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Approach to the Patient

Approach to the Patient With Glucocorticoid-induced Adrenal Insufficiency

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Abstract

Glucocorticoid-induced adrenal insufficiency is caused by exogenous glucocorticoid suppression of the hypothalamic-pituitary-adrenal axis and is the most prevalent form of adrenal insufficiency. The condition is important to diagnose given the risk of life-threatening adrenal crisis and impact on patients' quality of life. The diagnosis is made with a stimulation test such as the ACTH test. Until now, testing for glucocorticoid-induced adrenal insufficiency has often been based on clinical suspicion rather than routinely but accumulating evidence indicates that a significant number of cases will remain unrecognized. During ongoing oral glucocorticoid treatment or initially after withdrawal, ~50% of patients have adrenal insufficiency, but, outside clinical studies, ≤ 1% of patients have adrenal testing recorded. More than 70% of cases are identified during acute hospital admission, where the diagnosis can easily be missed because symptoms of adrenal insufficiency are nonspecific and overlap those of the underlying and intercurrent conditions. Treatment of severe glucocorticoid-induced adrenal insufficiency should follow the principles for treatment of central adrenal insufficiency. The clinical implications and thus indication to treat mild-moderate adrenal deficiency after glucocorticoid withdrawal has not been established. Also, the indication of adding stress dosages of glucocorticoid during ongoing glucocorticoid treatment remains unclear. In patients with established glucocorticoid-induced adrenal insufficiency, high rates of poor confidence in self-management and delayed glucocorticoid administration in the acute setting with an imminent adrenal crisis call for improved awareness and education of clinicians and patients. This article reviews different facets of glucocorticoid-induced adrenal insufficiency and discusses approaches to the condition in common clinical situations.

Key Words: adrenal insufficiency, hypothalamic-pituitary-adrenal axis, corticosteroids, glucocorticoids, adrenal crisis.

Abbreviations: ACTH, adrenocorticotrophic hormone; CRH, corticotropin-releasing hormone; HPA, hypothalamic-pituitary-adrenal; P-cortisol, Plasma-cortisol.

Case 1

Glucocorticoid-induced adrenal insufficiency was suspected in a 24-year-old woman with atopic disorder. For 1 year, she had been on high-dose inhaled budesonide (1400 µg/d), nasal fluticasone furoate (55 µg/d), and mometasone furoate cream (0.1%, European steroid group III, on hands, neck, and chest 3-7 times/wk) for asthma, rhinosinusitis, and dermatitis. For 6 months, she had felt increasingly unwell. Her major complaint was fatigue that only allowed her to attend university studies part time and have no other social activities. She reported dizziness, nausea, weight loss, cold sweats, tremors, and severe loss of energy during minor infections. The patient contacted the department of endocrinology herself because the general practitioner found no indication for referral.

Endocrine work-up included a 250-µg ACTH stimulation test, where plasma cortisol (P-cortisol) rose from 557 to 703 nmol/L (20.2 to 25.5 µg/dL) (local cutoff for normal 420 nmol/L [15.2 µg/dL] (1)). However, because she was using oral estrogen-containing contraception (inducing "falsely" high cortisol concentrations resulting from elevated cortisol-binding proteins), the test was inconclusive. A new test was scheduled after a pause in estrogen use for 2 months. Before retesting, her symptoms worsened and she was admitted to the local emergency department. Her primary complaint was severe general fatigue. Clinical examination and blood samples showed no signs of infection or exacerbation of asthma, blood pressure 100/80 mm Hg, sodium 143 mmol/L, and glucose 4.6 mmol/L. She remained hospitalized for observation without initiating any treatment. Given continuous weakness with inability to walk without support, oral hydrocortisone 10 mg twice daily was started at admission day 2. The symptom relief was striking and within days after discharge she could walk up stairs, bike, and stay up late without overwhelming fatigue; she reported she had not felt better in more than 6 months. The confirmatory ACTH test (performed 8 weeks after pausing estrogen and 6 weeks after commencing hydrocortisone, with no other changes in medication) showed severe adrenal insufficiency with stimulated P-cortisol of 30 nmol/L (1.1 µg/dL). She had otherwise normal biochemical pituitary workup including inappropriately low

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plasma ACTH within the normal reference range (no pituitary magnetic resonance imaging was performed), normal renin and aldosterone concentrations, no adrenal autoantibodies, and she was diagnosed with glucocorticoid-induced adrenal insufficiency. She continued hydrocortisone replacement treatment, 20 mg divided throughout the day (10 mg + 5 mg + 5 mg), received patient education in stress dose administration (Table 1), and was provided with the European steroid emergency card (2) and injectable hydrocortisone for rescue administration.

Case 2

A 71-year-old man with polymyalgia rheumatica had received prednisolone treatment for 26 months. In accordance with guidelines (6, 7), the starting dose was 37.5 mg/d. In suspicion of coexisting giant cell arteritis, the prednisolone dose had been ≥ 50 mg/d for 3 weeks on 2 occasions, followed by gradual tapering to 7.5 mg/d. He had experienced relief of musculoskeletal pain and no other complaints were recorded.

