



Review

Steroid-Induced Iatrogenic Adrenal Insufficiency in Children: A Literature Review

Shogo Akahoshi * and Yukihiro Hasegawa

Division of Endocrinology and Metabolism, Tokyo Metropolitan Children's Medical Center, 2-8-29 Musashidai, Fuchu, Tokyo 183-8561, Japan; yhaset@gmail.com

* Correspondence: shg.akhs@gmail.com; Tel.: +81-42-300-5111

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Abstract: The present review focuses on steroid-induced adrenal insufficiency (SIAI) in children and discusses the latest findings by surveying recent studies. SIAI is a condition involving adrenocorticotropic hormone (ACTH) and cortisol suppression due to high doses or prolonged administration of glucocorticoids. While its chronic symptoms, such as fatigue and loss of appetite, are nonspecific, exposure to physical stressors, such as infection and surgery, increases the risk of adrenal crisis development accompanied by hypoglycemia, hypotension, or shock. The low-dose ACTH stimulation test is generally used for diagnosis, and the early morning serum cortisol level has also been shown to be useful in screening for the condition. Medical management includes gradually reducing the amount of steroid treatment, continuing administration of hydrocortisone corresponding to the physiological range, and increasing the dosage when physical stressors are present.

Keywords: adrenal insufficiency; children; endocrinology; glucocorticoids; hypothalamic–pituitary–adrenal axis; therapeutics

1. Mainstem Concepts of Adrenal Insufficiency

1.1. Primary, Secondary, and Tertiary Adrenal Insufficiency

Adrenal insufficiency (AI) is defined as the inability of the adrenal cortex to produce sufficient amounts of glucocorticoid hormone. It can also be associated with mineralocorticoid deficiency, depending on the pathophysiology of the disease [1]. Severe AI, or adrenal crisis, can be life-threatening because glucocorticoids and mineralocorticoids play a central role in maintaining energy, salt, and fluid homeostasis [2]. AI is usually classified into the primary and secondary types, which are caused by adrenal diseases and hypothalamic/pituitary diseases, respectively. AI associated with hypothalamic dysfunction is sometimes called tertiary AI. The main causes of AI are described below (see Table 1).

Primary AI can be further divided into the congenital type, represented by congenital adrenal hyperplasia (CAH), and the acquired type, represented by Addison's disease [1]. One of the obvious differences in the clinical picture between primary, secondary, and tertiary AI is skin pigmentation, which is almost always present in primary AI (except in cases with a short duration) but is absent in secondary and tertiary AI [3]. Additionally, mineralocorticoid deficiency is generally associated with primary AI but not with secondary or tertiary AI because the renin–angiotensin–aldosterone system is not impaired in the latter [4]. In exceptional cases of CAH due to 11 beta-hydroxylase deficiency and 17 alpha-hydroxylase deficiency, mineralocorticoid excess occurs concurrently with glucocorticoid deficiency [5].

Table 1. Major causes of adrenal insufficiency.

Primary Adrenal Insufficiency	
Autoimmune adrenalitis	APS type 1, 2, 3
Infectious adrenalitis	Tuberculosis, HIV-1, cryptococcosis, Treponema pallidum
Bilateral adrenal hemorrhage	Meningococcal sepsis
Bilateral adrenal infiltration	Primary adrenal lymphoma, hemochromatosis
Drug-induced	Ketoconazole, fluconazole, phenobarbital, phenytoin, rifampicin
Genetic disorders	CAH, adrenoleukodystrophy, adrenal hypoplasia congenita
Secondary adrenal insufficiency	
Pituitary tumor	Craniopharyngiomas, adenomas, cysts
Pituitary injury	Trauma, surgery, irradiation, pituitary apoplexy
Pituitary infiltration	Lymphocytic hypophysitis, tuberculosis, meningitis
Genetic disorders	Combined pituitary hormone deficiency, isolated ACTH deficiency
Tertiary adrenal insufficiency	
Hypothalamic tumor	Craniopharyngiomas, metastasis
Hypothalamic injury	Trauma, surgery, irradiation
Hypothalamic infiltration	Hemochromatosis, tuberculosis, meningitis
Steroid-induced	Systemic, inhalation, topical, intra-articular
Other drug-induced	Chlorpromazine, imipramine
Abbreviations: ACTH, adrenocorticotropic hormone; APS, autoimmune polyendocrinopathy syndrome; CAH, congenital adrenal hyperplasia.	
(Modified from [2] E. Charmandari, et al. Adrenal insufficiency. <i>Lancet (London, England)</i> 2014, 383, 2152–2167.)	

