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REVIEW

Addison's Disease: Diagnosis and Management Strategies

Mara Carsote[1,2], Claudiu Nistor[3,4]

[1]Department of Endocrinology, Faculty of Medicine, "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania; [2]Department of Gonads and Infertility, "C.I. Parhon" National Institute of Endocrinology, Bucharest, Romania; [3]Department 4 – Cardio -Thoracic Pathology, Thoracic Surgery II Discipline, Faculty of Medicine, "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania; [4]Thoracic Surgery Department, "Dr. Carol Davila" Central Emergency University Military Hospital, Bucharest, Romania

Correspondence: Mara Carsote, Aviatorilor Ave, 34-38, Sector 1, Bucharest, 011683, Romania, Tel +40744 851 934, Email carsote_m@hotmail.com

Abstract: We aim to overview Addison's disease (AD) with regard to current diagnosis and management. This is a narrative review of full-length articles published in English between January 2022 and December 2022 (including online ahead of print versions) in PubMed-indexed journals. We included original studies in living humans regardless of the level of statistical significance starting from the key search terms "Addison's disease" or "primary adrenal insufficiency" in title or abstract. We excluded articles with secondary adrenal insufficiency. Briefly, 199 and 355 papers, respectively were identified; we manually checked each of them, excluded the duplicates, and then selected 129 based on their clinical relevance in order to address our 1-year analysis. We organized the data in different subsections covering all published aspects on the subject of AD. To our knowledge, this is the largest AD retrospective from 2022 on published data. A massive role of genetic diagnosis especially in pediatric cases is highlighted; the importance of both pediatric and adult awareness remains since unusual presentations continue to be described. COVID-19 infection is a strong player amid this third year of pandemic although we still not do have large cohorts in this particular matter as seen, for instance, in thyroid anomalies. In our opinion, the most important topic for research is immune checkpoint inhibitors, which cause a large panel of endocrine side effects, AD being one of them.

Keywords: Addison disease, cortisol, primary adrenal insufficiency, synacthen, congenital adrenal hyperplasia, immune checkpoint inhibitor, COVID-19

Introduction

Affecting one in 5000–7000 (varying from 1000–14,000) individuals, Addison's disease (AD) is mainly caused by destruction of the adrenocortical tissue caused by mononuclear infiltration of the inflammatory cells in 90% of adult cases (concerning geographic areas where tuberculosis is not highly prevalent) or by congenital adrenal hyperplasia (CAH) in the pediatric population.[1–3] The adult incidence of 4–6 cases per million per year has a less known correspondence in children.[2,3] Historically, AD was first described by Thomas Addison in 1855; the introduction of cortisone therapy in 1950 massively improved the prognosis; 21-hydroxylase deficiency was first recognized in 1957 followed by identification of other genetic defects in CAH after 1960; the genetics behind AD/CAH registered a great progress between 1984 and 2004; new data suggest other genes are involved such as CTLA4.[4,5]

The main etiological type is autoimmune AD which is due to an aberrant T cell profile.[6] A progressive adrenalitis is registered years before the actual clinical consequences.[7]

Due to life-threatening fulminant evolution unless adequately treated, AD represents a major point of interest for any clinician. While options such as allogeneic adrenocortical cell transplantation, stem cells derivate adrenal-like steroidogenic cells or gene therapy for CAH are still under development, in the meantime, glucocorticoid replacement remains the only lifesaving option, despite being associated with numerous limits such as decreased quality of life, repetitive acute crisis, lack of precise tools in order to assess adequate hormonal substitution and long-term consequences, with controversies around the use of different replacement regimes and formulas.[1]

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Aim

The paper is aiming to provide a 2022 retrospective on AD from a clinical perspective with regard to various data concerning its diagnosis and management.

Materials and Methods

This is a narrative review on full-length articles published in English between January 2022 and December 2022 (including online ahead of print versions) in PubMed-indexed journals. We included original studies in living humans regardless of the level of statistical significance starting from the key search terms "Addison's disease" or "primary adrenal insufficiency (AI)" on title or abstract. We excluded articles with secondary AI. Briefly, 199 and 355 papers, respectively were identified; we manually checked each of them, excluded the duplicates, and then selected 129 based on their clinical relevance in order to address our 1-year analysis. We organized the data in different subsections covering all published aspects on the subject of AD.

Results

Diagnosis of Addison's Disease: Clinical, Biochemical and Hormonal Findings

Clinical Presentation of Addison's Disease

Clinical manifestations of AD may be challenging due to its severity and heterogeneous aspects.[8] Interesting presentations have been reported such as: AD with mineralocorticoid–only deficiency; AD with spontaneous resolution; AD with symptomatic mineralocorticoid deficiency (not glucocorticoid); AD in the course of anti-phospholipid syndrome; AD with presentation as intractable nausea/vomiting.[9–11]

Psychiatric overlap was reflected by one case of a 28-year-old female with a psychotic syndrome at AD onset with complete resolution after starting glucocorticoid replacement.[12] Another 56-year-old male was admitted for organic delusional disorder at onset of tuberculosis-associated AD.[13]

Cardiologic anomalies were reported as a first step in identifying AD. A 63-year-old male was admitted for junctional rhythm requiring vasopressor support; another 26-year-old male was admitted for Brugada syndrome-like electrocardiogram elements.[14,15] A 40-year-old male had broad complex tachycardia, a cardiologic emergency that might not be related to ventricular tachycardia, but also to severe AD-associated hyperkalemia which, in this particular case, induced, as well, rapidly progressive muscle weakness to quadriparesis.[16] A woman in her 50s was admitted for cardiac tamponade as a consequence of AD.[17] So was a 39-year-old previously healthy male confirmed with APS (autoimmune poly-glandular syndrome)−2.[18]

We identified several articles on adrenal location of a lymphoma. One case of a 66-year-old female with primary adrenal lymphoma (bilateral adrenal masses) was reported with AD and very aggressive evolution.[19] Another women in her 70s, and a 73-year-old patient were reported with an adrenal B-cell lymphoma, a challenging differential diagnosis among AD-associated etiological types.[20,21] Another 67-year-old male was reported with the same condition (primary site of lymphoma generally accounts for less than 1% of all lymphoma cases) which developed into an adrenal crisis.[22] A retrospective study of 26 patients with primary adrenal lymphoma (which is the largest on this disease we identified in 2022) showed that 81% of subjects had suffered bilateral spreading and 63% of them developed AD.[23]

A first case of a 58-year-old female with primary gastric leiomyosarcoma with bilateral adrenal metastasis causing AD was reported with aggressive evolution.[24] A case of a 62-year-old female with prior history of colorectal cancer was found to have bilateral adrenal metastasis-associated AD; bilateral adrenalectomy was performed (in the absence of other metastasis) and confirmed the previous cancer adrenal spreading with a good post-operatory outcome, thus showing the importance of specifically addressing the cause of bilateral adrenal tumors.[25] AD following bilateral adrenalectomy or even unilateral procedure for adrenal tumors-associated hormonal excess still represents an area with many controversies and its clinical recognition might be done later after surgery.[26] Another forgotten presentation of AD amid an adrenal crisis is hypercalcemia.[27]

All these interesting cases we classified as the subsection dedicated to AD awareness due to clinical presentation include 17 case reports (each of a single case), a case series of 3 cases and one study of 26 patients, a total of 40 subjects. As mentioned, prompt recognition might be lifesaving, and the traditional picture of presentation might not be enough (Table 1).

