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REVIEW

Epidemiology, pathogenesis, and diagnosis of Addison's disease in adults

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Abstract

Background Addison's disease (AD) is a rare disorder and among adult population in developed countries is most commonly caused by autoimmunity. In contrast, in children genetic causes are responsible for AD in the majority of patients.

Purpose This review describes epidemiology, pathogenesis, genetics, natural history, clinical manifestations, immunological markers and diagnostic strategies in patients with AD. Standard care treatments including the management of patients during pregnancy and adrenal crises consistent with the recent consensus statement of the European Consortium and the Endocrine Society Clinical Practice Guideline are described. In addition, emerging therapies designed to improve the quality of life and new strategies to modify the natural history of autoimmune AD are discussed.

Conclusions Progress in optimizing replacement therapy for patients with AD has allowed the patients to lead a normal life. However, continuous education of patients and health care professionals of ever-present danger of adrenal crisis is essential to save lives of patients with AD.

Keywords Addison's disease · Primary adrenal insufficiency · Natural history of Addison's disease · Autoimmune polyendocrine syndromes · Therapy of Addison's disease

History

In 1563 one of the greatest anatomist of the Renaissance period, Bartolomeo Eustachius described the adrenals for the first time as "*de glandulis quae renibus incumbunt*" [1]. Three hundred years later, in 1855, Thomas Addison at Guy's Hospital in London described the symptoms and signs observed in 11 patients who died from a disease of the adrenals "*anaemia… fleebleness of the heart action… a peculiar change of color in the skin occurring in connection with a diseased condition of the suprarenal capsules defining this disorder melasma suprarenale*" [2]. In his report, Addison demonstrated that the adrenals in six of these patients were affected by tuberculosis, in three by cancer, by hemorrhage in one, and by idiopathic fibrosis in one. In the case of idiopathic fibrosis, he noted that "*The two adrenals together weighed 49 grains, they appeared exceedingly small and atrophied, so that the diseased condition did not result as usual from a deposit either of a strumous or malignant character, but appears to have been occasioned by an actual inflammation, that inflammation having destroyed the integrity of the organs, which finally led to their contraction and atrophy*". Almost certainly, this was the first published description of an autoimmune adrenalitis and of a multiple autoimmune syndrome, as the patient also presented with vitiligo [2]. In 1856, Trousseau termed the adrenal insufficiency as "*bronze Addison's disease*" [3] which later has become known widely as Addison's disease (AD).

Epidemiology

AD is a rare condition [4–6]. The reported prevalence in Europe has been increasing over time from 39 cases/million in England in 1968 [7], 60 in Denmark in 1974 [8], 93 in Coventry (UK) in 1992 [9], 110 in Nottingham (UK) in 1993 [10], 117 in Italy in 1996 [11] to 144 in Norway

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in 2007 [12] and 131 in Sweden in 2009 [13]. The highest prevalence has been reported in Iceland in 2016, with 221 cases/million [14]. Data from other parts of the world are sparse and report generally lower occurrence; for example, in Japan the prevalence is of 5 cases/million, 37% of which caused by tuberculosis [15].

The estimated incidence of AD in Europe range from 4.4 to 6.2 new cases/million/year in different studies [10, 12, 16].

Etiology and pathogenesis

The predominant cause of AD in Europe has varied over time. Tuberculosis (TBC-AD) was the most common cause (70%) during the 1930s [17] while subsequently, due to advancements in TBC prevention and management, decreased in the 1960s in the UK to 31% [7], to 17% in Denmark in 1970s [8], and most recently reported in only 3% of cases in Italy [6]. However, over the last seven decades, the overall prevalence of AD in industrialized countries has increased worldwide. For example, in Italy AD prevalence increased from 53% in the 1960s to 83.7% in more recent years [6]. At present, autoimmunity is the predominant cause of AD in Europe accounting for 75–96% of all the cases [6, 12, 18, 19] with TBC-AD accounting for 10—15% and other rare causes for only 5% [6, 18, 20]. In view of the substantial decrease of TBC-AD and the unchanged prevalence of the other non-autoimmune causes, the overall increased prevalence of AD represents a real increase of the autoimmune form [21].

The prevalence of the various forms of AD differs depending on patient geographical provenance and among adult or pediatric subjects. For example, 96% of Norwegian patients had autoimmune AD (AAD) [12]. Among South African patients with AAD 51% were of European origin, while none of the Asian or Black African patients had evidence of AAD [22]. In a recent survey of Swedish patients with AD, 83.3% had AAD [19]. In adult patients with AD in Padua, 77.7% of cases were attributed to autoimmunity, 9.0% to TBC, 4.6% to genetic forms, 1.6% to cancer, 1% to bilateral adrenalectomy, 0.6% to vascular disorders, 0.5% to other infections; while in 5.0%, the etiology was not established [6]. In children, by contrast, two studies performed in Canada [23] and in Turkey [24] reported that the great majority of AD was caused by genetic disorders (81–82%). Recent epidemiological study reported increased incidence and prevalence of AD in patients with type 1 diabetes mellitus (DM-1) in Sweden. The incidence of AD in patients with DM-1 was tenfold higher compared to healthy population, with two annual peaks in February–March and September–October. Furthermore, adrenal failure developed at a younger age [16]. In addition to AAD, several other disorders may induce adrenal gland insufficiency, including infections, causes related to vascular, neoplastic, infiltrative, dysmetabolic, or granulomatous diseases. Less frequently, use of some medicines or surgical procedures may lead to adrenal damage. A detailed list of different causes of AD is presented in Table 1.

Autoimmune Addison's disease (AAD)

AAD occurs more frequently in women and may present at any age, although most often develops between 30 and 50 years of age [6, 12, 19, 25]. About two-thirds of patients with AAD present with or may go on to develop other autoimmune diseases in the context of an autoimmune polyendocrine syndrome (APS) including autoimmune thyroid disease (AITD), autoimmune gastritis, DM-1, premature ovarian failure (POF), vitiligo, or coeliac disease (Table 1) [26]. In England, 58% of patients with AAD had associated hypothyroidism, 29% pernicious anemia, and 10% DM-1 [27]. Among Norwegian patients with AAD, 88% had one or more additional autoimmune diseases and only 12% had the isolated AAD [12]. In Swedish patients with AAD, 41.7% had hypothyroidism, 22.2% pernicious anemia, 11% DM-1, 9.5% hyperthyroidism, 6.3% gonadal failure, 4.8% vitiligo, 3.2% celiac disease, 1.6% alopecia and 6.3% other autoimmune disorders [19]. Similarly, 88.6% of Italian AAD patients had one or more additional autoimmune diseases [6].Based on the different combinations of associated autoimmune diseases, the patients with AAD can be grouped into APS-1, APS-2 or APS-4 according to previously published classifications [18, 28, 29] as summarized in Table 2.

Autoimmune polyendocrine syndrome type 2 (APS-2)

AAD most commonly presents in the context of APS-2 in association with AITD and/or DM-1. In addition, other autoimmune diseases (POF, gastritis, vitiligo, alopecia, hepatitis, hypophysitis, celiac disease, etc.) can be present in up to 11% of patients [18, 28–33]. APS-2 is linked to Class II HLA antigens [34, 35], specifically to HLA-DRB1*03-DQA1*0501-DQB1*0201(DR3/DQ2) and DRB1*0404-DQA1*0301 DQB1*0302(DR4.4/DQ8) haplotypes. There is also an association between AAD and the class I HLA MIC-A 5.1 allele [36]. Other gene polymorphisms contribute to the genetic risk for AAD, including CIITA (class II HLA trans-activator), cytotoxic T-lymphocyte antigen-4 (CTLA4), PTPN22, STAT4, NLRP1, PD-L1, NALP1, FCRL3, GPR174, GATA3, NFATC1, CYP27B1 and the vitamin D receptor [37–39]. In an Italian survey, out of all patients with AAD, 65.6% presented with APS-2 and AAD

Table 1 Classification of primary adrenal failure (Addison's disease) based on the etiology

Autoimmune	Isolated
Isolated or as a part of autoimmune polyglandular syndromes (APS)	APS-1 (associated with chronic candidiasis and/or chronic hypoparathyroidism) APS-2 (associated with autoimmune thyroid diseases and/or type 1 diabetes mellitus) APS-4 (associated with other autoimmune diseases)
Infectious	Tuberculous: *Mycobacterium hominis*, *Mycobacterium avium* Bacterial: *Neisseria meningitidis*, *Pseudomonas aeruginosa*, *Haemophilus influenza*, *Pasteurella multocida*, *Streptococci*, *Treponema pallidum*, *Escherichia coli* Fungal: *Pneumocystis carinii*, *Histoplasma capsulatum*, *Blastomyces dermatitidis*, *Paracoccidioides brasiliensis*, *Coccidioides immitis*, *Cryptococcus neoformans*, *Candida albicans* Parasitic: *Toxoplasma gondii*, *African trypanosomiasis* Viral: Human immunodeficiency virus, Cytomegalovirus, Herpes simplex virus, Echovirus type 11 and 12.
Infiltrative, dysmetabolic and granulomatous	Amyloidosis Hemochromatosis Xanthogranulomatosis Histiocytic disorders Sarcoidosis
Genetic and neonatal	Impaired steroidogenesis with congenital adrenal hyperplasia (CAH) 21-hydroxylase deficiency (*CYP21A2* mutation) 11β-hydroxylase deficiency (*CYP11B1* mutation) 3β-hydroxysteroid dehydrogenase type 2 deficiency (*HSD3B2* mutation) 17α-hydroxylase deficiency (*CYP17A1* mutation) P450 oxidoreductase deficiency (*POR* mutation) P450 side-chain cleavage deficiency (*CYP11A1* mutation) Aldosterone synthase deficiency (*CYP11B2* mutation) Cortisone reductase deficiency (*HSD11B1* mutation) Apparent cortisone reductase deficiency (*H6PDH* mutation) Congenital lipoid adrenal hyperplasia (CLAH) Disruption of the activity of the steroidogenic acute regulatory protein (*StAR*) responsible for rapid cholesterol transport into the mitochondrion Bilateral congenital adrenal hypoplasia or adrenal dysgenesis X-linked adrenal hypoplasia congenita (*NR0B1*/dosage-sensitive sex reversal X-linked gene 1 or *DAX-1* mutation) Steroidogenic factor 1 deficiency (*NR5A1* encoding or *SF-1* mutation) IMAGe syndrome (*CDKN1C* encoding cyclin-dependent kinase inhibitor 1C gene mutation) MIRAGE syndrome (*SAMD9* mutation) Pallister–Hall syndrome (*GLI3* mutation) Meckel syndrome (*MKS1* mutation) Pena–Shokeir syndrome (*DOK7, RAPSN* mutation) Pseudotrisomy 13 Hydrolethalus syndrome (*HYLS1* mutation) Galloway–Mowat syndrome (*WDR73* mutation) Familial glucocorticoid deficiency (FGD) and FGD-like conditions FGD type 1 (*MC2R* encoding the ACTH receptor or melanocortin 2 receptor mutation) FGD type 2 (*MRAP* encoding the MC2R-ancessory protein responsible for translocation of the ACTH receptor to the membrane mutation) FGD type 3 (*StAR* mutation, see CLAH) FGD type 4 (*NNT* encoding nicotinamide nucleotide transhydrogenase mutation) FGD-DNA repair defect *(MCM4* mutation, natural killer cell and glucocorticoid deficiency with DNA repair defect) Congenital adrenal destruction (e.g., adrenoleukodystrophy, adrenomyeloneuropathy, adrenal calcification, adrenalitis) *ABCD1* or *ABCD2* genes encoding for a peroxisomal membrane transporter protein, X-linked *PEX* 1 (neonatal adrenoleukodystrophy) *LIPA* gene mutation (bilateral adrenal calcification) *AIRE* gene mutation (lymphocyte autoimmune adrenalitis) ACTH receptor mutation (ACTH-R gene) Kearns–Sayre syndrome (mitochondrial DNA deletions) Cholesterol synthesis disorders Wolman disease (*LIPA* mutations) Smith–Lemli–Opitz syndrome (*DHCR7* mutations) Abeta-lipoproteinemia (*MTP* mutation) Familial hypercholesterolemia (*LDRL* gene mutation) Sitosterolemia (*ABCG5* gene mutation) Metabolic lysosomal disorders Sphingosine-1-phosphate lyase 1 deficiency (SPGL1 gene mutation) Triple A syndrome or Allgrove's syndrome (Triple A gene *AAAS* encoding WD-repeat protein *ALADIN*) Zellweger syndrome (PEX1 and other PEX genes mutation) Infantil Refsum disease (PHYH and PEX7 genes mutations) Maternal Cushing's syndrome (transient adrenal deficiency due to foetal pituitary–adrenal axis suppression) Autoimmune Polyglandular Syndrome type 1 (*AIRE* gene mutation, see above)