Secondary and tertiary AI can be divided into congenital and acquired types as well. Various genetic etiologies involving not only central nervous system malformations, such as holoprosencephaly, but also combined pituitary hormone deficiencies and isolated ACTH deficiency, have been identified [6]. Besides the drug-induced etiologies described below, acquired secondary AI can be caused by a tumor (e.g., craniopharyngioma), trauma, surgery, inflammation, or infarction involving the pituitary gland. It should be noted that secondary and tertiary AI may be latent or their onset may often be slow; congenital AI may become apparent around puberty (especially in septo-optic dysplasia [7] or hypopituitarism associated with perinatal problems [8]), while acquired AI can occur months to years after intracranial radiation [9] or traumatic brain injury [10,11]. Severe hypoglycemia in the neonatal period is rather exceptional and can be seen in congenital isolated ACTH deficiency caused by a *TBX19* gene mutation [12].

1.2. Iatrogenic Adrenal Insufficiency

Iatrogenic AI refers to primary, secondary, or tertiary hypoadrenocorticism associated with drug administration, surgery, or irradiation. This review focuses on the role of steroids, the most frequent etiology of tertiary AI [2], which induce iatrogenic adrenal insufficiency (steroid-induced iatrogenic adrenal insufficiency, or SIAI) when the hypothalamic–pituitary–adrenal (HPA) axis is suppressed by high dosages or prolonged use of the drugs followed by abrupt discontinuation or rapid tapering. Patients with leukemia, asthma, collagen disease, or inflammatory bowel disease and those who have undergone transplant surgery [13] and have received long-term synthetic glucocorticoid treatment are especially at risk of SIAI development. There is currently insufficient evidence on the epidemiology, treatment strategy, and recovery process in SIAI; therefore, the optimal diagnostic criteria and management of the condition are still controversial. However, with the chief aim of preventing life-threatening adrenal crises [14], we discuss below the approaches available for managing patients treated with corticosteroids and summarize our tentative recommendations in Table 2. Other known

causes of iatrogenic AI include drugs such as ketoconazole [15], mitotane [16], and etomidate [17], which inhibit the steroidogenesis pathway.

Table 2. Summary and recommendations for SIAI management.

Risk Factors	
Predisposing diseases	Asthma, leukemia, collagen disease, inflammatory bowel disease
Glucocorticoid dose	Doses higher than the physiological equivalent HDC (6–8 mg/m ²) and durations exceeding two weeks are associated with SIAI risk.
Clinical symptoms	
Chronic symptoms	Weakness, fatigue, anorexia, weight loss
Acute symptoms	Vomiting, diarrhea, abdominal pain, hypoglycemia, hypotension
Diagnostic evaluations	
Screening test	Serum cortisol level at 8–9 a.m. with cutoff <10 µg/dL
Dynamic test	Low-dose ACTH stimulation test with cutoff <18 µg/dL serum cortisol level 30 min after stimulation
Follow-up schedules	Initial testing 1–3 months after the end of pharmacological GC followed by dynamic testing every 3–6 months until recovery
Glucocorticoid supplementation	
Physiological replacement dose	po HDC 6–8 mg/m ² /day unless serum cortisol >5 µg/dL on morning testing
Stress dose	im/iv HDC 50–100 mg/m ² /day according to the physical stress unless peak cortisol >18 µg/dL on dynamic testing
Abbreviations: ACTH, adrenocorticotropic hormone; GC, glucocorticoid; HDC, hydrocortisone; im, intramuscular; iv, intravenous; po, orally; SIAI, steroid-induced iatrogenic adrenal insufficiency.	

