Hypopituitarism : clinical assessment in different conditions

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Chapter 2

Clinical review: Hypopituitarism following traumatic brain injury – the prevalence is affected by the use of different dynamic tests and different normal values

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Abstract

Objective: Traumatic brain injury (TBI) has emerged as an important cause of hypopituitarism. However, considerable variations in the prevalence of hypopituitarism are reported. These can partly be explained by severity of trauma and timing of hormonal evaluation, but may also be dependent on endocrine tests and criteria used for diagnosis of hypopituitarism.

Methods: Systematic review of studies reporting prevalence of hypopituitarism in adults ≥ 1 year after TBI focusing on used (dynamic) tests and biochemical criteria.

Results: We included data from 14 studies with a total of 931 patients. There was considerable variation in definition of hypopituitarism. Overall, reported prevalences of severe GH deficiency varied between 2 and 39%. Prevalences were 8–20% using the GHRH-arginine test (cut-off < 9 μg/L), 11–39% using the glucagon test (cut-off 1–5 μg/L), 2% using the GHRH test (no cut-off) and 15–18% using the insulin tolerance test (ITT) (cut-off < 3 μg/L).

Overall, the reported prevalence of secondary adrenal insufficiency had a broad range from 0 to 60%. This prevalence was 0–60% with basal cortisol (cut-off < 220 or < 440 nmol/L), 7–19% using the ACTH test and 5% with the ITT as first test (cut-off < 500 or < 550 nmol/L). Secondary hypothyroidism was present in 0–19% (free T_4) or 5–15% (TRH stimulation). Secondary hypogonadism was present in 0–29%.

Conclusion: The reported variations in the prevalence rates of hypopituitarism after TBI are in part caused by differences in definitions, endocrine assessments of hypopituitarism and confounding factors. These methodological issues prohibit simple generalizations of results of original studies on TBI-associated hypopituitarism in the perspective of meta-analyses or reviews.

Introduction

In recent years, an increasing number of studies have reported the presence of pituitary insufficiency in patients who experienced traumatic brain injury (TBI) (1–14). The prevalence of pituitary insufficiency after TBI appeared to be unexpectedly high (15;16). Remarkably, the prevalence rates varied considerably among the different studies, ranging from 15 to even 90% of the patients.

Several factors influence the prevalence of hypopituitarism after TBI. First, the time interval between TBI and the assessment of pituitary function, since hormone alterations mimicking pituitary insufficiency are prevalent in the early post-traumatic period. Second, the type and severity of the brain injury affects the prevalence of hypopituitarism, because persistent pituitary insufficiency is only frequent after severe TBI (7;15). Third, endocrine tests, assays, and criteria for the diagnosis of hypopituitarism differ between the studies. Although many reviews have addressed TBI-related hypopituitarism, a detailed comparison of these methodological issues between the different studies has not been performed for each pituitary axis.

We hypothesized that these methodological differences may have contributed, at least in part, to the discrepancies in prevalence rates of hypopituitarism after TBI, reported by the different studies. Therefore, the aim of this study was to critically compare the pituitary function tests, and definitions of hypopituitarism between studies that assessed the long term outcome of TBI on pituitary function.

Patients and methods

Search strategy

We performed a search in PubMed, EMBASE, Web of Science, and the Cochrane database, for all published studies on the association between TBI and hypopituitarism. The following search strategy was used: *(Traumatic Brain Injury OR Traumatic brain injuries) AND (traumatic OR trauma) AND (Hypopituitarism OR Hypopituitar* OR Hypothalamus Hypophysis System OR "Hypothalamopituitary dysfunction" OR "pituitary dysfunction" OR Hypothalamo-Hypophyseal System OR Pituitary Gland OR Hypophysis).*

In addition, the references of relevant articles were checked for additional articles. The search was performed on 23 March 2009. Only original articles were included. We used the following exclusion criteria: pediatric or adolescent population, publications concerning pituitary testing < 12 months after injury (a median of 12 months was accepted), and articles that evaluated pituitary insufficiency after subarachnoidal bleeding (SAB).

Data review

The following data were extracted from each study: 1) age and gender, 2) the endocrine tests used for assessment of each pituitary axis, 3) definitions used for pituitary insufficiency for each pituitary axis, 4) hormone assays, 5) reference values provided in the manuscript, and 6) use of control populations. Tables were constructed per pituitary axis. These tables are added as supplemental data files. The growth hormone (GH)-IGF-I axis (Table 2), the pituitary-adrenal axis (Table 3), the pituitary-thyroidal axis (Table 4), the pituitary-gonadal axis (Table 5), and prolactin (Table 6).

Results

We identified 278 articles, of which 218 were excluded on the basis of title and abstract. Of the remaining 60 articles, 46 were reviews. Finally, 14 original studies were included with a total of 931 patients. Details of these studies are summarized in Table 1. The number of patients evaluated by the different studies varied between 22 and 105.

Table 1. Studies on TBI and pituitary deficiency

Study	Year of publication	No. of patients	Time of testing post TBI [months (median)]	Trauma severity (GCS)	BMI (kg/m²)	Any pituitary deficiency (%)
Kelly *et al.*(6)	2000	22	3–276 (median 26)	3–15	25.1±6.5	37
Lieberman *et al.*(9)	2001	70	1–276 (median 13)	3–15 84% GCS ≤ 8	NR	69
Bondanelli *et al.*(3)	2004	50	12–64	3–15 54% GCS ≤ 8	24.6±0.4	54
Agha *et al.*(1)	2004	102	6–36 (median 17)	3–13 56% GCS ≤ 8	NR	28
Popovic *et al.*(10)	2004	67	12–264	3–13	24.8±0.5	34
Aimaretti *et al.*(2)	2005	70	12	3–15 21% GCS ≤ 8	23.8±0.4	23
Leal-Cerro *et al.*(8)	2005	99	>12	≤ 8	25.2±3.0 (n=44)	25
Schneider *et al.*(11)	2006	70	12	3–15	23.8±3.2	36
Tanriverdi *et al.*(12)	2006	52	12	3–15 25% GCS ≤ 8	NR	51
Herrmann *et al.*(5)	2006	76	5–47	≤ 8	25.8±4.2	24
Bushnik *et al.*(4)	2007	64	> 12 months	NR	NR	90
Klose *et al.*(7)	2007	104	10–27 (median 13)	3–15 38% GCS ≤ 8	25* (17–39)	15
Tanriverdi *et al.*(14)	2008	30	36	3–15 16.7% GCS ≤ 8	NR	30
Wachter *et al.*(13)	2009	55	NR	3–15 17% GCS ≤ 8	NR	25
Total No. of patients:		931				

BMI, body mass index reported as the mean ± SEM ; GCS, Glasgow Coma Scale sore; TBI, traumatic brain injury; NR, not reported. * reported as median (range)

The GH-IGF-I axis

The prevalence of GH deficiency (GHD) ranged between 2 and 66% (severe GHD 39%; Figures 1 and 2 and Suppl Table 2). The presence of GHD was associated with higher body mass index (BMI) values in some of the studies (Figure 1). In addition to basal serum GH and IGF-I values, all studies used a dynamic test to assess GH secretory reserve. However, different dynamic tests were used.

Three studies (196/931=21% of all patients) used the combined GHRH-arginine test as the first screening. The criterion for severe GHD was a peak GH level < 9.0 μg/L in all three, which was not adjusted for BMI. Prevalence rates of severe GHD varied between 8 and 20% (weighted mean 12%) (2;3;5). Schneider *et al.* (11) also used the GHRH-arginine test, but only in a subset of the patients (those with abnormal serum cortisol levels, n=32); the prevalence of GHD in this study was 10%.

Two studies (112/931=12% of all patients) used an insulin tolerance test (ITT) as the primary screening test (6;7). The criterion for severe GHD was a peak GH response < 3 μg/L in both, and the prevalence of GHD was comparable (18 and 15% respectively; weighted mean 16%).

