CLINICAL STUDY

Evaluation of pituitary function in the fatigued patient: a review of 59 cases

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Abstract

Objective: The aim of this study was to review the results of dynamic pituitary testing in patients presenting with fatigue.

Methods: We reviewed clinical histories and insulin tolerance test (ITT) results of 59 patients who presented with fatigue and other symptoms of glucocorticoid insufficiency over a 4-year period. All patients referred for ITT had an early-morning cortisol level of <400 nM and a low or normal ACTH level.

Results: Peak cortisol and GH responses following insulin-induced hypoglycaemia were normal in only seven patients (12%). Median age of the remaining 52 patients was 47 years (range, 17–67 years); all but five were female. Common presenting symptoms were neuroglycopenia ($n = 47$), depression ($n = 37$), arthralgia and myalgia ($n = 28$), weight gain ($n = 25$), weight loss ($n = 9$), postural dizziness ($n = 15$) and headaches ($n = 13$). Other medical history included autoimmune disease ($n = 20$); particularly Hashimoto's thyroiditis, Graves' disease and coeliac disease), postpartum ($n = 8$) and gastrointestinal ($n = 2$) haemorrhage and hyperprolactinaemia ($n = 13$). 31 subjects had peak cortisol levels of <500 nM (suggestive of ACTH deficiency; 18 of whom had levels <400 nM) and a further six had indeterminate results (500–550 nM). The remaining 15 subjects had normal cortisol responses (median 654 nM; range, 553–1062 nM) but had low GH levels following hypoglycaemic stimulation (5.9 mU/l; 3–11.6 mU/l).

Conclusion: Our results suggest that patients presenting with fatigue and symptoms suggestive of hypocortisolism should be considered for screening for secondary adrenal insufficiency, particularly in the presence of autoimmune disease or a history of postpartum or gastrointestinal haemorrhage. Whether physiological glucocorticoid replacement improves symptoms in this patient group is yet to be established.

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Introduction

Fatigue is a common symptom and diagnostic challenge in endocrine practice. Although accompanying symptoms often lead to the diagnosis of an endocrine condition, such as hypothyroidism, hypercalcaemia, diabetes or, rarely, primary adrenal failure, many patients undergo extensive investigation without identification of an obvious cause.

Secondary adrenal insufficiency is considered a rare and infrequent cause of fatigue, with an estimated prevalence of 150–280 per million (1). It is most commonly observed during or after chronic administration of exogenous glucocorticoids and in patients with hypothalamic-pituitary tumours, often in association with other pituitary hormone deficits (1). Presenting symptoms are variable and non-specific and include fatigue, reduced strength, myalgia, arthralgia, weight loss,

anorexia, postural dizziness and neuroglycopenia (1, 2). The diagnosis is suspected by finding a low morning cortisol in the absence of adrenocorticotrophic hormone (ACTH) elevation and is confirmed by the demonstration of suboptimal cortisol levels following dynamic testing.

In the absence of glucocorticoid treatment and organic pituitary or hypothalamic disease, ACTH deficiency, particularly isolated ACTH deficiency, is a rare condition of uncertain aetiology, with mostly small case series and case reports described (3–8). An autoimmune origin has been postulated, due to its frequent coexistence with other autoimmune diseases, particularly primary hypothyroidism secondary to chronic lymphocytic thyroiditis (1, 9). Among 102 Polish patients with secondary adrenal insufficiency of unknown aetiology, 25 reported associated autoimmune disorders: 23 exhibited evidence of thyroid

autoimmunity, 14 had overt hypothyroidism, three had subclinical hypothyroidism and three had treated Graves' disease (2). Other autoimmune diseases included type 1 diabetes, vitiligo, pernicious anaemia, autoimmune thrombocytopaenia and premature ovarian failure (2). Consistent with a probable autoimmune origin, ACTH deficiency is the most common endocrine abnormality reported in patients with autoimmune lymphocytic hypophysitis, present in up to 65% of cases (9–11). Lymphocytic hypophysitis classically, but not exclusively, affects females during late pregnancy or in the postpartum period (12) and is accompanied by hyperprolactinaemia in up to one-third of cases (10, 13). ACTH deficiency has also been described in patients with Langerhans cell histiocytosis, usually in the context of multiple pituitary hormone deficits, especially diabetes insipidus (14), and in rare cases of xanthomatous hypophysitis (15). Rare mutations in genes involved in corticotroph development or the synthesis or cleavage of pro-opiomelanocortin have been described in cases of early-onset isolated ACTH deficiency (1, 16, 17).

