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## CLINICAL STUDY

# Should anterior pituitary function be tested during follow-up of all patients presenting at the emergency department because of traumatic brain injury?

Anke W van der Eerden<sup>1</sup>, Marcel Th B Twickler<sup>2,6</sup>, Fred C G J Sweep<sup>3</sup>, Tjemme Beems<sup>4</sup>, Henk T Hendricks<sup>5</sup>, Ad R M M Hermus<sup>2</sup> and Pieter E Vos<sup>1</sup>

Departments of <sup>1</sup>Neurology, <sup>2</sup>Endocrinology, <sup>3</sup>Chemical Endocrinology, <sup>4</sup>Neurosurgery and <sup>5</sup>Rehabilitation Medicine, Radboud University Nijmegen Medical Centre, Internal address 935, PO Box 9101, 6500 HB Nijmegen, The Netherlands and <sup>6</sup>Department of Vascular Medicine, Academic Medical Centre, University of Amsterdam, Amsterdam, The Netherlands

(Correspondence should be addressed to P E Vos; Email: p.vos@neuro.umcn.nl)

## Abstract

**Context:** A wide range (15–56%) of prevalences of anterior pituitary insufficiency are reported in patients after traumatic brain injury (TBI). However, different study populations, study designs, and diagnostic procedures were used. No data are available on emergency-department-based cohorts of TBI patients.

**Objective:** To assess the prevalence of pituitary dysfunction in an emergency-department-based cohort of TBI patients using strict endocrinological diagnostic criteria.

**Methods:** Of all the patients presenting in the emergency department with TBI over a 2-year period, 516 matched the inclusion criteria. One hundred and seven patients (77 with mild TBI and 30 with moderate/severe TBI) agreed to participate. They were screened for anterior pituitary insufficiency by GHRH–arginine testing, evaluation of fasting morning hormone levels (cortisol, TSH, free thyroxine, FSH, LH, and 17 $\beta$ -estradiol or testosterone), and menstrual history 3–30 months after TBI. Abnormal screening results were defined as low peak GH to GHRH–arginine, or low levels of any of the end-organ hormones with low or normal pituitary hormone levels. Patients with abnormal screening results were extensively evaluated, including additional hormone provocation tests (insulin tolerance test, ACTH stimulation test, and repeated GHRH–arginine test) and assessment of free testosterone levels.

**Results:** Screening results were abnormal in 15 of 107 patients. In a subsequent extensive endocrine evaluation, anterior pituitary dysfunction was diagnosed in only one patient (partial hypocortisolism).

**Conclusion:** By applying strict diagnostic criteria to an emergency-department-based cohort of TBI patients, it was shown that anterior pituitary dysfunction is rare (<1%). Routine pituitary screening in unselected patients after TBI is unlikely to be cost-effective.

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## Introduction

In Europe, the yearly incidence of traumatic brain injury (TBI) is 100–300 per 100 000 persons (1, 2). Head trauma can cause damage to any region in the brain (3). Involvement of the posterior pituitary gland during the acute phase after severe head trauma has been acknowledged for years, but trauma-induced anterior pituitary dysfunction was considered rare (4). However, several recent studies have reported of a high frequency of anterior pituitary hormone insufficiency between 2 weeks and 1.5 years after TBI, varying from 15 to 56% of patients with moderate or severe TBI (Mod/STBI) (5–14).

Anterior pituitary hormone deficiencies are associated with cognitive impairment, depression, anxiety, fatigue, apathy, and impaired quality of life (15–17),

problems that are also frequently reported by TBI patients (18). Therefore, abnormal anterior pituitary hormone levels after TBI might contribute to the problems reported by TBI patients. Additionally, hypogonadism may limit fertility, and hypocortisolism and hypothyroidism can be disabling and life-threatening (19, 20). Consequently, it was proposed that pituitary function should be screened in all patients after Mod or STBI, even in the absence of symptoms of hypopituitarism (8, 21, 22).

It remains unknown whether the wide range of reported frequencies of abnormal hormone levels reflects true differences in the prevalence of pituitary dysfunction – attributable to regional differences in severity and treatment of trauma – or reflects differences in patient selection and diagnostic criteria applied to define pituitary dysfunction in the various studies.

The objective of the present study was to assess the prevalence of anterior pituitary function in an emergency-department-based cohort of TBI patients using strict endocrinological criteria. Contrary to previous studies, all consecutive patients who had presented at the emergency department (ED) with TBI were eligible.

## Subjects and methods

Since 1998, all TBI patients presenting at the ED of the Radboud University Nijmegen Medical Centre (RUNMC, a level I Dutch trauma center) are included in the Radboud University Nijmegen Brain Injury Cohort Study (RUBICS) if a neurologist and/or neurosurgeon is consulted. According to our hospital protocol, a neurologist and/or neurosurgeon is consulted at the ED in case a head trauma patient presents with i) a Glasgow Coma Scale (GCS) of 3–14, or ii) a GCS of 15 with loss of consciousness (LOC) and/or posttraumatic amnesia (PTA), or iii) a GCS of 15 without LOC and PTA, but fulfilling additional criteria: unclear or ambiguous accident history, persisting or progressive headache, nausea and vomiting, intoxication with alcohol or drugs, epileptic seizures, coagulation disorders, platelet aggregation inhibitors or oral anticoagulation use, confusion, disorientation, feeling dazed, retrograde amnesia, focal neurological deficits, age > 60 or < 2 years, high-energy accident, or visible trauma above the clavicles (including signs of skull (base) fracture) (23). According to the hospital admission GCS, TBI patients are classified as mild (GCS 13–15), moderate (Mod) (GCS 9–12), or severe (GCS ≤ 8) (23, 24). In RUBICS, we register various clinical variables obtained from the ambulance or helicopter trauma physician, the ED, the intensive care unit (ICU), and the neurological and neurosurgical ward. Six and twelve months after TBI, the patients' functional status is assessed by neurological examination and Extended Glasgow Outcome Score version (25). For the present study, injury characteristics were derived from the RUBICS database. Additionally, we assessed actual body weight and length.

The ethics committee of the RUNMC approved the present study protocol. All patients gave informed consent before study entry.