Of the eight remaining studies, three used a stimulation test with glucagon (n=209) (1;4;9) with prevalence rates for severe GHD between 11 and 39% (weighted mean 20%). The cut-off values differed considerably and varied between 1 and 5 μg/L between these studies. Just one study used a stimulation test with GHRH only (number of patients not recorded) reporting a GHD prevalence of 2% (13). Two studies (n=119) used the combined GHRH-GHRP6 test with a prevalence of 15 and 33% respectively (weighted mean 21%) (10;12). The cut-off values were similar (GH < 10 μg/L) within these studies, and were derived from another report (17).

Finally, two studies used a combination of these tests (8;14). For instance, Agha *et al.* (1) used a glucagon stimulation test for the initial screening in 102 subjects, and in case of incomplete GH response, they used an ITT (n=14) or combined GHRH plus arginine test (n=4) to confirm GHD.

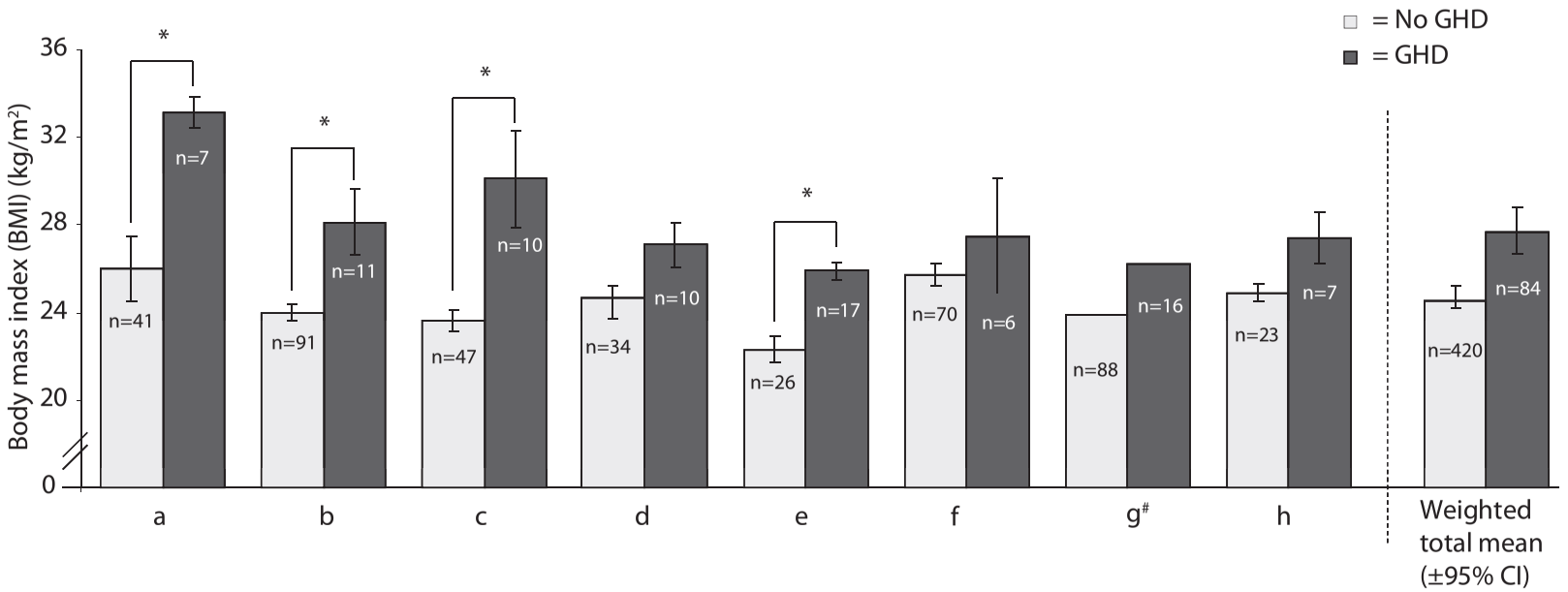

Figure 1. Body mass index in patients diagnosed with versus those without GH deficiency (data available only in 8 out of the 16 studies). a, Lieberman *et al.* 9); b, Agha *et al.*(1); c, Popovic *et al.* (10); d, Leal-Cerro *et al.* (8); e, Tanriverdi *et al.*(12); f, Herrmann *et al.*(5); g, Klose *et al.*(7); h, Tanriverdi *et al.*(14); i, weighted total mean (mean±95% CI: no GHD 24.5 (24.2–24.9) versus GHD 27.7 (26.7–28.8) kg/m^2). GHD, GH deficiency; BMI, body mass index; *P<0.05. #Data reported as median with range; not included in the total weighted mean.

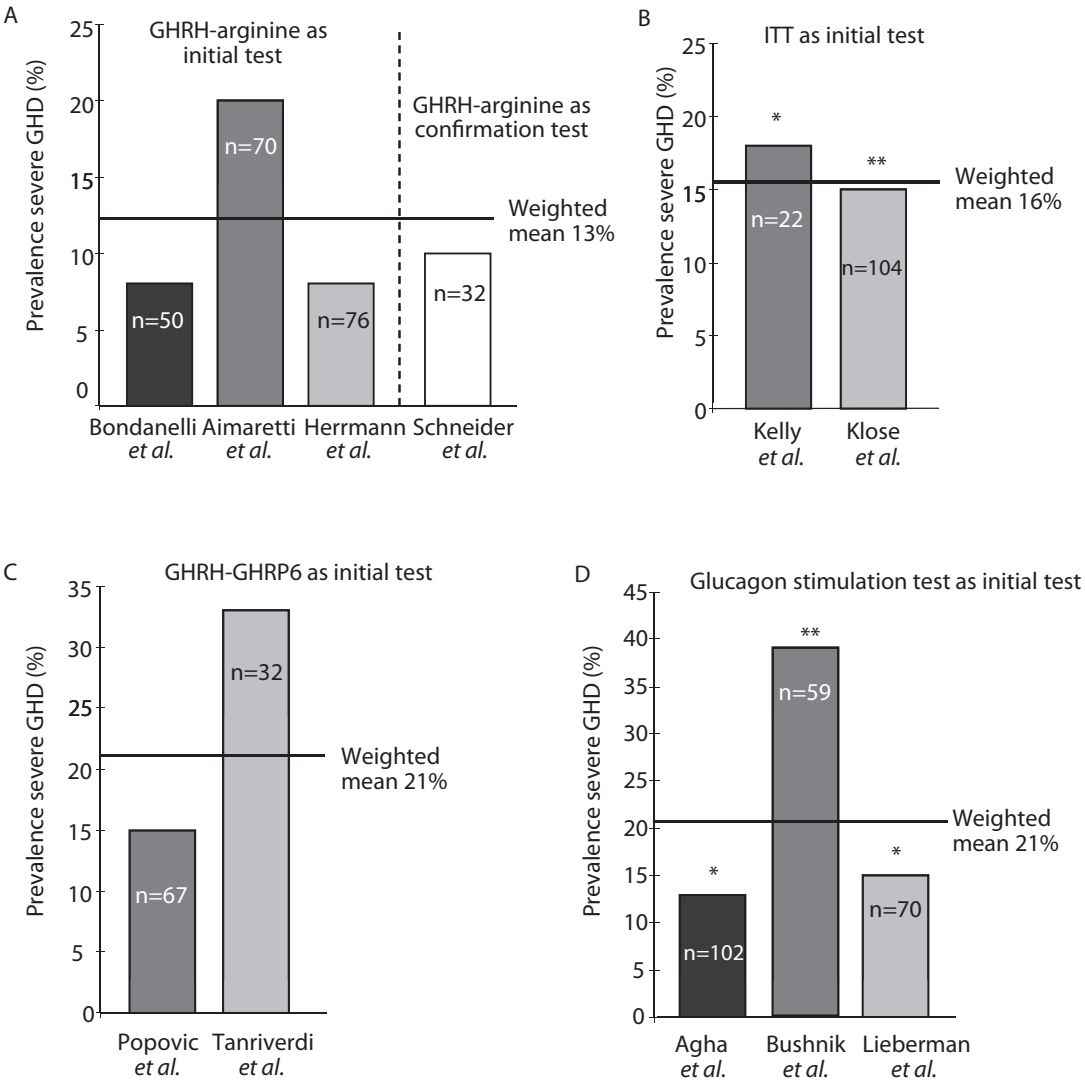

Figure 2. Absolute and weighted mean prevalence rates of severe GH deficiency (GHD) according to the stimulation tests used per study. The number of patients tested is depicted in each bar. *Panel A:* the combined GHRH-arginine test; definition severe GHD: peak GH < 9 µg/L for all four studies. *Panel B:* the insulin tolerance test (ITT); *definition severe GHD: GH < 95% CL according to AUC; **definition severe GHD: peak GH < 3 µg/L. *Panel C:* the combined GHRH-GHRP6 test; definition severe GHD: peak GH < 10 µg/L for both studies. *Panel D:* the glucagon stimulation test; definition severe GHD: *peak GH < 3 µg/L; **peak GH < 5 µg/L. *Panel E:* combined stimulation tests as initial screening followed by confirmation test; ΔGHRH-GHRP6 test as initial test; ITT and glucagon stimulation test as confirmation tests; ΔΔGHRH-GHRP6 test as initial test; glucagon stimulation test as confirmation test.