Table 1 A 2022 Retrospective of Challenging Clinical Presentations in Addison's Disease

First Author Reference Number	Type of Study Studied Population	Results
Howarth[9]	• Case series • 36-y-old female with AD, 1DM, pernicious anemia, autoimmune hypothyroidism (C1) • 51-y-old male with AD (C2) • 20-y-old female with AD, autoimmune hypothyroidism, premature ovarian failure (C3)	• C1: AD with mineralocorticoid-only deficiency • C2: AD with spontaneous resolution • AD with symptomatic mineralocorticoid deficiency, not glucocorticoid
Grabarczyk[10]	• Case report • 54-y-old male with AD in the course of anti-phospholipid syndrome	
Giri[11]	• Case report	• Onset of AD with intractable nausea and vomiting
Momayez Sanat[12]	• Case report • 28-y-old female with AD	• Onset of AD as psychotic syndrome
Govind[13]	• Case report • 56-y-old male with tuberculosis-associated AD	• Onset of AD as organic delusional disorder
Patel[14]	• Case report • 63-y-old male with junctional rhythm as AD onset	• Vasopressor support in addition to therapy for newly detected AD
Amusina[15]	• Case report • 26-y-old male with Brugada syndrome-like as AD onset	• Syncope and electrocardiogram anomalies at onset of AD
Ali N[16]	• Case report • 40-y-old male with broad complex tachycardia at AD onset	• Hyperkalemia also caused rapidly progressive muscle weakness to quadriparesis
Page[17]	• Case report • A female in her 50s with cardiac tamponade at AD onset	
Glick[18]	• Case report • 39-y-old male with cardiac tamponade at AD onset	• Confirmation of APS-2
Somasundaram[19]	• Case report • 66-y-old female with primary adrenal lymphoma	• AD due to adrenal lymphoma • Aggressive evolution
Kuhn[20]	• Case report • Female in her 70s with primary adrenal B-cell lymphoma	• AD masking as an adrenal lymphoma
Yousaf[21]	• Case report • 73-y-old female with primary adrenal B-cell lymphoma	• AD due to adrenal lymphoma
Zhang[22]	• Case report • 67-y-old male with primary adrenal lymphoma	• AD due to bilateral involvement
Zeng[23]	• Retrospective study • N = 26 patients with primary adrenal lymphoma	• 81% had bilateral involvement → 63% of them developed AD
Yashar[24]	• Case report • 58-y-old female with bilateral adrenal metastasis causing AD	• First reported case due to primary gastric leiomyosarcoma
Alberti[25]	• Case report • 62-y-old female with bilateral adrenal metastasis causing AD	• Bilateral adrenalectomy confirmed metastasis for a prior colorectal cancer • Good outcome after surgery

(*Continued*)

Table 1 (Continued).

First Author Reference Number	Type of Study Studied Population	Results
Shagjaa[26]	• Case report • 50-y-old female with post-adrenalectomy AD	• Prior unilateral adrenalectomy for primary aldosteronism and recent spare adrenalectomy for this recurrent condition
Aynaou[27]	• Case report • 30-y-old female with AD	• Presentation with hypercalcemia

Abbreviations: AD, Addison's disease; C, case; y, year.

Assessment of Electrolytes Anomalies Due to Addison's Disease

According to our method, we found 6 studies on sodium and potassium levels in AD. AD may be identified starting from very severe hyponatremia among other causes; for instance, this is the case of a young adult male admitted with a low serum sodium level of 88 mmol/L.[28] Inadequate sodium correction might lead to osmotic demyelination.[28]

One single-center retrospective pediatric study on 47 individuals admitted for hyperpotassemia identified 38 subjects with primary hypoaldosteronism (32 of them with CAH due to 21-hydroxylase deficiency) and 9 persons with aldosterone resistance; an additional 4 new cases of AD were identified starting from a clinical suspicion.[29] The data in the pediatric population are less abundant; mostly, genetic forms are detected; hyperkalemia might be a clue, but, generally, the associated aldosterone anomalies require further molecular testing.[29] A single center, retrospective study on 86 patients with hypoaldosteronism (55.4% males; median age of 77 y) showed that 94.6% of them experienced hyperpotassemia, while the diagnosis of AD was established only in 5% of all cases.[30]

Two studies focused on sodium content in tissues. Non-invasive assessment of tissue sodium content showed in 8 newly diagnosed patients with AD versus 22 chronic patients with AD a significant increase in muscle and skin relative sodium signal intensities after starting therapy through a[23] Na-magnetic resonance imaging (MRI-3T scanner) method.[31] A prospective study of 5 patients with AD versus 10 healthy individuals analyzed sodium tissue levels through Na-MRI (7.0 T.) in skeletal muscle; the method provided valuable insight of early metabolic anomalies accompanying adrenal cortex changes in AD including after substitution is started.[32] Of note, another MRI study analyzed gray and white matter brain in autoimmune AD (N = 52) versus 70 healthy controls and these were found to be similar, except for a 4.3% decrease of total brain volume (TBV) in AD, and reduced volume of parietal cortex (right superior area) in males with AD; higher dose of glucocorticoid replacement correlates with smaller TBV which should be the turning point of new concerns for daily practice[33] (Table 2).

Endocrine Tests for Addison's Disease Diagnosis

Particular attention is still needed for the pediatric population with subclinical AI requiring dynamic tests since a random cortisol assay might not be relevant.[38] New methods of plasma renin activity are being developed, this being an essential assessment in primary aldosteronism, but also in AD, CAH, Bartter syndrome, etc. One study introduced a semi-automated method of assay based on liquid chromatography and tandem mass spectrometry.[34] The method described by van der Gugten et al is applicable for other hormone measurements (for instance, aldosterone).[39]

We identified two surveys with respect to clinician's habits in treatment of AD. One survey from Riyadh included the endocrine practice of 162 physicians with respect to the use of a short synacthen test (SST); the indications of SST were: low blood pressure (78%), hyponatremia (65%), hypoglycemia (59%), and hyperkalemia (54%). The assays of baseline cortisol were the most frequent measurements (90%), followed by adrenocorticotropic hormone (ACTH) measurements (78%) whereas only 75% of clinicians assessed the hormones at 30 or 60 minutes, respectively; 93% of them considered the level of plasma cortisol of 550 nmol/L as the normal cutoff.[35] The other survey (among 221 practitioners in pediatric endocrinology) showed that 85% of them used high-dose SST for the diagnosis of AD, but with heterogeneous interpretations of the assays.[36]

Table 2 Studies with Electrolytes and Hormonal Findings in Patients with Addison's Disease (2022)

First Author Reference Number	Type of Study Studied Population	Results
Quigley[28]	• Case report • 26-y-old male admitted for extreme hyponatremia (88 mmol/L)	• Severe hyponatremia at onset of AD
Liu[29]	• Retrospective study • N = 47+4 pediatric patients with hyperpotassemia	• 4 new cases of AD • 38 cases of primary hypoaldosteronism (32 cases with 21 hydroxylase deficiency) • 8 cases with aldosterone resistance
Ruiz-Sánchez[30]	• N = 86 patients with hypoaldosteronism (median age: 77 y)	• 5% had AD
Chifu[31]	• N1 = 8 newly diagnosed patients with AD • N2 = 22 chronic patients with AD • ^{23}Na-MRI assessment	• Significant increase in Na signal intensities in muscle (p = 0.02) and skin (p <0.01) after treatment initiation
Zaric[32]	• Prospective study • N1 = 5 patients with AD • N2 = 10 healthy controls • ^{23}Na-MRI assessment	• Na concentration (skeletal muscle) was lower in AD than controls
Van't Westeinde[33]	• Controlled study • N1 = 52 patients with autoimmune AD • N2 = 70 healthy controls	• Similar MRI-based gray and white matter brain, except for: • AD: 4.3% ↘ of TBV • AD males: ↘ volume of parietal cortex (right superior area) • Higher dose of glucocorticoid replacement correlates with smaller TBV
van der Gugten[34]	• Lab study • New method of assay for plasma renin activity	• Semi-automated method based on liquid chromatography and tandem mass spectrometry
Butt[35]	• Survey-based study regarding the use of SST • N = 192 clinicians	Indications for SST: • Hypotension (78%) • Hyponatremia (65%) • Hypoglycemia (59%) • Hyperkalemia (54%)
Silva[36]	• Survey-based study • N = 221 pediatric clinicians (North America)	• 85% used high-dose SST for AD diagnosis
Mancillas-Adame[37]	• Control study • N1 = 20 patients with obesity • N2 = 20 controls • SST: weight-adapted dose (0.2 µg/kg) versus low dose (1 µg) versus high dose (10 µg)	• 1 µg (30 minutes): cortisol lower in studied group versus controls (p = 0.04) • Any cosyntropin dose (60 minutes): cortisol peak lower in studied group versus controls

Abbreviations: AD, Addison's disease; ACTH, Adrenocorticotropic Hormone; Na, sodium; MRI, magnetic resonance imaging; TBD, total brain volume; SST, short synacthen test; y, year; ↘, decrease.

One of the most interesting and controversial topics remains the use of STT. Since 50% of the patients diagnosed with autoimmune AD have a body mass index (BMI) above 25 kg/m^2, there is a question whether SST should be BMI-adjusted. We mention a study on 20 obese individuals (versus 20 controls) comparing a weight-adapted dose (0.2 µg/kg) versus low dose (1 µg) versus high dose (10 µg). At 30 minutes, cortisol levels were lower in the studied group after 1 µg versus controls (p = 0.04); at 60 minutes, cortisol peak was lower in obese group versus controls regardless of the dose of synacthen, thus the test with 1 µg might not be enough, and a 0.2 µg/kg body dose might be useful[37] (Table 2).