Table 1 (continued)

Vascular	Traumas Polyarteritis nodosa Systemic lupus erythematosus Primary antiphospholipid syndrome Waterhouse–Friderichsen syndrome (sepsis associated to *Meningococcus*, *Pneumococcus*, *Escherichia coli*, *Haemophilus* infections) Thrombocytopenia Treatment with anticoagulants (vitamin K antagonists, heparin, fondaparinux)
Pharmacological	Adrenolytic drugs Aminoglutethimide Trilostane Mitotane (o,p-ddd) Metyrapone Anticancer agents Tyrosine kinase inhibitors (sunitinib, imatinib) Immune check-point inhibitors: cytotoxic T-lymphocyte antigen-4 receptor (ipilimumab, tremelimumab) or Programmed death-1 receptor pathway (nivolumab, pembrolizumab) Other drugs Ketoconazole Fluconazole Etomidate Rifampicin Ciproterone acetate
Neoplastic	Bilateral primary cancer Lymphomas Bilateral adrenal metastasis Usually originating from lymphomas or solid-organ tumors (lung, breast, colon cancers and melanomas)
Surgical	Bilateral adrenalectomy for: Cushing's disease Bilateral pheochromocytoma Macronodular adrenal hyperplasia Primary pigmented nodular adrenocortical disease

developed at a mean age of 34.6 years (range 1–85), with female/male ratio of 2.3/1 and adult/children ratio of 16/1 (Table 2) [6].

Autoimmune polyendocrine syndrome type 1 (APS-1)

APS-1, which stands for Autoimmune-Poly-Endocrine-Candidiasis-Ectodermal-Dystrophy (APECED) syndrome [40], is a rare disorder characterized by combination of multiple autoimmunities presenting with at least two of the three main components: chronic candidiasis (CC), chronic hypoparathyroidism (CH) and AAD. Other autoimmune (POF, gastritis, AITD, vitiligo, alopecia, DM-1, intestinal dysfunction, hepatitis, hypophysitis) and non-autoimmune disorders (gall-bladder lithiasis, asplenia) or ectodermal dystrophy can be present in up to 31% of patients [18, 41–45]. Autoimmune diseases in APS-1 are manifested by respective autoantibodies detectable in patients' sera. Autoantibodies to NACHT leucine-rich repeat protein 5 (NALP-5Abs) and to calcium-sensing receptor (CaSRAbs) are found in CH, autoantibodies to 21-hydroxylase (21-OHAbs) in AAD, autoantibodies to side-chain cleavage enzyme (SCCAbs) or to steroid 17α-hydroxylase (17α-OHAbs) in POF, autoantibodies to tryptophane hydroxylase (TPHAbs) or L-glutamic acid decarboxylase (AADC) in autoimmune gastrointestinal dysfunction [42]. Moreover, 85–100% of the patients have autoantibodies to IFNsAbs [46–48]. APS-1 is a very rare, not sex-linked, monogenic, recessive disorder, characterized by mutations of Auto-Immune Regulator (AIRE) gene [33, 42]. In the thymus, AIRE gene is involved in immune tolerance by mediating the expression of many tissue-restricted antigens. When AIRE gene mutation occurs, autoreactive T cells can escape deletion and trigger an autoimmune response [33]. Mutations of AIRE gene result also in production of defective Treg cells at peripheral level leading to development of APS-1 in young individuals [42, 44, 49]. To date, approximately more than hundred different mutations have been found throughout the AIRE gene [44]. As a rule, APS-1 is inherited in autosomal-recessive manner, although dominant AIRE gene mutations have also been reported [50, 51]. There is no evidence of clear associations between genotype and phenotype expression in patients with APS-1 [49]. In our study of Italians patients with APS-1, AAD developed at a mean age of 15 years (range 2–41 years), with a female/male ratio of 2.1/1 and children/adult ratio of 1.5/1.

Homozygous or combined heterozygous AIRE gene mutations were found in 93% of the patients and different types of mutations were detected in patients coming from different regions in Italy [6, 29, 43, 45, 52, 53] (Table 2).

Autoimmune polyendocrine syndrome type 4 (APS-4)

APS-4 is characterized by AAD associated with other autoimmune diseases not included in APS-1 or APS-2, thus with the exclusion of CC, CH, AITD, or DM-1 [18, 29]. In our survey, 8.5% of the patients with AAD presented with APS-4, the mean age at onset of AD was 32 years (range 6–62) with a female/male ratio of 1.2/1 and adult/children ratio of 5.3/1. There was an association with HLA DR3 [6] (Table 2).

Isolated form

Isolated AAD is defined by the absence of other clinical or latent autoimmune diseases. In Italian patients, isolated AAD was determined in 11.4% of the all cases, and it developed at a mean age of 28 years with a male/female ratio of 1.7 [6] (Table 2).

Monitoring for associated autoimmune diseases

The European Expert Consensus [26] and the Endocrine Society [54] suggested that patients with AAD should be screened for thyroid and gastric autoimmunity, DM-1, POF or celiac disease annually. In addition, we suggest that patients with clinically isolated AAD should have other non-adrenal autoantibody status tested at diagnosis and periodically every 2–3 years to monitor for development of associated autoimmunities [6]. Positive patients would be considered at risk of developing subclinical or overt associated autoimmune diseases.

Pathological findings

The volume and weight of the adrenals in AAD may be normal or reduced [55]. Adrenal histology shows lymphocytic infiltration of all the layers of the adrenal cortex with plasma cells, macrophages and fibrosis. Islets of regenerating adrenocortical cells are also found. Immunohistochemistry shows infiltration by activated T lymphocytes. The adrenal medulla is spared, unlike in the other non-autoimmune forms of AD [56].

Family history of AAD and of other autoimmune diseases

In a Norwegian [12] and in a Swedish cohort [19] with AAD, 10% and 6.4% had another family member with AAD, respectively. In our study [6], a family history of AAD was found in 2% of AAD in APS-2 patients and in 25% of those with APS-1 (Table 2). Descriptions of twins with AAD have been rarely reported and in a cohort of 112,100 Swedish twins, there were 29 pairs with AAD. Five of 9 monozygotic pairs (55%) were concordant for AAD compared to none of 15 dizygotic pairs [57].

In the families of patients with AAD, the occurrence of other autoimmune diseases is higher compared to healthy population [21].

Pathogenesis

Adrenal cortex autoantibodies (ACA) were first detected in 1962 [58] by indirect immunofluorescence and for many years were the only markers of AAD [18]. In 1992, 21-OH was identified as the autoantigen [59–61] and subsequently radioimmunoassays (RIA) and ELISA for 21-OHAbs have been developed [62–65]. The prevalence of ACA and 21-OHAbs in our patients with AAD at the onset of the disease is summarized in Table 2. Two International Programs have been carried out for 21-OHAbs standardization assessing the sensitivity and specificity of different assays [66, 67]. 21-OH Abs are excellent markers of adrenal autoimmunity; however, they do not appear to be involved in the pathogenesis of AAD. For example, although 21-OHAbs inhibit 21-OH enzyme activity in vitro [68, 69], they do not have an effect in vivo [70]. However, structural studies have shown that 21-OHAb binding epitope is located close to the reductase binding site on the 21-OH molecule [71, 72]. Furthermore, 21-OHAbs that are of IgG class and can cross placenta do not cause hypoadrenalism in newborns [73]. AAD is a T cell-mediated disease due to cytotoxic effects of $CD8^+$ T lymphocytes infiltration, rather than an autoantibody-mediated disease. Patients with AAD have also an impaired suppressive function of $CD4^+CD25^+$ regulatory T cells [74] and a specific proliferative response of T cells against 21-OH peptide (amino acids 342–361) has been demonstrated in mice immunized with recombinant 21-OH [75]. Another study has shown that specific $CD8^+$ T cells from patients with AAD were able to lyse target cells expressing 21-OH [76]. In AAD, hypothetical pathogenic environmental factors (viral infections, stress, cigarette smoking, pollutants or other not yet defined agents) have been postulated. A hypothetical mechanism of autoimmune aggression against adrenal cortex cells is illustrated in Fig. 1 [77].

Table 2 Main features of autoimmune Addison's disease (AAD) according to the associations with other autoimmune diseases (personal data)

	AAD No. 498, mean age 36 years, range 1–85 years, female/male ratio 2.5			
Subgroups (%)	APS-2 (68%)	APS-1 (12%)	APS-4 (9%)	Isolated (11%)
Female/male ratio	2.3/1	2.1/1	1.2/1	0.6/1
Adult/children ratio	16/1	0.8/1	5/1	3.9/1
Mean age at onset of AAD (range)	34.6 years (1–85)	15.0 years (2–41)	32.0 years (6–62)	28.0 years (3–62)
Class II HLA antigen	DRB1*03/04	Absent	?	DRB1*03
AIRE gene mutation	Absent	93%	Absent	Absent
Family history for autoimmune Addison's disease	2%	25%	2%	2%
Family history for other autoimmune diseases	Present	Present	Present	Present
Main autoimmune diseases				
Chronic candidiasis	Absent	76%	Absent	Absent
Chronic hypoparathyroidism	Absent	90%	Absent	Absent
Autoimmune thyroid diseases (clinical or latent)	93.8%	41%	Absent	Absent
Type 1 diabetes mellitus (clinical or latent)	15.5%	6.0%	Absent	Absent
Autoimmune gastritis (clinical or latent)	12.1%	32%	11.9%	Absent
Premature ovarian failure (clinical or latent)	13.8%	39%	21.7%	Absent
Ectodermal dystrophy	Absent	Present	Absent	Absent
IFNω Autoantibodies	Absent	95.8%	Absent	Absent
Adrenal cortex antibodies (ACA) and/or	88%	90%	95%	94%
21-OHase antibodies at disease onset	93%	92%	100%	100%
Minor autoimmune diseases				
Vitiligo				
Alopecia				
Autoimmune hepatitis				
Hypophysitis	Up to 11%	Up to 31%	67%	Absent
Celiac disease				
Sjogren's syndrome				
Others				

Natural history

AAD is a chronic disease with a long prodromal period marked by the presence of ACA/21-OHAbs. The value of ACA/21OHAbs in predicting AAD was first described in 1983 [78]. They can be found in 30–47% of patients with CH and/or CC, in 5–10% with POF and in 0.5–2.0% with other autoimmune diseases [18, 77, 79–87]. Patients with ACA/21OHAbs should be evaluated by ACTH test using 250 µg of synthetic corticotropin [88]. This simple test can help to identify five stages of adrenocortical impairment [88] (Table 3). Stage 0 is characterized by a normal response to ACTH (potential AAD). Stage 1 is revealed by high plasma renin levels alone and can be considered the "point of no return" towards adrenal insufficiency for patients with APS-1 (Fig. 2). Stage 2 is characterized by increased renin, low aldosterone, normal basal cortisol and ACTH levels, but low cortisol response in ACTH stimulation test and is recognized as the "point of no return" in the progression to adrenal insufficiency for patients with APS2 or APS4 (Fig. 2). Stage 3 is indicated by elevation of ACTH with normal/low basal cortisol levels. Finally, Stage 4 is denoted by very high renin and ACTH levels with markedly low cortisol and aldosterone levels and is associated with the overt symptoms of adrenal failure [89]. The natural history of AAD is summarized in Fig. 2.