The Pituitary-Adrenal axis

The prevalence of secondary adrenal insufficiency deficiency ranged from 0 to 60% between the studies (Figure 3, Suppl Table 3).

Four studies (251/931=27% of all patients) only measured basal morning fasting serum cortisol and/or ACTH levels (2–4;10), resulting in prevalence rates between 0 and 60% (weighted mean 15%). The criteria for pituitary-adrenal insufficiency differed between three studies (cortisol < 220–440 nmol/L), and were not reported in the fourth study (10). The study reporting the highest prevalence of 60% used a cut-off value of 440 nmol/L (4).

Four studies (145/931=12% of all patients) used an ACTH stimulation test (Synacthen; either with 1 or 250 μg). However, only one study performed this test in all patients and the prevalence of ACTH deficiency was 7% (9). In the other three studies, only a subset of the patients (those with subnormal basal cortisol levels) underwent stimulation with ACTH. The prevalence in these studies varied between 7 and 19% (weighted mean 10%) (11;12;14).

One study (55/931=6% of all patients) used nonstimulated cortisol values between 1600 and 2000 h (reference values 63–339 nmol/L), which was followed by a corticotrope releasing hormone (CRH) test only in those with values below this reference range, or in those who responded confirmatory to a specific questionnaire (13).

In the remaining five studies (403/931=43% of all patients), the ITT was used in 169 patients as a primary test (n=112) resulting in a prevalence of 5% in both studies (6;7), or as a confirmation test in a subset of the patients. Two studies measured basal serum cortisol levels and used ITT as a confirmation test (prevalence of 3 and 11% respectively) (5;8). One study assessed primarily with a glucagon stimulation test (n=102), and used the ITT and ACTH tests to confirm ACTH deficiency (prevalence 13%) (1). The criteria for a normal cortisol response to hypoglycemia were a peak cortisol level > 550 nmol/L in one (8), and > 500 nmol/L in three other studies (1;5;7). The fifth study used a control group of 18 healthy subjects to define normal cortisol responses to ITT (cortisol response < 95% confidence limit according to the obtained area under the curve) (6). The CRH test was used in only one study and did not report the number of patients (13).

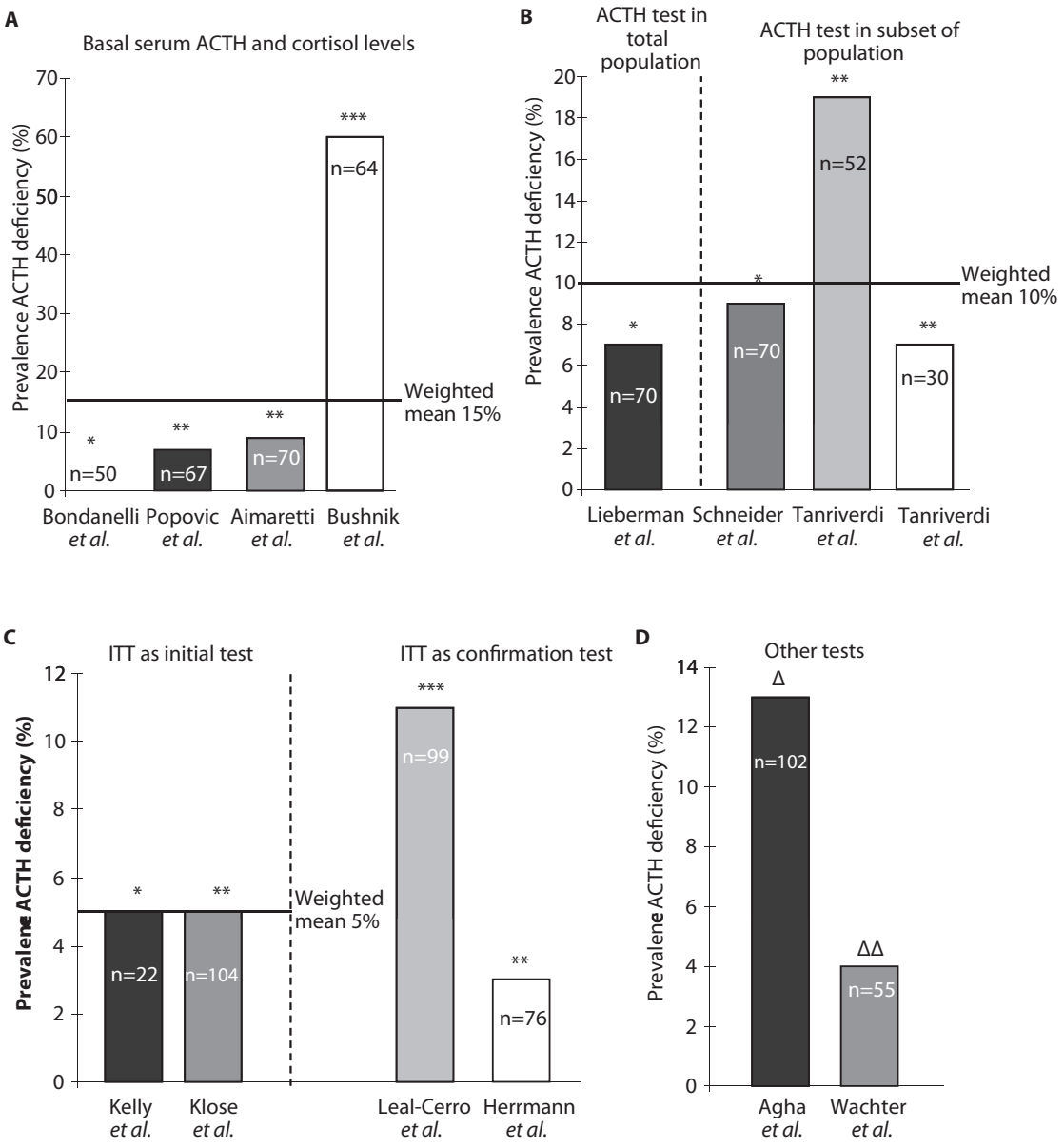

Figure 3. Absolute and weighted mean prevalence rates of corticotropin (HPA axis) deficiency according to the stimulation test used per study. The number of patients tested is depicted in each bar. *Panel A:* basal cortisol concentrations only using different cut-off levels; *cut-off level: NR; **cut-off level: cortisol < 220 nmol/L; ***cut-off level: cortisol < 440 nmol/L. *Panel B:* the ACTH stimulation test *using 250 µg ACTH and peak cortisol < 500 nmol/L; **using 1 µg ACTH and peak cortisol < 550 mol/L. *Panel C:* the insulin tolerance test (ITT); *peak cortisol < 95% CL according to AUC; **peak cortisol < 500 nmol/L; ***peak cortisol < 550 nmol/L. *Panel D:* other stimulation tests: Δthe glucagon stimulation test; ΔΔCRH test.NR, not reported.

The Hypothalamus-Pituitary-Thyroid axis

The prevalence of hypothalamus-pituitary-thyroid axis deficiency ranged from 0 to 19% between the studies (Suppl Table 4).