Various dynamic tests have been used to assess the integrity of the hypothalamic-pituitary-adrenal (HPA) axis, including low-dose (1 µg) and standard-dose (250 µg) corticotrophin tests, glucagon and metyrapone tests and the insulin-tolerance test (ITT; or insulin hypoglycaemia test) (1, 2, 18–20). Although the ITT is generally considered to be the 'gold standard' test of HPA function, it has been suggested that results should be interpreted with caution and in the clinical context in which the patient presents (1, 21, 22). The peak cortisol level used to delineate an 'adequate' from an 'inadequate' response is variable, with values of 500–600 nM used throughout the literature (19, 20, 22–24). Some of this variability may be due to immunoassay-related differences (25). Furthermore, there is considerable intra-subject variability in peak cortisol responses to insulin-induced hypoglycaemia, with inter-test differences of > 140 nM reported in some studies (21).

The aim of this report was to review the clinical histories and results of ITTs in patients presenting to an endocrine practice with fatigue and other symptoms of pituitary insufficiency over a 4-year period.

Subjects and methods

Subjects

We present a retrospective report of 59 fatigued patients who were evaluated between 2000 and 2004 (three patients presented through the general endocrinology outpatients clinic at St Vincent's Hospital, a teaching hospital in inner Sydney, Australia, and 56 patients through private general endocrinology consulting rooms at St Vincent's Clinic). One author (K S) consults for 2 days/week, the other (J R G) consults for 1/2 day each week. Fatigue was defined as lack of

energy or stamina and/or reduced vitality (1). Adrenergic symptoms of hypoglycaemia were defined as episodic diaphoresis or tremulousness, especially between meals or when meals were missed. Neuroglycopenic symptoms were defined as episodic poor concentration, word-finding difficulties and cognitive dysfunction. In fatigued patients who also reported symptoms suggestive of hypocortisolism, early-morning cortisol and ACTH levels were measured. As previous reports suggest that early-morning cortisol levels of at least 300–500 nM can be used to predict an adequate response following insulin-induced hypoglycaemia (1, 26–28), it was our practice that patients with early-morning cortisol levels of < 400 nM and low- or normal-range ACTH levels (< 12 pM) underwent an ITT. In addition, all patients with suboptimal ITT results underwent T1- and T2-weighted magnetic resonance scanning of the pituitary gland. The review was approved by the Research and Ethics Committee at St Vincent's Hospital.

ITT protocol

ITTs commenced between 0800 and 0900 h following an overnight fast. Patients remained supine throughout the test. A standardized protocol was followed: 0.1 IU/kg of human regular insulin (Actrapid®, Novo Nordisk, Denmark) was given intravenously to induce symptomatic hypoglycaemia (blood glucose, < 2.2 mM). Additional insulin boluses were given if required. Intravenous glucose was administered following severe hypoglycaemia. Glucose, cortisol, ACTH and growth hormone (GH) levels were measured at 0, 15, 30, 60, 90 and 120 min. As reviewed recently (1), a peak cortisol level of < 500 nM was considered suggestive of adrenal insufficiency, with values of > 550 nM indicative of a normal HPA axis. Values of 500–550 nM were considered indeterminate, with adrenal insufficiency not excluded (1). A peak GH level of > 13 mU/l (5 µg/l) was interpreted as a normal response (29–31). No serious adverse effects were experienced during the procedure.

Analytical methods

Blood glucose was measured immediately by the glucose oxidase method (model 2300 STAT PLUS 230V; Yellow Springs Instruments, Yellow Springs, OH, USA). Thyroid-function tests (reference ranges (RRs): free thyroxine, 10–21 pM; thyroid-stimulating hormone, 0.3–4 mIU/l), prolactin (RR, 50–370 mIU/l), follicle-stimulating hormone (RRs, premenopausal females, 1.6–33 IU/l; postmenopausal females, > 16 IU/l; males, 0.9–8.1 IU/l) and luteinizing hormone (RRs, premenopausal females, 2.5–130 IU/l; postmenopausal females, > 15 IU/l; males, 1.5–14 IU/l) were determined by a microparticle enzyme immunoassay (AxSYM system; Abbott Laboratories, Abbott Park, IL, USA). Cortisol (RR, 200–600 nM),

ACTH (RR, < 12 pM), GH and dehydroepiandrosterone sulphate (DHEAS; RRs, premenopausal females, $2.2\text{--}9.1$ μM ; postmenopausal females, $0.3\text{--}1.7$ μM ; males, $5.3\text{--}9$ μM) were assayed by chemiluminescent enzyme immunoassays (Diagnostic Products Corporation, Los Angeles, CA, USA); insulin-like growth factor (IGF)-I (RR, $0.4\text{--}1.6$ U/ml) by a double-antibody RIA (Bioclone IGF-1 RIA kit; Bioclone Australia Pty, Sydney, Australia) and α -subunit (RRs, males and premenopausal females, $0.05\text{--}0.4$ IU/l; postmenopausal females, $0.37\text{--}1.15$ IU/l) by a two-site immunoradiometric assay (free α -glycoprotein subunit IRMA kit; Bioclone Australia Pty, Sydney, Australia). Thyroid anti-microsomal antibodies were measured by a semi-quantitative microtitre particle agglutination test (Fujirebio, Tokyo, Japan).