### Selection of patients

We reviewed RUBICS data of all the consecutive patients ( $n=1425$ ) presenting within 24 h after TBI at the ED between November 2004 and November 2006. Inclusion criteria were age between 18 and 65 years, and speaking Dutch. Exclusion criteria were known neuroendocrine disorders, previous evaluation in the pre-TBI period for neuroendocrine disturbances, glucocorticoid therapy within 3 months before study entry, current alcohol or drug abuse limiting daily

functioning, other diseases substantially reducing life expectancy, inability to agree to participate (including mental retardation and dementia), obesity (body mass index (BMI) > 30 kg/m<sup>2</sup>), pregnancy, and lactation.

All 516 eligible patients (451 with a mild TBI (MTBI) and 65 with Mod to severe TBI (STBI); Fig. 1) received an invitation for hormonal evaluation. If pituitary dysfunction is a consequence of TBI, it seems reasonable to assume that the risk of pituitary dysfunction is higher in patients with more severe TBI. Therefore, in case of no response to the invitation within 4 weeks, we additionally contacted all patients with Mod/STBI and a random set of patients with MTBI by phone. Ultimately, of the 516 eligible patients, 107 agreed to participate (77 with MTBI and 30 with Mod/STBI), and they were evaluated for pituitary dysfunction.

### Study design

During the first visit, all patients were screened for insufficient function of the anterior pituitary gland. All patients with abnormal screening results were referred to the endocrinology department for extensive evaluation. The primary endpoint was pituitary dysfunction, which was confirmed by extensive endocrine evaluation.

### Screening for insufficient pituitary function

All patients were screened by a GHRH–arginine provocation test (100 µg GHRH i.v. bolus injection, immediately followed by infusion of an arginine solution (30 g in 30 min)). Baseline (0900 h in fasting state, 30 min after insertion of an i.v. catheter) serum levels of cortisol, TSH, free thyroxine (fT<sub>4</sub>), FSH, LH, and 17β-estradiol (E<sub>2</sub>) (females) or testosterone (males) were assessed. Additionally, premenopausal females were interviewed regarding their menstrual pattern.

Abnormal screening results were defined as 1) peak GH level below 3.5 µg/l (GHRH–arginine test) (26); 2) level of any of the fasting 0900 h end-organ hormones below the reference range of our laboratory (i.e. cortisol < 0.20 µmol/l, fT<sub>4</sub> < 8 pmol/l, total testosterone < 11 nmol/l in males, E<sub>2</sub> < 10 pmol/l in premenopausal females – not using oral contraceptives – in the follicular phase, and E<sub>2</sub> < 220 pmol/l in the luteal phase) with low or normal pituitary hormone levels (i.e. TSH < 4.0 mU/l; LH < 8.5 U/l and FSH < 11 U/l in males; LH < 16 U/l and FSH < 19 U/l in the follicular phase; LH < 19 U/l and FSH < 15 U/l in the luteal phase). Low gonadotropin levels in postmenopausal women were defined as LH < 12 U/l and FSH < 37 U/l. Premenopausal females who met the biochemical criteria of hypogonadism were classified as having an abnormal gonadal screening result if they were amenorrhic for more than 6 months.

Selection of patients

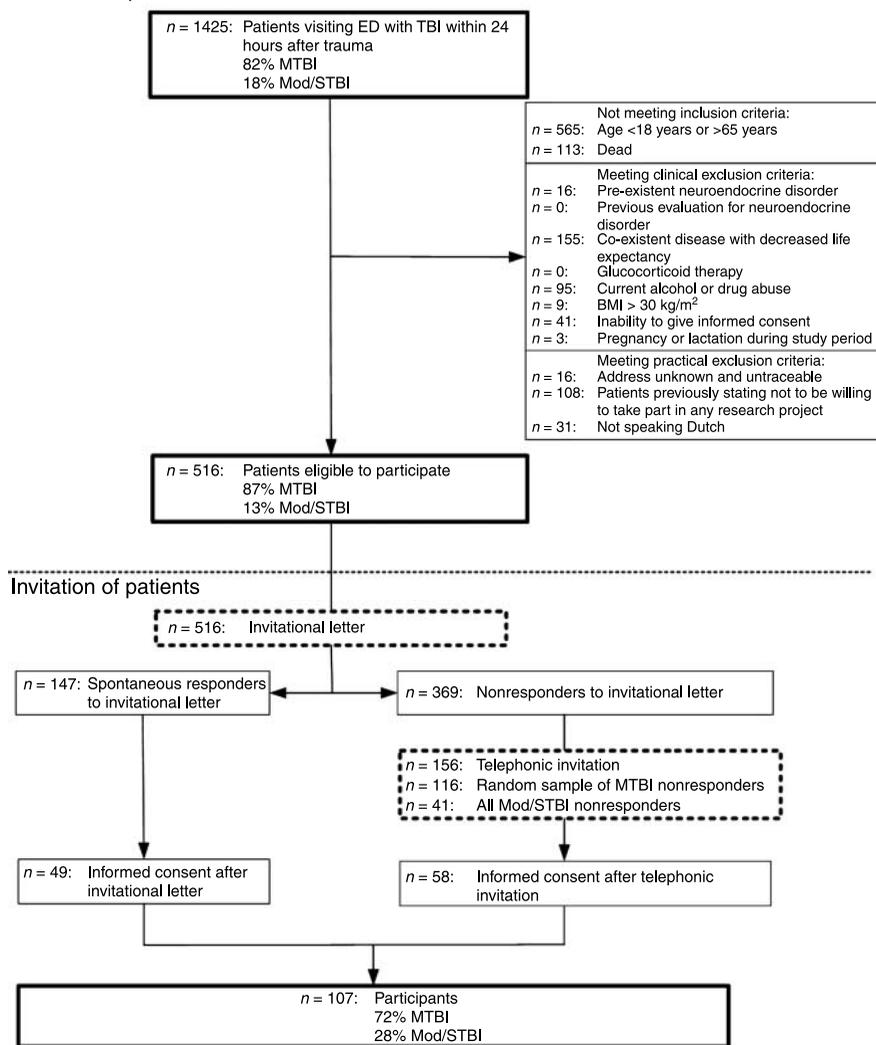


Figure 1 Patient selection flowchart.