The criteria for TSH deficiency were different. Nine studies used basal free thyroxine (fT_4) and TSH levels only. Within these studies, the cut-off value for decreased fT_4 varied between 8 and 12 pmol/L (2;5;7;11;14;18;19). In two studies, reference values were not reported (4;10), one of which (Bushnik *et al.*) reported the highest prevalence of secondary hypothyroidism.

The thyroid-releasing hormone (TRH) stimulation test was used in five studies, using i.v. doses of 200 (13) and 500 µg (5;6;8;9). The criterion for a normal response differed considerably: a TSH peak response > 7 mIU/L, a TSH peak between 5 and 30 mIU/L, or were not reported (12;13).

The prevalence rates between the studies that only measured basal fT_4 levels varied between 0 and 19% (weighted mean 5%) (1–5;7;10;11;14), and between 5 and 15% (weighted mean 8%) in those that also used TRH (6;8;9;12;13).

The Hypothalamus-Pituitary-Gonadal axis

The hypothalamus-pituitary-gonadal axis deficiency ranged from 0 to 29% (weighted mean 13%) between the studies (Table 5). Basal LH and FSH were measured in all but one study (4). Basal estradiol (E_2 in women) was measured in 9 studies, and the menstrual history was recorded in 10 out of 14 studies. Testosterone (in men) was measured in all studies. In four studies, a GnRH stimulation test was performed in a subset of the patients (6;8;9;13). The criterion for a normal test response differed between the studies (Suppl Table 5). The definition of secondary hypogonadism was mainly based on basal testosterone (in men) and E_2 concentrations (in women) below the reference ranges, in the presence of decreased or normal LH and FSH levels. A subset of the studies also incorporated the GnRH test result (see above) and menstrual cycle abnormalities in premenopausal females.

Prolactin

The prevalence of abnormal serum PRL concentrations ranged from 0 to 16% (Suppl Table 6). Abnormal PRL secretion was defined as hyperprolactinemia (8/14 studies) (1;2;5;7;9;11;12;14), hypoprolactinemia

(one study) (6), or both (3). In accordance, prevalence rates were between 3 and 12% using the definition of hyperprolactinemia, 0% using the definition of hypoprolactinemia, and 16% using the combination of both. Out of the 14 studies, 10 measured basal serum PRL concentrations only (1–3;5;7;9–12;14). Three studies also used a TRH test (doses 100 and 500 μg respectively) (6;8;13). Prevalence rates were not reported in two of these (8;13) and were 0% in the third (6).

Discussion

This review demonstrates that the endocrine evaluations and definitions of hypopituitarism differ considerably among the studies that have assessed TBI-related hypopituitarism. From the existing literature, the notion emerges that most of the tests that are currently used to establish the diagnosis of hypopituitarism in general, and GHD in specific, are not validated sufficiently regarding cut-off values, reproducibility, and dependence on confounding factors in TBI patients.

In general, there are hardly any data on reproducibility of tests or dependence on confounding factors in TBI patients. One factor that comes forward in the current review is the potential effect of increased BMI, which in general is associated with decreased GH responses to GH stimulation tests. Therefore, increased BMI may result in an inadvertently higher incidence rate of GHD, if the cut-off values for normal GH responses to GH stimulation tests are not adapted according to BMI. All these methodological issues limit the applicability of the individual studies, *i.e.* the decision whether the study results are valid for patients to whom the results are generalizable but who are subjected to a different endocrine diagnostic assessment than the original study population. Moreover, these methodological limitations prohibit simple generalizations of the results from the perspective of a meta-analysis or a review.

The question arises whether post-traumatic hypopituitarism, especially GHD, has been overdiagnosed on the basis of the older cross-sectional studies. Consensus guidelines for the evaluation of adult GHD state that different dynamic tests can be used to diagnose GHD, including the ITT, the glucagon stimulation test, the combined GHRH-arginine test, and the combined GHRH-GHRP6 test (20). The present assessment, however, documents a higher prevalence of GHD for the glucagon stimulation test and the combined GHRH-GHRP6 test, compared to the results of the combined GHRH-arginine test and the ITT. With the exception of the ITT (which was used in only 12%

of the patients (6;7)), the outcome of each test varied greatly (Figure 2) using different (glucagon stimulation test) or similar cut-off levels (other test). In addition, the studies that used two dynamic tests to assess GH reserve revealed a lower prevalence of GHD than the studies with only one test. Moreover, the results of GH stimulation tests are confounded by BMI, with higher BMI being associated with decreased GH responses. Although BMI-adjusted reference values have been reported (21), none of the studies on TBI-associated GHD reports adjusted their cut-off values for BMI. Moreover, the data indicate that BMI tends to be higher in the TBI patients with GHD (Figure 1). Finally, an important aspect is that most patients had only GHD or one additional pituitary hormone deficiency. Therefore, one test may not be sufficiently reliable and the use of two tests would increase the confidence in the diagnosis, although only if the two tests yield concordant results. However, the application of two tests may introduce an even greater uncertainty in case of discordant results. This discrepancy has been documented for instance in GHD in irradiated patients, in whom the attenuation in GH responses to the ITT was greater compared with the combined GHRH-arginine test (22). These factors impose major problems for an accurate assessment of GHD in these patients. Therefore, these methodological issues have contributed to the suspicion that GHD is probably over diagnosed in the older cross-sectional studies.

We observed similar variations in test results of the pituitary-adrenal axis (Figure 3). The use of different tests with different cut-off values resulted in prevalence rates that varied between 5 and 19%. ACTH deficiency can be diagnosed by measuring basal early morning cortisol levels: values below 100 nmol/L are indicative of ACTH deficiency, whereas cortisol values above 500 nmol/L essentially exclude ACTH deficiency. The ACTH stimulation test is reliable in diagnosing clinically significant adrenal insufficiency in patients who are at risk (23–25). ACTH stimulation tests, however, are not fully reliable in excluding the presence of mild secondary adrenal insufficiency (26). The ITT still remains the golden standard, and has the advantage that ACTH/cortisol and GH secretory reserve can be assessed simultaneously. If an ITT is contraindicated, a CRH test can be alternatively used (27). The effect of the initial choice for a specific stimulation test on the variation in outcome of adrenal insufficiency and GHD based on the available data after TBI is illustrated in Figure 4.