Statistical methods

Data are presented as medians (range) and were analysed using Statview 5 (SAS Institute, Cary, NC, USA). Simple regression analysis and analysis of variance were used to analyse normally distributed variables. Skewed data were analysed using non-parametric statistical methods. $P < 0.05$ was considered significant.

Results

Of the 59 patients who underwent an ITT, only seven had normal cortisol and GH responses to insulin-induced hypoglycaemia (median peak cortisol levels during ITT, 689 nM; range, $571\text{--}980$ nM; median GH levels during ITT, 39.2 mU/l; $13.8\text{--}49$ mU/l). Data on the remaining 52 patients are presented below.

Presenting symptoms

Median age was 47 years ($17\text{--}67$ years); all but five patients were female. Patients' presenting symptoms, concomitant diseases, medications and other relevant historical details are provided in Table 1. By definition, all patients reported fatigue. Symptoms of neuroglycopenia (episodic poor concentration, word-finding difficulties and cognitive dysfunction) were present in the majority of patients ($n = 47$). A history of depression was common ($n = 37$); 11 of these patients had received or were receiving antidepressant therapy. Arthralgia and myalgia were reported by 28 patients. Weight gain was present in 25 patients; weight loss was less frequent ($n = 9$). 15 patients reported postural dizziness. Headaches or migraines were reported by 13 patients.

Associated diseases

Autoimmune diseases were common (all women) and included Hashimoto's thyroiditis ($n = 11$), Graves'

disease ($n = 2$), coeliac disease ($n = 3$), pernicious anaemia ($n = 1$), Guillian Barre syndrome ($n = 1$), mixed connective tissue disease ($n = 1$), Raynaud's disease ($n = 1$) and vitiligo ($n = 1$; Table 1).

Eight patients had a history of significant postpartum haemorrhage and two reported significant previous gastrointestinal haemorrhage, occurring up to 39 years prior to diagnosis (Table 1). Both patients with gastrointestinal haemorrhage had been transfused (requiring 4 and 8 units of blood). Patient 36, an earthquake survivor, had received a blood transfusion of 5 units 28 years previously. In two other patients, symptoms had begun after the birth of a child, but there was no history of intra- or postpartum haemorrhage. Another patient had a cardiac arrest 1 month postpartum and a prolonged cardiac illness requiring intensive care support.

Pituitary imaging

Pituitary imaging by magnetic resonance imaging (MRI) revealed coincident microadenomas ($n = 6$), loss of the upper concavity of the pituitary (on the lateral image; $n = 10$), empty sella ($n = 6$), pituitary-stalk thickening ($n = 2$) and haemorrhage ($n = 1$; Table 1).

Pituitary function and other endocrine tests

Pituitary function tests at initial evaluation are presented in Table 2. Median early-morning cortisol level of all 52 subjects was 283 ($30\text{--}389$) nM. Thirteen patients had modest hyperprolactinaemia (two treated) and two of five males were diagnosed with hypogonadotropic hypogonadism. Anti-microsomal antibodies were positive in 15 of the 36 patients in whom they were measured. Low levels of DHEAS, an adrenal precursor of steroid biosynthesis, were common.

ITT results

ITT results are presented in Table 3. 31 subjects had peak cortisol levels of < 500 nM (18 of whom had levels < 400 nM) and six had values of $500\text{--}550$ nM, with or without impaired GH responses. The remaining 15 subjects had normal cortisol responses (median 654 nM; range, $553\text{--}1062$ nM), but had subnormal GH levels following hypoglycaemic stimulation (median 5.9 mU/l; $3\text{--}11.6$ mU/l).

Baseline morning cortisol levels at the time of the ITT allowed prediction of peak cortisol levels following hypoglycaemia ($r = 0.44$, $P = 0.001$). In contrast, there was no significant relationship between morning ACTH values and peak cortisol levels, nor between IGF-I and peak GH levels (data not shown).

Patients with ($n = 37$) and without ($n = 15$) a history of depression had similar peak cortisol responses following hypoglycaemia (463 nM (range $139\text{--}1062$ nM) versus 480 nM ($177\text{--}924$ nM) respectively; $P = 0.96$). Among those with a history of depression,

Table 1 Patient characteristics.