**Extensive evaluation after abnormal screening for insufficient pituitary function**

Patients with one or more abnormal screening results were further evaluated by an endocrinologist within 2 months of the initial screening. Patients with abnormal somatotrophic or corticotrophic screening results underwent an insulin tolerance test (ITT; with lowest glucose level <2.0 mmol/l). In case of contra-indication to ITT, in patients with abnormal somatotrophic screening results, the GHRH-arginine test was repeated, whereas in patients with abnormal corticotrophic screening results an ACTH stimulation test using 250 µg synthetic ACTH(1-24) was performed. In males with abnormal gonadal screening results, serum-free testosterone was both directly measured and calculated (27). In males with one or both measures of free testosterone below 120 pmol/l (28), the evaluation of total and free testosterone levels was repeated.

In patients with abnormal thyrotrophic screening results, the evaluation of TSH and fT<sub>4</sub> levels was repeated.

Definitive pituitary dysfunction was diagnosed if one of the pituitary axes was disturbed at the extensive endocrinological evaluation. GHD was diagnosed in case of low peak GH to both GHRH-arginine test and ITT (i.e. maximum GH response <3.5 µg/l to GHRH-arginine test and maximum GH response <3.4 µg/l during ITT (26)), or during two GHRH-arginine tests. Hypocortisolism was defined as a low basal cortisol level with a low cortisol response during ITT (i.e. maximum cortisol response <0.55 µmol/l) or synthetic ACTH(1-24) (i.e. maximum cortisol response <0.58 µmol/l). Central hypothyroidism was defined as low fT<sub>4</sub> with low or normal TSH at two consecutive occasions. Hypogonadism was defined as low total and free testosterone with low or normal FSH and LH at two consecutive occasions (males); persistent amenorrhoea with low E<sub>2</sub> and low or

normal FSH and LH at two consecutive occasions (premenopausal females); or low LH and FSH at two consecutive occasions (postmenopausal females).

### Analytical procedures

Serum GH was measured by RIA using an antiserum against recombinant human GH, which was raised in a guinea pig. The same preparation was used for radioiodination. The second (98/754) international standard for GH was used for the standard curve. Separation of bound and free hormone was performed by a second antibody technique. The detection limit was 0.536 µg/L. Within and between coefficient of variations (CV) were

7.1 and 10.5%, 4.3 and 8.2%, 5.4 and 10.9% at levels 2.01, 3.62, and 11.79 µg/l respectively. Serum TSH was measured by immunoluminometric assay (ILMA) incorporated in a random access analyzer (Architect, Abbott Diagnostics). Serum fT<sub>4</sub> was estimated by a luminescence enzyme immunoassay incorporated in a random access assay system (Vitros ECI, Ortho Clinical Diagnostics, Beerse, Belgium).

Serum testosterone was assessed by <sup>3</sup>H-RIA after ether extraction of the samples, including correction for procedural losses (29). Symmetric dialysis for the measurement of the free testosterone fraction (free/total ratio) was performed as described previously (29) with the following modifications: samples were diluted 1 + 1

**Table 1** Characteristics of the eligible patients before study entry. Data are separately presented for participants, and for patients meeting the selection criteria of this study but not participating in the endocrine evaluation (nonparticipants).

Variable	Participants		Nonparticipants	
	MTBI (n=77) <sup>†</sup>	Mod/STBI (n=30) <sup>†</sup>	MTBI (n=374)	Mod/STBI (n=35)
Pre-injury				
Age (years)	45 (22–63)*	36 (21–62)	35 (21–61)	36 (20–65)
Male gender	50 (65%)	20 (67%)	260 (70%)	28 (80%)
Physical comorbidity	52 (68%)*	17 (57%)	189 (51%)	14 (40%)
Prior head injury	4 (5%)	0 (0%)	15 (4%)	1 (3%)
Peri-injury				
Admission GCS	15 (3–15)	3 (3–12)	15 (13–15)	3 (3–12)
Mechanism of injury				
Traffic	34 (44%)	19 (63%)	183 (49%)	23 (66%)
Fall	23 (30%)	6 (20%)	91 (24%)	10 (29%)
Sports	9 (12%)	3 (10%)	36 (10%)	1 (3%)
Other	11 (14%)	2 (7%)	65 (17%)	1 (3%)
Hypoxia at entry in ED	5 (6%)	7 (23%)	10 (3%)	5 (14%)
Hypotension at entry in ED	5 (6%)*	7 (23%)	4 (1%)	5 (14%)
Loss of consciousness	44 (57%)	29 (97%)	188 (50%)	33 (94%)
Duration of PTA				
No PTA	38 (49%)	1 (3%)	175 (47%)	0 (0%)
PTA 1–30 min	30 (39%)	0 (0%)	142 (38%)	0 (0%)
PTA >30 min	9 (12%)	29 (97%)	57 (15%)	35 (100%)
Headache on admission	23 (31%)	1 (14%)	106 (29%)	0 (0%)
Headache not applicable <sup>a</sup>	2	23	3	23
Nausea or vomiting	10 (13%)	0 (0%)	63 (17%)	0 (0%)
CT characteristics				
No CT made	19 (25%)	0 (0%)	77 (21%)	0 (0%)
No traumatic abnormalities	41 (53%)	1 (3%)	233 (62%)	4 (11%)
Traumatic abnormalities	17 (22%)	29 (97%)	64 (17%)	31 (89%)
Additional extracranial injuries	59 (77%) <sup>†</sup>	25 (83%)	181 (48%)	25 (71%)
ISS	9 (2–41)	35 (10–62)*	6 (2–29)	20 (9–50)
Hospitalization	42 (55%)	30 (100%)	214 (57%)	35 (100%)
ICU	11 (14%)	27 (90%)	22 (6%)	29 (83%)
Other ward	31 (40%)	3 (10%)	192 (51%)	6 (17%)
Cranial surgery performed	1 (1%)	3 (10%)	5 (1%)	1 (3%)
Post-injury				
Interval between TBI and endocrine evaluation (months)	13 (5–29)*	14 (5–28)	18 (7–29)	19 (6–32)
GOS-E 3–9 months after TBI	7 (4–8)	6 (3–8)	7 (5–8)	6 (3–8)
GOS-E 9–15 months after TBI	8 (5–8)	7 (3–8)	8 (6–8)	6 (3–8)
BMI (kg/m <sup>2</sup> )	25 (19–30)	24 (21–29)	–	–

Data are shown as number (percentage) or as median (5–95th percentile). BMI, body mass index; GCS, Glasgow Coma Scale score; GOS-E, Extended Glasgow Outcome Scale Score version (range 1–8, higher score refers to a better functional outcome); ICU, intensive care unit; ISS, injury severity scale score (range 0–75, lower score refers to lower severity of injury to various body regions) (22); MTBI, mild traumatic brain injury; Mod/STBI, moderate to severe traumatic brain injury; n, number of patients; PTA, posttraumatic amnesia. \**P*<0.01 for the difference between participants and nonparticipants with a similar severity of TBI; <sup>†</sup>*P*<0.001.

