stimulation. FT4: serum free thyroxin level (pmol/l) ref. value 12–25. FSH, LH: maximum levels of follicle cell-stimulating and luteinizing hormones (μg/l) after LH-RH stimulation. IGF-I: insulin-like growth factor I (μg/l) ref. range 123–463. T/E: testosterone or estradiol (nmol/l) ref value 6–30.

* Unstimulated morning value.

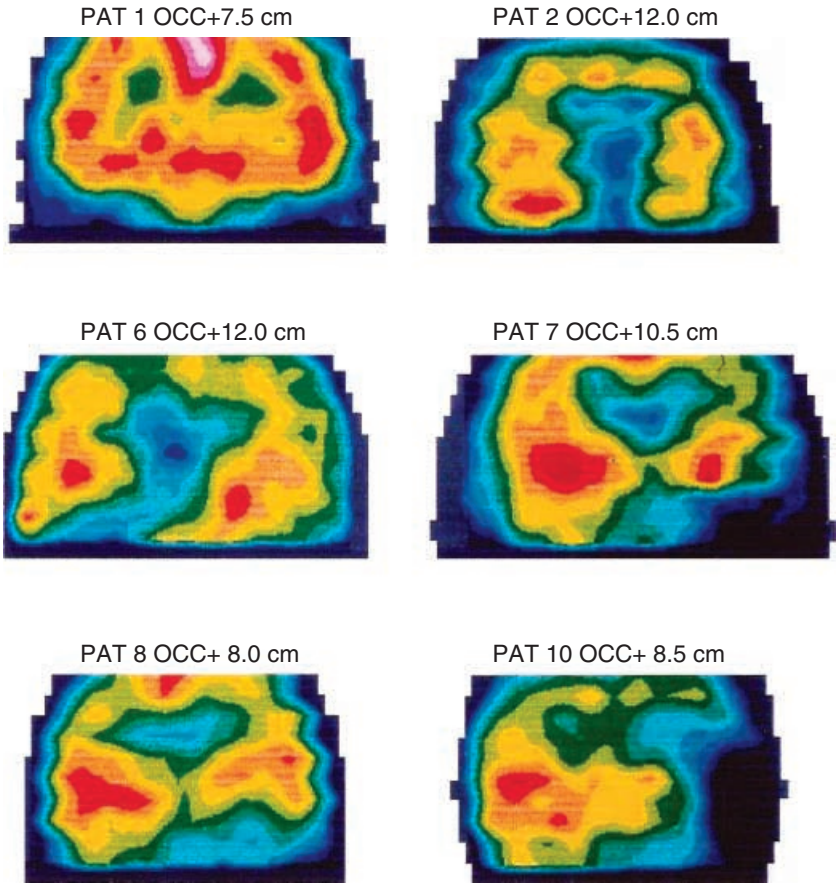

Figure 1. SPECT images with HMPAO. Coronal sections for one patient with no CBF disturbance (patient 1) and five patients with pronounced CBF reductions crossing the midline (patients 2, 6, 7, 8, and 10). Level of section with maximum CBF decrease is shown and given in centimetre in front of the occipital pole. Left in the picture is left in the patient. Blue denotes low flow. Red denotes high flow.

hypoglycemia was weak. Therefore, no conclusions could be drawn from the moderate GH reaction; as the IGF-I level was well within the reference range, GH release was judged to be preserved. No proven sign of ACTH insufficiency. Thyroid function normal.

No proven insufficiency. SPECT: Normal CBF distribution.

Patient number 2: Subnormal FSH reaction to LH-RH stimulation. The ACTH and cortisol reactions to hypoclycemia were comparatively low while the *GH reaction was clearly impaired*. Together these data indicate pituitary dysfunction with regard to GH and gonadotropin release. Thyroid function was normal.

Pituitary function partly impaired. SPECT: large CBF decreases which crossed the midline.

