Adrenal insufficiency

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Adrenal insufficiency is the clinical manifestation of deficient production or action of glucocorticoids, with or without deficiency also in mineralocorticoids and adrenal androgens. It is a life-threatening disorder that can result from primary adrenal failure or secondary adrenal disease due to impairment of the hypothalamic–pituitary axis. Prompt diagnosis and management are essential. The clinical manifestations of primary adrenal insufficiency result from deficiency of all adrenocortical hormones, but they can also include signs of other concurrent autoimmune conditions. In secondary or tertiary adrenal insufficiency, the clinical picture results from glucocorticoid deficiency only, but manifestations of the primary pathological disorder can also be present. The diagnostic investigation, although well established, can be challenging, especially in patients with secondary or tertiary adrenal insufficiency. We summarise knowledge at this time on the epidemiology, causal mechanisms, pathophysiology, clinical manifestations, diagnosis, and management of this disorder.

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Introduction

Adrenal insufficiency is a life-threatening disorder that can result from primary adrenal failure or secondary adrenal disease due to impairment of the hypothalamic–pituitary axis.[1–3] It is the clinical manifestation of deficient production or action of glucocorticoids, with or without deficiency also in mineralocorticoids and adrenal androgens. The cardinal clinical symptoms of adrenocortical insufficiency, as first described by Thomas Addison in 1855, include weakness, fatigue, anorexia, abdominal pain, weight loss, orthostatic hypotension, and salt craving; characteristic hyperpigmentation of the skin occurs with primary adrenal failure.[4,5] Whatever the cause, adrenal insufficiency was invariably fatal until 1949, when cortisone was first synthesised,[6–9] and glucocorticoid-replacement treatment became available. However, despite this breakthrough, the diagnosis and treatment of patients with the disorder remain challenging.

Epidemiology

According to the underlying mechanism, adrenal insufficiency is classed as primary, secondary, or tertiary. Primary adrenal insufficiency results from disease intrinsic to the adrenal cortex. Central adrenal insufficiency, the collective name for the secondary and tertiary types, is caused by impaired production or action of corticotropin. Secondary adrenal insufficiency results from pituitary disease that hampers the release of corticotropin or from a lack of responsiveness of the adrenal glands to this hormone. Tertiary adrenal insufficiency results from the impaired synthesis or action of corticotropin-releasing hormone, arginine vasopressin, or both, from the hypothalamus, which in turn inhibits secretion of corticotropin.

In Europe, the prevalence of chronic primary adrenal insufficiency has increased from 40–70 cases per million people in the 1960s[10,11] to 93–144 cases per million by the end of the 20th century,[12–16] with an estimated incidence now of 4·4–6·0 new cases per million population per year.[15] Tuberculosis was the most common cause of primary adrenal insufficiency during the first half of the 20th century,[17] but lately autoimmune adrenal insufficiency has become the most common form.[16] The increase in the frequency of primary adrenal insufficiency over the past few decades, associated with a decline in the prevalence of tuberculosis, is indicative of the rising proportion of cases of autoimmune adrenal insufficiency.[18] In a series of 615 patients with Addison's disease, studied between 1969 and 2009, the autoimmune form was diagnosed in 82% of cases, the tuberculosis-related form in 9%, and other causes in about 8% of cases.[19] Primary adrenal insufficiency occurs more frequently in women than in men, and can present at any age, although most often appears between the ages of 30 and 50 years.[12]

The frequency of the various forms of primary adrenal insufficiency in children differs substantially from that in the adult population; the genetic forms are more common. In a series of 103 children with Addison's

Search strategy and selection criteria

We searched PubMed and the Cochrane Library for original articles and reviews related to adrenal insufficiency, which were published in English between 1966 and April, 2013. We used the search terms "adrenal insufficiency", in combination with the terms "incidence", "prevalence", "cause", "origin", "diagnosis", "function test", "imaging", "hydrocortisone", "glucocorticoid", "mineralocorticoid", "dehydroepiandrosterone", "management", "treatment", "therapy", "replacement", "surveillance", "crisis", "bone mineral density", "quality of life", "well being", "pregnancy", "prognosis", "morbidity", and "mortality". We largely chose publications from the past 5 years, but we did not exclude commonly referenced and highly regarded older publications. We also searched the reference lists of articles identified by this search strategy and selected those we judged relevant. Several review articles or book chapters were included because they provide comprehensive overviews that are beyond the scope of this Seminar. The reference list was modified during the peer-review process on the basis of comments from reviewers.