Taken together, these observations suggest that the *zona glomerulosa* is first affected or the most susceptible to the autoimmune damage. The *zona fasciculata* is damaged later, probably protected by local release of glucocorticoids or its greater thickness. In some patients, adrenal failure does not progress through these chronological stages and the first abnormality found is an increase of ACTH [90, 91].

One study which included 143 patients followed for 1–33 years suggested that the risk of AAD is very high in patients with APS-1 but low in those with APS-2/APS-4. Patients developed AAD within 19 years from their first autoantibody detection, and after this period the risk was virtually absent [87, 89]. Three independent risk factors for progression to AAD were identified and these included male

gender, stage of hypoadrenalism and type of associated disease. Using this information, an algorithm for estimating the probability of survival free of AAD has also been developed [89].

Non-autoimmune forms

Infectious

The most common infection leading to AD is that with *Mycobacterium tuberculosis* which spreads to adrenals through blood. Adrenal involvement in patients with active TBC was found in 6% at autopsy [92]. TBC-related AD is predominant in older males and overt clinical manifestations may arise many years after the initial infection. However, up to 12% of patients with adrenal TBC may present with asymptomatic infection [93]. AD becomes apparent only when more than 90% of the adrenal glands is destroyed. The early phase of adrenal impairment can be accelerated to overt AD by precipitating factors including stressful events or administration of rifampicin which induces acceleration of cortisol metabolism [93]. The majority of patients with active or recently acquired disease (less than 2 years) have bilateral adrenal enlargement, while calcification and atrophy are typical for longer duration infection or inactive disease [56, 93, 94]. It has been reported that although some patients with acute pulmonary TBC presented with significantly lower basal and stimulated cortisol levels with adrenal enlargement, none developed overt AD. In these patients, cortisol concentrations increased and adrenal enlargement normalized after termination of anti-TBC therapy [95]. The patients with TBC-related AD have positive reaction to tuberculin or to interferon-γ release assays with *Mycobacterium tuberculosis* antigens [96]. In our study of AD patients, 57 patients (9%) had TBC-related AD and the disease occurred at a mean age of 52 years with a male/female ratio of 3/1. In 90% of cases, radiological imaging revealed increased adrenal volume usually with calcifications (Fig. 3b) and all the patients were negative for ACA/21-OHAbs [6].

In addition, infections with *Neisseria meningitides*, *Pseudomonas aeruginosa, Haemophilus influenza, Pasteurella multocida, Staphylococcus aureus* and *Streptococci group A* when associated with septicemia may lead to acute presentation of AD (Waterhouse–Friderichsen syndrome) with bilateral adrenal infarction caused by intravascular coagulation induced by endotoxins. Onset is acute with fever, nausea, myalgia, arthralgia, and erythematous rash which progresses to cutaneous ecchymosis and purpura fulminans [97, 98]. Other bacterial infections (*E. coli* and *group B Streptococci)* of the adrenals are rare and mostly occur in children, sometimes resulting in adrenal abscess. Spreading of the microorganisms to the adrenals is probably via blood supply [97, 99, 100]. The choice of treatment is usually determined by antibiotic susceptibility testing and targeting the bacteria from blood isolates.

Treponema pallidum infection may cause AD with extensive fibrosis and syphilitic gumma formation evident on pathology examination [17, 56].

Pneumocystis jiroveci (formerly carinii) is an opportunistic fungus, inhabiting the lung and infecting immune-compromised individuals and in the case of AD, adrenals appear bilaterally enlarged. The diagnosis should be confirmed by needle biopsy and followed by a standard treatment with trimethoprim–sulfamethoxazole [97, 98, 101]. Further, several fungal pathogens are responsible for infiltration and damage of the adrenals leading to AD. For example, *Histoplasma capsulatum* prevalent in the mid-western and south-central USA causes the disseminated disease commonly affecting immunocompromised subjects [102] but may also occur in immunocompetent hosts [103]. Symptoms include malaise, weight loss, indurated ulcers of the mouth, tongue and nose, fever, and chills. The adrenals are involved in more than 80% of the patients but only 5–10% may develop clinical AD. On CT scans, the adrenals are enlarged with attenuated center [104]. The treatment of choice is with amphotericin B or itraconazole [97]. *Blastomyces dermatitidis* is endemic in the south-eastern and south-central USA. Symptoms may be non-specific and, in general, involve the respiratory tract. The adrenals may be bilaterally enlarged. Cytology is helpful in confirming the pathogenesis, and standard treatment is with itraconazole or amphotericin B [97, 105].

Infections with *Paracoccidioides brasiliensis* (South American Blastomycosis) usually affect the lungs, skin and lymph nodes. Adrenal involvement is also commonly recorded and post-mortem studies revealed that 44–80% of infected patients had bilateral adrenal enlargement with calcifications [97, 106]. Standard treatment with sulfa- or imidazole derivates is indicated in these cases [97]. *Cryptococcus neoformans* is a fungus, commonly present in pigeon excrement. The majority of the affected patients are immunocompromised [107] and present with bilaterally enlarged adrenals on CT scans; while on MNR scans, bilaterally enlarged adrenals are hypointense compared to the liver. Fine needle aspiration may confirm the diagnosis [108]. Recommended treatment includes intravenous amphotericin B, together with flucytosine, followed by fluconazole [97]. A generalized infection with *Candida albicans* can also be a cause of adrenalitis leading to adrenal failure [97]. Fluconazole is the choice for the empirical treatment of disseminated candidiasis, unless a patient is suspected to be infected with an azole-resistant species (i.e., *Candida glabrata*, *Candida krusei*). Medicines with broader species coverage, such as echinocandins, may be preferred for empirical treatment of candidemia [109].

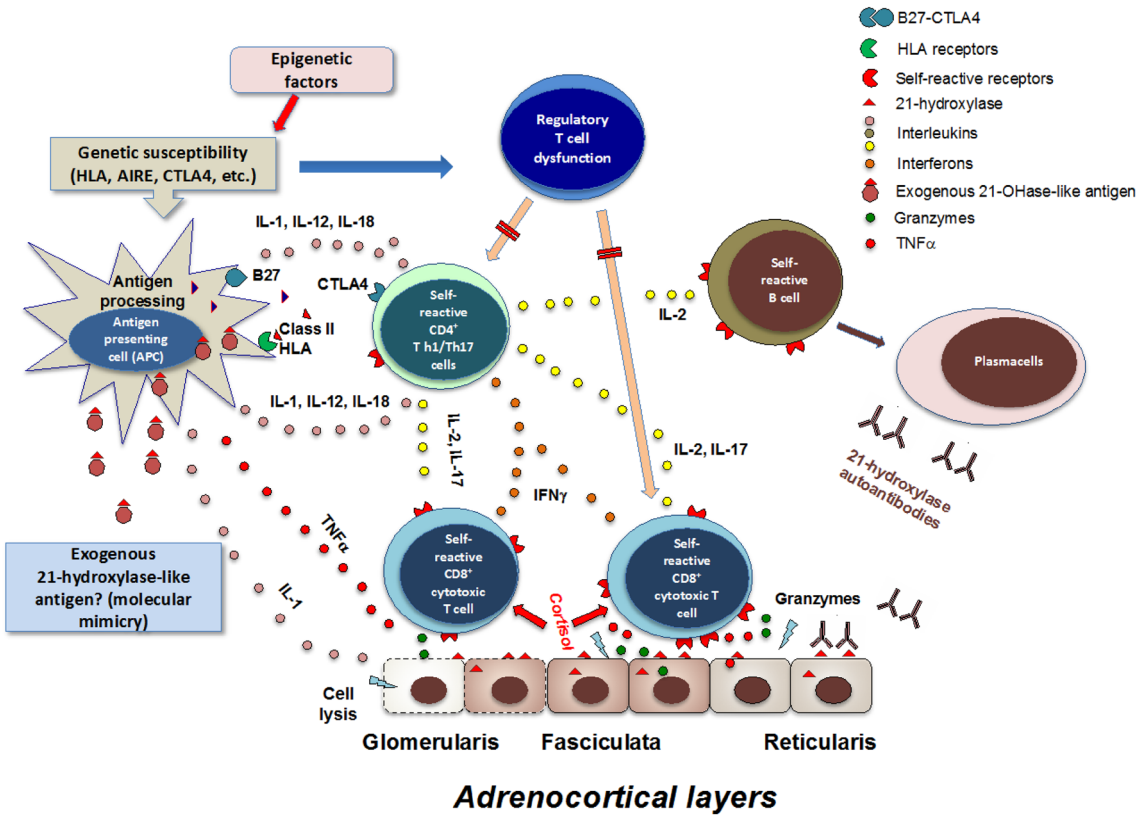

Fig. 1 Hypothetical pathogenesis of autoimmune adrenalitis. A currently unknown exogenous antigen (viruses, bacteria, chemicals) cross reactive with 21-hydroxylase (21-OH) may activate antigen presenting cells (APCs). After antigen uptake, APCs process and present 21-OH-like antigens to CD4+ T-helper 1 and T-helper 17 (Th1/Th17). In turn, T-helper cells promote activation and clonal expansion of cytotoxic T-lymphocytes to exogenous antigen, but also of autoreactive cytotoxic T-lymphocytes (CD8+) and autoreactive B cells which release self-destructive cytokines and steroid 21-OH autoantibodies (21-OHAbs), respectively. This self-reactive process might be allowed by possible deficiency in T-regulatory (T-reg) cells. The progressive destruction of glomerular, fascicular, and reticular cells of adrenal cortex is mediated by cytotoxic T cells through local production of cytokines. 21-OHAbs may also activate the complement system and antibody-dependent cellular cytotoxicity. However, these antibody-mediated mechanisms of damage have been demonstrated in vitro, but not in vivo. Local release of cortisol by zona fasciculata may hamper or delay this process (modified from [77], with permission of the Editor)

AD may occur in patients infected with human immunodeficiency virus [110, 111]. In these patients, AD is usually caused by adrenalitis secondary to opportunistic infections with *Cytomegalovirus*, *Mycobacterium tuberculosis, Pneumocystis jiroveci* or *Cryptococcus neoformans*, by neoplastic invasions of the adrenals, or by a combined side effect of drugs used for therapy of HIV infection (protease inhibitors) and concurrent opportunistic infections for example, rifampicin, ketoconazole and cotrimoxazole [111]. In a study of 192 patients with HIV, only 3 presented with adrenal insufficiency of different causes (one had AD, one had unspecified secondary adrenal insufficiency, and one had iatrogenic AD caused by withdrawal of inhaled steroids) [112]. Infections with *Herpes simplex virus* are rarely associated with AD [17, 113].