Gene Testing

Congenital Adrenal Hyperplasia Data

CAH recognition (while being distinctive from AD) remains a major challenge in pediatric cases due to its severity and epidemiologic impact among primary adrenal types. A pediatric retrospective study (over a 30-year period) included 28 patients with AI and 25% had CAH while most causes were due to secondary (pituitary) causes.[40]

Mostly remarkable data on CAH reveal new mutations as following. Two new cases of non-classic P450scc deficiency (*CYP11A1* gene) associating AD were identified after initially being misdiagnosed as familial glucocorticoid deficiency. The index of suspicion started with high plasma renin activity. Novel mutations at exon 8 were confirmed: missense (R466W (c1396C>T) and nonsense (c1315C>T). Of note, one sibling responded to hydrocortisone, another was unresponsive and was offered prednisolone.[41] Another report involves salt-wasting CAH in twins (Moroccan population) with pathogenic *HSD3B2* variant [biallelic c.969T > G (p.Asn323Lys)] concomitant with duplication on 10q22.3-q23.2.[42] A case of lipoid CAH (*StAR* mutations) was reported: a child with male external genitalia harboring heterozygous mutation c.772C>T/c.562C>T (of note, a total of previous 47 cases with non-classic lipoid CAH have been reported according to Lu et al).[43] Additionally, 3 novel pathogenic variants of *CYP11A1* in Indian patients with P450 side-chain cleavage deficiency and AD were reported in 2022.[44] A 17-year-old patient was found with AD since the age of 9; he inherited a tri-allelic heterozygous *CYP11A1* mutation and digenic *STAR* loss-of-function variants: c.465+1G>A and p.(E99K)[45] (Table 3).

Table 3 New Original Data on Gene Testing Concerning Addison's Disease (2022 Retrospective)

First Author Reference Number	Type of Study Studied Population	Results
Mosca[40]	• Retrospective study • N = 28 patients with primary and secondary AI	• 25% had CAH
Le[41]	• Case series • 2 siblings with non-classic P450scc deficiency	• Novel *CYP11A1* gene mutation (exon 8): missense (R466W (c1396C>T) + nonsense (c1315C>T)) • AD: • Responsive to hydrocortisone (1 sibling) • Non-responsive to hydrocortisone → switch to prednisolone (1 sibling)
Mellone[42]	• Case series • 2 Moroccan twins with salt-wasting CAH at birth	• Pathogenic *HSD3B2* variant [biallelic c.969T>G (p.Asn323Lys)] + duplication on 10q22.3-q23.2. 2.
Lu[43]	• Case report • 1 male child with lipoid CAH	• *StAR* heterozygous mutation (c.772C>T/c.562C>T)
Phadte[44]	• 3 Indian patients with P450 side-chain cleavage deficiency and AD	• 3 novel pathogenic *CYP11A1* variants ○ Homozygous p.Gly423Asp ○ Heterozygous p.Arg151Trp/p.Pro104Ser ○ Homozygous c.1351 C > T (p.Arg451Trp)
Ali[45]	• Case report • A 17-y-old male with AD since the age of 9	• Tri-allelic heterozygous *CYP11A1* mutation + digenic *STAR* loss-of-function variants: c.465+1G>A p.(E99K).
Gupta[46]	• Pediatric male case report with X-linked adrenoleukodystrophy	• AD onset before cerebral involvement
Wiersma[47]	• Case report • 11-y-old boy with 1 DM + AD	• Confirmation of X-linked adrenoleukodystrophy
Ghori[48]	• Case report • A 20-y-old male with AD confirmed with *ABCD1* mutation	• First case from Pakistan

(*Continued*)

Table 3 (Continued).

First Author Reference Number	Type of Study Studied Population	Results
Dong[49]	• Case series (a 27-y-old, and a 31-y-old male) with *ABCD1* variants	• 2 novel mutations: c.874_876delGAG (p.Glu292del) c.96_97delCT (p.Tyr33Profs*161)
Chen[50]	• Longitudinal study • Screening protocol at birth for *ABCD1* gene (NBS protocol Taiwan) • 12 males+10 females carriers of *ABCD1* variants	• Median follow-up: 2.28 y • 2 new cases (16.7%) of AD
Bonaventura[51]	• Setup of a pilot study (NBS protocol in Italy)	TBA
Gagnon[52]	• Single-center, retrospective study (12 y) • 7 Cases with peroxisomal biogenesis disorders (N = 6) + peroxisomal enzyme deficiency HSD17B4 (N = 1) • Mean age at diagnosis of 0.61 y	• AD prevalence: 4/7 • Heterozygous *PEX1* pathogenic variants of exon 13 (c.2097dupT and c.2528G>A) is at higher risk for AD
Liu[53]	• Single-center, retrospective study • 16 children with non-CAH AD	NGS confirmed a gene mutation (87.5%) as following: • *ABCD1* (37.5%) • *NR0B1* (25.0%) • *NR5A1* (12.5%) • *AAAS* (6.25%) • *NNT* (6.25%)
Ron[54]	• Case report • Newborn with adrenal calcifications	• *SGPL1* mutation
Wang[55]	• Case report • 21-y-old male with AD and hypogonadotropic hypogonadism (congenital adrenal hypoplasia)	• Novel frameshift mutation of *NR0B1* gene (c.1005delC, p.V336Cfs*36)
Ota[56]	• Case series • 2 siblings (a newborn and a 4-y-old boy) with congenital adrenal hypoplasia	• Novel *NR0B1* mutation (p.*471K)
Zhu[57]	• Case report • 26-y-old male with AD and hypogonadotropic hypogonadism (congenital adrenal hypoplasia)	• Novel frameshift mutation of *NR0B1* gene (c.1034delC)
Zhang[58]	• Case report • Transitory central precocious puberty by the age of 11 months remitted after hydrocortisone replacement for AD	• *NR0B1* mutation
Tao[59]	• Case report • 48-day-old Chinese male with Xp21 contiguous gene deletion syndrome underlying complex glycerol kinase deficiency	• Lethal outcome due to acute respiratory failure
Sadeghmousavi[60]	• Case report • 3-y-old boy with AD and tuberculosis	• Chromosome Xp21 deletion syndrome

(*Continued*)

Table 3 (Continued).

First Author Reference Number	Type of Study Studied Population	Results
Tong[61]	• Case report • Newborn male patient with AD and congenital hypothyroidism	• Novel *GNAS* mutation (heterozygous c.432 + 1G > A)
Dursun[62]	• Case report • 8-y-old boy with mitochondrial combined oxidative phosphorylation deficiency-40 (+AD)	• Novel biallelic *QRSL1* mutation (c.300T>A;Y100* and c.610G>A;G204R)
Krasovec[63]	• Case series • 3 siblings (4-y-old, 20-y-old, 21-y-old) with *NNT* mutation	• Novel NNT mutation (biallelic pathogenic variant, homozygous for c.1575dup): AD in oldest brothers
Rivelli[64]	• N1 = 6078 patients with Down syndrome • N2 = 30,326 controls	• Prevalence of AD: OR = 1.68 (95% CI: 1.18–2.4)
Seven Menevse[65]	• Non-CAH AD pediatric study based on TPS	• TPS provided AD diagnosis in 70% of cases with non-CAH AH (N = 29)

Abbreviations: AD, Addison's disease; AI, adrenal insufficiency; CAH, congenital adrenal hyperplasia; DM, diabetes mellitus; N, number; NBS, Newborn Screening protocol; NGS, next generation sequencing; OR, odds ratio; SST, short synacthen test; TBA, to be announced; y, year; TPS, targeted-gene panel sequencing.