disease seen over 20 years (1981–2001), the most frequent cause was congenital adrenal hyperplasia (72%), and other genetic causes accounted for another 6%; autoimmune disease was diagnosed in only 13%.[20]

Secondary adrenal insufficiency is more common than primary adrenal insufficiency.[1] It has an estimated prevalence of 150–280 per million and affects women more frequently than men.[14,21–24] The age at diagnosis peaks in the sixth decade of life.[22,23] A systematic review and meta-analysis of reported prevalences of hypopituitarism in adult patients who had received cranial irradiation for non-pituitary tumours showed that the point prevalence of any degree of hypopituitarism was 0·66 (95% CI 0·55–0·76) and the prevalence of corticotropin deficiency was 0·22 (0·15–0·30).[25] The most common cause of tertiary adrenal insufficiency is long-term administration of exogenous glucocorticoids, which leads to prolonged suppression of hypothalamic secretion of corticotropin-releasing hormone.[26]

Causal mechanisms

Primary adrenal insufficiency

The causes of primary adrenal insufficiency are listed in table 1. In developed countries, 80–90% of cases of primary adrenal insufficiency are caused by autoimmune adrenalitis, which can be isolated (40%) or part of an autoimmune polyendocrinopathy syndrome (60%).[1,2,19,32–34] Autoimmune Addison's disease is characterised by destruction of the adrenal cortex by cell-mediated immune mechanisms. Antibodies against steroid 21-hydroxylase are detected in about 85% of patients with idiopathic primary adrenal insufficiency,[16] but only rarely in patients with other causes of adrenal insufficiency.[35] In addition, other autoantigens, including steroid 17α-hydroxylase and the cholesterol side-chain cleavage enzyme, have been identified in patients with autoimmune Addison's disease, as well as patients with primary ovarian failure.[32,36] T cells and cellular immunity also have important roles in the pathogenesis of autoimmune Addison's disease, and the generation of

	Pathogenetic mechanisms	Clinical manifestations in addition to adrenal insufficiency
Autoimmune adrenalitis		
Isolated	Associations with HLA-DR3-DQ2, HLA-DR4-DQ8, MICA, CTLA-4, PTPN22, CIITA, CLEC16A, vitamin D receptor	None
APS type 1 (APECED)	*AIRE* gene mutations	Chronic mucocutaneous candidosis, hypoparathyroidism, other autoimmune diseases
APS type 2	Associations with HLA-DR3, HLA-DR4, CTLA-4	Thyroid autoimmune disease, type 1 diabetes, other autoimmune diseases
APS type 4	Associations with HLA-DR3, CTLA-4	Other autoimmune diseases (autoimmune gastritis, vitiligo, coeliac disease, alopecia), excluding thyroid disease and type 1 diabetes
Infectious adrenalitis		
Tuberculous adrenalitis	Tuberculosis	Tuberculosis-associated manifestations in other organs
AIDS	HIV-1	Other AIDS-associated diseases
Fungal adrenalitis	Histoplasmosis, cryptococcosis, coccidioidomycosis	Opportunistic infections
Syphilis	*Treponema pallidum*	Other syphilis-associated organ involvement
African trypanosomiasis[27]	*Trypanosoma brucei*	Other trypanosomiasis-associated organ involvement
Bilateral adrenal haemorrhage	Meningococcal sepsis (Waterhouse-Friderichsen syndrome), primary antiphospholipid syndrome	Symptoms and signs of underlying disease
Bilateral adrenal metastases	Mainly cancers of the lung, stomach, breast, and colon	Disease-associated clinical manifestations
Bilateral adrenal infiltration	Primary adrenal lymphoma, amyloidosis, haemochromatosis	Disease-associated clinical manifestations
Bilateral adrenalectomy	Unresolved Cushing's syndrome, bilateral adrenal masses, bilateral phaeochromocytoma	Symptoms and signs of underlying disease
Drug-induced adrenal insufficiency		
Anticoagulants (heparin, warfarin), tyrosine-kinase inhibitors (sunitinib)	Haemorrhage	None, unless related to drug
Aminoglutethimide	Inhibition of P450 aromatase (CYP19A1)	None, unless related to drug
Trilostane	Inhibition of 3β-hydroxysteroid dehydrogenase type 2	None, unless related to drug
Ketoconazole, fluconazole, etomidate	Inhibition of mitochondrial cytochrome P450-dependent enzymes (eg, CYP11A1, CYP11B1)	None, unless related to drug
Phenobarbital	Induction of P450-cytochrome enzymes (CYP2B1, CYP2B2), which increase cortisol metabolism	None, unless related to drug
Phenytoin, rifampicin, troglitazone	Induction of P450-cytochrome enzymes (mainly CYP3A4), which increase cortisol metabolism	None, unless related to drug