As part of an observational study to identify glucocorticoid-induced adrenal insufficiency (8), a 250-µg ACTH test was performed after pausing the daily 7.5 mg of prednisolone for 48 hours. Cortisol samples from the study were frozen and stored until analyzed in 1 batch when all patients had completed the study. If the rheumatologists found clinical suspicion of adrenal insufficiency while waiting for study ACTH test results, a new ACTH test was performed with immediate cortisol analysis. There was no obvious suspicion of adrenal insufficiency in this patient, which is why his ACTH test results only became available 1 year later. The 30-minute cortisol response was 92 nmol/L (3.3 µg/dL) (normal local cutoff 420 nmol/L [15.2 µg/dL] (1)), plasma ACTH was inappropriately low within the normal reference range, and, retrospectively, the patient therefore had had an unknown glucocorticoid-induced adrenal insufficiency for 1 year. During this year, he had tapered prednisolone to 2.5 mg/d and started to experience universal pain and fatigue. Because of low levels of C-reactive protein and normal muscle function, the rheumatologists had not considered symptoms related to polymyalgia rheumatica disease activity. After receiving the ACTH test results, the test was repeated and showed improved, but still a subnormal cortisol response to 351 nmol/L (12.7 µg/dL), confirming the diagnosis of glucocorticoid-induced adrenal insufficiency. With remission of the polymyalgia rheumatica and partial adrenal insufficiency, prednisolone 2.5 mg/d was switched to hydrocortisone replacement with 10 mg in the morning and 5 mg in the early afternoon. The patient was provided with the European steroid emergency card (2) and received patient education in glucocorticoid stress dose administration (Table 1).

Introduction

Glucocorticoid formulations are the key to managing numerous inflammatory conditions but can cause suppression of the hypothalamic-pituitary-adrenal (HPA) axis and result in adrenal insufficiency.

At any given time, 0.5% to 3% of the Western population receives systemic glucocorticoid treatment (9-12), and glucocorticoid-induced adrenal insufficiency is now the most frequent type of adrenal insufficiency (13, 14). Adrenal insufficiency is among the most dangerous side effects to glucocorticoid treatment because a life-threatening adrenal crisis may occur. Furthermore, subtle symptoms such as fatigue can have a large impact on patients' quality of life. However, the clinical severity of the measured "biochemical" glucocorticoid-induced adrenal insufficiency is uncertain and debated (15). Glucocorticoid-induced adrenal insufficiency exists as a spectrum from mild to severe deficiency, transient or long-lasting, and with need for glucocorticoid supplementation depending on the level of stress and ongoing (anti-inflammatory) glucocorticoid treatment dose. Few studies have presented suggestions for a guide to managing glucocorticoid-induced adrenal insufficiency, which has resulted in variability in patient management across centers and clinicians (16).

While awaiting more evidence, establishing some consensus on clinical management to improve patient safety and quality of life is beginning (16). This article reviews different facets and suggestions for approaching patients with glucocorticoid-induced adrenal insufficiency in different common clinical situations.

Glucocorticoid-induced Adrenal Insufficiency

Glucocorticoid-induced adrenal insufficiency results from suppression of corticotropin-releasing hormone (CRH) and ACTH by negative feedback from exogenous glucocorticoids (Fig. 1). Suppressed ACTH eventually leads to hypotrophy and atrophy of the adrenal cortex, with reduced cortisol production and is thus a central type of adrenal insufficiency with preserved mineralocorticoid function (14).

The endogenous cortisol production rate is approximately 10 mg/d in unstressed conditions. To ensure sufficient coverage, a daily oral intake of 20 mg hydrocortisone equivalent to 5 mg prednisolone is often used for replacement in unstressed conditions (17). The secretion increases many-fold with physical and emotional stress roughly proportional to the severity of the stress (18-22). In patients receiving ≥ 5 mg prednisolone equivalents daily, the unstressed glucocorticoid need is considered covered, but the increased glucocorticoid needs during stress might not be covered. The lower the anti-inflammatory glucocorticoid dose, the higher the risk, so that even daily glucocorticoid needs are not covered if the patient has adrenal insufficiency. Clinicians must therefore be aware of glucocorticoid-induced adrenal insufficiency during ongoing (especially low-dose) glucocorticoid treatment during tapering and after withdrawal.

Approach to Patient Identification

Occurrence and Risk Factors

Data from systematic reviews and 1 meta-analysis showed glucocorticoid-induced adrenal insufficiency in 38% to 48% of adult patients during or immediately after oral glucocorticoid use (23, 24), in 52% after intraarticular administrations, in 5% after topical administrations, in 4% after nasal glucocorticoids, and in 8% after inhaled glucocorticoids (23). Similar findings were reported in children (25, 26). Of note, individual variation in glucocorticoid sensitivity prevents a safe risk stratification with the definition of lower limits for glucocorticoid dose, duration, or administration type, where adrenal insufficiency does not occur (24, 27,

Table 1. Management of stress dose administrations of hydrocortisone in specific situations in patients with glucocorticoid-induced adrenal insufficiency

