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(Article begins on next page)

Secondary Adrenal Insufficiency: Where Is It Hidden and What Does It Look Like?

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Abstract

Adrenal failure secondary to hypothalamic-pituitary disease is a common although underestimated and underdiagnosed condition, with serious consequences. Corticotropin deficiency can be isolated or more frequently occur in association with other pituitary hormones deficiencies. The most frequent

endogenous cause of secondary adrenal insufficiency (SAI) is a tumor of the hypothalamicpituitary region, usually associated with panhypopituitarism secondary to tumor growth or to its treatment with surgery or irradiation. Less commonly, SAI is due to nontumoral disorders including infiltrative lesions, infective processes, vascular alterations, traumatic brain injury, empty sella or genetic

disorders. Finally, long-term administration of exogenous glucocorticoids can determine secondary and/or tertiary hypoadrenalism acting at the hypothalamic level and leading to prolonged suppression of the hypothalamic-pituitary-adrenal axis. It is essential to perform validated diagnostic

procedures in order to promptly diagnose hypoadrenalism so as to prevent an adrenal crisis. At the same time, diagnosis is complex as no single test has sufficient sensitivity to identify all patients with SAI. Therefore, clinical judgment and follow-up are crucial for the assessment of corticotropin deficiency. Patients with persisting suggestive symptoms and/or a clinical history of higher risk for adrenal insufficiency deserve careful subsequent reassessments.

Secondary adrenal insufficiency (SAI) may result from any disease that involves the hypothalamic-pituitary unit and be secondary to a defect in corticotropin [adrenocorticotrophic hormone (ACTH)] release or the lack of adrenal gland responsiveness to ACTH. Corticotropin deficiency can be isolated or occur in association with other pituitary hormone defects [1] .

There is generally a specific sequential failure of pituitary hormones that starts with growth hormone (GH) and is followed by gonadotropins (FSH and LH) and, finally, by thyrotropin-stimulating hormone (TSH) and ACTH [1] . The fact that ACTH is usually the last hormone to be lost may teleologically reflect its need for survival. However, in some patients with pituitary disorders (i.e. lymphocytic hypophysitis or genetic defects), ACTH deficiency can occur as a first and/or isolated hormone deficiency [1] . SAI is more common than primary adrenal deficiency, with an estimated prevalence of 150–280 cases per million, a predominance in women and a peak of age at diagnosis in the sixth decade [1] .

Where Is It Hidden?

All hypothalamic-pituitary disorders can potentially lead to SAI, which can be isolated or occur in the context of multiple hormone deficiency, up to panhypopituitarism if both the anterior and posterior pituitaries are involved [1] . Tumors of the hypothalamic-pituitary region are the most frequent cause of endogenous SAI [1] . Isolated ACTH deficiency is rare and has been described in association with a great

variety of conditions. An underlying immunological dysregulation has been hypothesized on the basis of the frequent association with extrapituitary autoimmune disorders and the identification of autoantibodies directed against the hypothalamus and pituitary, although the etiology remains to be elucidated [2] .

Pituitary Tumors

Pituitary adenomas account for about 10% of all intracranial tumors with a peak incidence between 30 and 60 years of age (females are usually younger at diagnosis than men, with the majority of the cases presenting in women between 20 and 45 years of age and in men between 35 and 60 years of age) [3] . Loss of pituitary function represents one of their major clinical manifestations, particularly in patients with large tumors. A high incidence of SAI has been reported in large series of patients with nonfunctioning

pituitary adenomas [4] . In prolactinomas – the most prevalent pituitary adenomas (45–66% of the cases; prevalence of 62 cases/100,000 individuals) – SAI is more frequent in patients with macro- than in patients with microadenomas, with an overall prevalence of 14–23% [5] . About 30% of the patients with GH-producing adenomas present insufficiency of at least one pituitary axis, with SAI reported in 12– 35% of them [6] . GH secretion appears to be a risk factor for the development of SAI per se, independently from adenoma size [6] . Transsphenoidal surgery (TSS), the treatment of choice in patients with symptomatic nonfunctioning pituitary macroadenomas and functioning adenomas, is another common cause of SAI. Particularly, data from the few available studies demonstrate that hypothalamic-pituitary-adrenal (HPA) axis function usually does not recover after

surgery and affects 13–60% of the patients (vs. 19–62% preoperatively), depending both on the number of patients included in the study and the time of hormonal assessment [7]. The prevalence of new-onset SAI after successful TSS of a GH-producing pituitary adenoma appears to largely depend on the timing of evaluation of HPA axis function. Indeed, the incidence rates 1 year after surgery and in the long term are comparable and lower than the incidence in the immediate postoperative period (about 14%) [8]. Retrospective data from cohorts of patients with ACTH-secreting adenomas show a prevalence of postoperative SAI of about 25–30% during remission, which appears to be secondary to the presurgical functional suppression of ACTH-producing cells induced by hypercortisolism [1, 9].