Infiltrative, dysmetabolic and granulomatous

In a study of 16 patients with kidney amyloidosis, 46% showed abnormal response to ACTH test and in 30% of patients who died of adrenal crisis amyloid depositions were found in the adrenals [114]. Further studies showed that 20–45% of patients with renal amyloidosis had subclinical AD [115–117].

In patients with haemochromatosis, AD is very rare [118] and the adrenals appear hyperdense on computed tomography [119]. Mutations of the High Iron Fe (HFE) gene of HLA are usually present [118].

Adrenal involvement in the course of sarcoidosis is rare. In a review of 145 patients with sarcoidosis, only one died of an Addisonian crisis [120]. Subsequently, 12 cases of sarcoidosis with AD were described [121–123]. However, 2 patients had adrenal histoplasmosis, one a TBC-AD, other 7

Table 3 Stages of adrenal cortical insufficiency based on the ACTH test in the ACA/21-OHAbs-positive patients

Addison's disease	Stage	ACA and/or 21OHAbs	Lymphocytic adrenalitis	Symptoms	Basal renin	Basal aldosterone	Basal ACTH	Basal cortisol	Cortisol response after i.v. ACTH (250 mcg)
Potential AAD	0	+	±	Absent	Normal	Normal	Normal	Normal	Normal
Subclinical deficiency of mineralocorticoids	1	+	+	Absent	↑	Normal/↓	Normal	Normal	Normal
Subclinical deficiency of mineralocorticoids and impaired reserve of glucocorticoids	2	+	++	Absent	↑	↓	Normal	Normal	Reduced or no response
Subclinical deficiency of both mineralcorticoids and glucocorticoids	3	+	+++	Absent	↑	↓	↑	Normal or at lower limits of normality	No response
Severe deficiency of mineralcorticoids and of glucocorticoids	4	+	++++	Present	↑↑	↓↓	↑↑	↓↓	No response

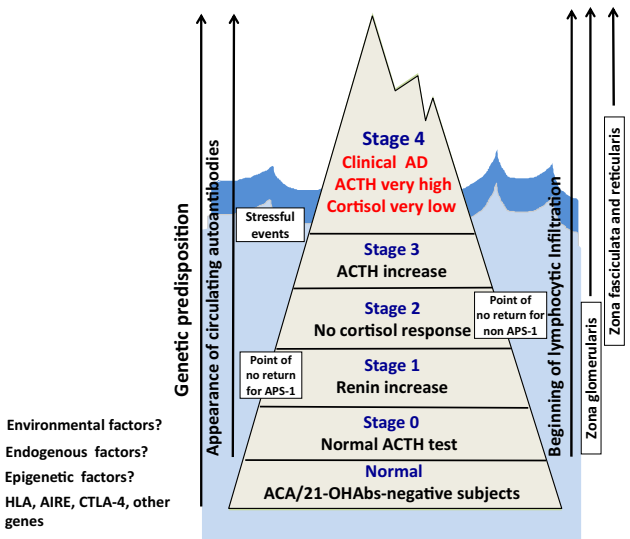

Fig. 2 The natural history of autoimmune Addison's disease in the adult. From subclinical to clinically overt stage

were ACA positive, and in 2 data were not available. Therefore, it is not clear whether sarcoidosis can cause AD.

Genetic

In the great majority of cases, genetic forms of AD are diagnosed in pediatric population [24, 124, 125] and then followed by adult medicine endocrinologists. Approximately, 5% of adult patients with AD are affected by genetic forms diagnosed during childhood. However, sometimes the diagnosis is made in the adulthood, for example, in the case of adrenoleukodystrophy.

In brief, main genetic forms can be classified into four major groups depending on pathogenesis: (1) impaired steroidogenesis with adrenal hyperplasia, (2) bilateral adrenal hypoplasia, (3) familial glucocorticoid deficiency (FGD) and FGD-like disorders, (4) adrenal lesions leading to gland destruction (e.g. adrenomyeloneuropathy, bilateral adrenal calcification) [24]. Among children with AD, 80–90% present with genetic forms [23–25, 30, 124, 126]. The most common cause is the classic or late-onset steroid 21-OH deficiency characterized by low production of glucocorticoids, and in many cases also mineralocorticoids, characterized by adrenal hyperplasia and hyperandrogenism. More rare causes include deficiency of 11β-hydroxylase, 17α-hydroxylase, 3β-hydroxysteroid dehydrogenase, P450 side-chain cleavage deficiency, P450 oxidoreductase, or

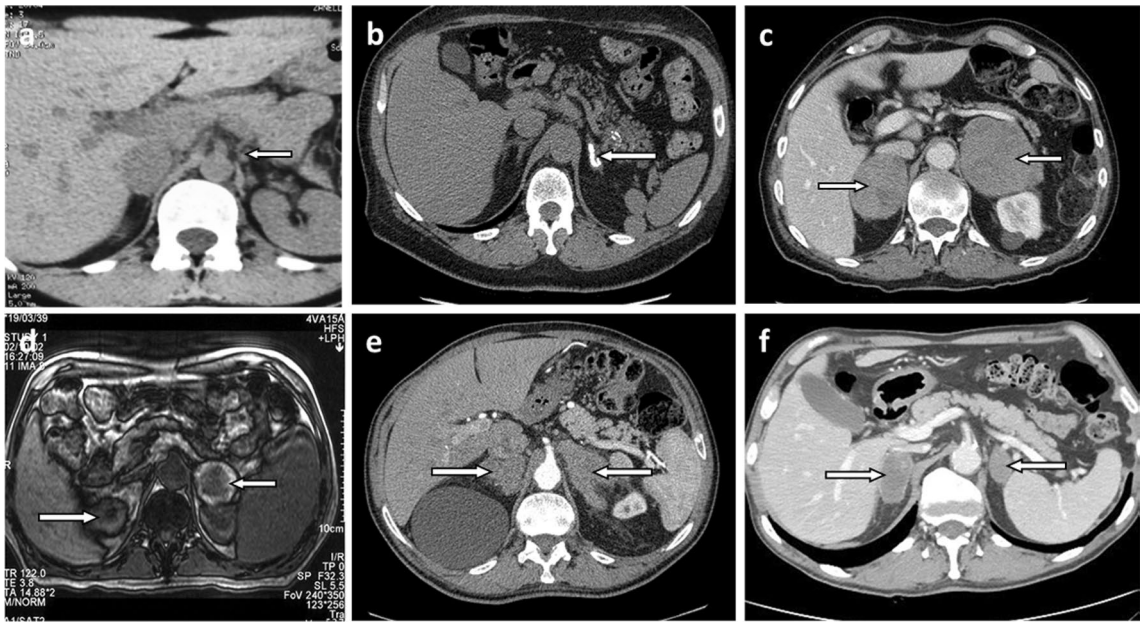

Fig. 3 Images of different cases of adrenal insufficiency (arrows denote abnormal adrenals). **a)** Autoimmune with small-atrophic adrenal glands, **b)** adrenals with calcifications in tuberculous infection, **c)** adrenal enlargement for bilateral primary adrenal lymphoma, **d)** bilateral adrenal hemorrhage in anti-phospholipid syndrome, **e)** adrenal enlargement with bilateral adrenal metastasis of lung cancer, **f)** adrenals with disseminated histoplasmosis

cortisone reductase (see detailed list in Table 1, modified from [125]).

Adrenoleukodystrophy is an inherited X-linked recessive condition due to a metabolic disorder characterized by elevated plasma levels of very long-chain fatty acids (VLCFA) accumulated in the adrenal cortex, brain, and other organs [127]. In a study of 18 Norwegian adult 21-OHAbs-negative men with AD one patient tested positive for VLCFA [128]. Clinical presentations of adrenoleukodystrophy are highly complex with AD being the predominant presentation in childhood (80%) while myelopathy in adulthood. In addition, gonadal function can also be affected. Approximately, 60% of patients develop progressive cerebral white matter lesions with a characteristic pattern on MRI which sometimes precede the symptoms. The adrenals on macroscopic examination are small, of normal shape, weighing from 1 to 2 g [129].

X-linked congenital adrenal hypoplasia (CAH) is a rare disorder characterized by a complete absence of the adrenal cortex accounting for 0.97% of all the causes of primary AD under the age of 18 years. CAH is caused by mutations or complete deletion of the NR0B1 gene (Nuclear Receptor subfamily 0, group B, member 1) that encodes the DAX-1 protein (Dosage-sensitive sex reversal, congenital Adrenal hypoplasia critical region on chromosome X, gene 19), a nuclear receptor expressed in steroidogenic tissues (gonads, adrenals), hypothalamus, and pituitary. CAH is characterized by AD in infancy and early childhood, and later by hypogonadotropic hypogonadism in males at puberty [130].

We found genetic forms of AD in 29 of our patients (4.3%), of whom 24 (all males) had adrenoleukodystrophy with a mean age at disease onset of 18 years (range 1–63). Other patients presented with genetic form of AD included two patients with 21-OH deficiency, one with X-linked CAH with mutation of DAX1, one with POEMS and one with ACTH receptor mutation. ACA and 21-OHAbs were negative in all patients [6].

Vascular

Vascular disorders related to anti-phospholipid syndrome, congenital bilateral hemorrhage, anticoagulation and Waterhouse–Friderichsen syndrome may rarely affect the adrenals and be responsible for AD [6, 131] (Fig. 3). In our observations, only 4 patients (0.6%) presented with vascular disorders: two with anti-phospholipid syndrome with bilateral hemorrhagic infarction of adrenals (Fig. 3d), one with congenital bilateral hemorrhage and one with Waterhouse–Friderichsen syndrome [6].

Drug induced

Several compounds inhibit adrenal steroidogenesis by interfering with the enzymes in the steroidogenic cascade. Ketoconazole, metyrapone, etomidate, and mitotane block

one or more of the enzymes in the cortisol and other steroids synthetic pathways [132] (Table 1). Mitotane inhibits steroidogenesis, but also exhibits adrenolytic activity by inhibiting CYP11B1 (11β-hydroxylase) and cholesterol side-chain cleavage (CYP11A1) enzymes. It is metabolized into an acyl-chloride that binds macromolecules in the mitochondria, causing destruction of adrenocortical cells both in normal adrenals and adrenocortical tumors. This mechanism renders mitotane useful for chemical adrenalectomy in patients with Cushing's disease [132].