Examples of stress	Hydrocortisone stress dose suggestions
Mild stress	
Fear of dentists, job interview, or regular exercise	Usually does not require stress-dose administration unless the patient has experienced that it is necessary. In that case, 5 to 10 mg of hydrocortisone can be added just before the event
Mild illness	
Mild symptoms of illness (eg, common cold) and body temperature below 38 °C	Usually does not require stress-dose administration unless the patient has experienced that it is necessary. In that case, 5 to 10 mg of hydrocortisone divided over the day can be added daily for a short period
Moderate stress	
Hard exercise (eg, exercise of more than 2 h in duration [swimming, running, cycling])	Will often require extra hydrocortisone; 5 to 10 mg 1 h before exercise and 10 mg in the afternoon or the next morning (whichever comes first)
Dentist procedure (except normal dental cleaning)	Will often require 5 to 10 mg hydrocortisone before the procedure but can require 10 mg twice daily for 2 days in patients with a fear of dentists
Traffic accident or other bodily injury	Patients may generally be advised to take 20 mg hydrocortisone immediately and seek medical advice for further guidance/treatment
Planned minor surgery or dental treatment performed on an outpatient basis and under local anesthesia	Patients can be advised to add 10 mg hydrocortisone twice daily (normal replacement dose is doubled) for 2 days
Moderate illness	
Symptoms of illness (eg, cough, sore throat) and temperature between 38 and 39 °C (measured in the rectum)	Addition of 10 mg hydrocortisone twice daily (normal replacement dose is doubled)
Short-term vomiting or diarrhea	Addition of 10 mg hydrocortisone twice daily (normal replacement dose is doubled)
Body temperature above 39 °C	Addition of 20 mg hydrocortisone twice daily (normal replacement dose is tripled). Patients may generally be advised to seek medical evaluation of the cause of the high fever that often requires treatment
Severe stress	
Such as a death in the family or traumatic experience	Will often require addition of 10 mg hydrocortisone twice daily (normal replacement dose is doubled) during the initial days but can be required for a longer period
Serious illness	
Persistent vomiting or diarrhea	The patient must be admitted to the hospital and immediately treated with parenteral hydrocortisone and fluid according to recommendations for an adrenal crisis
Acute adrenal crisis (Addison crisis), where the symptoms are persistent nausea and vomiting, loss of appetite, dizziness, pronounced fatigue, dehydration	Hydrocortisone 100 mg injection IV or IM immediately (can be with a self-administration kit), followed by hydrocortisone 200 mg/24 h as a continuous infusion for 24 h (alternatively 50-mg injection every 6 h), reduced to hydrocortisone 100 mg/d the following day. Switch to oral hydrocortisone is usually possible after 1 to 3 days or when the patient is free from gastrointestinal symptoms. The dose is thereafter tapered to normal replacement dose depending on clinical state
Any acute hospitalization for any reason	Addition of 10-20 mg oral hydrocortisone twice daily (normal replacement dose is doubled or tripled) or parenteral administration depending on condition
Planned moderate or major surgery under general anesthesia or surgery that requires hospitalization afterward	Treatment with 25-100 mg parenteral hydrocortisone injection when the anesthesia is inducted followed by continuous IV infusion of 75-200 mg hydrocortisone per 24 h. Depending on clinical state, switch to oral hydrocortisone with double replacement dose on days 2-3, often tapered to normal replacement dose the following day Alternatively, if dexamethasone 6-8 mg is used to prevent postoperative nausea and vomiting, it will suffice for 24 h[a]

Doses are suggestions that should be adjusted to the individual patient and situation. Patients with a near-normal ACTH test response (mild adrenal insufficiency) would be expected to require lower doses. Modified from (3-5).
[a]Dexamethasone has no mineralocorticoid activity, which is why it can be used in central, but not primary adrenal insufficiency.

28). Long-term glucocorticoid administration can cause adrenal insufficiency even during low-dose treatment because approximately one-half of patients receiving ongoing 5 mg or 5 to 7.5 mg of prednisolone daily developed insufficiency (29, 30). In patients receiving low-dose glucocorticoid treatment for chronic diseases or following organ transplantation, the treatment is often prolonged (31-34), with a risk of prolonged clinical implications of adrenal insufficiency. Among long-term treated patients, the strongest predictor for development of insufficiency may be the current dose (35) or the mean daily dose over the preceding 3 to 6 months (36), whereas calculating the precise treatment duration or cumulative dose does not seem to approve the prediction (29, 30, 35, 36) and is not feasible in daily clinical practice.

Other risk factors for glucocorticoid-induced adrenal insufficiency include high potency, long biological half-life of