Patient number	Age (years)/sex	Associated autoimmune disease(s)	Depression	Gastrointestinal symptoms (weight lost or gained)	Arthralgia/ myalgia	NG or AG	Pituitary imaging	Endocrine medications	Comments
1	26F	–	No	N	No	NG	Normal	–	Presyncope, seizures
2	52F	–	Yes*	WG (6 kg)	No	NG, AG	Empty sella	–	Migraines, PPH (24 years prior to presentation)
3	40F	Pernicious anaemia	Yes*	A, WG (20 kg)	Yes	NG	Normal	–	Onset of symptoms PP (fifth child), migraines, hyperprolactinaemia
4	59F	–	Yes	N	No	NG	Stalk thickening	–	Migraines, presyncope
5	67F	Hashimoto's thyroiditis	No	WG	Yes	NG	Empty sella	Thyroxine	–
6	61F	–	Yes	N, WG (40 kg)	Yes	NG	Normal	–	PPH (39 years prior to presentation), CFS
7	61F	Hashimoto's thyroiditis, coeliac disease	No	WL, A	No	NG	Normal	Thyroxine	Osteoporosis, premature menopause, taking inhaled steroids for asthma
8	38F	Coeliac disease	Yes	–	No	NG	Loss of the upper concavity of the pituitary	–	Presyncope, taking inhaled steroids for asthma
9	43F	Hashimoto's thyroiditis	No	A, WL	No	NG	Stalk thickening, loss of the upper concavity of the pituitary	Thyroxine	Presyncope
10	58F	–	Yes	N, WG (14 kg)	Yes	NG	Normal	–	Presyncope, GIH (transfused 4 U)
11	57F	Graves' disease	No	WG (18 kg)	Yes	NG	Loss of the upper concavity of the pituitary, 5 mm lesion (hypointense)	Thyroxine	Migraines, hyperprolactinaemia
12	25F	Hashimoto's thyroiditis	Yes	WG (30 kg)	Yes	NG, AG	Normal	Thyroxine	Hyperprolactinaemia
13	48F	Raynaud's disease	No	WG (7 kg)	Yes	NG	Normal	–	Hyperprolactinaemia
14	37F	–	No	WG	Yes	NG	Normal	–	Crohn's disease, postoperative hypotension
15	20M	–	Yes	WG (10 kg)	–	–	Normal	–	Headaches
16	34F	–	Yes	WG	–	NG, AG	Loss of the upper concavity of the pituitary	–	Secondary amenorrhoea
17	40F	Guillian Barre	Yes*	N	Yes	NG	Empty sella	–	PPH (24 years prior to presentation), CFS,
18	47F	–	Yes	A	No	NG	5 mm non-enhancing lesion	–	Presyncope, onset PP, headaches, BSO, hyperprolactinaemia
19	17F	Hashimoto's thyroiditis	No	N, A	No	NG	Loss of the upper concavity of the pituitary	Thyroxine	–
20	52F	–	Yes	N, A, WG	Yes	NG, AG	Small pituitary	Thyroxine†	GIH (transfused 8 U), presyncope,
21	30F	–	Yes	N, A, WL (5 kg)	No	NG	Haemorrhage	Thyroxine	Hyperprolactinaemia
22	59F	–	No	–	Yes	NG, AG	Normal	–	PPH requiring transfusion
23	39M	–	Yes*	N, WG (14 kg)	Yes	NG	4 mm hypointense lesion	Testosterone	Hypogonadotrophic hypogonadism
24	50F	Graves' disease	Yes	A	Yes	NG	Normal	PTU	Presyncope