Several factors have been demonstrated in the etiopathogenesis of postsurgical SAI in patients with ACTH-secreting adenomas, including hypothalamic corticotropin-releasing factor suppression, corticotroph resistance to corticotropin-releasing factor and lower ACTH potency in the adrenal gland [1]. The time for HPA axis recovery is largely variable and appears to depend on individual cortisol sensitivity, disease severity and duration, together with study population characteristics, surgical outcomes, type and doses of glucocorticoid (GC) replacement therapy, and diagnostic tests [1]. It is noticeable that the rate of the SAI is inversely proportional to the number of surgical interventions needed for disease cure [9]. SAI can also be secondary to radiotherapy (RT), which plays an integral role in the management of pituitary adenomas, especially in cases with residual or recurrent disease after TSS [10, 11]. Fractionated stereotactic conformal RT, stereotactic radiosurgery (SRS), Gamma Knife and linear accelerator have been recently developed as more accurate techniques allowing more precise tumor localization and irradiation, with a consequent reduction of irradiation in the surrounding tissues and long-term toxicity.

The risk of pituitary function defect is both a dose- and time-dependent phenomenon. Impairment of HPA axis function is reported in up to 60% of patients after 10 years from pituitary fractionated irradiation with doses of 30–50 Gy [11]. Studies in patients with acromegaly treated with conventional RT (mean dose of about 50 Gy) after unsuccessful pituitary surgery show a 35% prevalence of SAI with a mean onset at 6.5 years after treatment. SRS (mean dose of about 25 Gy) is associated with a drastic reduction in SAI occurrence (up to 14% after 2–4 years) [11]. Furthermore, after a second Gamma Knife irradiation, new-onset ACTH deficiency occurs with the same prevalence as the first time [11]. Post-RT SAI occurs less frequently in nonfunctioning pituitary adenomas treated with similar doses of RT (about 15% of the cases), especially in patients treated with SRS [11]. Post-RT data for Cushing's disease recurrence after TSS show a very low corticotroph deficiency (about 3%) during a 3.5-year biochemical remission period, while its rate is significantly higher when RT is the first-line treatment (15% of the cases with conventional RT, 12% with SRS) [11]. SRS was associated with an approximate 11% prevalence of SAI in patients with Cushing's disease during a 3.5-year disease-free period [11].

RT is rarely required in prolactinomas, and is mainly used as a third-line treatment.

A low incidence of SAI (0–14%) has been reported in patients who underwent RT after medical therapy failure, usually occurring at least 3 years after treatment [11]. Finally, the HPA axis appears to be relatively radioresistant in patients irradiated for nonpituitary disorders, as clinically apparent ACTH deficiency is uncommon (around 3%) in those receiving total radiation doses <50

Gy, while the incidence dramatically increases (27–35%) after intensive irradiation (50–70 Gy) [11].

Extrapituitary Tumors

SAI – isolated or associated to other pituitary deficiencies – is a well-known complication of nonadenomatous pituitary tumors (i.e. craniopharyngiomas, Rathke's cleft cysts and meningiomas), with variable pre- and postoperative prevalence depending also on the type of tumor. Patients with craniopharyngioma present the highest risk, with SAI present in 24–36% of the cases at diagnosis and in up to 90% after TSS [1]. Improvements in the HPA axis after craniopharyngioma removal are relatively uncommon (resolution rate: 0–22%) [12].

Surgery is the mainstay of treatment for symptomatic Rathke's cleft cysts, with transsphenoidal resection the preferred approach. Preoperative loss of adrenal function ranges from 6 to 46%. Postoperative resolution or improvement of adrenal insufficiency occurs frequently; permanent hypocortisolism may result while attempting to resect a cyst's capsule, which can be quite adherent to the pituitary lobes [12].

Very few studies have investigated HPA axis function in patients with parasellar meningiomas. Overall, preoperative loss of corticotroph function ranges from 6 to 15%; postoperatively, onset of hypocortisolism is relatively uncommon, while up to 30% of preexisting cases improve [12].

Nontumoral Disorders According to a recent multicenter study performed in more than 700 patients with hypopituitarism [13], nontumoral diseases, traditionally considered rare causes of hypopituitarism, account for the majority of cases (49.2%), especially in women (57.5%), with SAI the third most frequent defect after gonadotropic and thyrotropic defects. Increased prevalence can be largely attributed to the widespread use of head magnetic resonance imaging (MRI) and computed tomography (CT) imaging and improved clinician awareness.