Patient number 3: Weak reactions to LH-RH stimulation could be explained by long acting progesteron contraceptive therapy. The responses to hypoglycemic and TRH stimulation were adequate. The IGF-I level as well as the thyroid hormone levels were normal.

Normal pituitary functon. SPECT: CBF decreased in a restricted tissue volume.

Patient number 4: Adequate gonadotropin reactions in relation to normal *S*-testosteron level. Adequate reactions to hypoglycemia and TRH. Normal IGF-I and thyroxin levels.

Normal pituitary function. SPECT: CBF decreased in a restricted tissue volume.

Patient number 5: Regular menstrual bleedings as evidence of normal gonadotropin functions. Adequate reaction to hypoglycemia. Normal IGF-I level. Increased basal level of TSH and exaggerated response to TRH stimulation demonstrated previously undiagnosed primary hypothyroidism.

Normal pituitary function. SPECT: unifocal CBF reduction.

Patient number 6: A S-testosteron level in the lower part of the reference range without elevation of basal levels of LH but with a 10-fold increase after LH-RH might indicate a hypothalamic defect. Undiagnosed diabetes mellitus was revealed, not allowing hypoglycemic test. Basal *S*-cortisol 369–428 nmol/l in the morning. Normal IGF-I levels argues against GH deficiency. Thyroid function normal.

Impaired hypothalamic regulation of gonadotropin suspected. SPECT: large CBF decreases which crossed the midline.

Patient number 7: Gonadotropin function probably normal. Subnormal GH reaction to adequate hypoglycemia and a subnormal IGF-I level suggests GH dysfunction. Thyroid function normal.

Subnormal GH-reaction. SPECT: large CBF decreases which crossed the midline.

Patient number 8: Basal and stimulated gonadotropin levels low for post-menopausal age. Hypoglycemia was not induced because of neurological sequel. Basal morning *S*-cortisol level was adequate while the IGF-I level was subnormal. Increased basal level and exaggerated response for TSH after TRH indicated previously undiagnosed subclinical primary hypothyroidism. Because of moderate primary hypothyroidism no solid conclusion of GH function could be drawn.

Impaired gonadotropin function. SPECT: large CBF decreases which crossed the midline.

Patient number 9: Adequate gonadotropin reactions and normal testosteron level. Hypoglycemia not induced because of history of epileptic seizures. Basal levels of *S*-cortisol in the morning as well as the IGF-I level were however normal.

Pituitary incapacity not proven. SPECT: unifocal CBF reduction.

Patient number 10: Basal levels of gonadotropins clearly low for age. Hypoglycemia not induced because of neurological sequelae. Basal level of *S*-cortisol low – normal; glucocorticosteroid substitution therapy given. P-IGF-I low. Serum free thyroxine concentration normal.

Impaired pituitary function. SPECT: large CBF decreases which crossed the midline.

Discussion

None of the patients were known to suffer from endocrine dysfunction prior to the bleed, and five of them had still completely normal results concerning pituitary function at long-term follow-up. In two patients, only relatively weak indications of disturbances were detected while three individuals had significant disturbances concerning gonadotropin function and/or GH release. These endocrine functions are not of immediate concern with regard to survival in SAH patients, but may theoretically be of importance for later general well being.

The fact that clear-cut endocrine disturbances could be confirmed in only three of the 10 patients suggests a weak or non-existing correlation to the post-aneurysmal SAH syndrome. Furthermore, none of the patients had a complete loss of gonadotropin functions acccording to laboratory tests, and no clinical signs of unexpected hypogonadism. Pituitary–adrenal and thyroid functions were preserved in all cases studied.