(Table 1 continues on next page)

	Pathogenetic mechanisms	Clinical manifestations in addition to adrenal insufficiency
(Continued from previous page)		
Genetic disorders		
Adrenoleukodystrophy or adrenomyeloneuropathy	*ABCD1* and *ABCD2* gene mutations	Weakness, spasticity, dementia, blindness, quadriparesis. Adrenomyeloneuropathy is a milder variant of adrenoleukodystrophy with slower progression
Congenital adrenal hyperplasia		
21-hydroxylase deficiency	*CYP21A2* gene mutations	Hyperandrogenism
11β-hydroxylase deficiency	*CYP11B1* gene mutations	Hyperandrogenism, hypertension
3β-hydroxysteroid dehydrogenase type 2 deficiency	Mutations in 3β-*HSD2* gene	Ambiguous genitalia in boys, postnatal virilisation in girls
17α-hydroxylase deficiency	*CYP17A1* gene mutations	Pubertal delay in both sexes, hypertension
P450 oxidoreductase deficiency	Mutations in gene for P450 oxidoreductase	Skeletal malformation (Antley-Bixler syndrome), abnormal genitalia
P450 side-chain cleavage deficiency	*CYP11A1* gene mutations	XY sex reversal
Congenital lipoid adrenal hyperplasia	*StAR* gene mutations	XY sex reversal
Smith-Lemli-Opitz syndrome	*DHCR7* gene mutations	Craniofacial malformations, mental retardation, growth failure, hyponatraemia, hyperkalaemia, cholesterol deficiency
Adrenal hypoplasia congenita		
X-linked	*NR0B1* gene mutations	Hypogonadotropic hypogonadism in boys
Xp21 contiguous gene syndrome	Deletion of genes for Duchenne muscular dystrophy, glycerol kinase, and *NR0B1*	Duchenne muscular dystrophy, glycerol kinase deficiency, psychomotor retardation
SF-1 linked	*NR5A1* gene mutations	XY sex reversal
IMAGe syndrome	*CDKN1C* gene mutations	Intrauterine growth retardation, metaphyseal dysplasia, adrenal hypoplasia congenita and genital abnormalities
Kearns-Sayre syndrome	Mitochondrial DNA deletions	External ophthalmoplegia, retinal degeneration, cardiac conduction defects, other endocrine disorders
Wolman's disease	*LIPA* gene mutations	Bilateral adrenal calcification, hepatosplenomegaly
Sitosterolaemia (also known as phytosterolaemia)	*ABCG5* and *ABCG8* gene mutations	Xanthomata, arthritis, premature coronary artery disease, short stature, gonadal and adrenal failure
Familial glucocorticoid deficiency or corticotropin insensitivity syndromes		
Type 1	*MC2R* gene mutations	Hyperpigmentation, tall stature, characteristic facial features, such as hypertelorism and frontal bossing, lethargy and muscle weakness but normal blood pressure
Type 2	*MRAP* gene mutations	Hyperpigmentation, normal height, hypoglycaemia, lethargy, and muscle weakness, but normal blood pressure
Variant of familial glucocorticoid deficiency	*MCM4* gene mutations	Growth failure, increased chromosomal breakage, natural killer cell deficiency
Primary generalised glucocorticoid resistance or Chrousos syndrome[28–31]	Generalised, partial, target-tissue insensitivity to glucocorticoids	Fatigue, hypoglycaemia, hypertension, hyperandrogenism
Triple A syndrome (Allgrove's syndrome)	*AAAS* gene mutations	Achalasia, alacrima, deafness, mental retardation, hyperkeratosis

APS=autoimmune polyendocrinopathy syndrome. CTLA-4=cytotoxic T-lymphocyte antigen 4. ABCD=ATP-binding cassette, subfamily D. StAR=steroidogenic acute regulatory protein. DHCR7=7-dehydrocholesterol reductase. ABCG5=ATP-binding cassette, subfamily G, member 5. ABCG8=ATP-binding cassette, subfamily G, member 8. MC2R=melanocortin 2 receptor. MRAP=melanocortin 2 receptor accessory protein. MCM4=minichromosome maintenance complex component 4. AAAS=achalasia, adrenocortical insufficiency, alacrima syndrome.