2. Case Presentations of SIAI

Significant lessons can be learned from actual cases, especially in pediatrics, where the clinical research is still insufficient. For this reason, we have presented three cases below that illustrate the typical presentation and course of SIAI. Based on the findings of a study of the response of healthy adults to the corticotropin-releasing hormone (CRH) stimulation test [18] and the criteria for the low-dose ACTH stimulation test described below, we used a peak serum cortisol concentration <18 µg/dL in the CRH stimulation test as the cutoff value for diagnosing SIAI.

Case 1: A 1-year-old, male patient was treated for Kawasaki disease with intravenous immunoglobulin 2 g/kg and methylprednisolone (mPSL) 30 mg/kg followed by oral aspirin and prednisolone (PSL). PSL was started at 2 mg/kg/day, then tapered, resulting in a total hydrocortisone (HDC) equivalent glucocorticoid dose of 5500 mg/m² over three weeks. Thereafter, a physiological replacement dose of HDC (8 mg/m²/day) was started. A CRH stimulation test conducted one week after PSL discontinuation showed peak ACTH and cortisol levels of 52.9 pg/mL and 5.5 µg/dL, respectively. The normalization of his adrenal function was confirmed four months later by a CRH stimulation test, which showed peak ACTH and cortisol levels of 19.6 pg/mL and 55.5 µg/dL, respectively.

Case 2: A 13-year-old male patient was treated for ulcerative colitis with nutritional therapy, 5-aminosalicylic acid, and PSL. PSL was administered at an HDC equivalent dose of 2900 mg/m² for six weeks and afterwards switched to a physiological replacement dose. HDC was increased to a stress dose of 100 mg/m²/day for a colectomy and colostomy performed three weeks and months later, respectively. A CRH stimulation study conducted eight months later demonstrated a peak ACTH level of 61.4 pg/mL and a cortisol level of 9.5 µg/dL 30 min after stimulation. Thereafter, daily HDC

administration was discontinued, and no episodes of suspected SIAI have been observed to date. Nineteen months after the discontinuation of daily HDC, a CRH stimulation study showed recovery of the peak cortisol level to 17.4 µg/dL.

Case 3: A 5-year-old female patient was treated for acute tubulointerstitial nephritis with PSL 2 mg/kg/day initially, which was tapered by 0.5 mg/kg/day every two weeks to 0.25 mg/kg/day after two months of treatment. Three months after the start of treatment, when the cumulative dose of PSL was equivalent to HDC 8400 mg/m², she was admitted to the hospital emergency department due to recurrent vomiting and diarrhea. SIAI was diagnosed based on the serum cortisol value, which was 2.9 µg/dL more than 12 h after the PSL administration on the previous evening despite the physical stress. After a PSL stress dose of 15 mg/m² was administered on admission, her symptoms improved. Two days later, when the PSL dosage was reduced to 5 mg/m², vomiting recurred. Thereafter, PSL was reintroduced and tapered again, and the patient was discharged with a prescription for PSL at the pre-hospitalization dosage.

3. Effect of Steroid Dosage and Administration Duration on SIAI

3.1. Dose Dependency

A systematic review of adult patients showed that higher steroid doses and longer durations of use were associated with an increased SIAI risk [13] although the evidence in pediatrics is currently insufficient to demonstrate a dose-dependent risk of SIAI [19,20]. The timing of administration may also affect the severity of SIAI, as high steroid doses at night are believed to inhibit the early morning ACTH surge [21].