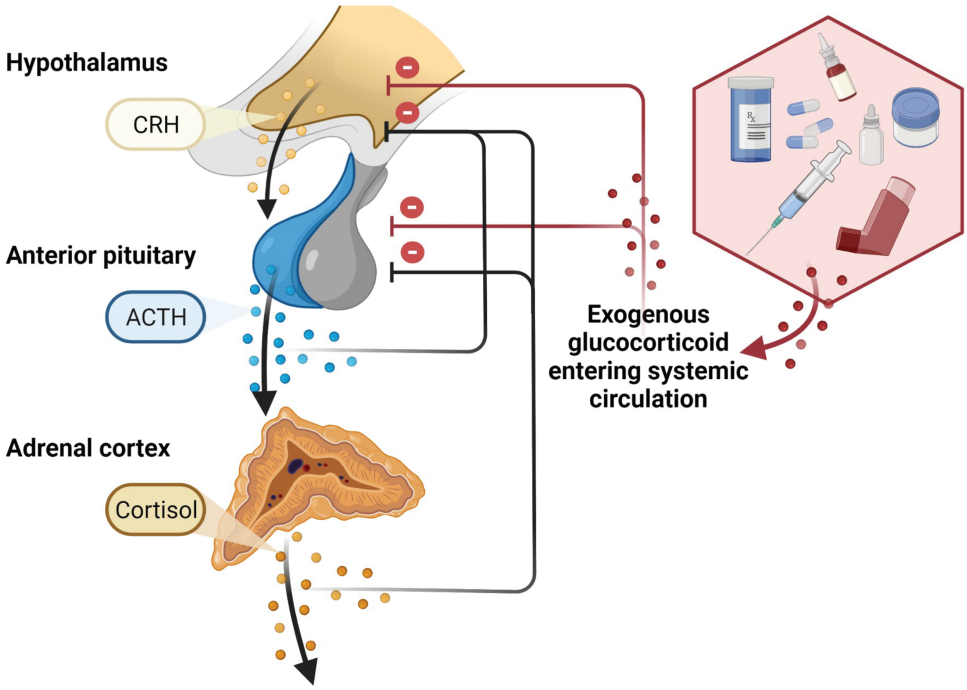

Figure 1. Negative feedback regulation of the hypothalamic-pituitary-adrenal axis. Black lines show normal endogen regulation with CRH from the hypothalamus stimulating production and release of ACTH from the anterior pituitary gland that in turn stimulates cortisol production and release from the adrenal cortex with cortisol and ACTH exerting negative feedback on the levels above. Red lines show inhibition on the axis by systemically absorbed glucocorticoid medications on the hypothalamic and pituitary level. Abbreviation: ACTH, adrenocorticotrophic hormone; CRH, corticotropin-releasing hormone. The figure was created with Biorender.com.

the glucocorticoid (37, 38), use of multiple glucocorticoid formulations (23, 39), as illustrated in case 1, and evening administration, which results in more pronounced suppression of the HPA axis by suppressing the natural early morning ACTH surge (37, 40, 41). Concomitant treatment with medications increasing glucocorticoid bioavailability by reducing glucocorticoid clearance (eg, CYP3A4 inhibitors such as amiodarone, cyclosporine, verapamil, itraconazole, several antiviral medications and grapefruit juice) or other HPA axis suppressors (eg, opioids) also increase the risk (42-44).

Predisposition

Individual glucocorticoid sensitivity and action predispose to substantial variation in adrenal suppression (45-48); these are modulated by multiple factors including thyroid and growth hormone, comorbidities or medications that affect cortisol binding globulin, prereceptor metabolism, hepatic metabolism, and glucocorticoid receptor isotypes, number, and action (42, 45-48). Some factors are influenced by genetic variation (49, 50), and environmental factors might also influence glucocorticoid sensitivity (51). The implication of individual glucocorticoid sensitivity is an unclear dose-response relationship between glucocorticoid dose and both clinical responsiveness and development of side effects, including HPA axis suppression (46, 52, 53).

Clinical Presentation at Diagnosis

Clinical identification of patients with adrenal insufficiency among glucocorticoid-treated patients is extremely challenging. At diagnosis, patients have often experienced a long period with unspecific symptoms and general health deterioration and/or been diagnosed in relation to an acute hospital admission. Signs and symptoms of glucocorticoid-induced adrenal insufficiency are nonspecific for the condition and often overlap those of the underlying disease for which glucocorticoids were prescribed (Fig. 2). Symptom onset of glucocorticoid-induced adrenal insufficiency may be insidious, and the degree of symptoms depends on the current level of stress. Furthermore, the cause of stress may contribute to overlapping signs and symptoms (Fig. 2) (53); therefore, symptoms of glucocorticoid-induced adrenal insufficiency might not be recognized by the patient or medical staff.

This may be more pronounced when clinicians are unfamiliar with the differences between the less specific signs and symptoms of central compared with primary adrenal insufficiency where the mineralocorticoid function is also absent. Thus, postural hypotension, high potassium, and to some extent hyponatremia are less frequent and ACTH-induced hyperpigmentation is absent in the central form (13).

An estimated two-thirds of patients consult more than 1 physician before the diagnosis of glucocorticoid-induced adrenal insufficiency (54). The resulting delay in the diagnosis is unknown, but even for primary and other causes of central adrenal insufficiency, the diagnosis is often delayed by more than a year (54). Consequently, patients might go undiagnosed until an event such as an infection, surgery, emotional stress, or glucocorticoid withdrawal eventually triggers an adrenal crisis (26, 53). Accordingly, in a retrospective study on 183 patients with glucocorticoid-induced adrenal insufficiency, the diagnosis was made during hospital admission in 71% and in mortality registers in 5% of cases (55).