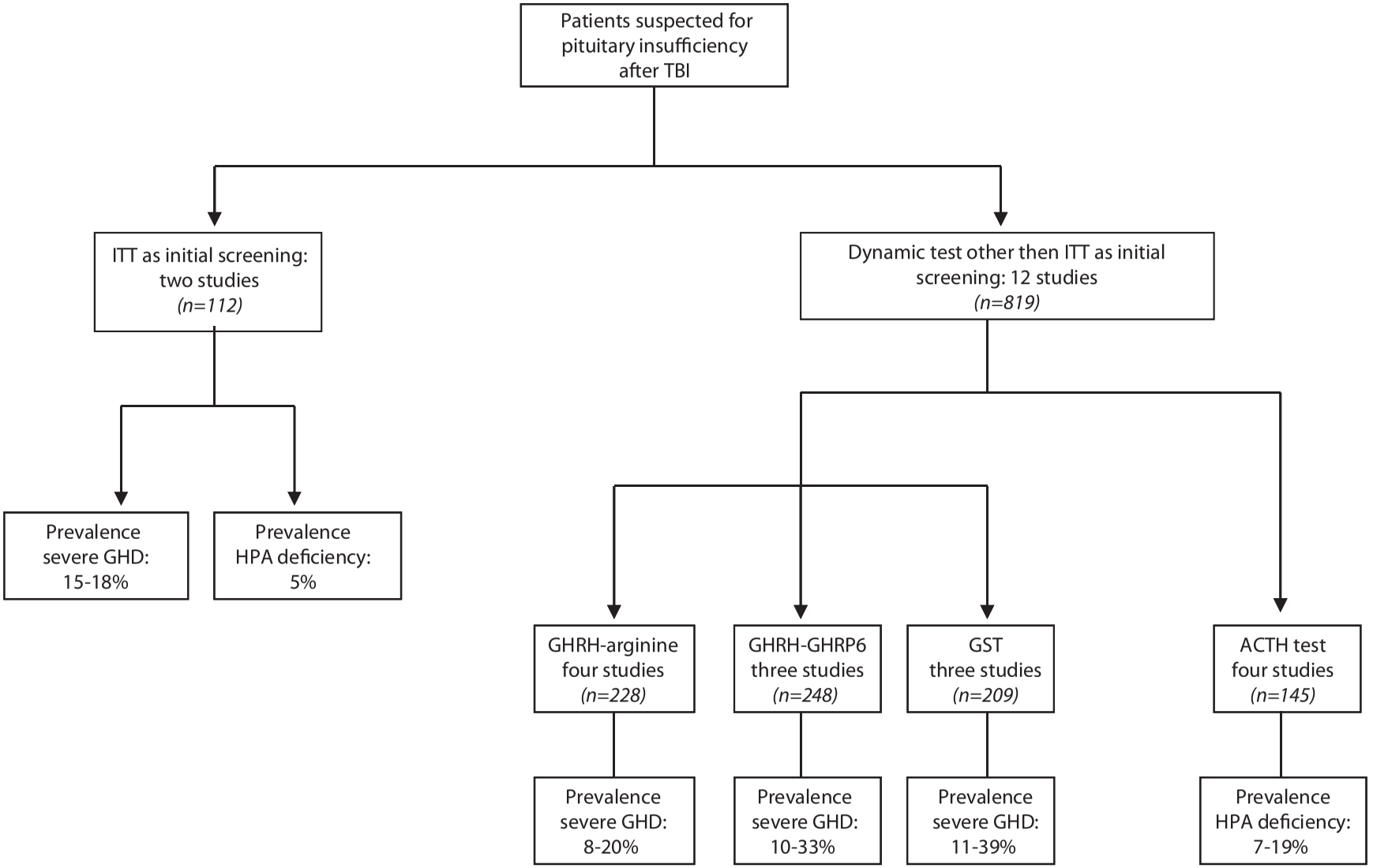

Figure 4. Example illustrating the effect of initial test choice on the variation in outcome of prevalence rates of severe GHD and HPA axis insufficiency.

The diagnosis of secondary hypothyroidism is usually made based on fT_4 values. However, basal fT_4 levels show a relatively small intra-individual variability, although inter-individual variability is large (28). As a consequence, a diagnosis of possible secondary hypothyroidism may not be straightforward, since fT_4 levels within the normal reference range can reflect hypothyroidism in one patient but euthyroidism in another patient. Basal TSH levels are also of limited help for the diagnosis of secondary hypothyrodism, since normal or even increased levels of TSH can be found (29). In addition, a TRH test is of limited value because patients with central hypothyroidism may show different patterns of TSH responses to TRH, with absent or exaggerated responses, which considerably overlap with those found in healthy volunteers. Moreover, the magnitude of the TSH peak is proportional to the injected TRH dose, is higher in women, and tends to decline with age (30). In accordance, the prevalence rates were not affected by the use of TRH stimulation. In analogy, the interpretation of the GnRH test is complex, and individual responses vary greatly in both adults and children (31). In men, it is sufficient to measure non-stimulated LH, FSH, and testosterone concentrations. In premenopausal women, the evaluation of the menstrual cycle is a prerequisite, whereas in postmenopausal women, the absence of increased LH and FSH levels almost invariably indicates hypogonadotropic hypogonadism.

Analytical factors will most likely also have affected the different outcomes of the studies. For instance, the GH and cortisol assays varied between studies, and it is known that the between-laboratory performance of the GH assay is not very good. Moreover, most were not validated sufficiently regarding normal cut-off values, reproducibility, and dependence on confounding factors even in a 'normal' population. None of these tests have been validated in TBI patients at all.

The time point of evaluation may also influence outcome; therefore, we focused only on studies in the chronic phase after TBI, *i.e.* one year after the trauma. Studies that analyzed patients with a median duration of 12 months after TBI, however, were also included. Thus, part of these patients was assessed within 12 months after TBI. In general, the transient effects of TBI mimicking pituitary insufficiency are almost exclusively reported only within the first six months after TBI (15). Therefore, it is unlikely that the pituitary results of the studies with a median duration of follow-up of 12 months of TBI are caused by the transient effects of

TBI. This is supported by similar results of additional analyses of the remaining studies, which included only patients with a follow-up of more than 12 months after TBI. Lastly, the underlying mechanisms of TBI-related hypopituitarism have not been resolved. It is unclear to that extent hypothalamic versus pituitary damage is present in TBI patients with hypopituitarism and what impact these processes may have on endocrine tests.

Recently, many clinical reviews have summarized the studies on pituitary insufficiency after TBI (15;16). These studies concluded that hypopituitarism is a common complication of TBI and might contribute to morbidity and poor recovery after brain injury (16). However, these reviews did not take into account the variability in diagnostic strategies and definitions of pituitary insufficiency. These discrepancies, in addition to differences in inclusion and exclusion criteria, limit the possibility to compare the results of studies on TBI. We agree with Klose and Feldt-Rasmussen that future studies should be designed to ensure a high diagnostic robustness for proper identification of reliable predictors, as the results may be highly dependent on diagnostic pitfalls (15).

In conclusion, the reported prevalence rates of pituitary insufficiency after TBI vary considerably, which is associated with major differences in endocrine and analytical methods of assessment and definitions used for hypopituitarism. This does not only apply to the case of TBI-related hypopituitarism, but most likely also to hypopituitarism caused by pituitary diseases. The same caution with respect to the evaluation of pituitary function should be considered in pituitary diseases, because the diagnosis of definitive hypopituitarism remains a challenge in clinical endocrinology. In pituitary pathology, definitive data on robust accuracy of basal or dynamic hormonal tests are incomplete.

Supplemental data

Table 2. GH-IGF-I Axis

Study	No. of patients	Basal serum GH	Basal serum IGF-I	ITT	GHRH-arginine test	Other dynamic test	Criterion GH deficiency		Assays GH / IGF-I	Outcome (%)
							GH	*IGF-I*		
Kelly *et al.* (6)	22	+	+	+ (n=22)	–	–	GH < 95% CL according to AUC[a]	16–24 yr: 182–780 µg/L 25–39 yr: 114–492 µg/L 40–54 yr: 90–360 µg/L	IFA/RIA*	18[b]
Lieberman *et al.*(9)	70	+	+	–	–	+[c] (GST; n=48)	Peak GH < 3 µg/L	NR	IRMA/RIA*	15
Bondanelli *et al.* (3)	50	+	+	–	+ (n=50)	–	Peak GH < 16.5 µg/L Severe GHD = GH < 9 µg/L Partial GHD = GH 9–16.5 µg/L	20–30 yr : 135–485 µg/L 31–40 yr: 120–397 µg/L 41–50 yr: 113–306 µg/L 51–60 yr: 100–250µg/L >60 yr: 92–229 µg/L	IRMA/RIA	Partial:28 Severe:8
Agha *et al.* (1)	102[d]	+	+	+ (n=14)	+ (n=4)	+[e] (GST; n=102)	GST: peak GH < 5 µg/L ITT: peak GH < 5 µg/L GHRH-arg: peak GH < 9 µg/L	IGF-I SDS: ln(IGF-I) – [5.9 –(0.0146xage in yrs)]/0.272	IRMA/ IRMA	11