Suppression of the HPA axis by exogenous glucocorticoids has been reported mainly in systemic and inhalation therapy and only rarely in topical applications [22,23] or intra-articular administration [13]. Studies of childhood asthma have suggested that patients using fluticasone ≥500 µg/day as a controller [24] or who received acute treatment with systemic steroids in the past [25] may be at higher risk of SIAI development. In a cohort study of children with asthma, the absolute risk of HPA suppression was 100% when using the beclomethasone dipropionate metered dose inhaler at a dose of 250–600 µg/m²/day for 6–42 months [26].

3.2. Dose Threshold for SIAI

There is no strict consensus on the cumulative steroid dose threshold for SIAI development. In the treatment of both adults [27] and children [28], even small doses and short-term administration of steroids can potentially cause SIAI. In adults, adrenal atrophy and functional decline are likely to occur after systemic administration of 30 mg or more of HDC equivalent steroids (>7.5 mg/day PSL or >0.75 mg/day dexamethasone) per day for three weeks or longer [4]. On the other hand, severe SIAI is reportedly unlikely to occur at a physiological replacement dose of glucocorticoids for up to two weeks of administration [29]. However, a prospective study of pediatric asthma showed that 11 patients receiving a PSL dosage of up to 2 mg/kg/day for five days, which is a shorter period of administration than in *Case 1* above, showed statistically significant blunting of the peak cortisol response in an insulin tolerance test three days after discontinuation of the PSL therapy [30]. Further studies are needed to determine the cumulative steroid dose threshold for SIAI development.

3.3. Adverse Effects of Glucocorticoid Pulse Therapy

Glucocorticoid pulse therapy, which consists of a small number of intravenous, high-dose mPSL administrations, is reportedly associated with fewer adverse effects than daily oral steroid therapy at the equivalent dose for suppressing inflammation and the autoimmune response [31]. In a randomized controlled trial enrolling adults, no significant difference in systemic side effects was observed between an mPSL 30 mg single-dose group and the placebo group [32]. In an observational study of mPSL pulse therapy for pediatric Kawasaki disease, only transient bradycardia and hyperglycemia were

observed [33]. However, a previous study reported that 22% of children with a rheumatic disease experienced unexpectedly diverse side effects of steroid pulse therapy, such as behavioral changes (10%), headache (5.2%), and abdominal complaints (4.7%) [34], underscoring the need for careful assessment of the safety of these treatments.

3.4. Factors Associated with SIAI Development

A study enrolling adults with various, underlying diseases demonstrated that possible predictors of adrenal suppression may include central obesity, nausea/vomiting, fatigue, low serum cholesterol, low serum sodium, and chronic kidney disease [35]. A pediatric study reported that responsiveness of the HPA axis to stress was more pronounced in female children than in male children [36], and another study of severely ill children reported that patients in an adrenal suppression group were older than subjects in the control group [37]. In addition, concurrent administration of other drugs may synergistically augment the potency of steroids and the severity of HPA axis suppression. For example, drugs that inhibit CYP3A4, such as ritonavir, suppress inhaled fluticasone clearance [38]. Drugs with an affinity for glucocorticoid receptors, such as progesterone derivatives, which are given to oncology patients in high doses, have also been linked to SIAI [39].

4. Clinical Manifestations of SIAI

4.1. Chronic Symptoms

Patients may present with chronic symptoms while recovering from HPA suppression. The common symptoms are weakness, fatigue, anorexia, and weight loss [40]. Frequent gastrointestinal complaints include nausea, vomiting, diarrhea, constipation, and abdominal pain, which are probably related to decreased bowel motility. These symptoms are more likely to occur with greater HPA suppression [1] and soon after stopping steroids [41]. In addition, adrenal insufficiency inevitably leads to a deficiency of dehydroepiandrosterone (DHEA), a substrate for peripheral sex hormone biosynthesis, which can lead to androgen deficiency in women. Its clinical manifestations include loss of axillary and pubic hair, dry skin, and decreased libido [42].