Data on Non-Congenital Adrenal Hyperplasia

X-linked adrenoleukodystrophy was the subject of a consensus-based approach.[66] Assessment of very-long-chain fatty acids and *ABCD1* testing are confirmatory. AD in boys represents an index of suspicion since AD may be identified prior to cerebral involvement.[46,47] Awareness of *ABCD1* mutations in young males with AD might help the neurologic outcome.[48] Two novel mutations were reported in a 27-year-old male harboring *ABCD1* mutation c.874_876delGAG (p.Glu292del), and a 31-year-old man with c.96_97delCT (p.Tyr33Profs*161) pathogenic variant.[49] X-linked adrenoleukodystrophy (the most common peroxisomal disorder in the majority carrying *ABCD1* mutations) has been addressed in a longitudinal study involving, among others, *ABCD1* sequencing (including whole exome sequencing): 16.7% (N = 2 males) of the 22 patients (male to female ratio of 12:10) carrying *ABCD1* variants developed AD after a median of 2.28 years. This study is part of the screening protocol at birth that has been added to a larger protocol concerning other peroxisomal diseases in Taiwan.[50] Similarly, a pilot Italian study was launched in 2021, also concerning NBS (newborn screening) of the same condition. The dramatic disease associates AD, adrenomyeloneuropathy and cerebral leukodystrophy (white matter progressive disease) requiring hematopoietic stem cell transplant for survival, thus the importance of early detection.[51]

Another single-center, retrospective study included data regarding peroxisomal diseases of patients who were followed for 12 years and identified peroxisomal biogenesis disorders in 6 individuals and one person with peroxisomal enzyme deficiency HSD17B4 (overall average age at diagnosis of 0.61 years); AD was identified in 4/7 individuals, requiring either daily glucocorticoids replacement in 3 subjects or hydrocortisone in stress circumstances in one case; the authors concluded that heterozygous *PEX1* variants of exon 13 (c.2097dupT and c.2528G>A) are at higher risk for clinical manifestations as AD.[52] A retrospective, single-center study (Northern China, between 2015 and 2021) on 16 pediatric patients with non-CAH AD showed through a next-generation sequencing analysis that 87.5% of them had a gene mutation, *ABCD1* being the most frequent (37.5%) followed by *NR0B1* (25.0%), *NR5A1* (12.5%), and 6.25% for each *AAAS*, and *NNT*.[53]

An interesting analysis on reported cases included 55 patients with sphingosine-1-phosphate lyase insufficiency syndrome (SPLIS) harboring *SGPL1* mutations; 71.2% of patients had AD and 32.7% had hypothyroidism with kidney disorders affecting 80% of them; among 30 *SGPL1* mutations, the most frequent was c.665G > A (p.Arg222Gln) in one-fifth of cases.[67] According to Ron et al, since 2017 when *SGPL1* mutations were first identified, 36 cases were reported

until 2022; the authors added a new case with prenatal adrenal calcifications and congenital nephrotic syndrome in addition to severe combined immunodeficiency.[54] However, Maharaj et al found 50 cases and identified a 64% prevalence of AD.[68] Novel *SGPL1* mutation has been reported in relationship with pediatric presentation without hyperpigmentation.[69]

More than 200 *NR0B1* mutations have been recorded so far. A novel frameshift mutation of *NR0B1* gene (c.1005delC, p.V336Cfs*36) was described in a young male admitted for AD and hypogonadotropic hypogonadism underlying congenital adrenal hypoplasia.[55] Another novel mutation of *NR0B1* (*DAX-1*) gene (p.*471K) was reported in two siblings with different clinical manifestations who inherited the mutation from their mother.[56] A novel frameshift mutation was described in adult X-linked onset congenital adrenal hypoplasia with delayed puberty in a male harboring *NR0B1 gene*: c.1034delC (exon 1).[57] Of note, a carrier of *NROB1* variant experienced transitory central precocious puberty by the age of 11 months that remitted after hydrocortisone replacement for AD.[58]

A dramatic male case with Xp21 contiguous gene deletion syndrome underlying complex glycerol kinase deficiency was reported with rapid fatal outcome due to acute respiratory failure following an infection.[59] Another 3-year-old boy was confirmed with the chromosome Xp21 deletion syndrome while being recognized with AD amid a tuberculosis infection.[60] A neonatal case of AD was reported in a male patient with congenital hypothyroidism carrying a novel *GNAS* mutation (heterozygous c.432 + 1G > A).[61] The case of an 8-year-old boy with AD and multiple somatic complications represents the longest survival with *QRSL1* mutation underlying mitochondrial combined oxidative phosphorylation deficiency-40; Dursun et al reported a novel biallelic mutation - c.300T>A;Y100* and c.610G>A;G204R.[62]

One family with 3 brothers carrying a novel *NNT* (nicotinamide nucleotide transhydrogenase) mutation (biallelic pathogenic variant, homozygous for c.1575dup) was reported with AD in the oldest brothers.[63] Also, we mention here a large study on patients with Down syndrome (N = 6078 versus 30,326 controls) over a 28-year period of time that evaluated 21 endocrine conditions, including AD which was found with a higher prevalence based on OR of 1.68 (95% CI: 1.18–2.4).[64] Another study on pediatric non-CAH AD showed a genetic diagnosis via targeted-gene panel sequencing in 70% of cases (N = 29)[65] (Table 3).

Management and Outcome in Addison's Disease

Etiology-Based Strategy

Disseminated tuberculosis remains an important cause of AD that requires additional anti-infectious drugs in addition with adrenal hormones replacement.[70,71] Other infectious causes might trigger AD requiring a collateral infectious management, as well.[72] Of note, one study from 2023 on North Indian patients enrolled 89 individuals with AD (age: 15–83 years; median of 5.9) between 2006 and 2019. Interestingly, due to infectious aspects of this geographic area, the most frequent cause of AD was histoplasmosis (45%) followed by tuberculosis (15%) and then autoimmune AD (25%), and lymphoma (6%). 42% of subjects were admitted due to an acute crisis. The prevalence of 21-hydroxylase antibodies, respective of thyroid antibodies was higher in autoimmune AD than infectious AD (41% versus 3%, respective 46% versus 5%). The highest mortality was registered in histoplasmosis-associated AD (45%) followed by tuberculosis-related AD (8%) and autoimmune AD (5%). Among the most frequent mortality causes, there were acute adrenal crisis and progression of histoplasmosis.[73]

However, a retrospective, cohort study from 2022 concerning Southern India included 36 patients with PAI between 2014 and 2021 (female to male ratio of 19:17, median age at diagnosis of 35 years) and 87% of patients had non-tuberculosis etiology which might show a shift of etiology even in countries where infectious AD was found to be more frequent than autoimmune AD.[74] Another retrospective Indian study identified 15 cases with adrenal incidentalomas, and 11/15 of them were adrenal histoplasmosis (82% males, 100% HIV negative); 4 individuals developed AD; anti-fungal therapy with itraconazole and/or amphotericin B was added to endocrine approach.[75] A single-center, retrospective study (Eastern India) between 2015 and 2019 included 9 cases of adrenal histoplasmosis; 77% of them had clinically suggestive features of AD; 100% had bilateral involvement; anti-fungal medication was added to standard AD care; the outcome showed that one (1/9) patient died, the response to medication was favorable without AD recovery (8/9)[76] (Table 4).

Table 4 Management in Addison's Disease; Outcome and Complications: A 2022 Retrospective of Original Studies

First Author Reference Number	Type of Study Studied Population	Results
Batool[70]	• Case report • 25-y-old female with disseminated tuberculosis (including brain)	• AD due to tuberculosis • Additional anti-tuberculosis medication (rifampicin, isoniazid, ethambutol and pyrazinamide for 2 months → rifampicin, isoniazid for 10 months)
Khan[71]	• Case report • 50-y-old male with tuberculosis	• AD due to infection • +Associating DM
Kaneto[72]	• Case report • 83-y-old female with AD due to mycobacterium abscesses	
Gunna[73]	• Longitudinal study • N = 89 patients with AD (age between 15 and 83 y)	• Median follow-up: 5.9 y • Causes: ○ Histoplasmosis (45%) ○ Tuberculosis (15%) ○ Autoimmune AD (15%) ○ Lymphoma (6%) • First diagnosis due to adrenal crisis: 42% • Mortality rate: ○ Histoplasmosis (45%) ○ Tuberculosis (8%) ○ Autoimmune AD (5%)
Sridhar[74]	• N = 36 patients with suspected AD (median age of 35 y)	• 87% with non-tuberculosis causes, mainly autoimmune AD
Pal[75]	• N = 11 patients with adrenal incidentaloma underlining adrenal histoplasmosis	• 4/11 experienced AD
Agrawal[76]	• Retrospective study • N = 9 patients with adrenal histoplasmosis	• 77% with AD • 100% with bilateral involvement • Outcome: • 1/9 patient died • 8/9 patients favorable outcome without AD recovery
Gasco[77]	• Longitudinal study (3, 6 months) • N = 21 patients switch from cortisone acetate and hydrocortisone to DH (N = 16; 25 mg/day twice a day, respective N = 5; 20 mg/day 3 times a day)	• Reduction of waist circumference ($p = 0.04$) and BMI ($p = 0.04$) • Improvement of AddiQoL total score ($p = 0.01$) • Increase of HDL-cholesterol ($p = 0.003$)
Ceccato[78]	• Retrospective study • N = 193 patients with AD under fludrocortisone substitution	• 50–75 µg/day (50% of cases) • Mineralocorticoid activity of fludrocortisone was dose dependent Fludrocortisone dose was correlated to sodium ($r = 0.132$, $p < 0.001$), • Potassium ($r = -0.162$, $p < 0.001$) • Renin ($r = -0.131$, $p < 0.001$)
Krutter[79]	• Pilot study on self-management telecare promoter "Addison Care"	TBA
Van't Westeinde[80]	• Case-control study • N1 = 67 patients with AD • N2 = 80 controls	• Similar cognitive tests • Females: more problems with emotional and cognitive regulation • All: more problems of executive functions associated with mental fatigue and lower doses of glucocorticoids
Blacha[81]	• N1 = 40 patients with AD • N2 = 20 controls	• General health, and daytime sleepiness more affected in N1>N2

(*Continued*)

Table 4 (Continued).