Some substances like rifampicin, growth hormone or levothyroxine may induce or worsen AD by increasing cortisol clearance or accelerating cortisol metabolism through stimulation of type 2 11ß-hydroxysteroid dehydrogenases (11ß-HSD2) which inactivates cortisol to cortisone [133, 134].

Kinase inhibitors (KIs) and monoclonal antibodies directed against kinases are an important class of anticancer drugs (sunitinib, imatinib). Endocrine side effects of KIs have been highlighted in some reports including effects on thyroid function, bone and glucose metabolism or gonadal and adrenal function [135]. Furthermore, immune check-point inhibitors introduced in therapies against cancer, including cytotoxic T-lymphocyte antigen-4 receptor (CTLA-4) inhibitors [ipilimumab, tremelimumab) or programmed death-1 (PD-1) receptor pathway inhibitors (nivolumab, pembrolizumab) have been reported to cause AD with a prevalence ranging from of 0.8 to 2.0% in different studies. AD may develop as a result of lymphocytic hypophysitis caused by this group of medicines [136]. The reported relative risk of developing hypophysitis and subsequent AD was 22.0 and 3.9, respectively [137]. However, more recently, 21-OHAb-positive cases of AD have been described following pembrolizumab immunotherapy [138].

Chronic use of corticosteroids inhibits the feedback of hypothalamic–pituitary–adrenal axis, which may cause AD after the cessation of corticosteroid treatment. In a meta-analysis performed on 3753 participants, manifestation of AD after corticosteroid withdrawal ranged from 4.2% for nasal administration to 52.2% for intra-articular administration. In patients with asthma on corticosteroid treatment, AD varied from 2.4% (low dose) to 21.5% (high dose) and from 1.4% (< 28 days) to 27.4% (> 1 year of therapy). The risk of AD cannot be safely excluded irrespective of the administration route, type of a condition requiring corticosteroids, size of a dose, or duration of treatment. Although the risk of developing AD after stopping corticosteroids decreases over time, up to 25% of patients may remain adrenal insufficient for more than 6 months [139].

Neoplastic

AD resulting from bilateral cancer metastases is probably underdiagnosed but would not contribute significantly to the prevalence of AD because the life expectancy in most such cases is limited [140]. Nevertheless, adrenal metastatic localization from kidney carcinoma, lung carcinoma, breast carcinoma, and melanoma or even adrenal lymphomas can lead to AD [141]. On imaging, bilateral adrenal masses are usually evident in all cases (Fig. 3e). In our cohort, bilateral metastases in the adrenals were found in 8 patients with AD (1.2%): 4 from renal carcinomas, 3 from non-Hodgkin lymphoma, and one from breast carcinoma. The mean age at onset of AD was 55 years (range 31–78 years) with a female/male ratio of 2.3. All had bilateral adrenal masses and were negative for ACA/21-OHAbs [6].

Surgical

Patients who undergo bilateral adrenalectomy for Cushing's syndrome, or for bilateral adrenal masses due to macronodular adrenal hyperplasia, primary pigmented nodular adrenocortical disease, or pheochromocytoma will present with AD if appropriate replacement therapy is not in place [25]. In our survey, we had 6 patients (0.9%) with AD following bilateral adrenalectomy: four for Cushing's syndrome, one for bilateral adrenal masses, and one for primary pigmented nodular adrenocortical disease [6].

Clinical manifestations

Clinical symptoms of AD are secondary to deficient production of glucocorticoids, mineralocorticoids, androgens and may vary depending whether AD is chronic or acute. AD is a "chameleon-like" disease masquerading under the guise of many other conditions, so that the diagnosis is frequently missed for a long time. About 60% of affected individuals are seen by various clinicians before the diagnosis is made [142]. Classical manifestations are weakness and fatigue (74–100%), weight loss (78–100%) with decreased appetite, weight loss with failure to thrive in children (61–100%), sometimes resembling anorexia, orthostatic hypotension and tachycardia (88–94%), skin and mucosal hyperpigmentation (80–94%), nausea, vomiting, diarrhea (75–86%) or recurrent abdominal pain (31%) which may even present as surgical emergency, amenorrhea or libido reduction (25–45%), depression (20–40%) and salt-craving (9–16%) [25, 56, 142, 143]. Salt craving is one of the symptoms that distinguish AD from the other salt-wasting disorders. In children, AD often presents with seizures following hypoglycemic crisis. Recurrent hypoglycemia can be a sign of AD in patients with DM-1 on insulin therapy [144]. AD

leads to dehydroepiandrosterone deficiency that is the major precursor for sex-steroid synthesis. This may result in severe androgen deficiency in women with AD presenting as loss of pubic and axillary hair or reduced libido [142]. It should be noted that patients with rapid onset of AD (due to infarction or hemorrhagic gland destruction) and short period of increased serum ACTH usually do not display characteristic hyperpigmentation [131]. Sometimes, AD can present with atypical manifestations of cerebral edema due to hyponatremia, persistent elevated transaminase levels associated with autoimmune hepatitis, anemia, vague abdominal pain, poor concentration and progressing fatigue [13]. There are additional signs of AD, for example, unexplained hyponatremia with increased TSH levels [145], moderate hyperkaliemia in the absence of renal failure or unexplained hypoglycemia after physical exertion. In healthy subjects, glucocorticoids enhance the synthesis of an enzyme which converts norepinephrine into epinephrine. In the case of AD basal and stress-induced epinephrine release may be impaired and be responsible for hypotension or hypoglycemia during crisis situations [146].

Acute adrenal insufficiency (Addisonian crisis)

Adrenal crisis is a life-threatening emergency in patients with AD. An overall incidence of Addisonian crisis in patients on long-term substitutive therapy has been reported between 5 to 10/100 patients/year, with a mortality rate of 0.5/100 patients/year [26, 147, 148]. The main precipitating events were infections, including gastroenteritis (23%), urinary tract infections (3%), fever (22%) and emotional stress (16%), surgery (16%), strenuous physical activity (9%), withdrawal of steroid therapy (3.6%), or unknown causes (10%) [148]. Patients with comorbidities had a higher risk compared to patients with AD alone [149]. Furthermore, adrenal crisis has been observed significantly more frequently in patients with primary (7.6/100 patients/year) than with secondary AD (3.2/100 patients/year). A higher prevalence of acute AD has been reported in patients with APS (10.9/100 patient/year) and with DM-1 (12.5/100 patient/year) [149]. The most frequent symptoms of adrenal crisis are malaise, fatigue, hypotension, nausea, vomiting, abdominal pain, muscle pain, mental confusion, somnolence, and coma. Typical laboratory findings are hypoglycemia, low plasma sodium and increased potassium levels, high plasma calcium levels, pre-renal insufficiency with high urea and creatinine [26].

Sexuality and fertility

Hypergonadotropic hypogonadism due to lymphocytic oophoritis affects 9–61% of females with AAD [6, 18, 150, 151]. Females with AD have reduced levels of circulating androgens that are essential for sexual function. In a postal survey, all 269 females in the Norwegian Addison's registry were invited to complete the Sexual Activity Questionnaire and registration of childbirths. Fertility was estimated as standardized incidence ratio for birth. Despite androgen depletion, females with AD did not report impaired sexuality. Fertility was reduced after diagnosis had been made, but the reasons for this remain unknown [152]. Sexual dysfunction was rarely investigated in men. In one study 12 males were examined at diagnosis of AAD and 2 months after initiating hormone replacement therapy. At baseline, low scores were found for erectile and orgasmic function, sexual desire, intercourse and overall satisfaction, and high scores for depression and anxiety. All these parameters improved significantly in the recovery phase following treatment compared with baseline [153].

Laboratory diagnosis

Measurements of concentrations of ACTH, cortisol, plasma renin and aldosterone in blood samples collected in the morning (at 8.00 a.m.) are required to confirm the diagnosis of AD. An increase of ACTH levels, i.e., more than twofold over the upper limit of the normal range (normal values 4.5–12 pmol/L or 20–52 ng/L) together with low levels of cortisol, i.e., less than 138 nmol/L or 5 µg/dl (normal values 275–550 nmol/L or 10–20 µg/dl) are diagnostic for AD [54]. Low cortisol levels with normal/low ACTH levels denote secondary AD [25, 54, 154].

The conventional ACTH test (an intravenous injection of 250 µg of synthetic corticotropin in adults or alternatively 125 µg intravenous or intramuscular administration in children less than 2 years old) is the gold standard for assessing adrenal function. This test has a superior diagnostic accuracy compared to other diagnostic tests routinely used in clinical practice, for example, the insulin tolerance test. A peak cortisol concentration of less than 500 nmol/L (18 µg/dl) at 30–60 min after ACTH administration is considered diagnostic for adrenal insufficiency [54, 154]. However, cut-off values for cortisol and other adrenal steroids after stimulation may differ significantly based on the method used for the measurements [154]. In contrast to the "high-dose" (250 µg) corticotropin test, the so-called "low-dose" corticotropin stimulation test employs 1 µg of synthetic corticotropin. Both tests give comparable results for serum cortisol concentration at least 30 min after stimulation; however,

the "high-dose" test has been better validated compared to the "low-dose" test. Therefore, it has been suggested that the "low-dose" corticotropin test is carried out only when ACTH is in short supply [54, 154]. It should be noted that the ACTH test is not required if AD diagnosis is obvious with already low basal cortisol levels (≤ 100 nmol/L) [155], or if patients are hemodynamically unstable.

The simultaneous measurements of plasma renin and aldosterone levels (in patients not on angiotensin-converting enzyme inhibitors therapy) confirm the presence of mineral corticoid deficiency [54]. At AD diagnosis serum levels of urea, creatinine, calcium and potassium are increased. Hypercalcemia due to increased intestinal absorption and decreased renal excretion of calcium can be present and is sometimes associated with Graves' disease [142]. In contrast, levels of sodium, glucose and osmolality are low. The low cortisol levels can induce anemia, lymphocytosis, and eosinophilia. TSH levels may be increased, usually between 4 and 10 IU/L, because of the lack of the inhibitory effect of cortisol on TSH production [156] or due to coexistent hypothyroidism with positive thyroid autoantibodies [26]. A multicenter retrospective study from Norway and Sweden on 272 patients hospitalized with new-onset AAD demonstrated that the most consistent biochemical finding was low sodium, present in 84% of the patients, while only 34% had elevated potassium [145]. It was suggested that in the case of unexplained low sodium and/or elevated TSH levels, a diagnosis of AAD should be considered [147]. The prevalence of AAD in patients with chronic thyroiditis is 1.4–5.3% and in patients with Graves' disease 0.1–1.7% [157, 158]. Based on the relatively low prevalence of AAD in patients with AITD (0–3%) [79–81], we suggest testing for 21-OHAbs only in selected patients, i.e., those who have personal or family history of other autoimmune diseases and/or those who display symptoms or signs of AD [91].

Imaging

Adrenal imaging is not required in patients with AAD positive for ACA/21-OHAbs [6, 54, 159] (Fig. 3a). However, adrenal NMR or TC scans should be performed in the case of AD patients negative for ACA/21OHAbs [6, 26, 54, 119, 159].