<sup>a</sup>Headache on admission only applicable for patients without loss of consciousness or with loss of consciousness for <30 min.

with HEPES buffer prior to dialysis. Aliquots, 180 µl, were taken to pipette on both sides of the membrane, and the dialysis time was 2.5 h. As a calibrator, we used pooled serum that had been spiked with 100 nmol/l testosterone, in which the free testosterone fraction had been assessed by equilibrium dialysis with total testosterone assessment. The within-assay CV was 5.4% ( $n=45$ ), and the between-assay CV (of duplicate means) were 4.6 and 6.4% at mean percent free testosterone levels 1.12 and 1.01% respectively ( $n=6$ ). We calculated a free testosterone index from total testosterone and sex hormone binding globulin (SHBG) concentrations using estimates based on the algorithm we recently developed to evaluate equilibrium constants of testosterone and SHBG or albumin from serum-free testosterone measurements by a near-reference method, i.e. symmetric dialysis (27). This free testosterone index perfectly matches with the free testosterone concentrations measured by symmetric dialysis. SHBG was measured by a commercial ILMA performed on an Abbott Architect Immunoanalyzer (Abbott).

E<sub>2</sub> was evaluated after ether extraction of 0.5 ml serum to which recovery tracer was added, followed by chromatography on Sephadex LH20 columns by RIA (30).

Serum FSH and LH were determined with fluorescenceimmunoassay (Abbott Diagnostics) using a random access analyzer (Type AxSYM; Abbott).

Serum total cortisol was measured by luminescence immunoassay on an Architect random access analyzer (Abbott).

### Statistical analyses

Data were analyzed using SPSS software version 12.0. To evaluate whether the participants with MTBI were a representative sample of all the eligible patients with MTBI and whether the participants with Mod/STBI were representative for all the patients with Mod/STBI,

participants, and nonparticipants (i.e. patients meeting the study criteria but not participating in the hormonal evaluations) were compared using the two-sample *t*-test in case of continuous measures, Wilcoxon–Mann–Whitney test for ordinal data, and  $\chi^2$  test for frequency data. To correct for multiple testings, a *P* value <0.01 was considered significant. Prevalences of pituitary dysfunction were described as percentages with exact 95% confidence intervals (CIs) of prevalences.

## Results

### Patient characteristics

Compared with nonparticipants with MTBI, participants with MTBI had more prognostically unfavorable characteristics (i.e. a higher age, more comorbidity, and more extracranial injury), and a shorter interval between TBI and endocrine evaluation (median 13 vs 18 months). Participants with Mod/STBI had higher injury severity scores (31) as compared with nonparticipants with Mod/STBI. No relation was found between the severity of TBI and interval between TBI and endocrine evaluation (Table 1).

### Endocrine evaluation

While screening the 107 patients for insufficient pituitary function, 15 patients (14.0%) with abnormal results were identified. The results of this initial screening were abnormal for the following axes: GH–insulin-like growth factor 1 (IGF1;  $n=1$ ), pituitary–gonadal ( $n=7$  males), pituitary–adrenal ( $n=6$ ), and pituitary–thyroid ( $n=1$ ) axes (Table 2).

In a subsequent extensive endocrine evaluation of all the 15 patients with initial abnormal screening results, 14 patients were found to have hormone levels within the reference levels of our laboratory (Table 2).

**Table 2** Results of extensive endocrine evaluation in patients with abnormal hormonal screening results.

Sex	Age (years)	Severity of TBI	Screening results	Results of extensive endocrine evaluation
F	31	MTBI	TSH 1.28 mU/l; fT <sub>4</sub> 7.9 pmol/l	Follow-up thyroid: TSH 1.69 mU/l; fT <sub>4</sub> 8.4 pmol/l
F	53	MTBI	Cort 0.15 µmol/l	ITT: peak cort 0.50 µmol/l, peak ACTH 62.2 pmol/l
F	39	ModTBI	Cort 0.14 µmol/l	ITT: peak cort 0.65 µmol/l, peak ACTH 39.2 pmol/l
M	34	MTBI	Cort 0.18 µmol/l	ITT: peak cort 0.57 µmol/l, peak ACTH 41.2 pmol/l
M	46	MTBI	Cort 0.19 µmol/l	ITT: peak cort 0.59 µmol/l, peak ACTH 36.3 pmol/l
M	58	MTBI	Cort 0.15 µmol/l	ITT: peak cort 0.58 µmol/l, peak ACTH 63.0 pmol/l
M	55	MTBI	Cort 0.15 µmol/l	ITT: peak cort 0.57 µmol/l, peak ACTH 24.2 pmol/l
M	33	MTBI	GHRH–arginine test: peak GH 2.35 µg/l	ITT contraindicated (epileptic seizures) GHRH–arginine test: peak GH 3.69 µg/l
M	36	MTBI	Test 10.3 nmol/l	fTest <sub>d</sub> 333 pmol/l; fTest <sub>c</sub> 294 pmol/l
M	59	MTBI	Test 8.04 nmol/l	fTest <sub>d</sub> 137 pmol/l; fTest <sub>c</sub> 155 pmol/l
M	22	MTBI	Test 10.6 nmol/l	fTest <sub>d</sub> 257 pmol/l; fTest <sub>c</sub> 288 pmol/l
M	41	MTBI	Test 9.3 nmol/l	fTest <sub>d</sub> 260 pmol/l; fTest <sub>c</sub> 231 pmol/l
M	44	STBI	Test 7.79 nmol/l	fTest <sub>d</sub> 223 pmol/l; fTest <sub>c</sub> 201 pmol/l
M	49	STBI	Test 8.47 nmol/l	fTest <sub>d</sub> 187 pmol/l; fTest <sub>c</sub> 202 pmol/l
M	41	STBI	Test 10.3 nmol/l	fTest <sub>d</sub> 139 pmol/l; fTest <sub>c</sub> 259 pmol/l

Cort, cortisol; F, female; fT<sub>4</sub>, free thyroxine; fTest<sub>c</sub>, calculated free testosterone; fTest<sub>d</sub>, determined free testosterone; GHD, GH deficiency; M, male; MTBI, mild TBI; ModTBI, moderate TBI; STBI, severe TBI; TBI, traumatic brain injury; Test, total testosterone.