Table 1: **Causes of primary adrenal insufficiency**

autoantibodies can be secondary to tissue destruction (figure 1).[37,38] Furthermore, several genes that confer susceptibility to autoimmune Addison's disease have been identified. In addition to the MHC haplotypes DR3-DQ2 and DR4-DQ8, cytotoxic T-lymphocyte antigen 4, protein tyrosine-phosphatase non-receptor type 22, and the MHC class II transactivator have been associated with the condition.[32–35,39–41] Now that large genome-wide screening projects are feasible, new susceptibility genes are likely to be identified in the near future.[32–35]

Primary adrenal insufficiency can also present in the context of autoimmune polyendocrinopathy syndromes. Autoimmune polyendocrinopathy syndrome type 1, which is also known as APECED (autoimmune polyendocrinopathy, candidosis, ectodermal dystrophy) syndrome, is a rare, autosomal recessive disorder caused by mutations in the autoimmune regulator (*AIRE*) gene.[32,42] It is most common among particular population groups—people from Sardinia and Finland and Iranian Jews—and is characterised by chronic mucocutaneous candidosis, adrenocortical insufficiency, hypoparathyroidism, hypoplasia of the dental enamel, and nail dystrophy; other autoimmune disorders, such as type 1 diabetes and pernicious anaemia, can develop later in life.[42,43] Antibodies