4.2. Symptoms as Side Effects of Glucocorticoids

Awareness of a variety of side effects of glucocorticoids is necessary when assessing SIAI. Particularly serious effects include immunosuppression, impaired growth, osteoporosis, and somewhat less frequently, but importantly, cataract formation and pancreatitis [43]. Medical Cushing's syndrome, i.e., central obesity, muscle atrophy, and hypertension, can also occur in infants [44]. Nonspecific symptoms include mood disorders, abdominal symptoms, and dizziness [34], which can be difficult to differentiate from the symptoms of SIAI.

4.3. Acute Symptoms in the Presence of Stressors

It is even more important to note that physical stressors, such as severe infection or surgery, can trigger acute symptoms. Nonspecific symptoms, such as vomiting and diarrhea seen in *Case 3*, are common [40]. Laboratory findings are often normal [35,45]. Hyponatremia can develop as a result of increased vasopressin secretion and water retention [46]. The most severe and acute form is adrenal crisis, which consists of tachycardia, hypoglycemia, hypotension, dehydration, and acute abdominal pain [40,47]. Although the incidence of adrenal crisis is unknown, a questionnaire study of physicians across the UK revealed that adrenal crisis associated with inhaled corticosteroids (ICSs) occurred in 28 children, one of whom died from the condition. The mean patient age, duration of ICS treatment, and dosage of fluticasone, which was administered to 94% of the patients, was 6.4 years, 1.7 years, and 980 µg/day (range of 500–2000 µg/day), respectively [48]. At the time of the study, only 16% of all asthma patients were reportedly using fluticasone in the UK, indicating the gravity of the risk of adrenal crisis associated with fluticasone use [24].

5. Diagnostic Approaches to SIAI

5.1. Variation in Diagnostic Approaches

The symptoms of SIAI are nonspecific, and the diagnostic criteria are basically based on dynamic testing rather than the symptoms. The insulin tolerance test (ITT) has traditionally been the gold standard for HPA axis assessment in adults [49], but this can be replaced by the safer, cheaper, and faster Synacthen test (SST) [50,51]. In pediatric medicine, the test most commonly used to diagnose secondary adrenal insufficiency is the low-dose ACTH stimulation test [52] because it is easy to administer, physiologically sound, safe, and reasonably sensitive. The glucagon [53] and CRH [14,54] stimulation tests (used in *Cases 1–3* above) are also administered. Furthermore, early morning cortisol levels can also be used in screening [55,56] and assessment [57] of HPA function.

5.2. Low-Dose ACTH Stimulation Test

Low-dose ACTH stimulation testing is performed by administering 1 µg/1.73 m² intravenous cosyntropin and assessing the subsequent increase in the serum cortisol level. A serum cortisol level of 16–20 µg/dL 30 min after cosyntropin administration is generally used as the threshold level although this may vary somewhat among assays [58–61]. Additional cortisol draws at 15 and 60 min may reduce the risk of false positive results [62]. We suggest performing this test at the initial evaluation 1 to 6 months after the end of the pharmacological dosing (depending on the duration of the steroid therapy), then every 3 to 6 months as needed in combination with early morning serum cortisol level testing, although the evidence and guideline recommendations supporting this approach are still inadequate. Once the values normalize, HDC maintenance therapy can be safely discontinued [41].

5.3. Early Morning Serum Cortisol Level

While random cortisol testing might be helpful in an emergency setting, as seen in *Case 3*, serum cortisol levels at 8 a.m. to 9 a.m. are often used when screening for SIAI. Previous studies have proposed an early morning cortisol level cutoff value of 8.5–10.3 µg/dL in adults [55,57]. A reference value of plasma cortisol, which is equivalent to that of serum cortisol [63–65], ≤3 µg/dL (83 nmol/L), may indicate SIAI, while a value >19 µg/dL (525 nmol/L) can be used to exclude SIAI [66]. A cohort study suggested a serum cortisol level of 5 µg/dL at 9 a.m. in children as a cutoff value for SIAI screening following steroid administration for Kawasaki disease [67].