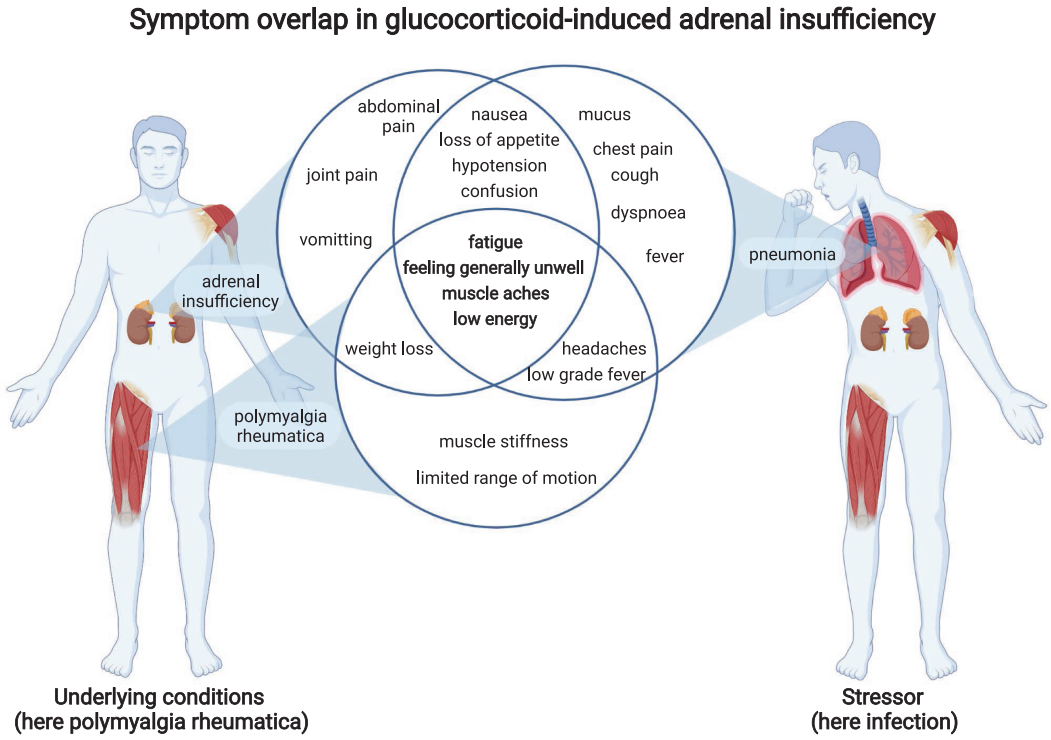

Figure 2. Symptom overlap in glucocorticoid-induced adrenal insufficiency. Overlap of the circles represents overlap of the symptoms of glucocorticoid-induced adrenal insufficiency and of the underlying disease, causing glucocorticoid prescription, here polymyalgia rheumatica. On the right side is the same person, now with an intercurrent illness (here pneumonia) adding further overlapping symptoms and potentially enhancing symptoms of adrenal insufficiency due to elevated glucocorticoid needs during stress. The figure was created with Biorender.com.

An empirical increase of glucocorticoid dose will typically alleviate symptoms independent of whether the cause of symptoms is a flare up of the underlying disease (56-58), symptoms of steroid withdrawal syndrome (59, 60), or adrenal insufficiency; a favorable glucocorticoid treatment response consequently cannot distinguish the underlying cause (36, 61). Accordingly, symptoms of glucocorticoid-induced adrenal insufficiency can be a contributing cause for prednisolone withdrawal reluctance, which might partly explain the extensive use of glucocorticoid treatment beyond the expected timeframe for diseases such as polymyalgia rheumatica and giant cell arteritis (61-63). A low threshold for testing the adrenal function should be considered in patients with unexplained symptoms, as illustrated in case 2.

An adrenal crisis occurs when the HPA axis is unable to mount an adequate cortisol response to stress. The clinical picture is not uniform but includes major impairment of general health and symptoms such as nausea, vomiting, severe fatigue, hypotension, and/or hypoglycemia, and can ultimately progress to cardiovascular collapse and death if untreated (64, 65). Immediate treatment with parenteral hydrocortisone and saline is lifesaving (64, 65). However, patient identification is challenging because an adrenal crisis can resemble the presentation of other medical emergencies such as sepsis and cardiovascular disease (64, 65). In a British survey, nearly 11% of identified cases of adrenal crises secondary to inhaled glucocorticoids were not correctly diagnosed at first presentation (66). In the acute setting where diagnostic workup is not possible, the safe patient approach is to apply parenteral hydrocortisone treatment whenever in doubt. Lack of awareness or a possible unjustified belief that it will compromise treatment of an infection seem to cause a general reluctance toward this approach (16). In case 1, hydrocortisone treatment was not initiated before the second day of the acute hospital admission despite awaiting a confirmatory ACTH test after pausing contraceptives. Even in patients with an established diagnosis of glucocorticoid-induced adrenal insufficiency, an American survey reported that only 19% of patients received prompt treatment for an adrenal crisis in the emergency department (54).

The number of adrenal crises in patients with adrenal insufficiency is unknown because of underreporting, but between 8.3 and 15 adrenal crises/100 patient-years have been described among patients with established adrenal insufficiency with an associated mortality rate of 0.5/100 patient-years (67, 68). The most common precipitating causes were gastrointestinal infection, other infections (67, 68), and emotional stress (~15% each) (68). Notably, these incidence rates occurred in patients educated in stress dose administration, which is not performed routinely for glucocorticoid-treated patients.

Diagnostic Approach

Measurement of basal (unstimulated) morning cortisol concentrations can provide an indication of HPA axis function, but definitive evaluation requires a stimulation test (69-71). Several tests are available, but the ACTH stimulation test (Synacthen, Cosyntropin, or corticotropin test) is simple and safe and has become the method of choice in most centers (3, 69, 72, 73). It assesses the HPA axis at the level of the adrenal glands and correlates well with the insulin tolerance test, which is historically considered the "gold standard" test of central adrenal insufficiency (69, 73, 74).

In glucocorticoid-treated patients, the HPA axis response to ACTH stimulation also correlated with the response to surgery (major stress) (75).