Table 1 Continued

Patient number	Age (years)/sex	Associated autoimmune disease(s)	Depression	Gastrointestinal symptoms (weight lost or gained)	Arthralgia/ myalgia	NG or AG	Pituitary imaging	Endocrine medications	Comments
25	53M	–	Yes	–	No	NG	Normal	Thyroxine	Hypogonadotrophic hypogonadism
26	46F	Hashimoto's thyroiditis	Yes*	N, A, WL	Yes	NG	Loss of the upper concavity of the pituitary	Thyroxine	PPH (15 years prior), migraines
27	34F	Coeliac disease	Yes	N	No	NG	2 mm hypointense lesion	Cabergoline	Hyperprolactinaemia
28	56F	–	No	N, WG	No	NG	Normal	–	Hyperprolactinaemia
29	48F	Hashimoto's thyroiditis	Yes	WG	Yes	NG	Loss of the upper concavity of the pituitary	Thyroxine	Premature menopause (37 years)
30	56F	–	Yes*	–	No	NG, AG	Normal	–	Premature menopause
31	51F	Hashimoto's thyroiditis	Yes	N, A, WL	Yes	NG	Empty sella	Thyroxine	Premature menopause (41 years), headaches, galactorrhoea, collapse, presyncope
32	41F	–	Yes*	A	Yes	NG	Loss of the upper concavity of the pituitary	–	Headaches
33	38F	–	Yes	N, A	No	NG	Normal	–	Migraines, hyperprolactinaemia
34	41F	–	Yes*	WL	Yes	NG	Normal	–	Presyncope, hyperprolactinaemia
35	56F	Hashimoto's thyroiditis	Yes*	N, A	Yes	NG, AG	Loss of the upper concavity of the pituitary	Thyroxine	Premature menopause
36	44F	–	Yes*	WG (3 kg)	Yes	NG	5 × 3 mm non-enhancing lesion	–	Earthquake survivor, transfused 5 U
37	47F	–	Yes	N, A, WL (5 kg)	Yes	NG	Normal	–	Sarcoidosis, premature menopause (42 years), migraines
38	56F	–	Yes	N, WG	Yes	NG	Empty sella	–	Premature menopause (42 years), migraines, presyncope, hyperprolactinaemia
39	50F	–	No	WG	No	AG	Normal	Cabergoline	Hyperprolactinaemia
40	31F	–	No	N, A, WL	No	NG	Normal	–	Onset PP after emergency CS
41	37M	–	Yes	–	No	–	Normal	–	Low libido, headaches
42	29F	–	Yes	WG	No	NG, AG	Normal	–	Presyncope, hyperprolactinaemia
43	53M	–	Yes*	–	Yes	NG, AG	Normal	–	Presyncope
44	49F	Vitiligo	Yes	WG	Yes	–	Normal	–	PPH, presyncope
45	39F	–	Yes	WL	No	–	Normal	–	–
46	46F	MCTD	Yes	–	Yes	NG	Normal	Thyroxine†	Perimenopausal
47	50F	Hashimoto's thyroiditis	No	–	Yes	NG	Normal	Thyroxine	–
48	45F	–	Yes	A, WG	Yes	AG, NG	3 mm adenoma	–	Cardiac arrest PP
49	55F	–	Yes	WG	–	NG	Empty sella	–	–
50	49F	–	No	WG	No	NG	Normal	–	PPH (22 years prior to presentation)

Table 1 Continued

Patient number	Age (years)/sex	Associated autoimmune disease(s)	Depression	Gastrointestinal symptoms (weight lost or gained)	Arthralgia/myalgia	NG or AG	Pituitary imaging	Endocrine medications	Comments
51	56F	–	No	WG	No	NG	Loss of the upper concavity of the pituitary	–	PPH (32 years prior to presentation)
52	42F	Hashimoto's thyroiditis, episcleritis	Yes	N, WG (4 kg)	Yes	NG	Normal	Thyroxine	Presyncope

F, female; M, male. Patients 1–37 had subnormal or indeterminate cortisol responses during the ITT, with or without suboptimal peak GH responses; patients 38–52 has suboptimal stimulated GH responses only. A, anorexia; AG, adrenergic glycopaenia; BSO, bilateral salpingo-oophorectomy (endometriosis); CFS, chronic fatigue syndrome; CS, Caesarian section; GIH, gastrointestinal haemorrhage; N, nausea; NA, neuroadrenergic glycopaenia; NG, neuroglycopaenia; PP, postpartum; PPH, postpartum haemorrhage; PTU, propylthiouracil; WG, weight gain; WL, weight loss; MCTD, mixed connective tissue disease.

*Depression treated;

†multinodular goitre.

Table 2 Pituitary function and other biochemical tests.