**Table 3** Selection criteria and baseline populations of ten previous key studies on the prevalence of pituitary dysfunction after traumatic brain injury (TBI).

Study	Baseline population	Duration of follow-up (m)	Trauma-related inclusion criteria	Exclusion criteria	n (% participation)	Age (years)	Sex (% male)	BMI (kg/m <sup>2</sup> )	ModTBI/STBI (%)	ICU (%)	Traumatic CT (%)	Cranial surgery (%)
Bondanelli (2004) (5) <sup>a</sup>	Admitted to neurosurgery sections of one of two general hospitals	12–64	–	Pre-existing metabolic, endocrine, neurological, cardiac, or pulmonary diseases; liver or renal failure; infectious disease; substance abuse; barbiturates or medication affecting GH secretion; parenteral nutrition, mechanical ventilation, GC treatment in previous 2 m	76 (63%), 50 of whom underwent all study procedures	37.6 (2.4)	80	24.6 (0.4)	68	NS	82	NS (≥28)
Aimaretti (2005) (6) <sup>a</sup>	Brain-injured patients NOS	3 and 12	NS	GC treatment in previous 2 m	70 (% NS)	39.31 (2.4)	71	23.8 (0.4)	53	NS	NS	NS
Agha (2004) (7) <sup>b</sup>	Admitted to neurosurgical unit in national neurosurgical center	17 (6–36)	Post-resuscitation pre-sedation GCS 3–13; ≥ 6 m post-TBI	Having suffered a prolonged hypotensive period ( $P_{syst} < 90$ mmHg for > 30 min); pregnancy; GC therapy; too ill to participate	102 (80%)	28 (15–65)	83	NS as a group value	NS <sup>c</sup> 56% GCS ≤ 8; 41% GCS 9–13	82	99	54
Leal-Cerro (2005) (9) <sup>d</sup>	Discharged from ICU of tertiary care level university hospital with a regional unit specialized in TBI	NS	Post-resuscitation GCS < 8; hospitalization GOS 3–5	Severe physical impairment	Questionnaire: 170 (68%); lab: 99	NS as group value	88	NS as group value	100	100	NS	NS
Agha (2005) (8) <sup>e</sup>	Admitted to neurosurgical unit in national neurosurgical center	12 d (7–20 d) and 6 and 12 m	Initial post-resuscitation and pre-sedation GCS ≤ 13	Too ill to undergo dynamic testing; pregnancy; having received GC therapy	12 d: 50 (93%); 6 m: 48 (92%); 12 m: 48 (92%)	37 (14)	76	24.3 (3.8)	NS <sup>c</sup> (64% GCS ≤ 8; 36% GCS 9–13)	NS (≥80)	100	50
Popovic (2004) (10) <sup>f</sup>	NS	46 (12–264)	GCS ≤ 13, hospitalized for TBI ≥ 1 y before	–	67 (% NS)	37.5	58	24.8	NS <sup>c</sup> (GCS mean 9.4)	NS	NS	NS
Schneider (2006) (11) <sup>e</sup>	Rehabilitation unit of neurological clinic	3 m (2 w) and 12 m (4 w)	TBI grades I–III, based on initial GCS	GC therapy in previous 3 w; GH therapy in previous 12 m; history of cranial irradiation; pre-existing pituitary disease, severe cardiac, renal, or hepatic diseases, sepsis; substance abuse	3 m: 78 (% NS); 12 m: 70 (% NS)	3 m: 36 (15.0); 12 m: 35.7 (14.8)	3 m: 67; 12 m: 67	3 m: 22.0 (3.1); 12 m: 23.8 (3.2)	NS (3 m: GCS 7.4 (4.5) 12 m: 7.5 (4.6))	NS	NS	NS

Table 3 Continued

Study	Baseline population	Duration of follow-up (m)	Trauma-related inclusion criteria	Exclusion criteria	n (% participation)	Age (years)	Sex (% male)	BMI (kg/m <sup>2</sup> )	ModTBI/STBI (%)	ICU (%)	Traumatic CT (%)	Cranial surgery (%)
Tanriverdi (2006) (12) <sup>e</sup>	Admitted to neurosurgery ICU	<24 h of ICU admission and 12 m	NS	NS	n = 52 (% NS)	35.9 (13.8)	83	NS	40.4% <sup>g</sup>	100	NS	NS
Herrmann (2007) (13) <sup>e</sup>	Discharged from neurosurgery departments; one neurosurgical rehabilitation and two general university hospitals	22 (10) NS	NS	Persistent alcohol abuse; apallic syndrome; too ill to undergo dynamic testing; known pituitary deficiencies/pituitary disease; pregnancy; GC in previous 3 m	n = 76 (% NS)	39 (14)	70	25.8 (4.2)	100	NS 100?	NS	NS
Klose (2007) (14) <sup>b</sup>	Admitted to neurosurgery departments; one university and one country hospital	13 (10–27)	–	Doubt of TBI; substance abuse; psychiatric disease; previous severe TBI/apoplexy; malign. disease; chronic GC use	104 (67%)	41 (18–64)	75	25 (17–39)	58	NS (≥50)	85	NS (≥2)
Present study	Consecutive patients with TBI, presenting within 24 h at ED of level 1 trauma center Nov 2004–Nov 2006	14 (5–28)	–	Pre-existent neuroendocrine disorder; glucocorticoid therapy; substance abuse; disorder reducing life expectancy; mental retardation; dementia; death; obesity; pregnancy; lactation; not speaking Dutch; address unknown; previously denied taking part in any future study	107 (21%)	41 (21–63)	65	25 (20–30)	28	36	43	4

BMI, body mass index; d, days; ED, emergency department; GC, glucocorticoid; h, hours; ICU, hospitalization at intensive care unit; m, months; n, number of patients; NOS, not otherwise specified; NS, not specified; p5, 5th percentile; p95, 95th percentile; P<sub>sys</sub>, systolic blood pressure; TBI, traumatic brain injury; w, weeks; y, years.  
<sup>a</sup>Numeric values presented as mean (s.e.m).  
<sup>b</sup>Numeric values presented as median (range).  
<sup>c</sup>Unclear how many patients had GCS 13, thus how many patients according to our definition had suffered MTBI.  
<sup>d</sup>Notation of numeric values not specified.  
<sup>e</sup>Numeric values presented as mean (s.d).  
<sup>f</sup>Numeric values presented as mean (range).  
<sup>g</sup>Based on GCS as soon as the patient was admitted to the ICU.