6. Recovery Course in SIAI

6.1. Long-Term Administration

In an observational study of the natural history of SIAI in adults, both ACTH and cortisol secretion were initially suppressed. Then, ACTH secretion quickly increased before dropping to the normal range while cortisol secretion increased in response to the ACTH increase and normalized over several months [68]. Figure 1 shows a schema of ACTH and cortisol levels in SIAI following glucocorticoid therapy. SIAI due to steroid treatment for chronic diseases tends to show slower recovery. Studies reviewing adult cases of leukemia, hemangioma, and asthma reported that six to 12 months were required for recovery from SIAI [69], while a study of glomerular disease reported that 8.7 ± 4.6 months (mean ± SD) [56] were required. A pediatric study reported that recovery after treatment for acute lymphocytic leukemia took an average of 8.5 months (95% confidence interval: 6.3–10.7 months) [70], and another study reported that 11% of patients still had adrenal suppression 20 months after treatment for a rheumatic disease [71]. In line with the results of these studies, the patient in *Case 2* did not show adequate cortisol secretion in the CRH stimulation test as late as eight months after the cessation of a six-week PSL treatment regimen.

6.2. Short-Term Administration

If the dosages are small or the treatment short-term, recovery tends to be faster. The above literature review found that adrenal function recovered rapidly when steroids were administered for less than 14 days [69]. In an interventional study where a high-dose, short-term glucocorticoid (HDC 25 mg twice daily for five days) was administered to healthy adult subjects, the peak cortisol response to the ITT significantly decreased two days after PSL discontinuation but nearly returned to pretreatment levels five days after the intervention [72]. An observational study of childhood asthma found that adrenal function normalized in all 11 patients ten days after the completion of short-term PSL treatment [30], and another study of PSL treatment for Kawasaki disease in children reported recovery in more than half the patients within two months [67].

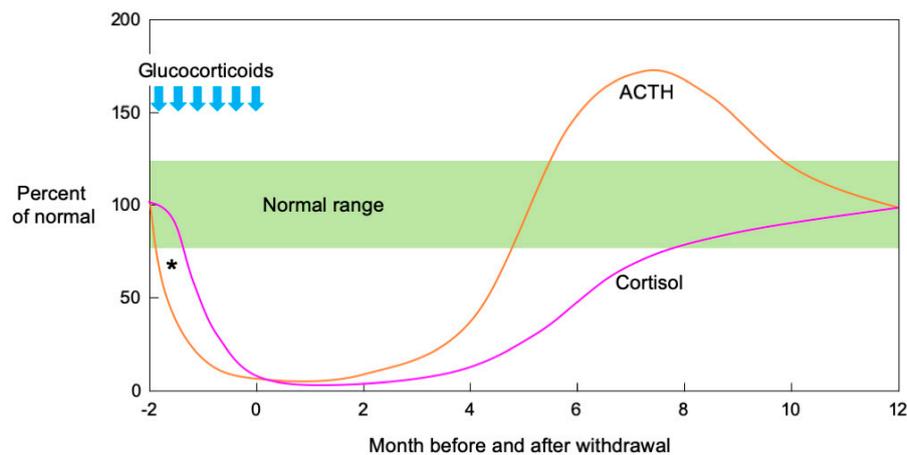


Figure 1. Schematic illustration of ACTH and cortisol levels after pharmacological glucocorticoid therapy. Both ACTH and cortisol secretion are initially suppressed when high-dose or long-term glucocorticoid administration is followed by abrupt cessation or rapid tapering. Theoretically, ACTH precedes cortisol in the suppression phase after pharmacological glucocorticoid therapy (*). In the recovery phase, ACTH secretion increases rapidly, then decreases to the normal range while cortisol secretion increases in response to increased ACTH and normalizes over several months. (Modified from [73] Kim E. Barrett, et al. *The Adrenal Medulla & Adrenal Cortex. Ganong's Review of Medical Physiology, 24th Ed.* 2012, Chapter 20).