Table 2. Continued

Study	No. of patients	Basal serum GH	Basal serum IGF-I	ITT	GHRH-arginine test	Other dynamic test	Criterion GH deficiency		Assays GH / IGF-I	Outcome (%)
							GH	*IGF-I*		
Popovic *et al.*(10)	67	+	+	–	–	+ (GHRH-GHRP6; n=67)	Severe GHD = peak GH < 10.0 µg/L GHI = peak GH < 10.0–20.0 µg/L	Normal levels matched for age and sex 11–35 nmol/L	IRMA/ RIA	Partial: 30 Severe: 15
Aimaretti *et al.*(2)	70	+	+	–	+ (n=70)	–	Peak GH < 16.5 µg/L Severe GHD = peak GH < 9.0 µg/L	25th centile age-related normal limits	IRMA/RIA	Partial: 39 Severe: 20
Leal-Cerro *et al.*(8)	99	+	+	+ (n=35)	+	+[f] (GHRH-GHRP6; GST n=44)	GHRH-GHRP6: peak GH ≤ 10 µg/L GST and ITT: GH 3 µg/L	IGF-I < 200 µg/L (±2SDS)	IRMA/ IRMA*	10
Schneider *et al.*(11)	70	+	+	–	+[g] (n=32)	–	GH < 9.0 µg/L	Age-dependent SDS[h]	CLA/CLA	10
Tanriverdi *et al.*(12)	52	+	+	–	–	+ (GHRH-GHRP6; n=52)	GH < 10 µg/L	IGF-I < 84 µg/L	IRMA/ IRMA*	33

Study	No. of patients	Basal serum GH	Basal serum IGF-I	ITT	GHRH-arginine test	Other dynamic test	Criterion GH deficiency		Assays	Outcome
							GH	*IGF-I*	GH / IGF-I	(%)
Herrmann *et al.*(5)	76	+	+	+ (n=7)	+ (n=76)	–	GHRH-arg: GH < 9 µg/L ITT: GH peak <3 µg/L	16–24 yr: 182–780 µg/L 25–39yr: 114–492 µg/L 40–54 yr: 90–360 µg/L ≥ 55 yr: 71–290 µg/L	CLA/IRMA	8
Bushnik *et al.*(4)	64	+	+	–	–	+ (GST; n=59)[i]	Severe GHD = peak GH < 3 µg/L Moderate: peak GH 3 –9.9 µg/L	IGF-I age-corrected normal levels	NR	Partial: 66 Severe: 39
Klose *et al.* (7)	104[j]	+	+	+ (n=90)	+ (n=14)	–	Severe GHD = ITT: peak GH< 3 µg/L GHRH-arg: GH< 9 µg/L Partial GHD: = ITT: peak GH 5 µg/L ≤ GH ≥ 3 µg/L GHRH-arg: peak 16.5 µg/L ≤ GH ≥ 9 µg/L	IGF-I SDS[k]	FIA/RIA	15
Tanriverdi *et al.*(14)	30	+	+	–	–	+ (GRHR-GHRP6 n=30; GST n=7)[l]	GRHR-GHRP6: severe GHD = GH < 10 µg/L GST: GH < 1.18 µg/L	18–30 yr: 197–476 µg/L 31–40 yr: 100–494 µg/L 41–70 yr: 101–303 µg/L	IRMA/ IRMA*	23

Table 2. Continued

Study	No. of patients	Basal serum GH	Basal serum IGF-I	ITT	GHRH-arginine test	Other dynamic test	Criterion GH deficiency		Assays GH / IGF-I	Outcome (%)
							GH	*IGF-I*		
Wachter *et al.*(13)	55	+	+	–	–	+ (GHRH; n=NR)[m]	NR	Age adjusted: 116–270 µg/L	NR	2

ACS, Automated chemiluminescence system; AUC, area under the curve; CL, confidence limit; CLA, chemiluminometric assay; FIA, fluoroimmunoassay; GHD, growth hormone deficiency; GHI, growth hormone insufficiency; GRHR, growth hormone releasing hormone; GHRH-GHRP6 test, growth hormone releasing hormone plus growth hormone releasing peptide 6; GST, glucagon stimulation test; IGF-I, insulin-like growth factor I; IRMA, immunoradiometric assay; ITT, insulin tolerance test; NR, not reported; RIA, radio immunometric assay

[a] Normal values defined by a group of healthy subjects (n=18)

[b] ¾ patients with GHD had been tested < 12 months post TBI (7,5,5 months)

[c] GST in n=48; n=20 underwent L-dopa test

[d] Cut-off values defined by 31 healthy control subjects

[e] All patients underwent GST; patients with abnormal results underwent ITT (n=14) or GHRH+arg test (n=4)

[f] Patients with IGF-I in lower range were tested with GHRH-GHRP6 (n=44,glucagon stimulation test (n=44) and ITT (n=35)

[g] 38 healthy controls underwent GHRH-arg test to test appropriatness of cut-off values

[h] Calculated according to Brabant *et al.*2003(31)

[i] GST: 0.03 mg kg-1 max 1 mg intramuscular

[j] 30 age- and BMI-matched healthy controls all underwent pituitary testing

[k] Calculated by Juul *et al.* 1994(32)

[l] Patients with uncertain levels of GH after GHRH-GRHP6 (GH 11–19 µg/L) test underwent GST (n=7)

[m] Hormonal stimulation tests were performed if abnormalities in basal hormone screening or if patients answered 'yes' to specific questionnaire. Not reported how many patients underwent stimulation tests. GHRH: 100 µg

* After acid-ethanol extraction

Table 3. Hypothalamic-Pituitary Adrenal Axis

Study	No. of patients	Basal serum cortisol	Basal serum ACTH	CRH test	ACTH test	ITT	Other dynamic test	Criterion for ACTH-deficiency	Assay cortisol/ ACTH	Outcome (%)
Kelly *et al.* (6)	22	+	+	–	–	+ (n=22)	–	Cortisol < 95% CI according to AUC[a]	RIA/IRMA	5
Lieberman *et al.* (9)	70	+	–	–	+ (n=70)[b]	–	–	Peak cortisol < 500 nmol/L	MSA/-	7
Bondanelli *et al.* (3)	50	+	+	–	–	–	–	Cortisol and ACTH below reported reference range (cortisol: 220 – 700 nmol/L ACTH: 1.5–11.5 pmol/L)	RIA/IRMA	0
Agha *et al.* (1)	102[c]	+	+	–	+ (n=8)[d]	+ (n=15)	+ (GST; n=102)[e]	Failing 2 tests: GST: peak cortisol < 450 nmol/L ITT: peak cortisol < 500 nmol/L SST: peak cortisol <500 nmol/L	FIA/IRMA	13
Popovic *et al.*(10)	67	+	–	–	–	–	–	NR	RIA/-	7
Aimaretti *et al.*(2)	70	+	–	–	–	–	–	Cortisol < 220 nmol/L 24h urinary free cortisol < 30 µg/24 h	RIA/-	9

Table 3. Continued

Study	No. of patients	Basal serum cortisol	Basal serum ACTH	CRH test	ACTH test	ITT	Other dynamic test	Criterion for ACTH–deficiency	Assay cortisol/ ACTH	Outcome (%)
Leal-Cerro *et al.*(8)	99	+	+	–	–	+[f] (n=NR)	–	Basal cortisol < 200 nmol/L Peak cortisol < 550 nmol/L Peak ACTH < 6.6 pmol/L	FIA / IRMA	11
Schneider *et al.*(11)	70	+	–	–	+ (n=33)[g]	–	–	Cortisol < 500 nmol/L	ECLIA/-	9
Tanriverdi *et al.*(12)	52	+	+	–	+ (n=12)[h]	–	–	Basal cortisol < 193 nmol/L ACTH test: Cortisol < 552 nmol/L	RIA/IRMA	19
Herrmann *et al.*(5)	76	+	+	–	–	+ (n=7)[i]	–	Cortisol and ACTH below reported reference range (cortisol 180–640 nmol/L; ACTH 3.74– 11.44 pmol/L) ITT: Peak cortisol < 500 nmol/L	IA/CL	3
Bushnik *et al.*(4)	64	+	–	–	–	–	–	Fasting serum cortisol < 440 nmol/L	NR	60
Klose *et al.* (7)	104[j]	+	+	–	+ (n=14)[k]	+ (n=90)	–	Peak cortisol < 500 nmol/L	ECLIA /-	5
Tanriverdi *et al.*(14)	30	+	+	–	+ (n=3)[l]	–	–	Basal cortisol < 193 nmol/L ACTH test: Cortisol < 550 nmol/L	RIA/IRMA	7

Study	No. of patients	Basal serum cortisol	Basal serum ACTH	CRH test	ACTH test	ITT	Other dynamic test	Criterion for ACTH–deficiency	Assay cortisol/ ACTH	Outcome (%)
Wachter *et al.*(13)	55	+	+	+ (n=NR)[m]	–	–	–	Cortisol below reported reference range (cortisol (16:00 – 20:00 h): 63 – 339 nmol/L)	NR	4