Partial hypocortisolism was diagnosed in one MTBI patient. Therefore, the prevalence of definitive pituitary dysfunction in our ED-based cohort of TBI patients was 0.9% (95% CI 0.0–5.0%).

## Discussion

In this study, <1% of the patients had pituitary dysfunction between 3 and 30 months after presentation at the ED with TBI. In all the 30 patients with Mod/STBI participating in our study, anterior pituitary function was normal. The prevalence of hypopituitarism after TBI that we report is considerably lower than the prevalences reported by recent studies (15–56%) (5–14). The aim of our study was to evaluate anterior pituitary function in a patient cohort representative for all the patients with TBI. Therefore, it is not surprising that our study showed a lower frequency of hypopituitarism compared with previous studies. In these previous studies (5, 7–14), the percentage of patients with Mod/STBI was higher (56–100%) than that of the patients in our study. In addition to the differences in the study cohorts, the wide range of reported prevalences of hypopituitarism (varying from 15 to 56%) may be attributed to the differences in diagnostic criteria (5–14). Furthermore, some studies included patients in whom, besides a history of TBI, alternative causes of pituitary dysfunction had not been ruled out, such as pre-existent hypopituitarism (6–10, 12, 14), BMI above 30 kg/m<sup>2</sup> (5–10, 12–14), and substance abuse (6–10, 12). These differences hinder the comparison of the findings of previous reports with our findings.

Table 3 summarizes the selection criteria and patient characteristics of ten previous studies on post-TBI hypopituitarism beyond the subacute phase, i.e. >5 months after TBI. Some authors did not unequivocally specify the population from which the study population was selected, or did not unequivocally define the selection criteria (6, 10, 12, 13). Consequently, the population in which the prevalence of pituitary dysfunction was assessed remained insufficiently defined. Contrary to our study, patients who were evaluated in all previous studies were selected from hospitalized patient populations only (at a general ward (5, 7, 8, 10, 13, 14), at an ICU (9, 12), or at a rehabilitation institute (11)). Therefore, these studies included patients with more severe brain injury. In our study, all patients presenting at our ED with TBI were eligible, whether or not hospitalized thereafter. This approach increased the probability that the sample of TBI patients we evaluated was representative for a general TBI population.

Some demographic and injury characteristics were unfavorable in MTBI patients participating in our study compared with MTBI patients who did not participate. In some previous studies, no association of pituitary

dysfunction with TBI severity was reported (6, 7, 10–13), whereas others found pituitary dysfunction to be more prevalent in patients with more severe TBI (5, 14). In their systematic review, Schneider *et al.* pooled the reported prevalences in severe (35.3%, 95% CI 27.3–44.2%), Mod (10.9%, 95% CI 5.1–21.8%), and MTBI (16.8%, 95% CI 10.9–25.0%) (22), showing that the risk of pituitary dysfunction is higher in patients with STBI than in patients with a MTBI. In order to prevent the underestimation of the prevalence of pituitary dysfunction, our study enrolment procedure implied that the largest effort was made to include patients with Mod/STBI, resulting in an overrepresentation of Mod/STBI patients. Therefore, the low prevalence of anterior pituitary dysfunction in our study cohort is unlikely to be an underestimation of the true prevalence of TBI-induced pituitary dysfunction.

Our results show that a strict differentiation should be made between definitive 'pituitary dysfunction' and 'abnormal results of hormonal screening'. Indeed, in our study, results of hormonal screening were frequently abnormal (14% of the patients), whereas definitive pituitary dysfunction was rare (<1% of the patients). Supplementary Table 1 (see section on supplementary data given at the end of this article) summarizes diagnostic criteria applied in ten previous studies and the reported prevalences of pituitary dysfunction.

We and four other groups used the GHRH-arginine test as the primary test to evaluate the GH-IGF1 axis (5, 6, 11, 13). Only one of those groups required confirmation by a second test, the ITT, like we did (13). For the GHRH-arginine test, previous authors used a peak GH of 9.0 µg/l as a cut-off value (5, 6, 11, 13), whereas recent clinical practice guidelines recommend 4.1 µg/l (26). Of our 107 patients, 13 patients (12%) had a peak GH response below 9.0 µg/l. This observation is in line with the results of previous studies defining GHD based on GHRH-arginine testing and using 9.0 µg/l as a cut-off value (median 9.5%, range 8–23%) (5, 6, 11, 13). Bondanelli *et al.* defined even patients with peak GH <16.5 µg/l as hypopituitaristic. Indeed, they reported a very high prevalence of hypopituitarism (i.e. 54%) (5). Such patients are unlikely to benefit from hormone substitution, and most health assurance companies will not reimburse GH substitution in these cases. Comparison of absolute hormone levels between the studies is intricate, as even after harmonization the performance of various immunoassays varies widely. For example, after harmonization, the interlaboratory CV of GH measurements is at least 7% (32).

The diagnosis of secondary hypogonadism is challenging as no consensus exists. Most preceding studies define hypogonadism as low or normal LH and FSH levels with a low total testosterone level (5–8, 10, 11, 13), or less frequently a low free testosterone level (9, 12, 14). Klose *et al.* were the only authors requiring

confirmation of low testosterone levels in a second visit (14). Seven percent of our male patients had onetime low total testosterone with low or normal LH and FSH. Leal-Cerro *et al.* used a GnRH provocation test, but they did not specify how patients were selected for GnRH testing (9). Two previous studies defined secondary hypogonadism in females as low levels of E<sub>2</sub>, LH, and FSH (5, 12). Most studies, however, included additional criteria, such as the presence of menstrual disturbances (6, 9, 10, 14) or secondary amenorrhea (7, 8, 11, 13), like we did. None of our female patients was amenorrheic with low E<sub>2</sub> and low or normal LH and FSH.