Patient number	Morning cortisol level (nM)	Morning ACTH level (pM)	IGF-I (U/ml)	Free thyroxine (pM)	TSH (mIU/l)	Prolactin (mIU/l)	LH (IU/l)	FSH (IU/l)	α -Subunit (IU/l)	AMA	DHEAS (μ M)
1	30	2.4	1.06	15.7	0.59	168	10.8	5.8	0.39	ND	ND
2	82	2.1	0.39	8	1.79	342	30.3	26.5	ND	ND	1
3	92	<1.5	0.88	11.9	2.2	781	1.6	1.9	0.19	–	1.5
4	125	<1.5	0.58	14.7	1.86	125	6.9	24.5	0.42	ND	0.9
5	186	1.5	0.62	16.9	0.19	117	44.2*	12.7*	0.26	+	ND
6	188	3	0.6	13.7	2.11	278	3.3*	7.1*	0.59	–	1.3
7	198	2.9	0.79	15.6	1.95	87	18.4*	42.7*	ND	+	<0.4
8	198	4.5	0.54	11	0.77	224	11.3	6.5	0.41	–	<1.0
9	210	1.3	0.87	15	2.21	ND	ND	ND	0.37	+	2.6
10	213	<1.5	0.92	16	0.86	253	ND	81.9	ND	ND	ND
11	219	3	0.57	16	3.09	1403	<0.5*	<0.5*	0.32	ND	ND
12	220	3.8	1.21	15	0.99	519	17.8	4.6	0.99	+	9.3
13	221	4.6	1.01	13	1.82	435	1.7	4.5	0.16	+	1.5
14	236	6	0.54	11.2	1.43	209	7.8	4.2	0.65	–	<0.9
15	237	5.1	0.99	11	1.1	141	8.5	1.9	0.38	–	6.0
16	264	7.0	0.89	ND	1.91	244	1.1	1.4	0.30	–	<0.9
17	264	1.2	1.14	13.5	3.04	377	10.1	4.3	1.38	–	1
18	268	2.3	0.73	14	1.59	495	7.1	2.1	0.24	–	ND
19	271	3.3	1.56	15.5	1.35	317	12.2	6	0.59	+	1
20	291	<1.5	0.46	13.4	2.43	247	28.9	13.6	0.82	–	ND
21	293	3.2	1.02	11.1	5.4	1260	7.4	6.6	0.18	–	3.7
22	295	1.8	0.25	15	3.1	280	14*	33*	0.88	ND	<0.2
23	306	2.1	0.59	11.7	1.64	216	3.4†	5.1†	0.39	ND	2.1
24	309	<1.5	0.52	11.9	0.8	266	2.5	5.6	ND	–	0.9
25	312	4.7	0.45	14	2.67	142	3.0†	5.0†	ND	ND	2.3
26	314	<1.5	0.48	19	3.28	275	5.2	13.7	0.34	+	1.7
27	317	1.8	0.69	12.2	1.55	644	2.4	6.1	0.2	–	4.2
28	318	3.2	ND	10.2	3.39	1492	36.4*	61.6*	1.1	–	ND
29	325	3.2	0.45	12	2.75	322	38.4*	63.6*	1.29	+	1.1
30	337	2.6	0.57	11	1.72	245	31.1*	60.5*	0.98	+	1.4
31	338	3.6	0.3	20	1.2	219	18	10	ND	+	ND
32	339	3.6	0.73	12.4	1.97	206	6.6	4.2	0.23	ND	2.2
33	350	5.3	0.82	12.7	0.97	627	0.7	2.7	ND	–	ND
34	352	2.1	1.62	12	1.89	570	3.9	8.2	ND	–	0.9
35	360	2.1	0.48	14	0.76	249	45.9*	21.1*	1.3	+	3.8
36	381	3.4	0.92	13.8	1.92	361	2.2	2.7	0.16	–	5.8
37	389	2.6	1.05	13	1.55	327	53.5*	87*	0.87	ND	ND
38	156	<1.5	0.62	11.2	1.5	768	11.6*	13.4*	0.52	ND	2.4
39	172	2.3	0.62	11.7	1.46	191	5.6	16.1	ND	ND	ND
40	193	2.4	1.06	12.2	0.59	138	ND	ND	0.11	–	ND
41	226	4.8	ND	ND	1.72	149	2.1	<1.0	0.34	ND	ND
42	236	3.0	0.71	12.5	1.23	492	2.8	5.3	0.17	–	3.2
43	276	9.3	0.58	17	2.01	80	6.7	6.4	0.34	+	6.2
44	279	2.4	0.48	13.9	1.01	280	6.4	4.8	0.66	+	ND
45	286	3.5	0.61	8.5	3.92	41	4.3	1.7	0.16	–	2.1
46	289	2.7	0.43	15	0.81	359	15.9*	36.8*	1.26	–	ND
47	299	1.6	0.19	16	3.2	151	9.7	3.4	0.42	+	ND
48	330	2.3	0.7	8	1.82	260	2.9	7.7	0.21	–	<0.4
49	338	1.5	0.64	ND	2.25	ND	6.4*	4.5*	ND	+	<1.0
50	339	4.1	0.45	ND	ND	203	13*	17.7*	0.5	ND	1.7
51	346	1.5	0.47	13	0.96	219	57	109	2.27	ND	2.7
52	358	2.2	0.37	13.4	2.33	289	3	5.5	0.51	ND	3.4

Patients 1–37 had subnormal or indeterminate cortisol responses during the ITT, with or without suboptimal peak GH responses; patients 38–52 had suboptimal stimulated GH responses only. +, positive; –, negative; AMA, antimicrosomal antibodies; FSH, follicle-stimulating hormone; LH, luteinizing hormone; ND, not done; TSH, thyroid-stimulating hormone.

†Postmenopausal, not receiving hormone-replacement therapy.

‡Male with low testosterone.

patients treated with antidepressants ($n = 11$) tended to have lower stimulated peak cortisol levels than untreated patients, although the difference was not statistically significant (435 nM (150–614 nM) versus 524 nM (139–1062 nM) respectively; $P = 0.09$).