Diagnostic work-up

Once clinical AD has been diagnosed further investigations aimed at establishing the etiology of the condition should be carried out (Fig. 4). The first line of tests in adults should include ACA or 21-OHAbs [26, 54, 65, 159]. In contrast, children should be first screened for baseline serum 17-hydroxyprogesterone (17-OHP) levels [54]. ACA/21-OHAbs-negative young or adult males with AD and normal 17-OHP should be tested for VLCFA for adrenoleukodystrophy [26, 54]. When ACA/21-OHAbs (Fig. 4) are present, a diagnosis of AAD can be made; however, it should be noted that 5–10% of AAD patients may be ACA/21OHAb negative at the time of testing [6, 65, 159]. Following diagnosis of AAD, further tests for other clinical, subclinical or potential autoimmune diseases should be carried out to define APS-1, APS-2, APS-4 or isolated AAD [18, 26, 54, 159]. In the case of young patients with isolated AAD, it is important to determine if AAD is the heralding component of APS-1. Thus, special attention should be given to the signs and symptoms of CC and/or CH, dental enamel dysplasia, keratitis, autoimmune hepatitis or malabsorption. Furthermore, tests for IFNAbs should be performed and if positive analysis for AIRE gene mutations should be carried out [26, 33, 92]. ACA/21-OHAb-negative adults with AD should be investigated using a combination of imaging and specific diagnostic tests [26, 54, 159] as shown in Fig. 4. The diagnosis of TBC-related AD is based on history of previous TBC infections and/or signs on the chest radiography, adrenals enlargement with calcifications, and positive tests indicating previous contact with the bacillus [6, 159]. The images of hyperdense adrenals would suggest haemochromatosis and specific genetic tests should be performed. On adrenal imaging, bilateral hyperdense lesions are characteristic for adrenal hemorrhage. In this case specific tests for coagulation parameters including anti-phospholipid antibodies and a treatment with anti-thrombotic agents or modification of anti-coagulation therapy are necessary [131, 160]. If CT scan of the adrenals in patients with a history of cancer reveal bilateral adrenal masses, an ultrasound-guided or CT-guided fine needle aspiration biopsy may be necessary to define the diagnosis [54]. When all the tests described above are negative, a diagnosis of idiopathic AD is justified [6, 54].

Pregnancy in patients with AD

During pregnancy, the feto-placental unit plays a major role in adrenal steroid hormone production because the placenta produces corticotropin releasing hormone (CRH) and ACTH, with a rise in maternal total and free cortisol. Free serum cortisol levels are initially similar to those of healthy women in early pregnancy and then rise 1.4- and 1.6-fold in the second and third trimester, respectively. However, to date, the amplitude of maternal cortisol (total and free) increase has not been fully determined and no trimester-specific cut-off reference levels have been yet defined. Circadian rhythm is maintained but can be blunted in the third trimester as placental CRH production does not follow a

diurnal pattern. During delivery, ACTH increases 15-fold and normalizes 24 h post-delivery. The fetus is protected from maternal hypercortisolism as cortisone is inactivated by placental 11β-hydroxysteroid dehydrogenase type 2 [161]. Renin–angiotensin–aldosterone system (RAAS) is activated during pregnancy, with consequent volume expansion and sodium retention. Angiotensin II increases, and aldosterone levels rise eightfold during mid-pregnancy and remain elevated till delivery. However, the anti-aldosterone effect of progesterone provides a balance against RAAS activation (by competing with aldosterone at the renal distal tubule) [161].

It is rare that AD develops during pregnancy and its diagnosis may be particularly challenging. In the first trimester, hyperemesis and hyperpigmentation presenting as *melasma* or *chloasma gravidarum,* caused by stimulation of melanocytes by female sex hormones, are the main two confounding symptoms/signs. In a Canadian study, prevalence of AD in pregnancy was of 5.5/100.000, increasing from 5.6 to 9.6/100.000 over a 9-year study period [162]. If AD is suspected during pregnancy, ACTH and cortisol levels should be measured first, followed by an ACTH test [163]. Pregnant women with known AD should continue with their therapy during the first trimester. In the case of nausea and vomiting, supplementing with intravenous or intramuscular hydrocortisone is recommended. In the third trimester, the physiological increase in serum cortisol associated with anti-mineralocorticoid effect of progesterone may need to be corrected with increased doses of glucocorticoid and fludrocortisone [26]. Usually, the required additional hydrocortisone dose during the third trimester is of 2.5–10 mg/day [26, 163] but this increment is dependent on the individual clinical course [54]. Major adjustments to the substitutive therapy are considered to be unnecessary because of physiological adaptations in cortisol clearance observed in women with AD [20]. The preferred glucocorticoid to be used in pregnancy is hydrocortisone rather than cortisone acetate. The developing fetus is no longer dependent on maternal cortisol concentrations from the third trimester because fetal adrenals begin their production of cortisol. Thus, supplementary treatment in the third trimester of pregnancy still remains controversial. During the active phase of delivery, additional dose of hydrocortisone is recommended. For example, a single injection of 100 mg i.v. followed by 50–100 mg within 24 h [54, 163]. Furthermore, parenteral injections of 100 mg hydrocortisone i.v. or i.m. should be administered before and after cesarean delivery, repeated at the same dose at 24 h [26, 163]. Assessment of adrenal function in infants from mothers with AD who were on adequate hormone replacement therapy is not necessary and there is no contraindication for breast feeding [163].

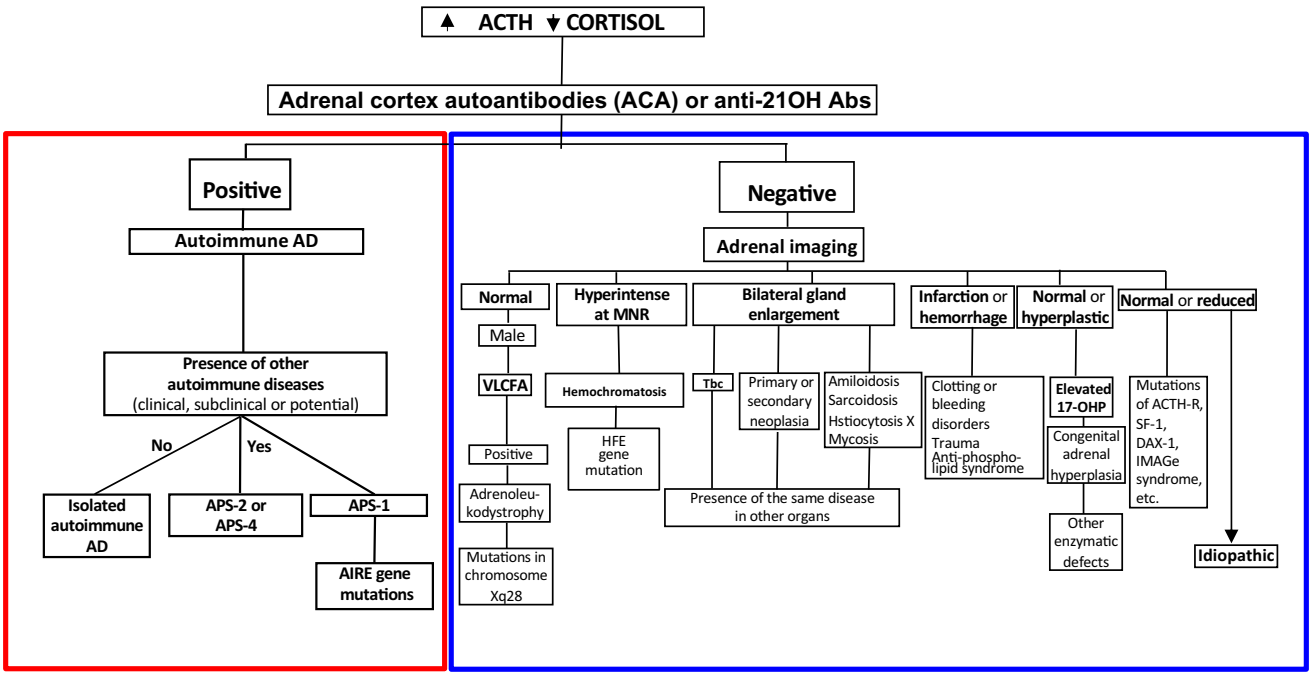

Fig. 4 Suggested flow-chart for the diagnosis of different forms Addison's disease. The conditions not included may be diagnosed as "idiopathic form" (e.g., adult females negative for 21-OH antibodies with normal adrenal imaging without genetic mutations, or adult males negative for 21-OH antibodies with normal adrenal imaging and normal VLCFA). *ACA* adrenal cortex antibodies, *APS* autoimmune polyglandular syndrome, *VLCFA* very-long-chain free fatty acids, *Tbc* tuberculous infection, *MNR* magnetic nuclear resonance. See text for details

In a study of pregnancy outcomes, patients with AD were more likely to deliver preterm, by cesarean section, have impaired wound healing, develop infections and thromboembolism, require transfusions, and have prolonged post-partum hospital admissions. Maternal mortality was significantly higher. Congenital anomalies and small-for-gestational-age infants were more likely in pregnancies in women with AD [162].

Therapies

Conventional therapy with oral glucocorticoids

Glucocorticoids are secreted in a circadian fashion, with a peak at 8.00 o'clock in the morning and a nadir at 24.00 h. Adults produce 9–11 mg of cortisol daily/m^2 of body surface, corresponding to about 15–25 mg of hydrocortisone/day [26, 164, 165]. Treatment of AD aims at replacing the hormones secreted by the adrenal cortex together with a standard care for the conditions that caused the adrenal failure. Recommended adrenal replacement therapy in AD is based on a daily dose of hydrocortisone at 10–12 mg/m^2 of body surface administered in 2 or 3 doses and fludrocortisone at 0.05–0.20 mg in the morning when patients wake up [25, 26, 54]. The Consensus Statement of the Euradrenal European Consortium suggests 15–25 mg hydrocortisone or 18.75–31.25 mg of cortisone acetate [26] and the Endocrine Society, 15–25 mg hydrocortisone or 20–35mg cortisone acetate in 2–3 oral daily doses. The highest dose should be taken when wakening early in the morning, a smaller dose after 4–6 h and sometimes a third small dose around 17.00 h, at least 4–6 h before sleep to avoid insomnia and nocturnal insulin resistance with potential adverse metabolic consequences [154]. Cortisone acetate is absorbed through the intestine quickly (half-life 80 min) and as a pro-hormone requires activation by the hepatic enzyme 11β-hydroxysteroid dehydrogenase type 1. Glucocorticoids with longer half-lives, like dexamethasone at a dose of 0.25–0.75 mg or prednisone at 2.5–7.5 mg/day, may be considered for replacement therapy only when hydrocortisone or cortisone acetate is not available. In children, only hydrocortisone should be used for replacement therapy because its short half-life allows for better control. The starting dose in children is about 6–10 mg/m^2 of body surface divided in 3 doses [26, 54]. Night workers must modify the dosing based on changes in the day-time/night-time activity. Monitoring glucocorticoid replacement therapy in AD should be based on body weight, postural blood pressure, energy levels and signs of excessive or insufficient bioavailability [26, 54, 166]. Insufficient replacement therapy is manifested by nausea, poor appetite, asthenia, weight loss, hyperpigmentation, while excessive replacement is associated with weight increase, hypertension, insomnia, peripheral edema. Plasma ACTH and cortisol levels are not useful markers in the assessment of the effectiveness of the substitutive therapy in patients with AD. However, in case of a clinical doubt or if required, the samples for ACTH and cortisol measurements should be collected at least 1–2 h after the normal replacement dose [26, 54].