Measurement of cortisol concentrations is subject to substantial interassay variation (76). Cortisol concentrations are measured with the highest specificity by mass spectrometry, but this is a demanding method and unavailable in most routine laboratories. Newer immunoassay generations using antibodies with improved specificity show results at sufficient reliability such that mass spectrometry is not needed in daily clinical practice (77). Using these methods, a lower cutoff limit has been defined as ACTH-stimulated 30-minute cortisol readings in the range of 375 to 440 nmol/L (1, 78, 79). In glucocorticoid-treated patients, cross reactivity from other glucocorticoids in cortisol immunoassays is a major concern (80). Cross reactivity by prednisolone is up to 171% in some assays (80, 81), but 8% in assays using more specific antibodies (82). Glucocorticoid treatment must therefore be paused (typically 24-48 hours depending on the drug) to ensure more reliable cortisol measurements. A short glucocorticoid pause of 24 hours will reduce the risk of a flare up of the underlying disease. On the other hand, a slightly longer pause will segregate patients with a fast recovery, so the ideal timing of HPA axis function assessment must be decided based on the clinical situation. High total cortisol concentrations are seen in pregnancy and during treatment with oral estrogen-containing contraceptive drugs, regardless of cortisol assay, caused by elevated cortisol-binding globulin. Measurement of cortisol should be carefully evaluated or avoided in these situations and treatment guided by symptoms and clinical relevance (83). The estrogen effect on cortisol concentrations can be substantial, as illustrated by the 2 ACTH tests performed at the time of diagnosis in case 1; P-cortisol rose to 703 nmol/L while she was using an oral contraceptive vs 30 nmol/L after pausing it for 2 months. In this specific case, commencing hydrocortisone replacement 4 weeks before the second test could potentially have suppressed the HPA axis further and contribute to the difference. The opposite effect (low total cortisol concentrations because of low cortisol-binding globulin concentrations) is seen in patients with cirrhosis, nephrotic syndrome, or critical illness (42).

To date, clinical guidelines for monitoring side effects to low-dose glucocorticoid treatment does not recommend routine screening for adrenal insufficiency in daily practice (84). The dominating strategy is to test for glucocorticoid-induced adrenal insufficiency based on clinical suspicion, but accumulating evidence indicates that this inevitably results in underdiagnosis. Thus, an English retrospective register-based cohort study found that ≤ 1% of 70 638 patients receiving oral glucocorticoids had ACTH or cortisol testing recorded (55). This and the absence of clear biomarkers of the risk make a case for routine screening for glucocorticoid-induced adrenal insufficiency, but implementation of such recommendations awaits further determination of the clinical implications of the condition. Meanwhile, a low threshold to test adrenal function seems relevant following long-term glucocorticoid treatment, during ongoing treatment, and tapering below basal daily glucocorticoid needs (5 mg prednisolone equivalents). Should a broader screening be implemented, strategies to reduce the needed number of ACTH tests will be important for feasibility. A morning P-cortisol above approximately 350 nmol/L (depending on assay) seems to safely predict a normal cortisol response to an ACTH test, reduces the number of needed ACTH tests by half (70, 71), and has already been implemented as part of the initial test strategy at some centers (35).

Adrenal Recovery and Approach to Retesting

Adrenal recovery is also associated with individual variations (53). Short-term (<1 month), high-dose, oral glucocorticoid treatment has been associated with recovery within weeks to months in most patients (23, 25, 85). Therefore, the retest strategy could focus on identifying the majority of patients with fast adrenal recovery (eg, with retest of identified cases after 3 months). Glucocorticoid-induced adrenal insufficiency after long-term glucocorticoid treatment is associated with more prolonged suppression, with reports of continued insufficiency in 25% to 86% after 6 to 12 months (23, 86, 87).

A retrospective evaluation of 110 patients with repeated ACTH tests for glucocorticoid-induced adrenal insufficiency found delta cortisol of the initial ACTH test (difference between the 30-minute cortisol concentration and baseline above or below 100 nmol/L [3.6 µg/dL]) to be the best predictor for future adrenal recovery, with delta cortisol > 100 nmol/L indicating more swift recovery. Combining the delta cortisol with a random cortisol measured 1 year later refined prognostic ability; no patients with delta cortisol < 100 nmol/L and random cortisol < 200 nmol/L recovered adrenal function within 4 years (86). Such an approach could help guide the retest timing to, for example, 6 months vs 1 year in patients with high vs low likelihood of recovery, but results are conflicting (35) and the thresholds need to be validated in larger cohorts.

Back to the Cases

Case 1

More than 3 years after diagnosis and after discontinuing inhaled budesonide treatment, the patient still has adrenal insufficiency, with the latest ACTH-stimulated cortisol at 32 nmol/L (1.2 µg/dL). She has experienced 2 adrenal crises. The first crisis resulted from an infection during a vacation in Southern Europe where she received prompt treatment after showing her international steroid emergency card. The precipitating cause for the second crisis was mental stress while studying for an examination and she has needed a high hydrocortisone replacement dose of 30 mg/d in periods with high-performance demands. Despite very good compliance with the hydrocortisone replacement treatment, she has been unable to work full-time. She has now adjusted her life situation accordingly, reducing stress and consequently her hydrocortisone need, thus improving her overall wellbeing.

This case illustrates first the prolonged period with insidious, nonspecific but devastating symptoms, second the acute hospitalization before the condition was diagnosed, and third the risk of missing the diagnosis because of oral contraceptive drug use. Finally, outside the endocrine department, the patient was met with reluctance to consider adrenal

insufficiency, which could have been fatal had she not had the unusual knowledge and capability herself to pursue this suspicion.

To reduce the risk of systemic side effects, the lowest effective glucocorticoid dose should always be used. For this patient, pulmonary specialists were able to reduce the inhaled glucocorticoid dose without compromising asthma control. However, at that point, the patient had developed severe longstanding adrenal insufficiency.

Case 2

Weeks after the adrenal insufficiency diagnosis was confirmed, the patient was admitted to a local emergency department. He presented with acute respiratory symptoms and continuous vomiting. He had pneumonia, but whether the infection had triggered an adrenal crisis was not considered, despite the recent documentation of adrenal insufficiency in the electronic medical records. No parenteral glucocorticoid was administered but upon suspicion of asthma he was given oral prednisolone 37.5 mg/d. At the endocrine department, the patient received continued patient education, slowly adapting to the replacement regimen, getting confident in self-management of the disease, and experiencing a substantial reduction of fatigue, especially when adding 5 mg of hydrocortisone before hosting larger social events. After 5 years of hydrocortisone replacement, his adrenal function has not recovered. The latest ACTH-stimulated P-cortisol level was 200 nmol/L (7.3 µg/dL).