Aimaretti *et al.* defined hypocortisolism as onetime low serum cortisol or a decreased level of 24-h urinary free cortisol (6). Six percent of our patients had a low serum cortisol level at screening, but hypocortisolism was confirmed in only one patient. The prevalence of low basal serum cortisol levels in our TBI population is similar to the prevalence in an unselected sample from the general Dutch population (33). Some authors did not specify their criteria for hypocortisolism (5, 10). However, most authors diagnosed hypocortisolism with a hormone provocation test (such as ITT (7, 9, 13, 14), glucagon stimulation test (7, 8), or short ACTH stimulation test (7, 11, 14)). Groups basing their definition of hypocortisolism on basal cortisol levels, glucagon stimulation test, or ACTH stimulation test found a relatively high prevalence of hypocortisolism (range 5–19%) (6–8, 11, 12). Like we did, four other groups used an ITT (7, 9, 13, 14), two of which specified the selection criteria for patients to undergo ITT (7, 14). Three of them found a low prevalence of hypocortisolism: 1–6% (9, 13, 14), whereas Agha *et al.* found 13% (7). Klose *et al.* found that 3.3% of their age- and BMI-matched controls had a cortisol response meeting their definition of hypocortisolism (14).

Hypothyroidism was mostly assessed by low fT<sub>4</sub> and low or normal TSH according to local reference ranges (5, 6, 12, 13), or without a specification of local reference ranges (7, 8, 11). One percent of our patients had onetime low fT<sub>4</sub> with low or normal TSH. Klose *et al.* were the only authors requiring persistence of low fT<sub>4</sub>, like we did (14). Leal-Cerro *et al.* additionally used a TRH stimulation test (in some, but not in all patients) (9).

A limitation of this study is that because of the very low frequency of hypopituitarism, no risk factors for pituitary dysfunction could be identified. Another limitation is the use of a stimulation test of the pituitary–adrenal axis only in patients who had low basal cortisol levels. This strategy cannot unequivocally exclude relative pituitary–adrenal dysfunction. However, a low basal cortisol level does exclude absolute pituitary–adrenal dysfunction.

In conclusion, our findings show that the results of hormonal screening are abnormal in a significant proportion of patients who originally presented at the

ED with TBI, but that definite pituitary dysfunction is rare. Therefore, routine screening for hormone disturbances in unselected patients after TBI is unlikely to be cost-effective. However, screening should be advised in all patients with symptoms and signs of hypopituitarism and a history of TBI, and based on earlier reports, probably also in patients with more severe forms of TBI (e.g. those necessitating neurosurgical intervention or admission to an ICU).

### Supplementary data

This is linked to the online version of the paper at <http://dx.doi.org/10.1530/EJE-09-0436>.

### Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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### Author contribution statement

P E Vos initiated the study. A W van der Eerden, P E Vos, M Th B Twickler, F Sweep, and A R M M Hermus designed the study. A W van der Eerden acquired the data. F C G J Sweep coordinated the evaluation of the serum samples. A W van der Eerden, P E Vos, M Th B Twickler, F C G J Sweep, T Beems, H T Hendricks, and A R M M Hermus analyzed and interpreted the data, and prepared the manuscript. All authors had full access to all the data and had the final responsibility for the decision to submit for publication.

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### References

- 1 Tagliaferri F, Compagnone C, Korsic M, Servadei F & Kraus J. A systematic review of brain injury epidemiology in Europe. *Acta Neurochirurgica* 2006 **148** 255–268.
- 2 Hirtz D, Thurman DJ, Gwinn-Hardy K, Mohamed M, Chaudhuri AR & Zalutsky R. How common are the “common” neurologic disorders? *Neurology* 2007 **68** 326–337.
- 3 Povlishock JT & Katz DI. Update of neuropathology and neurological recovery after traumatic brain injury. *Journal of Head Trauma Rehabilitation* 2005 **20** 76–94.
- 4 Edwards OM & Clark JD. Post-traumatic hypopituitarism. Six cases and a review of the literature. *Medicine* 1986 **65** 281–290.
- 5 Bondanelli M, De Marinis L, Ambrosio MR, Monesi M, Valle D, Zatelli MC, Fusco A, Bianchi A, Farneti M & degli Uberti EC. Occurrence of pituitary dysfunction following traumatic brain injury. *Journal of Neurotrauma* 2004 **21** 685–696.