Long-term administration of exogenous GC represents a very common cause of secondary and/or tertiary hypoadrenalism, associated with prolonged suppression of the HPA axis starting at the hypothalamic level [1].

Infiltrative Lesions

Infiltrative lesions can be classified into primary and secondary hypophysitis (i.e. sarcoidosis, Langerhans' cell histiocytosis or histiocytosis X, Wegener's granulomatosis, hemochromatosis, Takayasu's disease, and Cohan's syndrome) depending on the intra- or extrapituitary origin of the disease, respectively [14, 15].

Lymphocytic hypophysitis is the most common form of primary disease (incidence: 1 case/9 million persons/year; less than 400 reported cases). According to the affected pituitary portion, we can distinguish adenohypophysitis, which is more common in younger women (F:M ratio 6: 1) especially during or shortly after pregnancy, and infundibulo-neurohypophysitis and

panhypophysitis, which tend to occur in older subjects and have a less remarkable predilection for females [14, 15] .

Patients may be pauci- or asymptomatic for a long period of time and then manifest with overt neurological (i.e. headache, impaired vision and nausea) and systemic symptoms secondary to pituitary insufficiency. SAI is the most common (about 40% of the cases) and earliest defect in adeno- and panhypophysitis, followed by hyperprolactinemia (30%), hypothyroidism (20%), hypogonadism (15%) and GH deficiency (10%) [14] . Diabetes insipidus is almost invariably present in neuro- and panhypopituitarism, but only in about 20% of the patients with adenohypophysitis, who in turn typically present with visual disturbances and anterior pituitary dysfunction [14] . The disease typically progresses from inflammation to fibrosis, with subsequent atrophy of pituitary and empty sella. Spontaneous remission is rare [14] .The pathogenic and diagnostic role of antipituitary and antihypothalamic antibodies remains debated [14, 16] . Moreover, these antibodies are poorly specific, as they have been detected in many extrapituitary autoimmune and nonautoimmune disorders, and their prevalence is also highly variable, depending on the study and the diagnostic technique applied [14, 16] .

Secondary hypophysitis typically presents with multiple hormone deficiency, irreversible in most of the cases and sometimes associated with hyperprolactinemia and neurological symptoms, while isolated ACTH deficiency is uncommon [15] .

Infective Processes

Pituitary infections are very rare but potentially life-threatening disorders, commonly affecting people from developing countries or immunocompromised patients. Although microorganisms of all species (i.e. bacteria, viruses, parasites and fungi) can spread to the pituitary, tuberculous hypophysitis, pyogenic abscess, aspergillosis and coccidioidomycosis are the most common infections [15] .

Typical presentation includes neurological (i.e. headache, visual and cognitive disturbances) and endocrinological symptoms due to concomitant panhypopituitarism, and more rarely hyperprolactinemia. Isolated ACTH deficiency is uncommon. Acute adrenal insufficiency can be precipitated by antitubercular drugs. Other diseases' pathognomonic signs and symptoms or evidence of systemic infection can (but not invariably) be present [15] . Diagnosis is suggested by MRI features, but can be confirmed only by surgical exploration or histological exam on surgical biopsy [15] .

Vascular Alterations

Pituitary apoplexy is caused by a sudden increase in pituitary size secondary to hemorrhagic infarction, typically occurring in patients with pituitary macroadenomas or in the postpartum period (Sheehan's syndrome). Increased vulnerability to ischemia secondary to estrogen-induced pituitary enlargement and hypervascularization, small sella size, disseminated intravascular coagulopathy and autoimmunity have been hypothesized in the pathogenesis of Sheehan's syndrome [1, 14] .

GH deficiency is the most common alteration affecting almost all patients, and is associated with TSH, gonadotropin, prolactin and ACTH deficiency in more than 80% of the cases, with a positive correlation between antipituitary and hypothalamic antibodies and the number of affected pituitary axes [1, 14, 16] .

Subarachnoid hemorrhage typically affects patients aged 40–60 years, with an estimated yearly incidence of 6/100,000. Pituitary dysfunction is reported in 0–68% of the patients, varying according to the evaluation timing and diagnostic criteria [17] . Delayed-onset hypogonadism and SAI (0–33% of the cases) are typical. The etiology is complex and includes increased intracranial pressure, pituitary ischemia secondary to arterial vasospasm or microinfarctions, venous stasis, surgical procedures, neuroinflammatory responses, autoimmunity, and genetic predisposition [17] .