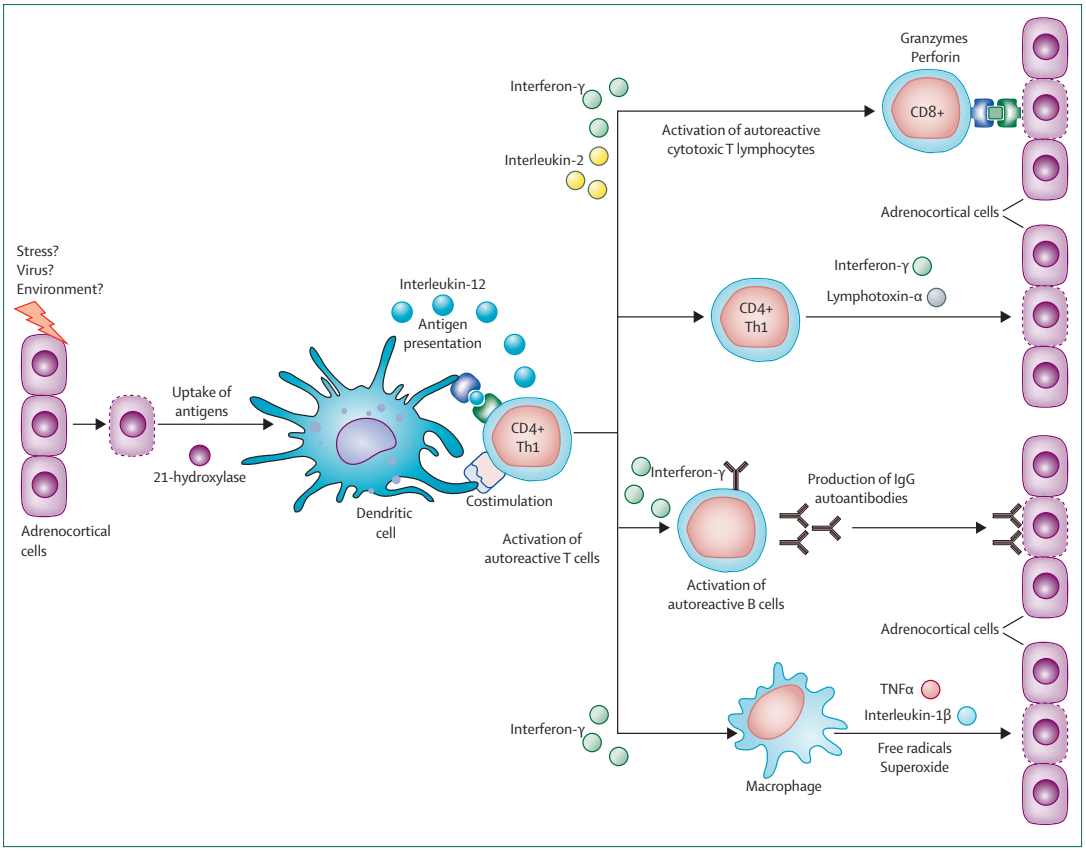

Figure 1: **Molecular immunopathogenesis of primary adrenal insufficiency**
A persistent subclinical viral infection or an aberrant response to inflammatory stressors could cause adrenocortical cell apoptosis or necrosis, leading to dendritic-cell activation by cellular components, including peptides derived from 21-hydroxylase. After activation, dendritic cells transport and present adrenocortical antigens to CD4-positive T-helper-1 (Th1) cells within the local draining lymph node. Activated specific CD4-positive Th1 cells could provide help for the activation and clonal expansion of cytotoxic lymphocytes and autoreactive B cells producing anti-21-hydroxylase and other antibodies. The continuing progressive destruction of adrenal cortex is mediated by several different mechanisms: direct cytotoxicity by apoptosis-inducing cytotoxic lymphocytes via perforin and granzyme B or by the FasL-Fas pathway; direct cytotoxicity by interferon-γ and lymphotoxin-α secreted by CD4-positive Th1 cells; autoantibody-induced activation of the complement system or antibody dependent cellular cytotoxicity; cytotoxic effects of inflammatory cytokines (tumour necrosis factor-α [TNFα], interleukin-1β) and free radicals (nitric oxide, superoxide) released by monocytes and macrophages or by the adrenocortical cells themselves.

against interferon-ω and interferon-α are both sensitive and specific for type 1 autoimmune polyendocrinopathy syndrome, and mutational analysis of the *AIRE* gene confirms the diagnosis in more than 95% of cases.[44] Type 2 autoimmune polyendocrinopathy syndrome is characterised by autoimmune adrenal insufficiency and autoimmune thyroid disease, with or without type 1 diabetes; it is more prevalent than the type 1 form. It is often associated with other autoimmune conditions, affects women more commonly than men, and generally presents in the fourth decade of life.[32–34,43,45,46] Autoimmune polyendocrinopathy syndrome type 4 is a rare syndrome characterised by the association of autoimmune Addison's disease with one or more minor component autoimmune diseases (eg, hypogonadism, atrophic gastritis, pernicious anaemia, coeliac disease, myasthenia gravis, vitiligo, alopecia, and hypophysitis) but excluding the major component disease characteristics of types 1 and 2 (chronic candidosis, hypoparathyroidism, thyroid autoimmune diseases, type 1 diabetes).[45]

Table 1 lists several infectious, drug-induced, and other causes of primary adrenal insufficiency, then genetic disorders. Of the genetic causes, adrenoleukodystrophy, is an X-linked recessive disorder that affects one in 20 000 men and boys and is caused by mutations in the ATP-binding cassette, subfamily D, member 1 (*ABCD1*) gene. These mutations prevent normal transport of very-long-chain fatty acids into peroxisomes, thereby preventing their β-oxidation and breakdown. Accumulation of abnormal amounts of these fatty acids in affected organs (CNS, Leydig cells of the testes, adrenal cortex) is thought to be the underlying pathological process. The clinical features include neurological impairment resulting from white-matter demyelination

and primary adrenal insufficiency, which presents in infancy or childhood. The two major forms of adrenoleukodystrophy are the cerebral form (50% of cases; early childhood manifestation with rapid progression) and adrenomyeloneuropathy (35% of cases; onset in early adulthood with slow progression) in which demyelination is restricted to the spinal cord and peripheral nerves. Since adrenal insufficiency can be the initial clinical manifestation, adrenoleukodystrophy should be considered in young male patients with adrenal insufficiency and confirmed biochemically by measurement of plasma concentrations of very-long-chain fatty acids.[1–3,47]

Primary adrenal insufficiency occasionally presents acutely as a consequence of bilateral adrenal haemorrhage in patients with antiphospholipid syndrome. It is characterised by recurrent arterial and venous thrombosis, complications during pregnancy, and the presence of autoantibodies to phospholipids. The condition can be isolated or manifest in the context of connective tissue disorders or malignant disorders.[48,49]