ACS, Automated chemiluminescence system; ACTH, adrenal corticotrope hormone; AUC, area under the curve; CL, confidence limit; CLA, chemiluminometric assay; CRH, corticotrope releasing hormone; ECLIA, electrochemiluminiscence immunoassay; FIA, fluoroimmunoassay; GST, glucagon stimulation test; IA, Immunoassay; IRMA, immunoradiometric assay; ITT, insulin tolerance test; MEIA, microparticle enzyme immunoassay; MSA, magnetic separation assays; NR, not reported; RIA, radio immunometric assay; SST, short synacthen stimulation test

[a] Normal values defined by a group of healthy subjects (n=18)

[b] ACTH test: 250 µg cosyntropin

[c] Cut-off values defined by 31 healthy control subjects

[d] ACTH test: 250 µg Synacthen

[e] Patients with subnormal response to GST (n=23) underwent ITT (n=15) or SST (n=8)

[f] Patients with subnormal basal serum cortisol and ACTH values underwent ITT; not reported how many patients cortisol < 200nmol/L

[g] ACTH test: 250 µg Synacthen

[h] ACTH test: 1 µg Synacthen

[i] Patients with subnormal basal serum cortisol and ACTH values underwent ITT (n=7)

[j] 30 age- and BMI-matched healthy controls all underwent pituitary testing

[k] ACTH test: 250 µg Synacthen

[l] ACTH test: 1 µg Synacthen

[m] Hormonal stimulation tests were performed if abnormalities in basal hormone screening or if patients answered 'yes' to specific questionnaire. Not reported how many patients underwent stimulation tests; CRH test: 100 µg corticotrope releasing hormone

Table 4. Hypothalamus Pituitary Thyroid Axis

Study	No. of patients	Basal serum fT_3	Basal serum fT_4	Basal serum TSH	TRH	Criterion TH deficiency	Assay TSH/FT_4	Outcome (%)
Kelly *et al.*(6)	22	–	+	+	+ (n=22)[a]	TSH < 95% CL according to AUC[b]	ICL/ RIA	5
Lieberman *et al.*(9)	70	–	+	+	+ (n=27)[c]	TSH: 0.49–4.7 mIU/L fT_4: 9.7 – 23.8 pmol/L Insufficient ↑ TSH (5–30 mIU/L); peak TSH not within 60 min	MPIA/ MPIA	15
Bondanelli *et al.*(3)	50	–	+	+	–	Low serum fT_4 with normal or low serum TSH TSH: 0.4–4.2 mIU/L fT_4: 10.3–19.4 pmol/L	ACS/ACS	10
Agha *et al.*(1)	102[d]	–	+	+	–	Low fT_4 without elevation TSH TSH: 0.5 –4.2 mIU/L fT_4: 8–21 pmol/L	FIA/FIA	1
Popovic *et al.* (10)	67	–	+	+	–	NR	IRMA/RIA	4
Aimaretti *et al.* (2)	70	–	+	+	–	fT_4 < 10.29 pmol/L with normal or low TSH	IRMA/RIA	6
Leal-Cerro *et al.*(8)	99	–	+	+	+ (n=NR)[e]	fT_4 ≤ 7.74 pmol/L with normal or low TSH TRH test: TSH peak ≤ 7 mIU/L	RIA/RIA	6

Study	No. of patients	Basal serum fT_3	Basal serum fT_4	Basal serum TSH	TRH	Criterion TH deficiency	Assay TSH/FT4	Outcome (%)
Schneider *et al.*(11)	70	–	+	+	–	fT_4 < 11.97 pmol/L; TSH not elevated	ECLIA/ ECLIA	4
Tanriverdi *et al.*(12)	52	+	+	+	+ (n=NR)[f]	fT_4 < 10.3 pmol/L without appropriate elevation TSH	fT_3, fT_4: RIA TSH: IRMA	6
Herrmann *et al.*(5)	76	+	+	+	–	Low serum fT_4 without appropriate elevation in serum TSH TSH: 0.3–3.0 mIU/L fT_4: 10–25 pmol/L	IA/IA	3
Bushnik *et al.* (4)	64	–	+	+	–	Low serum fT_4 with low or normal TSH Normal reference values: NR	NR	19
Klose *et al.*(7)	104[g]	–	+	+	–	Subnormal fT_4 (<12 pmol/L) with inappropriate low TSH	ECLIA/ ECLIA	2
Tanriverdi *et al.*(14)	30	+	+	+	–	fT_4 < 10.3 pmol/L without appropriate elevation TSH	fT_3, fT_4: RIA TSH: IRMA	0

Table 4. Continued

Study	No. of patients	Basal serum fT_3	Basal serum fT_4	Basal serum TSH	TRH	Criterion TH deficiency	Assay TSH/FT4	Outcome (%)
Wachter *et al.* (13)	55	–	+	+	+ (n=NR)[h]	Criterion for TRH test: NR fT_4: 12–22 pmol/L TSH: NR	NR	6

ACS, Automated chemiluminescence system; AUC, area under the curve; CL, confidence limit; ECL, Electrochemiluminiscence immunoassay; FIA, Fluoroimmunoassay; fT_3: free triiodothyronine; fT_4, free thyroxine; IRMA, immuno radiometric assay; ICL, Immunochemoluminiscense; MPIA, microparticle enzyme immunoassay; NR, not reported; RIA, radio immunoassay; TRH, thyroid releasing hormone; TSH, thyroid stimulating hormone

[a] TRH test: 500 µg

[b] Normal values defined by a group of healthy subjects (n=18)

[c] Abnormal TSH and fT_4 values underwent TRH stimulation test (n=27); 0.5 mg TRH; IV, TSH at T0, 15, 30, 60, 90 min

[d] Cut-off values defined by 31 healthy control subjects

[e] TRH test: 500 µg Protirelin

[f] Not reported how many patients underwent TRH testing and how the test was performed

[g] 30 age- and BMI-matched healthy controls all underwent pituitary testing

[h] Hormonal stimulation tests were performed if abnormatlities in basal hormone screening or if patients answered 'yes' to specific questionnaire. Not reported how many patients underwent stimaltionsts. TRH: 200 µg

Table 5. Hypothalamus pituitary gonadal Axis

Study	No. of patients	Basal serum LH	Basal serum FSH	Basal serum E_2/T	Menstrual history	GnRH Stimulation test	Criterion for hypogonadism	Assay LH/FSH/T/E_2	Outcome (%)
Kelly *et al.* (6)	22	+	+	+	+	+ (n=18)	LH and FSH < 95% CL according to AUC [a] F: increase LH <10 IU/L after GnRH administration T: 10.3 – 36.2 nmol/L E_2: (early follicular phase) 73.4–550.7 pmol/L	LH, FSH: FIA T: RIA E_2: direct assay	23
Lieberman *et al.*(9)	70	+	–	T+	+	+[b] (n=NR)	T below reported reference range (9.7 – 30.5 nmol/L) LH below reported reference rage (M= 2–12 IU/L) Normal response GnRH test: M: peak LH <12 IU/L and increase in LH < 7 IU/L F: peak LH < 10 IU/L and increase in LH < 5 IU/L	T: RIA LH: MEIA	0

Table 5. Continued

Study	No. of patients	Basal serum LH	Basal serum FSH	Basal serum E_2/T	Menstrual history	GnRH Stimulation test	Criterion for hypogonadism	Assay LH/FSH/T/E_2	Outcome (%)
Bondanelli *et al.*(3)	50	+	+	+	NR	–	LH below reported reference range: F: follicular phase 2.5–10 IU/L; menopausal 40–104 IU/L M: 1–10 IU/L FSH below reported reference range: F: follicular phase 2.5–10 IU/L; menopausal 34–96 IU/L M: 1–7 IU/L T below reported reference range (10.1–34.7 nmol/L) E_2 below reported reference range (follicular phase 74–555 pmol/L; menopausal <180pmol/L)	LH, FSH: CLIA T, E_2: RIA	14
Agha *et al.*(1)	102[c]	+	+	T+	+	–	M: low T; inappropriately low LH and FSH Premenopausal F: amenorrhea with low E_2 without ↑ LH and FSH Postmenopausal F: LH and FSH in range of premenopausal	LH, FSH: FIA	12
Popovic *et al.* (10)	67	+	+	T+	+	–	NR	LH, FSH: IRMA T: RIA	9
Aimaretti *et al.*(2)	70	+	+	+	+	–	M : T < 12.1 nmol/L with low or normal FSH and LH Premenopausal F: menstrual disturbances, low E_2 < 73.4 pmol/L with normal or low LH and FSH	LH, FSH: IRMA T,E_2: RIA	11