Very rarely, ACTH deficiency has been reported in association with intracranial aneurism, sickle cell anemia [1] and hemorrhagic fever with renal syndrome (a severe systemic infection presenting with hypovolemic shock and renal failure caused by hantavirus) [18] .

Traumatic Brain Injury

In the last decade, pituitary insufficiency has been increasingly reported in patients with traumatic brain injury (TBI). For this reason, several authoritative authors have outlined the importance of defining the burden of pituitary disorders in TBI patients, and of criteria for the early identification of high-risk patients deserving systematic screening [19] . Reported prevalence of TBI-induced hypopituitarism differs considerably among reported studies ranging from 5 to 90%, similarly to the prevalence of SAI ranging from 5 to 13%. This variability could be attributed to the different timing of evaluation, severity of the trauma, diagnostic criteria, methods and assays to test endocrine function [19] .

Transient hypopituitarism has been almost exclusively reported in the first 6 months after TBI. Therefore, an early assessment of pituitary function after the event could lead to overestimate the prevalence of pituitary dysfunction in these patients, especially if patients with a more severe trauma are included. Indeed, the chance to develop hypopituitarism is directly related to the severity of trauma [19] .

Empty Sella

Empty sella is defined as the herniation of the subarachnoid space within the sella turcica associated with elongated pituitary stalk and flattened pituitary. It can be partial (<50% of the sella is filled with cerebrospinal fluid) or total. According to the etiology, it can be classified into: primary , of unknown origin, and secondary, resulting from spontaneous or treatment-induced pituitary adenoma shrinkage, pituitary apoplexy or hypophysitis. In the majority of the cases, it is asymptomatic and incidentally discovered during head CT or MRI; less frequently, patients present with neurological, visual or endocrinological signs secondary to liquor-induced compression on the pituitary gland and stalk and nearby structures. Some degrees of pituitary deficiency –typically GH and less frequently

other hormones – have been reported in 8–60% of the cases, often in association with hyperprolactinemia [20] .

Genetic Disorders

Very rarely, SAI can be secondary to mutations of genes involved in pituitary development, POMC (proopiomelanocortin) synthesis and processing, and sex-determining region Y, or develop in the context of Prader-Willi syndrome [1] . Diagnosis is usually performed during childhood; in the majority of the cases, patients present with multiple pituitary hormone deficiencies (except for POMC mutations), sometimes associated with other physical or cognitive disorders (table 1) [1] .

Exogenous Glucocorticoid Administration

Chronic GC administration inhibits HPA axis function at the hypothalamic-pituitary level by negative feedback, which can induce adrenal insufficiency and, eventually, adrenal atrophy [1, 21, 22] . Because of the large diffusion of GC treatments, they represent one of the most frequent causes of SAI [1, 21, 22] .

HPA suppression has been traditionally reported to occur after systemic administration of 20 mg of prednisone (or equivalent dose of other steroids) per day for more than 3 weeks. Indeed, HPA axis suppression is uncommon after sudden cessation of therapy in patients treated with any dose of steroids for shorter periods, although some authors have demonstrated that patients receiving 20–30 mg/day of prednisone (or equivalent dose of other steroids) for more than 5 days are at risk for SAI [23] . Inhaled and topical GC can also cause adrenal suppression in a dose-dependent fashion [1] .

According to a recent meta-analysis [22] , 1,190 out of the 3,753 (31%) patients treated with GC from the included studies were diagnosed with adrenal insufficiency, with the risk associated with the route of administration (oral higher than inhalation, topical and nasal), dose and duration of treatment. Because of the considerable interindividual variability in response to GC, there are no absolute cutoff values for type of GC, dose, route of administration or duration of treatment [1] . Moreover, symptoms are often absent or nonspecific and, although not frequent, the coadministration of drugs that affect GC metabolism (i.e. CYP3A4 inhibitors and GC receptor agonists) has to be considered [1] . For all these reasons, SAI cannot be safely excluded a priori in any patient treated with GC [1, 22] . Finally, although prevalence of adrenal insufficiency after GC discontinuation declines over time, a considerable number of patients were still affected after 6 months [1, 22] .

How Does It Look?

Clinical Presentation

Differently from primary adrenal insufficiency, clinical manifestations of SAI result only from GC deficiency, as aldosterone and adrenal androgens secretion is preserved.

Moreover, SAI rarely manifests with an acute adrenal crisis, although acute presentation can be precipitated by stress like surgery, trauma or infection [24] .

At the same time, patients can present with some signs (i.e. hyponatremia and volume expansion) typical of primary adrenal insufficiency caused by the so-called ‘inappropriate increase in arginine vasopressin secretion’ [1] . Symptoms and signs secondary to deficiency of other anterior pituitary hormones as well as neurological signs can coexist.