First Author Reference Number	Type of Study Studied Population	Results
Li[82]	Tri-center study (US) N = 529 subjects with AI (42.2% with AD).	• Abnormal physical scores associated with: • Female sex (OR = 3.3, 95% CI: 1.8–6) • Replacement dose of hydrocortisone higher than 25 mg per day (OR = 2.3, 95% CI: 1.2–4.6) • Worsen mental scores associated with: • Female sex (OR = 2.1, 95% CI:1.08–4) • Poor family support (OR = 9.1, 95% CI: 2.3–33.3)
Gaw[83]	• Survey-based study • 18 dental teaching hospitals (UK)	• 29% have a written guidance with respect to glucocorticoid replacement
Quinkler[84]	• N = 75 patients with AD evaluated via ISAQ	• Rate of adrenal crisis: 8.8 → 2.4/100 patient-years (pre-pandemic versus pandemic) • ISAQ is similar regardless of the adrenal crisis
Sekhon[85]	• Population-based study (Alberta)	• Patients with AI: • Number of visits per year is 2.3 (as an emergency), and 17.8 (as outpatients)
Zdrojowy-Wełna[86]	• N1 = 29 patients with autoimmune AD (62% females; mean age: 49.7±11.7 y; AD duration: 13.2±13.6 y) • N2 = 33 healthy, age-, sex- and body mass index-matched controls	• Similar DXA results (BMD, T-scores, TBS) • Sclerostin: 44.7±23.5 versus 30.7±10.4 pmol/L (p = 0.006)
Guarnotta[87]	• Longitudinal study • N1 = 35 patients with AD and standard glucocorticoid replacement • N2 = 35 patients with AD and HD	After 60 months: N1 versus baseline • Higher BMI (p = 0.004) • Lower osteocalcin (p = 0.002) • Lower bone alkaline phosphatase (p = 0.029) • Decreased lumbar T-score (p <0.001) • Increased vertebral fractures prevalence (p = 0.021) N2 versus baseline: • Increased alkaline phosphatase (p = 0.019) • Increased lumbar T-score (p = 0.032) • Increase femoral neck T-score (p = 0.023)
Yazidi[88]	• Cross-sectional study • N = 37 patients with AD under hydrocortisone replacement	Prevalence of: • Osteoporosis 14.3% • Osteopenia 34.3% Lumbar and femoral neck BMD associated with: • Daily HC dose (r = −0.36, p = 0.03, r = −0.34, p = 0.02) • Cumulative dose (r = −0.43, p <0.01) Osteocalcin associated with: • Cumulative HC dose (r = −0.43, p <0.01), • Disease duration (r = −0.38, p = 0.02) • Daily HC dose of ≥12 mg/m^2 = independent risk factor for osteoporosis, osteopenia: OR = 9, 95% CI: 1.1–74.6, (p = 0.04)
Conrad[89]	• Population-based study • N = 446,449 patients diagnosed with 19 types of autoimmune diseases	• Risk of cardiovascular disease: • For any autoimmune disease: HR = 1.56 (95% CI: 1.52–1.59) • For AD: HR = 2.83 (95% CI: 1.96–4.09)

Abbreviations: AD, Addison's disease; AI, adrenal insufficiency; AddiQoL, Health-related Quality of Life in Addison's disease; BMI, body mass index; BMD, bone mineral density; CI, confidence interval; DH, dual-release hydrocortisone; DXA, Dual-Energy X-Ray Absorptiometry; HR, hazard ratio; HC, hydrocortisone; ISAQ, immune system assessment questionnaire; OR, odds ratio; N, number of patients; TBA, to-be-announced; TBS, trabecular bone score; y, years.

Considerations of Hormonal Replacement Regimes

One of the causes regarding a suboptimal outcome and poor quality of life (HRQoL) in AD involves suboptimal standard glucocorticoid replacement. Dual-release hydrocortisone (DH) formulation might overcome these negative aspects. A longitudinal study on 21 patients (male to female ratio of 17:4) included 16 patients treated with cortisone acetate (25 mg/day twice a day) switched to DH and 5 subjects treated with hydrocortisone (20 mg/day 3 times a day) that was switched to DH; the results showed a statistically significant reduction of waist circumference and BMI after 3 and 6

months with DH, as well as an improvement of HRQoL, but with a significance decrease of HDL cholesterol, thus the potential benefits of this new regime should be carefully followed.[77]

Fludrocortisone (mineralocorticoid replacement) was studied in a single-center, cohort study on 193 patients with AD (130/193 with autoimmune AD). Doses of 50–75 µg/day were stable in 50% of cases; mineralocorticoid activity of the drug was dose-dependent being correlated with serum Na ($r = 0.132$, $p < 0.001$), potassium ($r = -0.162$, $p < 0.001$) and renin ($r = -0.131$, $p < 0.001$); this indicated the usefulness of renin and plasma electrolytes to adjust the doses of mineralocorticoid replacement in AD as lifespan indication[78] (Table 4).

Quality of Life in Patients with Addison's Disease

As a general note, HRQoL in AD remains lower than in the general non-AD population. One team proposed the launch of a self-management telecare promoter namely "Addison Care", as a new alternative to survey-based assessments in patients older than 65 years. The results of this one-arm, non-randomized pilot study are yet to be published.[79]

A few studies specifically addressed HRQoL evaluation based on interviews. A Swedish study of 67 persons with autoimmune AD (and 80 controls) showed that females (N = 39) experienced more problems with emotional and cognitive regulation versus controls, while both sexes were affected at the level of executive functions in association with mental fatigue and lower doses of glucocorticoids.[80] One study on 40 persons with AI (versus 20 controls) showed that questionnaire-based quality of life was significantly affected in terms of general health and daytime sleepiness regardless of primary or secondary type while increased hydrocortisone replacement is negatively correlated with mental health.[81] One tri-center study from the USA assessed quality of life in 529 subjects with AI (42.2% had AD). Abnormal physical scores were associated with female sex (OR = 3.3, 95% CI: 1.8–6), a replacement dose of hydrocortisone higher than 25 mg/day (OR = 2.3, 95% CI: 1.2–4.6), while worse mental scores were associated with female sex (OR = 2.1, 95% CI: 1.08–4) and poor family support (OR = 9.1, 95% CI: 2.3–33.3).[82]

Moreover, quality of life in terms of preventing adrenal crisis is also reflected by the adjustment of the hormonal replacement when dental procedures and treatment is provided. A survey-based study in 18 dental teaching hospitals (UK) showed that only 29% of them have written guidance for these patients with various doses of glucocorticoids.[83] Interestingly, one study (N = 75 patients with AD) evaluated via ISAQ (immune system assessment questionnaire) the accuracy of predicting an adrenal crisis: ISAQ score was similar pre-pandemic versus pandemic, while the rate of adrenal crisis decreased from 8.8 to 2.4/100 patient-years due to new (pandemic) regulations.[84] A significant disease burden is due to frequent hospitalizations and presentations at hospital. A population-based study from Alberta included patients with AI; the study pointed out that the average number of medical visits compared with regular controls for their endocrine condition was 17.8 per year (as outpatients), and 2.3 per year for presentation as an emergency (this being 3–4 times higher than the average resident population)[85] (Table 4).

Bone Status in Patients Diagnosed with Addison's Disease

We found 3 studies dedicated to an issue that is still a matter of discussion, namely bone status and fracture risk in AD. A study on 29 patients with autoimmune AD (62% females; mean age of 49.7 ± 11.7 years) versus 33 healthy, age-, sex- and BMI-matched controls showed similar results at central DXA (Dual-Energy X-Ray Absorptiometry) in terms of bone mineral density and T-score and TBS (Trabecular Bone Score), but higher sclerostin ($p = 0.006$) with a negative correlation between TBS and AD duration and age that might explain a certain influence of AD on bone status.[86]

A longitudinal study comparing DH (N = 35) to standard glucocorticoid replacement (N = 35) in AD showed after 60 months a higher BMI in standard group ($p = 0.004$) in addition to a lower osteocalcin ($p = 0.002$) and bone alkaline phosphatase ($p = 0.029$) and decreased lumbar T-score ($p < 0.001$) and increased vertebral fractures prevalence ($p = 0.021$) versus baseline. DH groups showed increased bone formation marker alkaline phosphatase ($p = 0.019$), lumbar and femoral neck T-score ($p = 0.032$ and $p = 0.023$, respectively) versus baseline, thus suggesting to be a better option for bone status consideration.[87] A small sized, uncontrolled study on 37 patients with AD under hydrocortisone replacement showed a prevalence of osteoporosis of 14.3%, and osteopenia of 34.3%; lumbar and femoral neck BMD associated with daily hydrocortisone dose ($r = -0.36$, $p = 0.03$, and $r = -0.34$, $p = 0.02$, respectively), and cumulative dose ($r = -0.43$, $p < 0.01$); osteocalcin levels associated with cumulative dose ($r = -0.43$, $p < 0.01$), and disease duration ($r = -0.38$, $p =$

0.02); multivariate regression showed that daily hydrocortisone dose of ≥12 mg/m^2 was an independent risk factor for osteoporosis/osteopenia (OR = 9, 95% CI: 1.1–74.6, p = 0.04)[88] (Table 4).