7. Practical Management of SIAI

7.1. Tapering from the Therapeutic to Physiological Replacement Dose

Weeks or months may be required to taper steroids until normal adrenal function is restored, and measures should be taken to prevent adrenal crisis during episodes of stress. In adults, the PSL dosage may be reduced from the pharmacological to the physiological level for several weeks. For example, depending on the patient's condition, PSL may be reduced by 1 mg per day every two to four weeks [21]. Alternatively, HDC may be reduced weekly by 2.5 mg/day and maintained at 10 mg/day, which corresponds to endogenous cortisol synthesis as measured by isotope dilution [74].

In children, dose tapering to levels equivalent to the physiological dose (6–8 mg/m²/day of HDC [75–77]) is believed to be important to prevent symptoms of SIAI, although it has not been shown to restore adrenal cortical function [78]. Despite the lack of a consensus on how HDC should be prescribed, oral HDC administration once a day may be feasible and can improve compliance. Another option is to divide the total daily dose into four doses, two on waking, one at noon, and one in the evening, which may be acceptable to some patients [41].

7.2. Stress Doses

When the patient is under stress, the rescue method should be chosen according to the degree of the stress and the symptoms. Expert opinion [1,2] on steroid dosages for adults during stress was shown to be valid by a clinical study enrolling adults [79]. The stress dose for children is estimated by converting the adult dose into HDC per body surface area. For moderate physical stressors, such as infection associated with high fever (>38.5 °C), minor trauma, or dental treatment, three-fold the maintenance dosage or 50 mg/m²/day of HDC is administered orally in three to four divided doses [40,80]. If vomiting, lethargy, or other reasons make oral intake difficult, 50 mg/m² HDC may first be injected intravenously. If an intravenous line cannot be placed, an intramuscular injection may be used [80]. In both adult and pediatric patients who are under severe stress, such as that caused by sepsis or major surgery, intravenous HDC 100 mg/m²/day administered continuously or every six hours in divided doses is recommended until recovery is achieved [40,47,80–82].

7.3. Patient Education

It is important that patients understand how to manage their condition, including knowing how much hydrocortisone to take or inject outside the hospital during episodes of stress. Patients are encouraged to wear a tag or a pin containing medical information, such as measures required in an emergency, hospital contact information, etc., which can enable others to provide assistance when needed [2,40,41,82,83].

8. Further Considerations Regarding SIAI

8.1. Pathophysiological and Pharmacological Research

Despite the availability of hydrocortisone replacement therapy and the asymptomatic clinical course in most cases, it is essential to recognize that any patient with SIAI who has been receiving prolonged glucocorticoid therapy may experience reduced quality of life and have a risk of experiencing adrenal crisis [84,85].

New oral hydrocortisone drugs that allow sustained absorption through delayed or biphasic release are being developed as a promising method of mimicking the physiological cortisol profile [86,87]. Additionally, a deeper understanding of steroid activity pathways and how these change in different target tissues may enable the development of tissue-specific glucocorticoid analogs, such as those that can suppress inflammation without causing osteopenia or other symptoms of Cushing's syndrome [88–91].

8.2. Clinical and Epidemiological Research

The methods of diagnosing adrenal insufficiency and the administration of physiological and stress doses addressed in this review are all based on various studies of patients with different backgrounds. In particular, the criteria for continuing/discontinuing physiological and stress doses need to be discussed in terms of the treatment target. For example, our interpretation of dynamic test results will differ depending on whether the goal is to prevent chronic and acute symptoms or adrenal crisis. Furthermore, adrenal crisis is difficult to define in clinical studies because its physical and laboratory findings are nonspecific, and endocrinological testing is often difficult in the acute phase. Further research is warranted to optimize practical management of the disease, and clinical studies enrolling an adequate number of cases with a sufficient follow-up period are needed to standardize the diagnostic criteria and treatment methods.

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