Endocrinological Evaluation (table 2)

Diagnosis of SAI is often delayed because of unspecific symptoms and diagnostic issues [25] . Indeed, despite more than 50 years of clinical research, the choice of the most appropriate test for the assessment of HPA axis alterations in patients with hypothalamus-pituitary disorders remains largely debated [1] .

Currently available tests measure total cortisol concentration and not the biologically active free cortisol, leading to false-normal results in the presence of high concentrations of cortisol-binding globulin (e.g. women receiving oral estrogens or in pregnancy), and falsely hypocortisolism in the presence of low cortisol-binding globulin (e.g. patients with cirrhosis) [1] .

Salivary cortisol concentration might be a useful alternative, although the normal cutoff is not fully validated [1] . On the contrary, urinary free cortisol concentrations are not helpful for diagnosis of adrenal insufficiency mainly because the lower reference range levels are not contributory; the same is true for measurement of basal plasma ACTH concentration, which is required only for differential diagnosis with primary forms [1] .

A morning serum cortisol concentration below 80–110 nmol/l (30–50 µg/l; blood drawing between 7.00 h and 9.00 h) is strongly suggestive of adrenal insufficiency, whereas values more than 400–500 nmol/l (150–180 µg/l) are consistent with an intact HPA axis. For values between 80–110 and 400–500 nmol/l, adrenal insufficiency cannot be excluded and dynamic tests are required [1] .

The insulin tolerance test has been conventionally used as the reference gold standard test for the diagnosis of ACTH insufficiency, as it examines the integrity of the whole HPA axis by stimulating corticotropin-releasing hormone (CRH), ACTH and, subsequently, cortisol release [1] . Insulin (0.10–0.15 U/kg) is given to induce hypoglycemia (<2.2 mmol/l), and cortisol concentrations are measured every 30 min for at least 90 min; a peak serum cortisol >500–550 nmol/l (180–200 µg/l) is considered a normal response [1] . However, this test is labor-intensive, presents several limitations and is contraindicated in patients with cardiovascular and cerebrovascular disease or who have a history of seizures [26] . Therefore, alternative tests have been proposed over the years, namely the overnight metyrapone, CRH and ACTH stimulation tests.

The overnight metyrapone test has so far been considered a convenient and sensitive method, with a good correlation with the insulin tolerance test [26] . The metyrapone test (30 mg/kg administered orally with a snack at midnight) inhibits adrenal 11β-hydroxylase and the conversion of 11-deoxycortisol (11-DOC) to cortisol. The diagnostic accuracy of this test has been shown to depend on the ACTH and/or 11-DOC cutoff used [27] . Shortcomings of the metyrapone test are the limited

availability of reliable 11-DOC assays and the fact that the drug is not widely available due to local restrictions [27] .

The CRH test is used to differentiate secondary from tertiary adrenal insufficiency. It entails intravenous administration of CRH (dose of 1 µg/kg, up to a maximum of 100 µg) and measurement of serum cortisol and plasma ACTH concentrations at baseline, every 15 min to 1 h, then every 30 min up to 2 h after stimulation. Patients with SAI present a little or no ACTH response, whereas response is exaggerated in patients with tertiary forms. However, this test is not of great diagnostic help because individual responses to exogenous CRH are highly variable, while cutoffs and ranges of normal reference values have not been univocally defined yet [28] .

The ACTH test at the standard dose of 250 µg has been used over the years as an alternative tool to diagnose SAI, providing an indirect assessment of the integrity of corticotroph function in chronic ACTH deficiency [29] . It is based on stimulation of the adrenal glands by pharmacological doses of exogenous ACTH 1–24 peptide, administered intravenously or intramuscularly. Serum cortisol levels are measured at baseline and at 30 and 60 min after stimulation. A peak cortisol concentration above 500 nmol/l (180 µg/l) is generally considered a normal response, although different cutoffs have been proposed [29] .

Although the ACTH test is considered to be safe, reliable and accurate, it has been suggested that the dose of 250 µg is largely supraphysiological, so it would elicit very high circulating ACTH levels and induce many false-normal responses, especially in patients with mild or recent-onset SAI [28] . Therefore, several studies have explored the use of low-dose (1.0 µg) ACTH, in the attempt to increase ACTH test sensitivity, with controversial results. In fact, the 1.0-µg ACTH test has been indicated as a more useful tool for the evaluation of SAI by some authors, while others have shown that even this test lacks diagnostic sensitivity and does not give real advantages in comparison with the standard dose test [29] . Moreover, technical issues – caused by the need to dilute the commercially available dose ampule of 250 µg of ACTH 1–24 to 1 µg, and the potential binding of such a small hormone amount to the surface of injection devices – can impair test accuracy [30] .