Cardiovascular Risk in Addison's Disease

One of the most complex studies published in 2022 is represented by a population-based analysis in UK (22 million persons); newly identified subjects with any of 19 types of autoimmune diseases (N = 446,449), including AD, were analyzed considering the cardiovascular risk. The autoimmune cohort (mean age of 46.2 years) displayed a higher risk than controls expressed as HR of 1.56 (95% CI: 1.52–1.59), especially younger individuals and those with multiple autoimmune conditions, AD being among the diseases with highest HR of 2.83 (95% CI: 1.96–4.09)[89] (Table 4).

Discussion

New Insights of Distinct Entities in Addison's Disease

Autoimmune Poly-Endocrine Syndrome Type 1 and 2

Awareness for APS, including for AD, is required at any time in life if the patient is already identified with an autoimmune endocrine disease.[90–94] Recognition of AD is essential, including in children and teenagers that associate a general rate of an adrenal crisis of 6–8 crisis per 100 patient-years.[95–97] One Australian study analyzed the admission rates in children and teenagers with AI: from 3386 admissions, 24% were caused by an adrenal crisis.[98] Pregnancy also represents a hallmark of clinical approach in females with APS.[99] One multi-center, register-based study on 321 females with APS-1 evaluated 43 of them while being pregnant, a total of 83 pregnancies with a delivery rate of 72%; 36% of them had AD.[100]

APS-2, having a prevalence of one case in 1000–20,000 individuals may mimic other conditions, for instance, a young male was misdiagnosed with Crohn's disease, being in fact AD with a good response to hormonal replacement and a normalization of colonoscopic aspects.[101] New conditions might be identified despite a long-term history of different autoimmune disorders, for instance, a case of ocular sarcoidosis was reported in an 86-year-old female with APS-2.[102] APS-2 was detected starting from Takotsubo cardiomyopathy when AD was confirmed.[103] Subacute degeneration of spinal cord due to pernicious anemia in combination with APS-2 led to the AD identification in another presentation.[104] An unusual evolution to end-stage renal disease was reported in a 45-year-old male with APS-2.[105] A first case with APS (specifically APS-2), multiple endocrine neoplasia syndrome (MEN) type 2A and Kabuki syndrome was reported in a 16-year-old male (which is also the first report of a teenager carrying *RET* and KMT2D pathogenic variant).[106]

In 2022, an exceptional case of a 4-year-old girl was identified with both autoimmune APS-1 (*AIRE* mutation) and lacrimo-auriculo-dento-digital syndrome (*FGFR* mutation).[107] A novel *AIRE* mutation namely c.1024C>T (exon 9) was identified in a 36-year-old male with APS-1.[108] A small study on 7 patients with APS-1 (Southern Croatia) evaluated *AIRE* R257X mutations; the patients, who were followed for 17.8 years, had an average age at APS onset of 6.5 years.[109] One study on APS-1 (11 patients from unrelated families of Iranian non-Jewish origin) identified 2 novel mutations: homozygous (c.308–1G>C), and a combination of 2 heterozygotes (c.1496delC + c.232T>C).[110] A post-mortem study on a potential eye donor with APS-1 harboring a mutation at R257X (C to T substitution) at exon 6 showed pigmentary deposits at the level of inner retinal vessels causing retinal atrophy, thus confirming retinitis pigmentosa as part of an APS-AD picture.[111] A novel *AIRE* mutation was identified in a 7-year-old girl with APS-1 complicated with AD-associated left ventricular systolic dysfunction.[112]

A first study exploring the prevalence of APS in the pediatric population included 879 Danish subjects diagnosed with type 1 diabetes mellitus, autoimmune thyroid disease (ATD) or AD who were followed for a decade. Out of 35 individuals identified with APS, 65.7% had APS-3 and none had APS-1. Patients with APS-associated type 1 diabetes and ATD experienced the conditions earlier than non-APS (7.7 versus 9.3 years, p = 0.04; 7.7 versus 13.1 years, p <0.01).[113]

The burden of AD in one family was analyzed in a study on 116 subjects with AD; 74% of them had at least one relative diagnosed with an autoimmune condition (most frequent were Hashimoto thyroiditis, followed by Graves' disease and vitiligo). A correlation between the number of autoimmune comorbidities in one subject with AD and the number of affected relatives was confirmed (p = 0.031); also, female sex was more affected in first- and second-degree relatives.[114]

An interesting study performing screening for autoantibodies against IL22 and IGN-ω, as signature elements of APS-1 detected 29 patients with positive antibodies (a cohort of 675 patients with AD and 1778 subjects with autoimmune endocrine diseases) and further gene testing for *AIRE* showed four new cases of APS-1.[115]

A large study on 912 subjects with autoimmune AD evaluated the prevalence of ATD which is known to be the most frequent endocrine comorbidity of autoimmune AD. This is a nationwide registry-based study (Norwegian National Registry of Autoimmune Diseases); 48% of individuals had ATD; 42% of all patients experienced autoimmune hypothyroidism, while 9% had Graves' disease (but 21% of these were first identified with autoimmune hypothyroidism).[116] A pediatric, single-center, cross-sectional study from Bangladesh (between 2012 and 2016) evaluated 277 children with thyroid diseases; 145 of them had acquired hypothyroidism; the most frequent comorbidity was short stature (35%); 34.4% had autoimmune hypothyroidism, while AD was identified in 1.4% of all pediatric cases with hypothyroidism[117] (Table 5).

Table 5 Autoimmune Poly-Endocrine Syndrome: A 2022 Analysis on PubMed Published Data

First Author Reference Number	Type of Study Studied Population	Results
Jamal[90]	• Case report • 23-y-old male with Hashimoto thyroiditis	Diagnosis of AD 7 months after identification of ATD (APS-2)
Abdullah[91]	• Case report • 20-y-old male newly diagnosed with APS-2	de novo recognition of AD, hypothyroidism
Murphy[92]	• Case report • Female teenager with arrested puberty	Newly diagnosis of APS-2 (hypothyroidism and AD)
Bakkour[93]	• Case report • 9-y-old male with APS-2	AD since the age of 3 HT, CD since the age of 9
Tenório[94]	• Case report • 42-y-old female with APS-1	• Predominant oral manifestations (candidiasis, microdontia, enamel hypoplasia)
Silajdzija[96]	• Case report • 33-y-old male with APS-2	• DR3/DR4+DQ8/DQ2 heterozygosity • AD + HT+ vitiligo + pernicious anemia
Graf[97]	• Case report • 16-y-old male with newly diagnosed 1DM and AD	
Rafique[99]	• Case report • Successful pregnancy in APS-2 female	• Pre-pregnancy counseling • Hyponatremia during labor • Newborn: 90th centile for fetal growth
Laakso[100]	• Multi-center, register-based study • N = 321 females with APS-1 • 36% of them had AD	• 43 females with 83 pregnancies • Delivery rate of 72%
Gonciarz[101]	• Case report • 27-y-old male with APS-2	AD misdiagnosed as Crohn's disease
Pinheiro[102]	• Case report • 86-y-old female with APS-2	Sarcoidosis revealed by uveitis
Batta[103]	• Case report • 50-y-old female with hypothyroidism	Synchronous diagnosis of AD and Takotsubo cardiomyopathy (APS-2)
Bapat P[104]	• Case-report • 50-y-old male with APS-2	Subacute degeneration of spinal cord due to pernicious anemia + AD + HT (+vitiligo)
Ismaeel[105]	• Case report • 45-y-old male with APS-2	Evolution to end-stage renal disease

(*Continued*)

Table 5 (Continued).