There was no difference between subjects with and without depression in peak stimulated GH responses ($P = 0.25$). Among patients with depression, treatment with antidepressants had no effect on peak GH levels ($P = 0.18$).

Table 3 Biochemical results during ITTs.

Patient number	Baseline cortisol (nM)	Minimum blood glucose (mM)	Peak cortisol (nM)	Peak GH (mU/l)
1	79	1.3	189	44.8
2	394	1.0	330	<0.4
3	<30	1.6	150	22.8
4	39	2.1	139	5.9
5	188	1.4	495	1.9
6	251	1.7	264	5.1
7	159	1.6	492	4.9
8	160	1.9	450	40.3
9	213	1.6	177	0.7
10	215	1.4	173	1.1
11	128	2.2	359	4.5
12	311	1.7	301	4.3
13	125	1.6	296	4.8
14	236	1.3	322	23
15	241	1.7	548	10.4
16	228	1.5	448	4.6
17	395	1.1	440	6.2
18	256	1.4	489	<0.4
19	140	1.7	429	48.7
20	421	1.5	528	0.4
21	293	1.6	293	1.0
22	64	2.0	408	25
23	272	1.6	472	<0.4
24	177	1.7	312	<0.4
25	358	1.7	519	4.3
26	310	1.8	292	6.2
27	188	2.0	199	0.4
28	231	1.6	480	5.6
29	307	1.7	536	31.5
30	304	1.9	321	<0.4
31	273	1.4	509	11.9
32	167	1.2	209	0.5
33	331	1.6	537	5.8
34	433	1.2	435	27.7
35	333	1.1	448	0.9
36	254	0.88	463	0.5
37	389	2.1	344	14
38	550	1.8	897	4.7
39	71	2.1	553	11.4
40	346	1.6	924	4.7
41	277	1.9	631	9.4
42	171	2.0	564	4.2
43	213	1.7	614	4.3
44	277	1.6	1062	11.6
45	578	1.9	610	5.9
46	367	1.4	745	6.9
47	211	1.6	684	4.1
48	313	1.1	682	10.5
49	306	1.8	627	10.5
50	239	1.3	663	6.3
51	319	1.4	560	3.0
52	228	1.5	645	4.7

Patients 1–37 had subnormal or indeterminate cortisol responses during the ITT, with or without suboptimal peak GH responses; patients 38–52 had suboptimal stimulated GH responses only. To convert GH from mU/l to ng/ml ($\mu\text{g/l}$), divide by 2.6.

Discussion

This study reviewed the results of dynamic pituitary testing in 59 patients who presented with fatigue and other symptoms suggestive of HPA deficiency, in whom morning cortisol levels were <400 nM and ACTH levels were

normal or low. 31 patients were found to have suboptimal peak cortisol responses to insulin-induced hypoglycaemia and six had indeterminate results. Although these findings suggest that some patients presenting with such symptoms should be considered for screening for secondary adrenal insufficiency, particularly in the

presence of autoimmune disease or a history of postpartum or gastrointestinal haemorrhage, the results should be considered in the context of limitations relating to the interpretation of ITT results. First, intra-subject, inter-test variability in peak cortisol responses of $>20\%$ has been reported in some studies and patients with non-diagnostic results may therefore require repeat testing (21). Second, variability between cortisol immunoassays may limit the validity of interpreting ITT results based on cortisol cut-offs established in other laboratories, particularly in the absence of a local control group (25). Although our study was uncontrolled, stimulated cortisol levels in the seven patients categorized as having normal ITT results (689 nM; range, 571–980 nM) and the 15 patients with normal stimulated cortisol levels (654 nM; 553–1062 nM) but suboptimal GH responses were comparable to levels reported previously in healthy subjects (18). Despite these limitations, a significant number of patients in the current series clearly demonstrated suboptimal cortisol responses to hypoglycaemia.

Autoimmune diseases were common, suggesting that ACTH deficiency may be of autoimmune origin in some cases. Indeed, seven of 31 patients (23%) with suboptimal stimulated cortisol levels had a prior diagnosis of autoimmune hypothyroidism and two had Graves' disease. This observation is consistent with a recent Japanese review of the literature, which reported that 24% of cases of isolated ACTH deficiency were associated with hypothyroidism, most commonly Hashimoto's thyroiditis (6). Similarly, thyroid autoimmunity, with or without subclinical or overt hypothyroidism, was found in $\sim 25\%$ of Polish patients with secondary adrenal insufficiency of uncertain aetiology (2). As cortisol is a physiological regulator of thyrotrophin secretion (1), resolution of biochemical hypothyroidism following adequate glucocorticoid therapy has been reported (32–34) and thyroid function should therefore be reassessed after adequate glucocorticoid replacement.