For all the abovementioned reasons, it has to be emphasized that no single test is able to correctly identify all patients with SAI: mild SAI can be missed, while even healthy individuals might show abnormal values. Therefore, clinical judgment remains important and follow-up is crucial for assessment of ACTH deficiency. Patients with persisting suggestive symptoms or risk factors for adrenal insufficiency deserve careful, sometimes subsequent, reassessment [31] .

Imaging

Head MRI should be performed to exclude tumors and other lesions of the sellar and parasellar region once SAI has been confirmed [1–4] . Typical MRI features of primary hypophysitis include symmetrical pituitary enlargement with homogeneous contrast enhancement, a parasellar dark signal on T2-weighted sections, a thickened (rarely displaced) pituitary stalk and loss of posterior pituitary T1 hyperintensity when neurohypophysis is involved [32] . Diagnosis of secondary hypophysitis is suggested by MRI features, i.e. sellar mass associated with pituitary stalk's thickening and nodularity in tuberculous hypophysitis, and round cystic lesions with peripheral gadolinium enhancement in pituitary abscess [14, 32] . Traumatic damage can present with pituitary stalk deviation, associated with hemorrhage, infraction, or empty sella [32] .

Conclusions

SAI is an underestimated and underdiagnosed condition, which can be isolated or occur in association with other pituitary hormone defects, that has potentially severe clinical consequences. Diagnosis is complex as no single hormonal evaluation is able to correctly identify all patients with this condition, and mild SAI can be missed. Therefore, clinical judgment and follow-up are crucial for the assessment of corticotropin deficiency, in order to avoid an adrenal crisis.

References

- 1 Crowley RK, Argese N, Tomlinson JW, Stewart PM: Central hypoadrenalism. *J Clin Endocrinol Metab* 2014; 99: 4027–4036.
- 2 Hannon MJ, O'Halloran DJ: Isolated acquired ACTH deficiency and primary hypothyroidism: a short series and review. *Pituitary* 2011; 14: 358–361.
- 3 Davis JR, Farrell WE, Clayton RN: Pituitary tumours. *Reproduction* 2001; 121: 363–371.
- 4 Greenman Y, Stern N: Non-functioning pituitary adenomas. *Best Pract Res Clin Endocrinol Metab* 2009;23: 625–638.
- 5 Tirosh A, Benbassat C, Lifshitz A, Shimon I: Hypopituitarism patterns and prevalence among men with macroprolactinomas. *Pituitary* 2015; 18: 108–115.
- 6 Sherlock M, Reulen RC, Alonso AA, Ayuk J, Clayton RN, Sheppard MC, Hawkins MM, Bates AS, Stewart PM: ACTH deficiency, higher doses of hydrocortisone replacement, and radiotherapy are independent predictors of mortality in patients with acromegaly. *J Clin Endocrinol Metab* 2009; 94: 4216–4223.
- 7 Dekkers OM, Pereira AM, Romijn JA: Treatment and follow-up of clinically nonfunctioning pituitary macroadenomas. *J Clin Endocrinol Metab* 2008; 93: 3717–3726.
- 8 Burgers AM, Kokshoorn NE, Pereira AM, Roelfsema F, Smit JW, Biermasz NR, Romijn JA: Low incidence of adrenal insufficiency after transsphenoidal surgery in patients with acromegaly: a long-term follow-up study. *J Clin Endocrinol Metab* 2011; 96:E1163–E1170.
- 9 Aranda G, Ensenat J, Mora M, Puig-Domingo M, Martinez de Osaba MJ, Casals G, Verger E, Ribalta MT, Hanzu FA, Halperin I: Long-term remission and recurrence rate in a cohort of Cushing's disease: the need for long-term follow-up. *Pituitary* 2015; 18: 142–149.
- 10 Darzy KH: Radiation-induced hypopituitarism after cancer therapy: who, how and when to test. *Nat Clin Pract Endocrinol Metab* 2009; 5: 88–99.
- 11 Fernandez A, Brada M, Zabulienė L, Karavitaki N, Wass JA: Radiation-induced hypopituitarism. *Endocr Relat Cancer* 2009; 16: 733–772.
- 12 Dusick JR, Fatemi N, Mattozo C, McArthur D, Cohan P, Wang C, Swerdloff RS, Kelly DF: Pituitary function after endonasal surgery for nonadenomatous parasellar tumors: Rathke's cleft cysts, craniopharyngiomas, and meningiomas. *Surg Neurol* 2008; 70: 482–490.
- 13 Tanriverdi F, Dokmetas HS, Kebapci N, Kilicli F, Atmaca H, Yarman S, Ertorer ME, Erturk E, Bayram F, Tugrul A, Culha C, Cakir M, Mert M, Aydin H, Taskale H, Ersoz N, Canturk Z, Anaforoglu I, Ozkaya M, Oruk G, Hekimsoy Z, Kelestimur F, Erbas T: Etiology of hypopituitarism in tertiary care institutions in Turkish population: analysis of 773 patients from Pituitary Study Group database. *Endocrine* 2014; 47: 198–205.
- 14 Caturegli P, Newschaffer C, Olivi A, Pomper MG, Burger PC, Rose NR: Autoimmune hypophysitis. *Endocr Rev* 2005; 26: 599–614.
- 15 Carpinteri R, Patelli I, Casanueva FF, Giustina A: Inflammatory and granulomatous expansive lesions of the pituitary. *Best Pract Res Clin Endocrinol Metab* 2009; 23: 639–650.
- 16 De Bellis A, Sinisi AA, Pane E, DelloIacovo A, Bellastella G, Di Scala G, Falorni A, Giavoli C, Gasco V, Giordano R, Ambrosio MR, Colao A, Bizzarro A, Bellastella A; Italian Hypophysitis