First Author Reference Number	Type of Study Studied Population	Results
Park[106]	• Case report • 16-y-old male with APS-2	First report with co-diagnosis of MEN2A and Kabuki syndrome
Zhu[107]	• Case report • 4-y-old girl	APS-1 + lacrimo-auriculo-dento-digital syndrome
Qian[108]	• Case report • 36-y-old male with APS-2	Novel *AIRE* mutation c.1024C>T (exon 9)
Skrabic[109]	• Case series • 7 patients with APS-1	• Mean age at diagnosis: 6.5 y AD was present in 5 cases The age at presentation of AD was between 7 and 14 years
Setoodeh[110]	• Genetic study on 11 patients from unrelated families of Iranian non-Jewish origin	• 2 novel mutations: • Homozygous (c.308–1G>C), • Combination of 2 heterozygotes (c.1496delC + c.232T>C)
Culp[111]	• Case-report • 23-y-old male with APS-1 and fatal outcome	• *AIRE* mutation at R257X (C to T substitution) at exon 6 • Post-mortem confirmation of retinitis pigmentosa
Özer[112]	• Case report • 7-y-old girl with APS-1	• AD-associated left ventricular systolic dysfunction. • Novel AIRE mutation: p.Cys322Arg (c.964T>C)
Bouça[113]	• Observational study (10-y) • 879 Danish children with 1DM, ATD or AD	• 35/879 had APS-3 (65.7%) • Age of onset: • APS-DM versus non-APS-DM: 7.7 versus 9.3 y (p = 0.04) • APS-ATD versus non-APS: 7.7 versus 13.1 y (p <0.01)
Fichna[114]	• Observational study • 116 patients with AD and 221 relatives	• 74% of patients with AD had at least one relative with an autoimmune disease, respectively: • 100/221 - Hashimoto thyroiditis • 25/221 – Graves' disease • 24/221 – vitiligo • 23/221 – 1DM • 15/221 – psoriasis • 12/221 – rheumatoid arthritis • 11/221 – pernicious anemia • 8/221 – multiple sclerosis • 8/221 – premature ovarian failure
Sjøgren[115]	• Cross-sectional study • 675 patients with AD + 1778 subjects with autoimmune endocrine diseases • Testing for autoantibodies against IL22 and IGN-ω	• 29 patients had positive antibodies • 4 new cases of APS-1 (*AIRE* testing)
Meling Stokland[116]	• Nationwide registry-based study (Norwegian National Registry of Autoimmune Diseases) • N = 912 patients with autoimmune AD	Prevalence of: • Autoimmune thyroid conditions (48%) • Autoimmune hypothyroidism (42%) • Graves' disease (9%)
Mahbuba[117]	• Cross-sectional study • N = 145 children with acquired hypothyroidism	Prevalence of: • Autoimmune hypothyroidism (34.4%) • AD (1.4)

Abbreviations: ATD, autoimmune thyroid disease; AD, Addison's disease; APS, autoimmune poly-glandular syndrome; CD, celiac disease; DM, diabetes mellitus; HT, Hashimoto thyroiditis; Il, interleukin; N, number of patients; MEN, multiple endocrine neoplasia; y, years.

Adrenal Hemorrhage

New data on this exceptional event, namely adrenal hemorrhage, are provided in 2022, but the level of statistical evidence remains that of case reports. A young female with APS-2 (Hashimoto thyroiditis and AD) developed adrenal hemorrhage under apixaban for a prior thrombosis; a senior female presented with AD-associated adrenal hemorrhage due to rivaroxaban for thrombosis prevention amid femur surgery.[118] A 45-year-old male was confirmed with bilateral adrenal hemorrhage while being treated with apixaban in addition to a newly detected anti-phospholipid syndrome.[119] Another adult female was reported with bilateral adrenal infarction due to COVID-19 infection; she was known to have autoimmune hepatitis and anti-phospholipid syndrome, as well.[120] Interestingly, 3 more cases of the severe condition were reported due to motor vehicle accidents.[121] An unusual cause was described on a 64-year-old male after a fall complicated with a hip fracture.[122] A new case of Waterhouse-Friderichsen syndrome due to methicillin-resistant *Staphylococcus aureus* bacteremia was reported, too[123] (Table 6).

Immune Checkpoint Inhibitors – Induced Adrenal Failure

ICPs represent a new anti-cancer category and almost 40% of oncologic patients are candidates to this class. Unfortunately, immune-related adverse effects represent a major concern and 10% of these subjects develop endocrine side effects in almost every gland, including primary AI, ICP being the core of a new etiological group of AD.[124] 1–2% of patients under a single ICP develop AD, while those under 2 different types of ICPs have a 5% risk of suffering from AD.[125] Primary and secondary AI might not be reflected by random cortisol measurement, thus the importance of periodic dynamic tests.[126] Among the complex constellation of various side effects, AD is mandatory to be taken into consideration due to its severity.[127–130] A study on newly detected cases of ICP-associated AD included 1134 suspected cases and 46 confirmed AD (US FDA Adverse Event Reporting System); males and elderly had a higher risk of AD ($p < 0.001$ and $p = 0.009$, respectively); lower body weight was associated with a poor outcome in AD (OR = 0.984, 95% CI: 0.969–0.998, $p = 0.029$); anti-CTLA-4 plus anti-PD-1 had a higher risk than anti-PD-1-only regarding AD ($p < 0.001$).[131] One case report also introduced a 74-year-old male with pulmonary malignancy who developed AD under nivolumab, while large trials focused on a large panel of ICP-induced side effects.[129–132] Of note, a compressive study on published cases involving patients that were offered ICPs identified 206 cases of primary and secondary AI and only 5.2% of them

Table 6 Reported Cases with Adrenal Hemorrhage Causing Primary Adrenal Insufficiency

First Author Reference Number	Type of Study Studied Population	Results
Sheklabadi[118]	2 case reports with AH: • 35-year-old female (C1) • 89-year old female (C2)	C1: APS-2 (HT+AD) + apixaban C2: rivaroxaban
Tan[119]	Case report • 45-year-old male with AH	Apixaban + anti-phospholipid syndrome
Machado[120]	Case report • 46-y-old female with bilateral adrenal infarction	COVID-19 infection Co-presence of: autoimmune hepatitis + anti-phospholipid syndrome
Szwarcbard[121]	Case series with AH: • 60-y-old male • 88-y-old female • 46-y-old male	All cases due to motor vehicle accident
Khakwani[122]	Case report • 64-y-old male with AH	Fall + hip fracture +Chronic alcoholism
Kalinoski[123]	Case report 58-y-old male with Waterhouse-Friderichsen syndrome	Methicillin-resistant *Staphylococcus aureus* bacteremia + History of intravenous drug use

Abbreviations: C, case; AH, adrenal hemorrhage; AD, Addison's disease; HT, Hashimoto's thyroiditis; APS, autoimmune poly-endocrine syndrome.

were AD, thus confirming that secondary rather than primary AI is at higher risk.[133] A practical approach from an endocrine perspective was released on behalf of AACE (American Association of Clinical Endocrinology) in 2022 concerning ICPs. Adrenal complications, despite being less frequent that those located in the thyroid and pituitary glands, might create a life-threatening scenario[134] (Table 7).

Also, tyrosine kinase inhibitors such as lenvatinib might induce AD. One study on 13 patients with thyroid cancer showed that 54% of these experienced AD, while 85% of them reported fatigue without requiring cessation of anti-cancer drugs.[135] Another type of drug-induced AD has been reported in relationship with fluconazole use as prophylaxis for hematopoietic cell transplantation (a first such case was reported in 2022).[136]

COVID-19 Infection and Addison's Disease

The COVID-19 pandemic involved at least two practical points when it comes to AD. Early recommendations during the COVID-19 pandemic included patients with AI of any type who were asked to double or triple the doses of daily glucocorticoids (or switch to injectable substitution) when suffering even mild forms of infection or at the moment of each vaccine dose.[137,138] Awareness was mandatory since going through COVID-19 infection required intensive glucocorticoid replacement in severe forms.[139,140] Another aspect concerns two types of virus-induced AI: either primary (for instance, due to adrenal hemorrhage or due to the infection itself acting as trigger for a previously undiagnosed AD) or secondary (as seen in hypophysitis).[141]