However, the mean IGF-1 value of our patients (167.8 μg/l, $n = 9$) was in the lower part of the reference range (mean 239, range 2 SD = 123–463 μg/l, $n = 83$) presented by the laboratory, suggesting that GH deficiency may appear in a number of patients after aneurysmal SAH. This is in accordance with data from a recent report Kelly et al. (11) who had included two SAH patients and found that both had a GH deficiency. This is of interest since adult patients with acquired GH deficiency have a poorer quality of life in terms of

e.g. energy, emotional distress and social isolation (13). These symptoms remind to some extent of what has been reported to occur in SAH patients (3, 5, 8). Although not solely responsible for the post-aneurysmal SAH fatigue, GH deficiency should be ruled out in such cases. The present profile of minor pituitary or hypothalamic dysfunctions in SAH patients are in accordance with general endocrine experience, that gonadotropin and GH regulation are more easily damaged than, e.g. ACTH or TSH release in patients suffering pituitary tumors (14). Although the destructive process differs between a slowly growing pituitary adenoma and the sudden SAH trauma, endocrine dysfunctions seem to appear in similar order. Insufficient GH secretion alone or in combination with impaired secretion of gonadal hormones has been reported in patients who had SAH from non-aneurysmal origin, where the source of bleeding was supposed to be a pituitary adenoma necrosis (15). Impaired secretion of these hormones may not necessarily originate from pituitiary changes alone, and former data indicate that hypothalamic disturbances were responsible (16). This latter notion agrees with the present CBF-SPECT findings among our patients.

In the present study measurement of CBF was performed by injection of ^{99m}Tc-HMPAO. This tracer substance is lipid soluble at the time of injection and is distributed in proportion to the blood flow. In the brain cells, the carrier molecule HMPAO is, within a few minutes, converted to a water-soluble form, which cannot cross the cell membrane. Hence, the amount of ^{99m}Tc trapped in the brain cells is proportional to the CBF distribution prerequisite the brain cells are intact. A reduced flow will, therefore, represent either structural cell damage or an impaired cellular functioning, considering the brains normal metabolic-CBF coupling. In five of our patients, SPECT clearly demonstrated reduced CBF in the central suprasellar and subfrontal region, indicating a persistent organic defect in this area. Three of these patients also demonstrated some degree of endocrine dysfunction. In these three patients, the SPECT pathology crossed the midline, but no conclusions could be drawn because this was also the case in two other patients in whom endocrine dysfunction was not so clearly proven.

SPECT pathology most probably reflects a varying degree of neuronal damage with subsequent reduction of CBF, and not necessarily only gross tissue loss (17). Neuronal deactivation in the area surrounding the primary lesion may also contribute to the extent of CBF decrease. Thus, comparing computerized tomography (CT), magnetic resonance imaging (MRI) and SPECT, the latter gives the most relevant indirect information about neuronal function. Recently, SPECT has been used to predict cerebral infarction because of reduced vasodilator capacity in SAH patients (18). In patients operated for an intracranial aneurysm after SAH, late SPECT pathology may represent damage from an array of sources; trauma from the initial bleed, brain retraction during surgery, temporary arterial occlusion, consequences of delayed ischemia from vasospasm, increased intracranial pressure, etc. The intraoperative trauma may differ widely between patients, depending on, i.e. aneurysm location, brain swelling or surgical technique and skill.

To summarize the present 10 SAH patients, three were clearly found to have some degree of pituitary dysfunction. Interestingly, in these three individuals there was a corresponding area of decreased CBF, crossing the midline in the hypothalamic and subfrontal region, but not related to the location of the ruptured aneurysm per se. Thus, obvious pituitary dysfunction was only detected in these three patients where SPECT-pathology crossed the midline in the basal region. This flow pattern was, however, also seen in two further patients, in whom pituitary dysfunction was only weakly verified, but not in any of those five patients with sufficient pituitary capacity.

The present results do not support that the frequently observed post-SAH-fatigue may, in general, be explained by a pituitary–hypothalamic insufficiency. It is not excluded, however, that such incapacity in some patients adds to the consequence of other SAH-induced brain damage. Evaluation of pituitary function seems to be justified in subjects suffering post-aneurysmal SAH fatigue. SPECT could be valuable for demonstration of relevant brain damage in such patients.

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