- 6 Aimaretti G, Ambrosio MR, Di Somma C, Gasperi M, Cannavò S, Scaroni C, Fusco A, Del Monte P, De Menis E, Faustini-Fustini M, Grimaldi F, Logoluso F, Razzore P, Rovere S, Benvenega S, Degli Uberti EC, De Marinis L, Lombardi G, Mantero F, Martino E, Giordano G & Ghigo E. Residual pituitary function after brain injury-induced hypopituitarism: a prospective 12-month study. *Journal of Clinical Endocrinology and Metabolism* 2005 **90** 6085–6092.
- 7 Agha A, Rogers B, Sherlock M, O'Kelly P, Tormey W, Philips J & Thompson CJ. Anterior pituitary dysfunction in survivors of traumatic brain injury. *Journal of Clinical Endocrinology and Metabolism* 2004 **89** 4929–4936.
- 8 Agha A, Phillips J, O'Kelly P, Tormey W & Thompson CJ. The natural history of post-traumatic hypopituitarism: implications for assessment and treatment. *American Journal of Medicine* 2005 **118** 1416e1–1416e7.
- 9 Leal-Cerro A, Flores JM, Rincon M, Murillo F, Pujol M, Garcia-Pesquera F, Diequez C & Casanueva FF. Prevalence of hypopituitarism and growth hormone deficiency in adults long-term after severe traumatic brain injury. *Clinical Endocrinology* 2005 **62** 525–532.
- 10 Popovic V, Pekic S, Pavlovic D, Maric N, Jasovic-Gasic M, Djurovic B, Medic Stojanoska M, Zivkovic V, Stojanovic M, Doknic M, Milic N, Djurovic M, Dieguez C & Casanueva FF. Hypopituitarism as a consequence of traumatic brain injury (TBI) and its possible relation with cognitive disabilities and mental distress. *Journal of Endocrinological Investigation* 2004 **27** 1048–1054.
- 11 Schneider HJ, Schneider M, Saller B, Petersenn S, Uhr M, Husemann B, von Rosen F & Stalla GK. Prevalence of anterior pituitary insufficiency 3 and 12 months after traumatic brain injury. *European Journal of Endocrinology* 2006 **154** 259–265.
- 12 Tanriverdi F, Senyurek H, Unluhizarci K, Selcuklu A, Casanueva FF & Kelestimur F. High risk of hypopituitarism after traumatic brain injury: a prospective investigation of anterior pituitary function in the acute phase and 12 months after trauma. *Journal of Clinical Endocrinology and Metabolism* 2006 **91** 2105–2111.
- 13 Herrmann BL, Rehder J, Kahlke S, Wiedemayer H, Doerfler A, Ischebeck W, Laumer R, Forsting M, Stolke D & Mann K. Hypopituitarism following severe traumatic brain injury. *Experimental and Clinical Endocrinology and Diabetes* 2006 **114** 316–321.
- 14 Klose M, Juul A, Poulsgaard L, Kosteljanetz M, Brennum J & Feldt-Rasmussen U. Prevalence and predictive factors of post-traumatic hypopituitarism. *Clinical Endocrinology* 2007 **67** 193–201.
- 15 Van Aken MO & Lamberts SW. Diagnosis and treatment of hypopituitarism: an update. *Pituitary* 2005 **8** 183–191.
- 16 Sternbach H. Age-associated testosterone decline in men: clinical issues for psychiatry. *American Journal of Psychiatry* 1998 **155** 1310–1318.
- 17 Deijen JB, de Boer H & van der Veen EA. Cognitive changes during growth hormone replacement in adult men. *Psychoneuroendocrinology* 1998 **23** 45–55.
- 18 Mittenberg W, Canyock EM, Condit D & Patton C. Treatment of post-concussion syndrome following mild head injury. *Journal of Clinical and Experimental Neuropsychology* 2001 **23** 829–836.
- 19 Yamamoto T, Fukuyama J & Fujiyoshi A. Factors associated with mortality of myxedema coma: report of eight cases and literature survey. *Thyroid* 1999 **9** 1167–1174.
- 20 Bouillon R. Acute adrenal insufficiency. *Endocrinology and Metabolism Clinics of North America* 2006 **35** 767–775 ix.
- 21 Schneider HJ, Stalla GK & Buchfelder M. Expert meeting: hypopituitarism after traumatic brain injury and subarachnoid haemorrhage. *Acta Neurochirurgica* 2006 **148** 449–456.
- 22 Schneider HJ, Kreitschmann-Andermahr I, Ghigo E, Stalla GK & Agha A. Hypothalamic dysfunction following traumatic brain injury and subarachnoid hemorrhage. A systematic review. *Journal of the American Medical Association* 2007 **298** 1429–1438.
- 23 Vos PE, Battistin L, Birbamer G, Gerstenbrand F, Potapov A, Prevec T, Stepan ChA, Traubner P, Twijnstra A, Vecsei L, von Wild K & European Federation of Neurological Societies. EFNS guideline on mild traumatic brain injury: report of an EFNS task force. *European Journal of Neurology* 2002 **9** 207–219.
- 24 Mild Traumatic Brain Injury Committee. Definition of mild traumatic brain injury. *Journal of Head Trauma Rehabilitation* 1993 **8** 86–87.
- 25 Wilson JT, Pettigrew LE & Teasdale GM. Structured interviews for the Glasgow Outcome Scale and the extended Glasgow Outcome Scale: guidelines for their use. *Journal of Neurotrauma* 1998 **15** 573–585.
- 26 Molitch ME, Clemmons DR, Malozowski S, Merriam GR, Shalet SM, Vance ML. Endocrine Society's Clinical Guidelines Subcommittee, & Stephens PA. Evaluation and treatment of adult growth hormone deficiency: an Endocrine Society Clinical Practice Guideline. *Journal of Clinical Endocrinology and Metabolism* 2006 **91** 1621–1634.
- 27 Ross HA, Meuleman EJ & Sweep FC. A simple method for estimating equilibrium constants for serum testosterone binding resulting in an optimal free testosterone index for use in elderly men. *Clinical Chemistry and Laboratory Medicine* 2005 **43** 613–616.
- 28 Van Uytvanghe K, Stöckl D, Kaufman JM, Fiers T, Ross HA, De Leenheer AP & Thienpont LM. Evaluation of a candidate reference measurement procedure for serum free testosterone based on ultrafiltration and isotope dilution-gas chromatography-mass spectrometry. *Clinical Chemistry* 2004 **50** 2101–2110.
- 29 Swinkels LM, van Hoof HJ, Ross HA, Smals AG & Benraad TJ. Concentrations of salivary testosterone and plasma total, non-sex-hormone-binding globulin-bound, and free testosterone in normal and hirsute women during administration of dexamethasone/synthetic corticotropin. *Clinical Chemistry* 1991 **37** 180–185.
- 30 Thomas CM, Corbey RS & Rolland R. Assessment of unconjugated oestradiol and progesterone serum levels throughout pregnancy in normal women and in women with hyperprolactinaemia, who conceived after bromocriptine treatment. *Acta Endocrinologica* 1977 **86** 405–414.
- 31 Baker SP, O'Neill B, Haddon W Jr & Long WB. The injury severity score: a method for describing patients with multiple injuries and evaluating emergency care. *Journal of Trauma* 1974 **14** 187–196.
- 32 Ross HA. Reporting growth hormone assay results in terms of one consensus recombinant standard preparation offers less than optimal reduction of between-method variation. *Clinical Chemistry and Laboratory Medicine* 2008 **46** 1334–1335.
- 33 Enderit E, Ouwehand A, Fliers E, Prummel MF & Wiersinga WM. Establishment of reference values for endocrine tests. Part IV: adrenal insufficiency. *Netherlands Journal of Medicine* 2005 **63** 435–443.

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