- Network Group: Involvement of hypothalamus autoimmunity in patients with autoimmune hypopituitarism: role of antibodies to hypothalamic cells. *J Clin Endocrinol Metab* 2012; 97: 3684–3690.
- 17 Karaca Z, Tanriverdi F, Dagli AT, Selcuklu A, Casanueva FF, Unluhizarci K, Kelestimur F: Three years prospective investigation of pituitary functions following subarachnoid haemorrhage. *Pituitary* 2013; 16: 76–82.
- 18 Stojanovic M, Pekic S, Cvijovic G, Miljic D, Doknic M, Nikolic-Djurovic M, Micic D, Hrvacevic R, Nesic V, Popovic V: High risk of hypopituitarism in patients who recovered from hemorrhagic fever with renal syndrome. *J Clin Endocrinol Metab* 2008; 93:2722–2728.
- 19 Lauzier F, Turgeon AF, Boutin A, Shemilt M, Cote I, Lachance O, Archambault PM, Lamontagne F, Moore L, Bernard F, Gagnon C, Cook D: Clinical outcomes, predictors, and prevalence of anterior pituitary disorders following traumatic brain injury: a systematic review. *Crit Care Med* 2014; 42: 712–721.
- 20 Guitelman M, Garcia Basavilbaso N, Vitale M, Chervin A, Katz D, Miragaya K, Herrera J, Cornalo D, Servidio M, Boero L, Manavela M, Danilowicz K, Alfieri A, Stalldecker G, Glerean M, FainsteinDay P, Ballarino C, Mallea Gil MS, Rogozinski A: Primary empty sella (PES): a review of 175 cases. *Pituitary* 2013; 16: 270–274.
- 21 Schlaghecke R, Kornely E, Santen RT, Ridderskamp P: The effect of long-term glucocorticoid therapy on pituitary-adrenal responses to exogenous corticotropin- releasing hormone. *N Engl J Med* 1992; 326: 226–230.
- 22 Broersen LH, Pereira AM, Jorgensen JO, Dekkers OM: Adrenal insufficiency in corticosteroids use: systematic review and meta-analysis. *J Clin Endocrinol Metab* 2015; 100: 2171–2180.
- 23 Axelrod L: Perioperative management of patients treated with glucocorticoids. *Endocrinol Metab Clin North Am* 2003; 32: 367–383.
- 24 Hahner S, Loeffler M, Bleicken B, Drechsler C, Milovanovic D, Fassnacht M, Ventz M, Quinkler M, Allolio B: Epidemiology of adrenal crisis in chronic adrenal insufficiency: the need for new prevention strategies. *Eur J Endocrinol* 2010; 162: 597–602.
- 25 Bleicken B, Hahner S, Ventz M, Quinkler M: Delayed diagnosis of adrenal insufficiency is common: a cross-sectional study in 216 patients. *Am J Med Sci* 2010; 339: 525–531.
- 26 Jones SL, Trainer PJ, Perry L, Wass JA, Bessser GM, Grossman A: An audit of the insulin tolerance test in adult subjects in an acute investigation unit over one year. *Clin Endocrinol (Oxf)* 1994; 41: 123–128.
- 27 Fiad TM, Kirby JM, Cunningham SK, McKenna TJ: The overnight single-dose metyrapone test is a simple and reliable index of the hypothalamic-pituitaryadrenal axis. *Clin Endocrinol (Oxf)* 1994; 40: 603–609.
- 28 Schmidt IL, Lahner H, Mann K, Petersenn S: Diagnosis of adrenal insufficiency: evaluation of the corticotropin- releasing hormone test and basal serum cortisol in comparison to the insulin tolerance test in patients with hypothalamic-pituitary-adrenal disease. *J Clin Endocrinol Metab* 2003; 88: 4193–4198.
- 29 Ospina NS, Al Nofal A, Bancos I, Javed A, Khalid B, Kapoor E, Lteif AN, Natt N, Murad MH: ACTH stimulation tests for the diagnosis of adrenal insufficiency: systematic review and meta-analysis. *J Clin Endocrinol Metab* 2015, Epub ahead of print.
- 30 Wade M, Baid S, Calis K, Raff H, Sinai N, Nieman L: Technical details influence the diagnostic accuracy of the 1 microg ACTH stimulation test. *Eur J Endocrinol* 2010; 162: 109–113.
- 31 Dickstein G: Hypothalamo-pituitary-adrenal axis testing: nothing is sacred and caution in interpretation is needed. *Clin Endocrinol (Oxf)* 2001; 54: 15–16.
- 32 Buchfelder M, Schlaffer S: Imaging of pituitary pathology. *Handb Clin Neurol* 2014; 124: 151–166.