In children, the most common cause of primary adrenal insufficiency is congenital adrenal hyperplasia, a group of autosomal recessive disorders resulting from deficiency of one of the enzymes needed for synthesis of cortisol in the adrenal cortex. The most common form is classic 21-hydroxylase deficiency, a condition characterised by low synthesis of glucocorticoids and, in many cases, mineralocorticoids, adrenal hyperandrogenism, and impaired development and function of the adrenal medulla.[50–52] More rare forms are caused by deficiency of 11β-hydroxylase, 17α-hydroxylase, 17,20-lyase, 3β-hydroxysteroid dehydrogenase, or P450 oxidoreductase.

Central adrenal insufficiency

Secondary adrenal insufficiency results from any process that involves the pituitary gland and interferes with corticotropin secretion (table 2). The corticotropin deficiency can be isolated or can occur in association with deficiencies of other pituitary hormones. Isolated corticotropin deficiency generally results from an autoimmune process, as shown by the frequent association with other autoimmune endocrine disorders (thyroiditis, type 1 diabetes).[53,54] Genetic causes of corticotropin deficiency include loss-of-function mutations in the genes encoding pro-opiomelanocortin gene and proprotein convertase subtilisin or kexin type 1 inhibitor, which also result in early-onset severe obesity,[53,55] as well as mutations in TPIT, a T-box factor that controls transcription of the pro-opiomelanocortin gene in corticotrophs only.[53,56]

Tertiary adrenal insufficiency results from processes that involve the hypothalamus and interfere with secretion of corticotropin-releasing hormone, arginine vasopressin, or both (table 3). Suppression of the hypothalamic-pituitary-adrenal (HPA) axis by long-term administration of high doses of glucocorticoids is the most common cause. Therefore, in most cases, slow withdrawal of glucocorticoid treatment over 9–12 months is needed for full recovery of the HPA axis.[26,57–59] Tertiary adrenal insufficiency also occurs in patients cured of Cushing's syndrome, since the persistently high serum cortisol concentrations before treatment suppress the HPA axis in the same way as high exogenous doses of glucocorticoids.[60–63] Finally, drugs such as mifepristone, a glucocorticoid receptor antagonist, antipsychotics, and antidepressants cause target-tissue resistance to glucocorticoids through impairment of glucocorticoid signal transduction.[60]

Pathophysiology and clinical presentation

The adrenal cortex has three distinct zones, which secrete the various hormones under the direct control of well understood feedback mechanisms. Aldosterone is synthesised in the outermost zone, the zona glomerulosa. Its secretion is predominantly regulated by the renin–angiotensin system and extracellular potassium concentrations; therefore, it is not impaired in secondary and tertiary adrenal insufficiency. Cortisol secretion from the zona fasciculata is primarily regulated by corticotropin, which is released from the anterior pituitary in response to the hypothalamic neuropeptides corticotropin-releasing hormone and arginine vasopressin.[50,60,64] In healthy people, cortisol secretion is pulsatile, and circulating cortisol concentrations fluctuate naturally in a circadian fashion, highest in the early morning (0600–0800 h) and lowest around midnight.[60,64–67] The adrenal androgens, androstenedione, dehydroepiandrosterone, and the sulphate ester of dehydroepiandrosterone, are synthesised in the innermost zona reticularis.[50] Dehydroepiandrosterone and its sulphate show a characteristic, age-associated pattern, with very high concentrations in the neonatal period, a decline to very low concentrations during the first few months of life, and a continuous increase starting between age 6 and 10 years, termed adrenarche. Peak concentrations of these two hormones are achieved during the third decade of life; they then decline steadily from the fifth decade (adrenopause) with concentrations decreasing to 10–20% of the maximum at around age 70 years. The age-related decline in dehydroepiandrosterone sulphate does not reflect a general loss of adrenocortical output because cortisol concentrations are maintained and even slightly rise with age.[50,68]

The clinical manifestations of primary adrenal insufficiency (table 4) result from deficiency of all adrenocortical hormones (aldosterone, cortisol, androgens); they can also include signs of other concurrent autoimmune conditions. Most of the symptoms are non-specific and can delay diagnosis and treatment of the condition. Hypoglycaemia can be the presenting sign in children with adrenal insufficiency, and it can lead to deterioration of glycaemic control and

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