Two patients in the current series had developed symptoms in the postpartum period and 13 had associated moderate hyperprolactinaemia. Although these observations raise the possibility of autoimmune lymphocytic hypophysitis, circulating anti-pituitary antibodies were not measured (as a reliable assay was not locally available) and histological confirmation was not within the scope of this study. Furthermore, three patients in our series had concomitant coeliac disease, which has been associated with the development of lymphocytic hypophysitis (35). Of note, two of these patients were receiving treatment with inhaled corticosteroids, which have been reported, albeit uncommonly in adult patients (36), to suppress the HPA axis. Whether their use contributed to the patients' symptoms and suboptimal stimulated cortisol responses is speculative. Finally, seven patients gave a history of premature menopause, raising the possibility of primary ovarian failure of autoimmune origin, which has been reported previously in ACTH deficiency (2).

Our results suggest that HPA function should also be evaluated carefully in fatigued patients with a history of significant blood loss, even if the event predated the onset of symptoms by many decades. In our series, eight patients reported postpartum haemorrhage 15–39 years prior to the onset of symptoms of hormonal deficiency; two had a history of massive gastrointestinal haemorrhage requiring transfusion and another, an earthquake survivor, also required transfusion. Two of these patients (patients 2 and 17) and four others were reported as having an empty sella on MRI. Acute hypopituitarism in the context of obstetric haemorrhage, as described initially by Sheehan in 1937 (37), refers to ischaemic pituitary infarction occurring as an immediate response to an obstetric haemodynamic insult. Two recent Japanese reports collectively described a total of seven cases of complete or partial hypopituitarism (with an empty sella on MRI) 3–48 years after massive obstetric blood loss (38, 39). Our observations indicate that a significantly fatigued patient with a history of postpartum haemorrhage, significant gastrointestinal blood loss or shock requiring transfusion or intensive-care support should be carefully evaluated for underlying pituitary deficiency, irrespective of when the haemorrhage occurred relative to presentation.

Studies of the HPA axis in depression have yielded conflicting and inconsistent results (40). It has been postulated that melancholic depression is associated with activation of hypothalamic corticotrophin-releasing hormone (CRH) secretion (41, 42), basal hypercortisolism, intact negative feedback and a blunted ACTH response to ovine CRH (43). Early studies demonstrated that some patients with severe major depression had impaired cortisol responses to hypoglycaemia, which improved on recovery (44, 45). These results contrast with our findings and a previous study of ambulatory depressed patients (46), which found that cortisol responses to hypoglycaemia were similar in subjects with and without a history of depression. Taken together, these studies suggest that the degree of HPA impairment in depressed patients may depend on the severity of the depressive illness and whether patients are studied during the active phase of their disease or following remission.

The ITT is considered to be the test of choice for diagnosing GH deficiency (30, 47, 48). However, the peak GH level that most appropriately and accurately differentiates a 'normal' GH response from adult GH deficiency is subject to inter-assay and intra-subject variability (48–50). A stimulated GH level of $<5 \mu\text{g/l}$ ($\sim 13 \text{ mU/l}$) following insulin-induced hypoglycaemia has been reported to accurately differentiate subjects with organic GH deficiency from age-, gender- and body-mass-index matched controls (29). Indeed, this cut-off has been shown to have a sensitivity of 95% and a specificity of 92% for the diagnosis of adult GH deficiency (48). The Growth Hormone Research Society

defined severe GH deficiency as a stimulated GH level of $<3 \mu\text{g/l}$ ($\sim 8 \text{ mU/l}$) (30). In the current study, 43 patients had stimulated GH levels of $<13 \text{ mU/l}$, 36 of whom had levels of $<8 \text{ mU/l}$. However, only three of these patients had IGF-I levels lower than the RR ($<0.4 \text{ U/ml}$). The finding of a suboptimal peak GH level following hypoglycaemia in the absence of a low or borderline IGF-I level should be interpreted with caution, particularly in the absence of multiple pituitary hormone deficits and/or structural pituitary disease (30, 49). Furthermore, a low stimulated GH level in a glucocorticoid-deficient patient is of questionable diagnostic significance and requires re-evaluation following stable hormone replacement (30). Finally, obesity, which suppresses GH release (47, 48), may have contributed to these findings in some patients.

In summary, this case series suggests that the diagnosis of secondary adrenal failure should be entertained in patients presenting with fatigue, adrenergic hypoglycaemia, neuroglycopenia and a change in mood or weight, especially when accompanied by autoimmune disease or a history of postpartum or gastrointestinal haemorrhage. Whether steroid replacement improves symptoms in this patient group is yet to be determined. The significance, if any, of a suboptimal GH response to hypoglycaemia, in the absence of structural hypothalamic-pituitary disease and multiple pituitary hormone deficits, remains unknown.

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