Therapy with oral modified-release or parenteral hydrocortisone

Supplementing hydrocortisone in 2–3 subdivided doses induces 2 or 3 peaks of serum cortisol with possible intermediate periods of hypocortisolemia which can be associated with symptoms of asthenia. To counteract these fluctuations, a dual-release formulation hydrocortisone tablet has been developed [167]. This drug consists of an outer layer containing hydrocortisone for immediate release and an inner nucleus for 12-h discharge. This method of drug delivery produces a more physiological cortisol release than the standard formulations used for supplementation [167]. An open randomized crossover trial showed that once daily dual-release dose regimen was associated with reduction of body mass index (BMI) and improvement in blood pressure and glucose metabolism in AAD patients with DM-1 [168]. In a study of diabetic patients with primary and secondary adrenal failure or congenital adrenal hyperplasia, both BMI and glycated hemoglobin were significantly reduced on therapy with dual-release formulation compared to conventional supplementation [169]. An open-label study on dual-release hydrocortisone replacement has demonstrated that plasma cortisol profiles resembling normal daily profiles were reached in 31 healthy volunteers [170]. Furthermore, in an analysis of 19 patients with AAD, the dual-release hydrocortisone delivery was found to be effective in reducing central adiposity, improving glucose and lipids metabolism, as well as the Quality of Life (QoL) [171]. Therefore, this formulation appears to have a favorable metabolic impact and may be chosen for patients with high cardiovascular risks such as patients with diabetes mellitus. A recent single-blind randomized controlled trial in subjects with AD indicated that administration of glucocorticoids multiple times a day has been associated with weight gain, metabolic impairment, pro-inflammatory state and a weakened immune response; therefore, restoration of a more physiological circadian glucocorticoid rhythm with a once-daily modified-release regimen may result in reduction in BMI, normalization of the immune cell profile, reduction in recurrent infections, and improvement in the QoL [172]. In addition, a 36-month study of 13 patients with primary and 36 patients with secondary adrenal insufficiency has shown a significant decrease in BMI, waist circumference, glycated hemoglobin, and an increase in HDL-C in all patients treated

with dual-release hydrocortisone, in particular in patients with prediabetes (impaired fasting glucose or impaired glucose tolerance) when compared to those with normal glucose tolerance [173]. Analysis of salivary cortisol measurements in patients on treatment with dual-release hydrocortisone has confirmed that cortisol levels were lower in the afternoon and in the evening than in the morning thus achieving a cortisol profile closer to the healthy controls [174]. Currently, there is an ongoing PlenadrEMA trial which is an investigator-initiated open-label switch pilot trial of the effect of dual-release hydrocortisone versus conventional hydrocortisone on fatigue in patients with secondary adrenal insufficiency [175]. The outcome of this trial together with the observations described above may lead to changes in the routine strategies for delivering the replacement therapy in patients with AD.

Another oral formulation containing multiparticulate modified-release hydrocortisone for replacement therapy administered twice-daily has become available and consists of tablets with an insoluble barrier coat protecting all but the outer surface [176]. The formulation is designed to be taken at 15 mg at 10 p.m. with drug release starting 4 h after administration resulting in serum cortisol increase after midnight and very early in the morning with the maximum concentrations at 8 h after administration. This design is intended to mimic the physiological morning cortisol peak. However, the drug delivery in this formulation is not sufficient to cover the whole day following administration in the previous evening and another dose should be taken later in the morning. Twice-daily administration of this novel hydrocortisone formulation at starting doses of 10 mg (07:00 a.m.) and 20 mg (11:00 p.m.) resulted in more effective decrease of ACTH levels and androgen secretion in patients with classical congenital adrenal hyperplasia [177–179]. Overall, future case-controlled studies designed for long follow-up in larger cohorts of patients with AD should be carried out to verify the promising observations on the innovative hydrocortisone formulations discussed above [180].

Until recently, there were no licensed, dose-appropriate formulations of hydrocortisone for young children with AD. The dosing relied either on parents crushing tablets or pharmacists making up appropriate preparations from adult medicines. This unsatisfactory situation has been improved with the availability of an immediate-release hydrocortisone preparation based on multilayered technology [181]. This formulation has the maximum granules diameter controlled by passing through a 0.8-mm sieve and permits swallowing even by neonates. The granules are presented within a capsule that is opened for dosing of 0.5, 1.0, 2.0, and 5.0 mg [181]. A phase 3 open-label single-dose study has been performed in three cohorts of children with AD aged from 1 day to 6 years. This study has demonstrated that the formulation was well tolerated, easy to administer, and showed good absorption with cortisol levels at 60 min similar to physiological levels as observed in healthy children [178, 182]. Very old patients with difficulty in swallowing (for example with neurologic dysphagia) may benefit from these new formulations.

One strategy for mimicking the circadian rhythm of cortisol is using subcutaneous administration of hydrocortisone which normalizes ACTH levels within 24 h [183]. This approach may be useful as initial treatment of newly diagnosed patients or in the case of Addisonian crisis. Intravenous infusion of hydrocortisone by pump in patients with AD can be used when standard measures are not expected to guarantee sufficient cortisol replacement in special clinical situations, for example in patients with unceasing vomiting, loss of consciousness, inability of swallowing, or in patients with contraindications for nasogastric tube for oral administration [184]. Rectal suppositories of 100-mg prednisone have been studied for emergency treatment. Although sufficient drug levels were observed with ACTH suppression by more than 50% of baseline values, rectal way cannot be regarded as equivalent to parenteral glucocorticoid administration for treatment of adrenal emergencies [185].

Therapy with mineralocorticoids

Concerning mineralocorticoid substitution, the current standard treatment comprises fludrocortisone which exhibits tenfold higher mineralocorticoid potency compared to aldosterone. In adult patients, it is recommended at 0.05–0.20 mg taken once daily in the morning at awakening, as physiological aldosterone secretion follows a circadian rhythm similar to that of cortisol. Restriction of salt intake is not required [26, 54]. Starting dose of fludrocortisone dose should be of 0.05–0.1 mg daily and then titrated in steps of 0.025–0.05 mg. Substitution therapy aims at achieving normal blood pressure, normal potassium serum levels, and obtaining plasma renin activity in the upper normal range. A higher dose is required in newborns and children because their mineralocorticoid sensitivity is lower than adults, as well as in the last trimester of pregnancy when high levels of progesterone counteract the effects of mineralocorticoids [26, 54]. Temporary dose increments may also be recommended in hot climates and conditions that promote excessive sweating, such as long-lasting exercise. Licorice potentiates the mineralocorticoid effect of glucocorticoids and should be avoided. Some patients with adrenal failure may be insufficiently replaced with fludrocortisone if they report symptoms and signs indicating chronic under replacement such as salt craving and postural dizziness [186]. Glucocorticoid over replacement may reduce the need of mineralocorticoid but increases the risk for cardiovascular disease. It has been demonstrated that cognitive function and mood in patients with adrenal failure are in part related

to mineralocorticoid-receptor occupation [187]. High blood pressure, rapid weight gain, and hypokalemia indicate overtreatment with mineralocorticoids, while the hypotension, weight loss, asthenia, and hyperkaliemia suggest insufficient dosing. In case of doubt, measurement of plasma renin is indicated to reassess mineralocorticoid replacement therapy. In patients who develop hypertension while receiving fludrocortisone, a reduction in the dose should be considered [54]. If blood pressure remains uncontrolled, initiating antihypertensive treatment while continuing with fludrocortisone is indicated. Fludrocortisone tablets should be stored in a refrigerator (between 2 and 8 °C) in a tightly closed container, even though according to the new formulation instructions, the decay rate is as low 0.1% over the first 6 months at room temperature (up to 25 °C) [188].

Therapy with androgens

Substitutive therapy with dehydroepiandrosterone (DHEA) at 25–50 mg/day has been suggested to improve the QoL in women with AD receiving optimal glucocorticoid and mineralocorticoid therapy who are still suffering from symptoms of low libido, depressive symptoms, or low energy. This is particularly relevant in post-menopausal patients or those presenting with concomitant primary ovarian insufficiency with loss of ovarian androgens [25, 26, 54]. However, the effectiveness of additional treatment with DHEA is currently unconfirmed or controversial, and if there is no beneficial effect after 6 months, DHEA should be discontinued [20, 54, 154].

Prevention and management of adrenal insufficiency in patients on replacement therapy during stressful events

The glucocorticoid dose needs to be adjusted dynamically according to specific stressful circumstances [20, 26, 54]. Table 4 summarizes proposed oral or parenteral interventions in the case of acute febrile illness, in major and minor surgical or dental procedures and in critical medical conditions (septic shock, myocardial infarction, ischemic or hemorrhagic stroke, acute pancreatitis, gastroenteritis with vomiting and diarrhea, intestinal obstruction with fluid loss or sequestration, etc.) according to the European Expert Consensus Statement [26] and the Endocrine Society Clinical Practice Guidelines [54].

In physiological conditions, cortisol levels rise in response to stress of surgery. It is estimated that adults secrete 75–100 mg of cortisol/day in reaction to major surgery and 50 mg/day in the case of minor surgery [54, 189]. Available data indicate that cortisol secretion rarely exceeded 200 mg in the first 24 h after surgery, and that the secretion rate correlated with the duration and extent of surgery [189]. However, in the event of surgery, the principal aim is to cover increased demand for corticosteroids caused by trauma and also to cover any potential additional demand if unexpected complications ensue. According to the Endocrine Society Guidelines, in the case of major surgery, hydrocortisone should be given intravenously at an initial dose of 100 mg in adults followed by a continuous infusion of 200-mg hydrocortisone over the following 24 h, together with intravenous fluid replacement to counteract dehydration. For patients with secondary AD, lower doses of supplementary hydrocortisone (25–75 mg over 24 h) may be sufficient to cover surgical stress [54]. The effects of the physiological stress response during surgery on cortisol levels have been assessed in a study on 93 euadrenal patients undergoing elective surgery, and a positive correlation between the severity of surgical intervention and peak serum cortisol levels has been found [190]. In this study, the post-surgical cortisol peak was only 2–3 times higher than pre-surgical basal levels, and the levels of cortisol tended to return to baseline by post-operative day one even after major surgery [190]. A recent meta-analysis including 2,953 patients from 71 studies has shown that on the day of surgery, the cortisol output levels increases by three- to fourfold in the case of moderate–high invasive surgical procedures, while only approximately twofold after minimally invasive procedures. Thus, replacement doses currently advocated by guidelines to cover surgical stress may lead to cortisol levels that exceed the physiological requirement even after major surgery. Yet, it should be kept in mind that invasive surgical intervention give rise to more pronounced and prolonged cortisol surges in older subjects, in females, in patients undergoing open surgery and general anesthesia [191]. Table 4 summarizes the most frequent stress-associated situations requiring corticosteroid supplementation and the recommended management strategies.