This case illustrates several of the issues addressed in this paper. The patient was identified with quite severe glucocorticoid-induced adrenal insufficiency because of participation in a study. Because case identification based on risk factors and symptoms is difficult, routine screening should be considered for patients at high risk. There was a marked improvement in the ACTH-stimulated cortisol concentration when tested on 2.5 mg prednisolone/day compared with 7.5 mg/d. When tapering from 7.5 to 2.5 mg prednisolone/day, the patient had unspecific symptoms of steroid withdrawal, adrenal insufficiency, or both, whereas the rheumatologists did not find polymyalgia rheumatica disease activity. He later experienced clinical improvement when adding hydrocortisone stress doses in situations of mild-moderate stress. These symptoms could likely have been alleviated earlier had the condition been known and had stress doses been applied when the patient tapered to prednisolone ≤ 5 mg/d.

Like other reports (54), this case also indicates inappropriate management of adrenal-insufficient patients at emergency departments. Continuous vomiting should have led to parenteral glucocorticoid administration. Both cases 1 and 2 also demonstrate lack of recovery of adrenal function in these patients despite physiological replacement with the short-acting physiological cortisol equivalent hydrocortisone, and in the second case despite using a low daily dose (with partially suppressed adrenal function).

Approach to Patient Management

Indication to Treat Glucocorticoid-induced Adrenal Insufficiency?

As the clinical consequences and the effect of treatment of especially mild-moderate glucocorticoid-induced adrenal insufficiency are inadequately investigated, there is no evidence guiding the treatment of this type of adrenal insufficiency. While waiting for evidence, caution must be taken not to neglect treatment needs. Clear guidelines for managing primary and secondary adrenal insufficiency exist and the indication to treat these "classical" types of adrenal insufficiency are globally accepted (3, 14). Primary and secondary adrenal insufficiency are associated with reduced life expectancy compared with that of the general population, with adrenal crises, infections, and cardiovascular diseases as the major causes of death (88-90). Underreplacement with hydrocortisone is dangerous, potentially leading to adrenal crises, but chronic glucocorticoid overexposure leads to features of Cushing syndrome, with higher rates of metabolic and psychiatric comorbidities compared with matched controls (91). A survey study reported the highest number of symptoms of both hypo- and hypercortisolism and poorest self-perceived health in patients with glucocorticoid-induced compared with primary and secondary adrenal insufficiency (54). Patients with glucocorticoid-induced adrenal insufficiency were less frequently equipped with injectable glucocorticoids (51%) or medical alert gear at home (58%) and they less frequently reported improved self-management of adrenal insufficiency with time since the diagnosis (52%) compared with patients with primary and secondary adrenal insufficiency (54). This implies inadequate management.

There are 2 central questions to the clinical relevance of a mild-moderate biochemically abnormal ACTH test in glucocorticoid-induced adrenal insufficiency: first, whether patients have symptoms justifying treatment and, second, whether the risk of an adrenal crisis justifies treatment of apparently asymptomatic patients. Clinically relevant glucocorticoid-induced adrenal insufficiency has been documented in numerous cases of adrenal crises (53). English (55) and Danish (92) population-based register studies further described higher mortality (55) and incidence rates of registered diagnoses suggestive of untreated adrenal insufficiency (hypotension, gastrointestinal symptoms, hypoglycemia, and hyponatremia) (92) the first months after oral glucocorticoid cessation. Potential biomarkers for monitoring the adequacy of glucocorticoid replacement are being explored (93, 94), but none have yet shown sufficient reliability for implementation in clinical practice. The sole basis for treatment monitoring is therefore still clinical evaluation including patient reported symptoms (95-97). Few studies (54, 98-100) on glucocorticoid-induced adrenal insufficiency have systematically registered symptoms suggestive of hypocortisolism, asking patients to report the occurrence of up to 13 symptoms of adrenal insufficiency. None of the studies used a validated patient-reported outcome instrument, and the 3 studies specifying symptoms used in total 21 different symptoms/wordings of symptoms. Some (54, 98) but not all (99, 100) found a relationship between glucocorticoid-induced adrenal suppression and symptoms suggestive of hypocortisolism.

As illustrated in both patient cases, fatigue is the predominant complaint in adrenal insufficiency (68, 97, 101, 102). Daily variation in fatigue depending on stress level and how closely the replacement regimen mimics the natural circadian cortisol rhythm have been reported in patients with primary

and secondary adrenal insufficiency (97, 101-104), but this has not been investigated in patients with glucocorticoid-induced adrenal insufficiency. Such symptom variation during the day might not be captured in retrospective questionnaires using a long recall period. Real-time reporting of symptoms may be more sensitive as may specific instruments to capture symptoms throughout the day, as suggested in secondary adrenal insufficiency (104).