The papers concerning COVID-19 infection and AD in 2022 include unusual clinical presentation of AD under these recent circumstances. One teenager with coronavirus-associated myocarditis was identified with AD due to this trigger infection.[142] One male in his 20s was confirmed with AD while being identified COVID-19 positive. This is the first case of AD in a patient with a history of autoimmune disseminated encephalomyelitis that experienced the coronavirus infection.[143] A first case of 4A syndrome (alacrima, achalasia, and AI and autonomic nervous system anomalies) was suspected of COVID-19 and reported.[144] Collaterally, we mention a matched case-control study on 6769 patients with achalasia (versus 27,076 controls) that was strongly associated with AD as reflected by an OR of 3.83 (95% CI: 1.83–8.04).[145] Moreover, an adult male with APS-2 developed an adrenal crisis while going through COVID-19 infection.[146] A 14-year-old girl previously known with vitiligo was confirmed with adrenal crisis due to COVID-19 infection; she developed multisystem inflammatory syndrome in children (MIS-C), this being the first pediatric case of autoimmune AI and hypothyroidism that were diagnosed due to the infection.[147]

Of note, a study analyzing medical deprivation rate in patients with endocrine disease during pandemic showed that individuals with AD had the lowest rate (of 0%) as opposed, for instance, with high rates for differentiated thyroid carcinoma (of 89%).[148]

Table 7 Immune Checkpoint Inhibitors-Induced Addison's Disease

First Author Reference Number	Type of Study Studied Population	Results
Lu[131]	FAERS (US FDA Adverse Event Reporting System) N1 = 1134 suspected AD N2 = 46 confirmed AD	• ICP inducing AD: • Males had a higher risk of AD (p <0.001) • Elderly had a higher risk (p =0.009) • Lower body weight associated with a poor outcome in AD (OR = 0.984, 95% CI: 0.969–0.998, p = 0.029) • Anti-CTLA-4 + anti-PD-1 had a higher risk than anti-PD -1-only of AD (p <0.001)
Galliazzo[132]	Case report 74-y-old male with pulmonary cancer treated with nivolumab	• Newly detected AD
Cui[133]	Sample case series study 206 cases with ICPs-induced primary and secondary AI	• Rate of AD: 5.3%

Abbreviations: AD, Addison's disease; AI, adrenal insufficiency; CI, confidence interval; ICP, immune checkpoint; OR, odds ratio; y, year; N, number of patients; p, p-value.

One questionnaire-based study on 88 individuals with AI who were referred for the first and the second dose of vaccination against coronavirus showed that adjustment of glucocorticoid replacement within the first week after vaccine was necessary only in 8% of them concerning the oral regimes, and none required non-oral administration of glucocorticoids[149] (Table 8).

Unexpected clinical presentations of AD might still surprise us; gathering the data on primary adrenal lymphoma might be one of the most useful trans-disciplinary initiatives to be explored in future. Cutting edge in electrolytes assaying seems to be Na-MRI in AD. Survey-based studies showed a large variation of SST protocols. Further trials on using BMI-adjusted SST are needed. 9 novel mutations on CAH were reported; additionally, 2 novel mutations of *ABCD1*, 3 of *NROB1*, and one of each – *SGPL1, GNAS, QRSL1*, and *NNT*. Studies on infectious AD are mostly provided by India. The spectrum of quality of life assessment in AD goes from studies on using DH regimes (N = 21), and different fludrocortisone doses (N = 193) to questionnaire-based cohorts (N of 40, 67 and 529, respectively) including

Table 8 Data on Addison's Disease Associated with Coronavirus Infection (2022)

First Author Reference Number	Type of Study Studied Population	Results
Eguchi[139]	• Case report • 77-y-old male with previous maintenance hemodialysis and AD with COVID-19 infection	During COVID-19 infection: • Hydrocortisone ↗ to 35 mg/day (non-dialysis days) + 55 mg/day (dialysis days) X 3–4 doses per day (20 mg in the morning, 20 mg before dialysis, 10 mg in the afternoon, and 5 mg in the evening) fludrocortisone ↗ to 0.5 mg/day
Tremblay[140]	• Case report • 8-y-old boy diagnosed with AD during COVID-19 infection	Diagnosis of AD amid infection (autoimmune family history: mother with 1DM)
Sánchez[141]	• Case report • 68-y-old female with AD triggered by COVID-19 infection	Diagnosis of AD amid infection (comorbidities: hypothyroidism and 2DM)
Eskandari[142]	• Case report • 18-y-old male with COVID-19 myocarditis	Diagnosis of AD amid infection and its complications
Beshay[143]	• Case report • Male in his 20s diagnosed with AD during COVID-19 infection	First case with autoimmune disseminated encephalomyelitis and newly diagnosed AD amid infection
Azmoodeh[144]	• Case report • 24-y-old male with 4A syndrome	Suspected of COVID-19 due to presentation
Suryadevara[146]	• Case-report • 65-y-old male with adrenal crisis during COVID-19 infection	History of APS-2
Flokas[147]	• Case-report • 14-y-old girl with adrenal crisis during COVID-19 infection	• History of vitiligo • Newly diagnosed autoimmune hypothyroidism amid infection • First pediatric case with AD and hypothyroidism due to COVID-19
Bozkur[148]	• Retrospective study • N = 3903 patients with endocrine diseases	• Medical deprivation rate in patients with AD of 0% amid pandemic
Pilli[149]	• Questionnaire-based study • N = 88 individuals with AI going through first and the second dose of vaccination against coronavirus	• 8%: adjustment of oral glucocorticoid regimes

Abbreviations: AD, Addison's disease; AI, adrenal insufficiency; DM, diabetes mellitus; y, year; APS, autoimmune poly-glandular syndrome; □, increase.

ISAQ with a poor prediction of an adrenal crisis. New data suggest a pandemic reduction of acute forms rates (8.8. ↘2.4/100 patient-year); while the outcome is highlighted by 2.3–17.8 visits/year in one patient with AD.

The 3 clinical studies specifically addressing bone status and fracture risk in AD offered heterogeneous results (a total of 126 subjects with AD). Most impressive UK cohort on different autoimmune entities pointed out a statistically significant higher cardiovascular risk in AD of 2.83.

We separately acknowledged 4 distinct entities based on practical points. APS domain provided novel genetic combinations: RET+KMT2D, AIRE+FGFR and 4 more new *AIRE* mutations. Five studies (2 observational, 2 cross-sectional and one national cohort) also analyzed different autoimmune-associated risks in AD patients. An additional 9 new cases of adrenal hemorrhage were identified according to our methodology. The strongest new entry in AD field is, in our opinion, ICP. Cui et al gathered 206 published cases of AI and primary type represented only a small fraction of them (5%).[133] Awareness of tyrosine kinase inhibitors-associated fatigue regarding AD might expand the connection with oncologic drugs.[135] Nevertheless, an AD spectrum of a traditional side effect related to with anti-fungal medication might be re-shaped amid increased number of transplantations and a first such case was reported in 2022.[136]

During the third year since the COVID-19 pandemic started, we identified on PubMed 8 new case reports with AD triggered by the infection. New data showed that patients with AI did not suffer from new restrictions for a certain period of time as opposed to other endocrine patients and that the first two doses of vaccines required a higher glucocorticoid dose in less than one out of 10 individuals.[148,149]

Overall, this review covers a recent, wide area of topics related to AD. As limits of the current work, we acknowledge that we followed a limited timeframe and only using PubMed as literature search might bring a potential bias.

Conclusion

To our knowledge, this is the largest retrospective on published data with regard to a 2022 analysis on AD. We are aware than by searching only one database, some papers may be missed. However, consistent data are found. A massive role of genetic diagnosis especially in pediatric cases is highlighted; the importance of both pediatric and adult awareness remains since unusual presentations continue to be described. COVID-19 infection is a strong player amid this third year of pandemic, although we still do not have large cohorts in this particular matter as seen, for instance, in thyroid anomalies. In our opinion, the most important topic is ICPs causing a large panel of endocrine side effects, with AD being one of them, not particularly frequent, but mostly severe, and further studies are expected to provide the statistical impact of it.

Abbreviations

AI, Adrenal insufficiency/adrenal failure; ACTH, Adrenocorticotropic Hormone; AD, Addison disease; AACE, American Association of Clinical Endocrinology; APS, autoimmune poly-endocrine syndrome; ATD, autoimmune thyroid disease; BMI, body mass index; CAH, congenital adrenal hyperplasia; DH, dual-release hydrocortisone; DXA, Dual-Energy X-Ray Absorptiometry; HR, hazard ratios; HRQoL, Health-related quality of life; ICP, immune checkpoint inhibitors; ISAQ, immune system assessment questionnaire; MEN, multiple endocrine neoplasia; MIS-C, multisystem inflammatory syndrome in children; MRI, magnetic resonance imaging; N, number of patients; NBS, Newborn Screening; NNT, nicotinamide nucleotide transhydrogenase; SST, short synacthen test; SPLIS, sphingosine-1-phosphate lyase insufficiency syndrome; TBV, total brain volume; TBS, Trabecular Bone Score.

Disclosure

The authors report no conflicts of interest in this work.

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