AD patients who undertake regular and time-limited physical activity do not generally need to modify daily doses of glucocorticoids [26]. In contrast, in the case of a prolonged, intensive and unusual exercise, an increase of hydrocortisone (5–10 mg) and salt intake is generally suggested [26, 54]. However, an extra-dose of hydrocortisone administered in a study performed on 10 women with AD who underwent short strenuous physical exercise has not shown benefit [192]. To date, the requirements for administration of additional doses of hydrocortisone during different types of physical activities have not been assessed in appropriate clinical studies. Stress adjustment of mineralocorticoid replacement is not required.

Interferences with glucocorticoids and mineralocorticoid therapy

Anticonvulsants drugs, such as phenytoin, phenobarbital, carbamazepine, or topiramate stimulate cytochrome CYP3A4, thereby inducing synthesis of liver enzymes responsible for glucocorticoid metabolism and induce a decrease in available glucocorticoids with the associated clinical symptoms [26]. Consequently, patients who are on anti-epilepsy medications require higher replacement doses of glucocorticoids. In contrast, anti-retroviral drugs, such as ritonavir, inhibit CYP3A4 activity leading to delayed glucocorticoid metabolism and increased serum concentrations of glucocorticoids [25].

Some dietary products including large quantities of grapefruit juice or licorice may have effect on bioavailability of glucocorticoids and should be avoided in patients on a substitutive therapy for AD [26]. Contraceptive medicines containing drospirenone displaying anti-mineralocorticoid properties should not be prescribed to avoid increased demand for fludrocortisone [20].

Therapy of AD crisis

Adrenal crisis is a medical emergency and must be promptly treated with rapid infusion of 100 mg of hydrocortisone and 1 l of intravenous isotonic saline solution in the first 1–2 h. During the following 24–48 h, 100 mg of hydrocortisone must be given intravenously every 6 h, and 1 l of saline solution also every 6 h. After 2–3 days, if precipitating events improve, treatment may be continued using oral medications. Mineralocorticoid therapy is not necessary during infusion of high doses of hydrocortisone. However, it may be restored when hydrocortisone replacement falls below 50 mg/day. Admission to intensive care unit depends on the severity of underlying or co-occurring diseases [26, 54]. About half of the patients at the onset of AD may present with increased levels of TSH [131]. A high TSH level could indicate untreated autoimmune hypothyroidism but also

Table 4 Prevention and management of adrenal insufficiency during stressful events in adults

Special condition, medical or surgical stress	Corticosteroid supplementation
Management of mild to moderate illness with fever (e.g., respiratory or urinary infections, skin and soft tissue infections, etc.)	Hydrocortisone or cortisone acetate replacement doses doubled (body temperature > 38 °C) or tripled (> 39 °C) until recovery (usually within 2 to 3 days). Increased consumption of electrolyte-containing fluids (2–3 L) if tolerated. Antibiotic therapy
Gastroenteritis with vomiting and diarrhea or traumas with inability to take oral medications	Hydrocortisone 100 mg i.m. or i.v. b.i.d. until recovery. Infusion of 2.000 mL isotonic saline with in the first 24 h (or more based on total fluid loss, with additional 5% glucose solution if hypernatremia or hypoglycemia are present). Return to oral fluids intake if ability to drink is restored and switch to oral regimen tapering to normal corticosteroid dose depending on clinical state
Critical medical illness (septic shock, myocardial or bowel infarction, ischemic or hemorrhagic stroke, pneumonia with acute respiratory insufficiency, acute pancreatitis, persistent vomiting and diarrhea, intestinal obstruction with fluid loss or sequestration, etc.)	50–100 mg i.v. every 6–8 h or 0.18 mg/kg/h by continuous infusion for 48–72 h or until recovery of acute phase. Replace fluids in case of loss or negative balance, being careful if heart failure occurs
Major surgery with long recovery time, potential blood loss greater than 500–1.000 ml and usual post-operative intensive care unit stay	100 mg hydrocortisone per i.v. injection just before anesthesia followed by continuous i.v. infusion of 200 mg hydrocortisone in 24 h (alternatively 50 mg every 6 h i.v. or i.m.) for 2–3 days. Then double the oral dose for other 2–3 days and finally begin tapering to normal oral dose after post-operative day 7 within 2–3 days (if patient is hemodynamically stable or has no infections)
Minor surgery (inguinal hernia repair, tonsillectomy, rhinoplasty, arthroscopy, etc.) or major dental surgery	50–100 mg hydrocortisone i.m. just before anesthesia. Double oral dose for 24 h, then return to normal dose
Common dental procedure	Extra morning dose 1 h prior to surgery.
Other invasive procedures with or without sedation (fiber-optic gastroscopy, bronchoscopy, cystoscopy, coronary angiography, etc.)	50–100 mg hydrocortisone i.m. just before start of procedure. Double oral dose for 24 h, then return to normal dose
Minor procedures (breast or skin biopsy, thoracentesis, paracentesis, bone marrow biopsy or aspiration, rachicentesis, etc.)	Usually not required Extra-dose (e.g., 10–20 mg hydrocortisone) if symptoms
Invasive bowel procedures requiring laxatives (colonoscopy, colon computed tomography, barium enema, etc.)	Hospital admission overnight with 50–100 mg hydrocortisone i.m. or i.v. and fluids administration. Repeat the dose before starting the procedure
Labor and vaginal birth	100 mg hydrocortisone i.m. just at the onset of labor. Double oral dose for 24–48 h after delivery, then taper to normal dose

could be related to the decreased inhibitory effect of cortisol on TSH production. Thus, it is recommended that in AD patients with hypothyroidism, adrenal function is adequately supported before commencing replacement with levothyroxine to avoid adrenal crisis resulting from increased glucocorticoids demand after restoration of thyroid function [25]. TSH needs to be reassessed when AD is compensated [26]. In the case of clinically hyperthyroid patients with AD, the dose of glucocorticoids should be increased to compensate increased cortisol clearance and stress related to hyperthyroidism [25].

Emergency card

It has been recognized that the best strategy for prevention of the adrenal crisis is continuous improvement in the awareness of this life-threatening condition, together with education of patients and health professionals [193, 194]. Patients with AD should be informed when and how to increase steroid doses during concurrent illnesses or injury. Furthermore, training in intramuscular/subcutaneous administration of glucocorticoids may be very helpful for the effective prevention of acute adrenal crisis by patients themselves [195]. Patients should be advised to wear a medic alert bracelet and carry a card stating their daily dose of the steroids to enable health care professionals to act as appropriate in the event of an emergency. The Euradrenal Consortium proposed a Standard Emergency Card which has been now produced in collaboration with different national associations of patients with AD and made available for distribution in different European countries [26]. On the card, there are specific instructions on to how to manage Addisonian crisis in the national language on one side and in English on the reverse side. This card is a simple and effective strategy to save lives of patients with AD [188].

Therapy to modify the natural history of AAD

Immunosuppressive drugs

De Bellis et al. have made an interesting observation that some ACA-positive patients in stage 1–2 became ACA negative and showed restoration of adrenal function after treatment with high doses of steroids for Graves' ophthalmopathy [196]. One of these patients remained in remission for more than 100 months [197]. More recently, targeting autoimmune responses have shown some promise in prevention or treatment of DM-1, Graves' disease, multiple sclerosis and other autoimmune conditions [198–203]. Rituximab is a monoclonal antibody able to block CD20 molecules on B-lymphocytes and is thought to affect the ability of B cells to cooperate in antigen presentation and cytokine secretion. Potential benefit of rituximab has been tested in 6 patients with new-onset AAD. Although serum cortisol and aldosterone concentrations remained low in 5 subjects, one patient showed a steady improvement in both serum cortisol and aldosterone, allowing discontinuation of steroids at 15 months following rituximab therapy [204]. Furthermore, the patient remained well without medication for 12 months thereafter [204]. However, these early observations need to be confirmed in studies with greater number of patients at the onset of clinical AAD or in ACA/21-OHAbs-positive patients with subclinical AAD.

Regenerative therapy

The adrenal cortex has a great potential for regeneration as the progenitor or stem cells present in the adrenals respond to stimulation with ACTH [205]. Consequently, stimulation with ACTH may lead to increased regeneration of glucocorticoid-producing cells. A 20-week trial of regular administration of ACTH in 13 patients with clinical AAD of more than 1-year duration showed an improvement in cortisol and aldosterone concentrations in two patients [206]. One remained well without steroids for 28 months, while the other responder had to resume glucocorticoid replacement after 7 months [205]. It should be noted that this approach may only be effective if there is sufficient residual adrenal function. Advances in understanding adrenocortical stem cell biology will be helpful in designing new therapeutic avenues to modify the natural history of AAD.

Evaluation of quality of life

The Euradrenal Consortium developed a Disease-Specific QoL Questionnaire for patients with AD (AddiQoL) with the purpose to quantify altered well-being and treatment effects [207]. Full validation of the questionnaire requires obtaining responses from a large number of subjects. Hence, the original English version of AddiQoL questionnaire translated into various languages had been distributed to all the members participating to the European Consortium and enabled collection of information in a large group of 623 European patients with AD [208]. The outcome of this initiative is likely to improve the understanding of the impact of this condition on the QoL and benefit the patients with AD in the future.

Prognosis and mortality

The mortality rate for patients with AD is more than double compared to the background population [209–211]. The main causes of death were acute AD (15%) and infectious diseases (10%). Sudden death accounted for 9.2%, compared to 5.3% in the general population [210]. It is likely that Addisonian crisis contributed to the increased deaths in all of these causes of mortality. One study based on data from the National Swedish Hospital and Cause of Death Registers reported for the patients with AD a risk ratio of 2.19 for all the causes of mortality in men and 2.86 in women. The increase in mortality compared to the background population was due to cardiovascular disorders, malignancies and infectious diseases [209]. These observations were confirmed in a study on all patients with AAD admitted to the Swedish hospitals which reported a mortality rate of 2.9 for women and 2.5 for men. Patients with APS-1 had the highest mortality rate at 4.6 compared to 2.1 for patients with APS-2 [210]. This study also highlighted a high incidence of cancer among the APS-1 patients [210]. In a different study, a mortality rate for patients with AD in Norway was 1.10 for males and 1.18 for females. Furthermore, an increased rate was reported in males who were diagnosed with AD before 40 years of age. Acute adrenal failure was the major cause of death and infections, and sudden deaths were more frequent than in the general population [211].

Between 1996 and 2012, a nationwide observational cohort study cross-referencing the Swedish National Diabetes Register identified 226 patients with diabetes and AD that were matched with 1,129 controls. Patients with diabetes and AD had an increased frequency of metabolic complications and 28% of these patients died during the observation period compared to 10% of diabetic controls. The estimated relative risk of mortality in diabetic and AD group was 3.89 (95% confidence interval 2.84–5.32) compared to controls with diabetes. The most common cause of death was cardiovascular in both groups, but patients with diabetes and AD showed an increased death rate from diabetes complications, infectious diseases and other unknown causes [212]. More detailed analyses of survival and mortality of patients with AD of different etiology should be carried out in future.

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Compliance with ethical standards

Conflict of interest JF is an employee of RSR Ltd. RSR Ltd is a developer of medical diagnostics including kits for measuring 21-OH autoantibodies.

Ethical approval No data have been fabricated or manipulated (including images) to support our conclusions No data, text, or theories by others are presented as if they were the author's own. Proper acknowledgements to other works are given and permissions are secured for material that is copyrighted.

Informed consent Informed consent by patients was not applicable in the present paper, being a review on previous works.

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