Study	No. of patients	Basal serum LH	Basal serum FSH	Basal serum E_2/T	Menstrual history	GnRH Stimulation test	Criterion for hypogonadism	Assay LH/FSH/T/E_2	Outcome (%)
Leal-Cerro *et al.*(8)	99	+	+	+	+	+ (n=NR)	M: T < ref val with normal LH and FSH F: menstrual disorder or amenorrhea after TBI, E_2 <0.08 nmol/L normal or low LH and FSH	T: RIA E_2, LH, FSH: FIA	29
Schneider *et al.*(11)	70	+	+	+	+	–	M: T < 12.1 nmol/ without ↑ LH and FSH Premenopausal F = no menses Postmenopausal F = low FSH, LH	All: ECL	29
Tanriverdi *et al.*(12)	52	+	+	+	NR	–	M: T < reference values; normal or ↓LH and FSH Premenopausal F: E_2 < 40.4 pmol/L; inappropriate low LH and FSH Postmenopausal F: LH and FSH in rage of premenopausal women	T: RIA E_2: CLIA LH, FSH: RIA	8
Herrmann *et al.*(5)	76	+	+	+	+	–	M: ↓T; inappropriately low LH and FSH Premenopausal F: amenorrhea ↓E_2 without ↑LH and FSH Postmenopausal F: LH and FSH in premenopausal range	All: IA	17
Bushnik *et al.* (4)	64	–	–	T+	–	–	M: testosterone deficiency: T < 9.0 nmol/L	NR	17
Klose *et al.*(7)	104[d]	+	+	+[e]	+	–	M: T < 10 nmol/L; inappropriate low LH; inhibin B and SHBG Premenopausal F: amenorrhoea/ oligomenorrhoe; low E_2, LH,FSH Postmenopausal F: inappropriate low LH,FSH for age	All: ECL	2

Table 5. Continued

Study	No. of patients	Basal serum LH	Basal serum FSH	Basal serum E_2/T	Menstrual history	GnRH Stimulation test	Criterion for hypogonadism	Assay LH/FSH/T/E_2	Outcome (%)
Tanriverdi *et al.*(14)	30	+	+	+	+	–	M: T < normal (total T < 4.6 nmol/L; free T < 11.5pg/ml); normal or ↓LH, FSH Premenopausal F: E_2 < 40.4 pmol/L; inappropriate low LH, FSH Postmenopausal F: LH, FSH in rage of premenopausal women	T: RIA E_2: CLIA LH, FSH: RIA	0
Wachter *et al.*(13)	55	+	+	T+	–	+ (n=NR) [f]	T below reported reference range (9.7– 27.7 nmol/L) E_2 below reported reference range: (follicular phase 48–709 pmol/L; midcycle peak 316–1828 pmol/L; luteal phase 162–775 pmol/L; postmenopausal < 128 pmol/L) Abnormal response LHRH test: NR	NR	13

ACS, automated chemiluminescence system; AUC, area under the curve; CL, confidence limit; CLIA, chemiluminometric immunoassay; E_2, estradiol; ECL, electrochemiluminiscence; F, female; FIA, fluoroimmunoassay; FSH, follicle stimulating hormone; GHD, growth hormone deficiency; GnRH, gonadotrope releasing hormone; IA, Immunoassay; IRMA, immunoradiometric assay; LH, luteinizing hormone; LHRH, luteinizing hormone releasing hormone; M, male; MEIA, microparticle enzyme immunoassay; MSA, magnetic separation assays; NR, not reported; RIA, radio immunometric assay; T, testosterone

[a] Normal values defined by a group of healthy subjects (n=18)

[b] Patients with abnormalities in basal testosterone levels or menstrual history underwent GnRH; only LH measurements

[c] Cut-off values defined by 31 healthy control subjects

[d] 30 age- and BMI-matched healthy controls all underwent pituitary testing

[e] In case of suspected hypogonadism in men, evaluation was repeated with measurement of inhibin B and SHBG

[f] Hormonal stimulation tests were performed if abnormatlities in basal hormone screening or if patients answered 'yes' to specific questionnaire. Not reported how many patients underwent stimaltions tests; LHRH: 100 µg

Table 6. Prolactin secretion

Study	No. of patients	Basal serum PRL	TRH	Criterion for abnormal PRL secretion	Assay PRL	Outcome (%)
Kelly *et al.* (6)	22	–	+ (n= NR)	Hypoprolactinemia: PRL < 95% CL according to AUC [a]	RIA	0
Lieberman *et al.*(9)	70	+	–	Hyperprolactinemia: M: > 565 pmol/L F: > 1160 pmol/L	MSA	0
Bondanelli *et al.*(3)	50	+	–	Hyperprolactinemie = PRL above reported reference range Hypoprolactinemia = PRL below reported reference range (M: 87 – 696 pmol/L; F: 174 – 1043 pmol/L)	ACS	16
Agha *et al.* (1)	102[b]	+	–	Hyperprolactinemia = basal level PRL > than the locally derived normal assay reference range (M: 83–414 mIU/L; F: 90–523 mIU/L)	FIA	12
Popovic *et al.*(10)	67	+	–	NR	IRMA	12
Aimaretti *et al.*(2)	70	+	–	Hyperprolactinemia: NR	IRMA	6
Leal-Cerro *et al.*(8)	99	+	+[c] (n=NR)	NR	NR	NR
Schneider *et al.*(11)	70	+	–	Hyperprolactinemia: PRL > 1087 pmol	ECLIA	NR

Table 6. Continued

Study	No. of patients	Basal serum PRL	TRH	Criterion for abnormal PRL secretion	Assay PRL	Outcome (%)
Tanriverdi *et al.*(12)	52	+	–	Hyperprolactinemia: basal level greater than the normal reference range (M: 87 –1783 pmol; premenopausal F: 122–1261 pmol; postmenopausal F:78–870 pmol)	RIA	8
Herrmann *et al.*(5)	76	+	–	Hyperprolactinemia: PRL above reported reference range (M:870 pmol; F: <1087 pmol)	IA	3
Bushnik *et al.*(4)	64	–	–	–	–	–
Klose *et al.* (7)	104[d]	+	–	Hyperprolactinemia: PRL > 510 mIU/L	ECLIA	NR
Tanriverdi *et al.*(14)	30	+	–	Hyperprolactinemia: basal level greater than the normal reference range (M: 87 –1783 pmol; premenopausal F: 122–1261 pmol; postmenopausal F: 1.8–20 ng/ml)	RIA	NR
Wachter *et al.*(13)	55	+	+[e] (n=NR)	NR	NR	NR

AUC, area under the curve; ACS, automated chemiluminescence system; CL, confidence limit; ECLIA, Electrochemiluminiscence immunoassay; FIA, Fluoroimmunoassay; IA, Immunoassay;
IRMA, immunoradiometric assay; MSA, magnetic separation assays; NR, not reported; PRL, prolactin; RIA, radio immunometric assay; TRH, thyroid releasing hormone
[a] Normal values defined by a group of healthy subjects (n=18)
[b] Cut-off values defined by 31 healthy control subjects
[c] TRH test: 500 ug
[d] 30 age- and BMI-matched healthy controls all underwent pituitary testing
[e] Hormonal stimulation tests were performed if abnormalities in basal hormone screening or if patients answered 'yes' to specific questionnaire. Not reported how many patients underwent stimulation tests. TRH: 100 µg

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