Treatment After Glucocorticoid Withdrawal

Treatment of glucocorticoid-induced adrenal insufficiency generally follows the principles for treatment of central adrenal insufficiency, with some special concerns. First, whether the patient needs immunosuppressive or replacement treatment or both need to be established. Relapse of the inflammatory disease is frequent and when the anti-inflammatory glucocorticoid treatment is altered, so is the need for replacement. Second, the type/level of replacement treatment must be decided. Unlike patients with primary adrenal insufficiency, who generally develop complete adrenal insufficiency, patients with glucocorticoid-induced adrenal insufficiency have variable degrees of glucocorticoid insufficiency and a chance to recover adrenal function. Supplementation with hydrocortisone can therefore be considered at several levels ranging from rescue treatment only in situations of severe stress to full replacement treatment. In 2 observational studies on adrenal insufficiency after glucocorticoid withdrawal, adrenal insufficient children with rheumatic diseases (100) or adults with exacerbated chronic obstructive pulmonary disease (99) did not receive daily glucocorticoid replacement but were instructed to take hydrocortisone and to seek professional help if they experienced symptoms suggestive of hypocortisolism. Clinical follow-up to evaluate the efficacy of this approach was limited, but no hospitalizations or deaths were reported as a result of adrenal crisis, which is why the authors found the "stress dose only" approach safe (99, 100). In the presented cases, the daily replacement doses were based on the degree of adrenal suppression in addition to other factors such as weight and they were tapered to lowest dose necessary to alleviate clinical symptoms of adrenal insufficiency. At a minimum, patients with glucocorticoid-induced adrenal insufficiency must receive patient education and medical alert gear including steroid emergency card (2) aiming to self-manage adrenal crises.

The ideal clinical situation seen from the point of view of the endocrinologist is when a patient no longer needs the anti-inflammatory effect of glucocorticoid treatment and thus can be handled as a pure endocrine patient. Hydrocortisone has the same chemical structure as endogenous cortisol and is therefore the preferred drug for replacement (3), but other glucocorticoid formulations such as cortisone acetate and prednisolone are also used (3, 105, 106). Hydrocortisone has a short half-life (90 minutes), and administration is therefore recommended in 2 to 3 daily doses, with the highest dose given early in the morning to approximate the endogenous circadian cortisol rhythm (69). A 2-dose regimen avoiding late afternoon administrations will theoretically offer the best opportunity for adrenal recovery with lowest suppressive effect on the early morning ACTH surge (60). Prednisolone 3 to 5 mg divided in 1 to 2 daily doses has mainly been used in patients with reduced compliance to multiple dosing or in countries where this is the only available glucocorticoid (3, 105, 106), but a general usefulness of prednisolone is being revisited (107).

Continuous efforts are made to optimize both anti-inflammatory and replacement glucocorticoid treatment targeting the early morning rise in proinflammatory cytokines or mimicking the circadian cortisol rhythm as closely as possible (103, 108-111). This has led to development of modified-release formulations of both prednisolone for anti-inflammatory treatment (110) (releases prednisolone around 2 am after bedtime intake) and slow (111) or dual-release (103) hydrocortisone for replacement treatment. The improved timing may improve clinical outcomes in some patients compared with the same dose of the conventional formulation (103, 110, 111), but evidence is still based on small cohorts. Administration of modified-release prednisolone to patients with rheumatoid arthritis provided clinical arthritis improvements without further suppression of the adrenal function (110).

Patient Approach During Ongoing Low-dose Glucocorticoid Treatment

The clinical focus on glucocorticoid-induced adrenal insufficiency has primarily been after glucocorticoid withdrawal, but as described previously, and illustrated in cases, patients receiving ongoing low-dose glucocorticoid-treatment (≤5 mg prednisolone equivalents) are at risk of symptomatic adrenal insufficiency even during minor self-managed infections or mental stress (29). If adrenal function testing is not possible, a safe approach is to advise self-administration of stress doses in all patients, as recommended by the British Endocrine and Rheumatologic societies during the COVID-19 pandemic (16). Patient education in sick-day rules and hydrocortisone self-administration must be handled by trained health care providers within endocrinology. This poses an organizational challenge to manage patients receiving ongoing glucocorticoid treatment with a main affiliation to a nonendocrine department. It demands close collaboration between medical specialities to ensure adequate education of health care providers and subsequently of patients.

Controversies and Areas of Uncertainty

In this article, we have emphasized the importance of identifying clinical manifestations of glucocorticoid-induced adrenal insufficiency. The major shortcomings in the tailored management of patients with possible glucocorticoid-induced adrenal insufficiency are the low screening rates for case identification. Had that been done, subsequent evaluation of the clinical implications could have been properly studied in randomized controlled clinical trials. The lack of evidence-based guidance results in huge gaps and variations in management. The high rates of diagnosis during an adrenal crisis and delayed glucocorticoid administration in patients with an established diagnosis of glucocorticoid-induced adrenal insufficiency indicate room for improved management. Prospective randomized studies evaluating the impact of hydrocortisone replacement are needed. Such studies should focus on evaluating symptoms of adrenal insufficiency using validated patient-reported outcome instruments, including daily variation of symptoms, symptoms during mild-moderate stress,

and risk of adrenal crises both during ongoing low-dose glucocorticoid treatment and after withdrawal. With colleagues, the authors of this paper are engaged in such investigations in the project Double Edge, including 2 randomized clinical trials (EudraCT numbers 2020-006121-65 and 2021-002528-18). Introducing a classification of mild-moderate-severe adrenal insufficiency might ground a more balanced patient approach with treatment strategies ranging from rescue doses only in case of major stress to full replacement treatment in cases of more severe adrenal insufficiency. Validation of clinical biomarkers for glucocorticoid sensitivity and action could help determine the adequacy of the glucocorticoid replacement dose, thereby avoiding both over- and underreplacement.

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Disclosures

The authors have nothing to declare.

Data Availability

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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