Table 1. Genetic causes of SAI

Gene	Chromosome	Inheritance mode	Endocrinological manifestation in addition to adrenal insufficiency	MRI findings	Associated malformations
<i>Transcription factors</i>					
HESX homeobox 1	3p21	Recessive	Panhypopituitarism, short stature, delayed puberty	Hypoplastic/hyperplastic anterior pituitary	Cognitive changes, septo-optic dysplasia
Orthodentical (OTX) homeobox 2	1q23	Dominant/negative	Panhypopituitarism	Hypoplastic anterior pituitary, ectopic posterior pituitary	Eye malformations
LIM homeobox 4	1q25	Dominant	Panhypopituitarism	Hypoplastic anterior pituitary, ectopic posterior pituitary	–
PROP paired-like homeobox 1	3p11	Recessive	Panhypopituitarism	Normal, hypoplastic, hyperplastic or cystic anterior pituitary	–
<i>POMC</i>					Severe obesity, hyperphagia, red hair pigmentation
Sex-determining region Y (SOX-3)	Xq27	X-linked recessive	Panhypopituitarism	Hypoplasia anterior pituitary, infundibular hypoplasia, ectopic posterior pituitary; severe hypoglycemia and jaundice (neonates with T-box mutations)	Mental retardation
<i>Prader-Willi syndrome</i>					
Deletion of the paternal copies of the small nuclear riboprotein polypeptide N, NDN gene and clusters of snoRNAs	15q11-13	Deletion or silencing of genes in imprinting center	Hypogonadism		Hypotonia, obesity, mental retardation

Table 2. Biochemical diagnosis of SAI

Test	Procedure	High probability of adrenal insufficiency	Adrenal insufficiency excluded
Early morning cortisol	Serum cortisol (07.00–09.00 h)	<80–110 nmol/l (30–50 µg/l)	>400–500 nmol/l (150–180 µg/l)
ITT	Serum glucose and cortisol every 30 min for 90 min after insulin i.v. (0.1–0.15 U/kg)	Peak cortisol <500 nmol/l (180 µg/l)	Peak cortisol >500–550 nmol/l (200 µg/l)
MET	Serum 11-DOC and ACTH at 08.00 h after MET 30 mg/kg p.o. at 23.00 h the night before	11-DOC <200 nmol/l (7–9 µg/dl) and/or ACTH <16.5–44 pmol/l (75–200 pg/ml)	11-DOC >200–260 nmol/l (7–9 µg/dl) and/or ACTH >16.5–44 pmol/l (75–200 pg/ml)
CRH	Serum cortisol and plasma ACTH at 0, every 15 min to 1 h and every 30 min to 2 h after CRH i.v. (1 µg/kg, up to a maximum of 100 µg)	Peak ACTH >33 pmol/l (100 pg/ml); peak cortisol >500–550 nmol/l (180–200 µg/l)	Peak ACTH >33 pmol/l (100 pg/ml); peak cortisol >500–550 nmol/l (180–200 µg/l)
ACTH test	Serum cortisol at 0 and 30 or 60 min after ACTH 1–24 i.v.	Peak cortisol <500 nmol/l (180 µg/l)	Peak cortisol >500 nmol/l (180 µg/l)