Review Article

A narrative review: an update on primary adrenal insufficiency (PAI) in pediatric population※

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Background and Objective: This article aims to provide an update on etiology, diagnosis, and management of primary adrenal insufficiency (PAI), also known as Addison's disease in pediatric population, while focusing on rare monogenic causes. PAI is a rare condition which results in destruction of the adrenal cortex leading to cortisol and aldosterone deficiency. Autoimmunity, infections, malignancy, genetic and metabolic disorders, and iatrogenic causes such as medications that cause adrenal hemorrhage (anticoagulants) or impairs glucocorticoid synthesis and action are known etiologic factors. Although autoimmunity is the most common cause of PAI in adolescents and adults, genetic causes are more common in children. Despite significant advancements made in understanding the pathogeneses of PAI, availability of diagnostic tools and treatment, in many cases, PAI remains unrecognized until the affected individual presents in acute adrenal crisis.

Methods: Literature was searched from PubMed, MedlinePlus, Science Direct, and Google Scholar, using appropriate search terms. We included articles up to November 2021, focusing on new developments since 2019.

Key Content and Findings: There are a large number of genetic and non-genetic causes of PAI, which can occur at a variety of times and with a variety of co-occurring symptoms across the lifespan. Knowledge of the time of onset of various causes of PAI and chronology of later-onset symptoms can aid the clinician in determining the utility of genetic testing in patients with PAI of unknown etiology.

Conclusions: PAI has a number of potential underlying etiologies and can affect a broad spectrum of patients, from pediatrics to geriatrics. Since its first description by Addison, significant advancements have been made in understanding adrenal gland development and function. While PAI remains a relatively rare condition, it has severe and precipitous implications when it arises. Having a high index of suspicion is the key for early diagnosis of PAI and the prevention of life-threatening adrenal crisis. Corticosteroid and mineralocorticoid replacement is necessary to prevent morbidity and life-threatening adrenal crisis.

Keywords: Primary adrenal insufficiency (PAI); Addison's disease; steroidogenesis; autoimmunity; stress dose

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Introduction

Primary adrenal insufficiency (PAI), also known as Addison's disease, is characterized by glucocorticoid (cortisol) and mineralocorticoid (aldosterone) deficiency and can be a potentially life-threatening condition if unrecognized. The association between clinical features of PAI and pathological changes of adrenal glands on 11 patients was first described by Dr. Thomas Addison, a British surgeon, in 1855 (1). PAI was a fatal disease until the discovery of synthetic steroids in 1940s (2).

PAI is a rare disorder, though its prevalence is noticeably increased from 40 to 70 per million in the 1960s to 110–140 per million in the 2000s (3-5). In adults, the incidence of PAI is estimated at 4.4–6.0/million/year (6) and is primarily due to autoimmune destruction of the adrenal cortex. There are no data on the incidence of PAI in children other than congenital adrenal hyperplasia (CAH) due to 21 hydroxylase deficiency, which is the most common cause of PAI in children with the incidence of 1:15,000 to 1:20,000 worldwide (7).

Other causes of PAI include infectious diseases, malignancies, rare genetic disorders, iatrogenic factors, infiltrative, and metabolic conditions (*Table 1*). Regardless of the etiologic factor, PAI continues to present significant challenges regarding diagnosis in early stages due to its rarity and nonspecific signs and symptoms in either children or adults. Despite advancements in our understanding of pathogenesis of PAI and availability of diagnostic tools and treatment, most patients with PAI seek medical attention from two or three physicians before the correct diagnosis is made (28). In many cases, it remains unrecognized until the affected individual presents in acute adrenal crisis.

This narrative review aims to provide an update on etiology, including recently added new genetic causes, diagnosis, and management of PAI in pediatrics. We present this article in accordance with the Narrative Review reporting checklist (available at https://pm.amegroups.com/article/view/10.21037/pm-22-2/rc).

Methods

A literature search was performed using the following scholarly search engines: PubMed, MedlinePlus, Science Direct, and Google Scholar. Appropriate search terms were utilized with a time range up to November 2021. Particular focus was given to articles published since 2019. Search terms focused on pathologic conditions with a significant presentation of PAI and genetic dysfunctions that highlight important molecular mechanisms within the adrenal gland (*Table 2*).

Etiology

PAI may present at any age. However, the frequency of etiology varies noticeably in relation to the patient's age and gender. While tuberculosis was the main cause of PAI until the early 20th century, autoimmune destruction of all three layers of the adrenal cortex became the leading cause in developed countries and is being the most common etiologic factor in adolescents and adults. Autoimmunity may occur isolated or as a part of autoimmune polyglandular syndrome type 1 (APS-1) or autoimmune polyglandular syndrome type 2 (APS-2). Autoimmune PAI is more common in women than men (female to male ratio 1.5–3.5:1) (29,30). In infants and children, however, genetic causes, especially steroidogenic enzyme defects known as CAH, are the most common cause of PAI (19). In addition to CAH, mitochondrial disorders, Wolman disease, and the Smith-Lemli-Opitz syndrome are rare causes of PAI due to impaired steroidogenesis. While mutations in genes responsible for adrenal gland development including *DAX-1* [X-linked adrenal hypoplasia congenita (XL-AHC)], steroidogenic factor 1 (*SF1*), melanocortin 2 receptor (*MC2R*), MC2R accessory protein (*MRAP*), *CDKN1C*, sterile alpha motif domain containing 9 (*SAMD9*), and polymerase epsilon-1 (*POLE1*) result in adrenal gland dysgenesis or hypoplasia, APS, infections, amyloidosis, sarcoidosis, adrenal leukodystrophy, adrenal metastases or hemorrhage can cause adrenal gland destruction and lead to PAI (*Table 1*).

Adrenal gland dysgenesis

XL-AHC—DAX1 (NR0B1)

DAX1 (NR0B1) (dosage sensitive sex reversal, adrenal hypoplasia congenita critical region on the X chromosome) is an orphan protein of the nuclear receptor superfamily that is a key regulator of appropriate adrenal and gonadal development. The protein regulates transcription when bound to its ligand, acting on both promoters and transcription factor targets (31). Mutations have been characterized in the protein-encoding gene that lead to either protein truncation or alterations in ligand binding activity, resulting in partial loss of function (19). *DAX1* mutation is a relatively common and likely underdiagnosed

Table 1 Causes of primary adrenal insufficiency*

Syndrome	Protein	Gene	Locus
Adrenal gland dysgenesis			
X-linked adrenal hypoplasia Congenita (8)	DAX1	*NR0B1*	Xp21.2
Steroidogenic factor-1 (SF1) (9)	SF-1	*NR5A1*	9q33.3
ACTH resistance syndromes			
Familial glucocorticoid deficiency type 1 (10)	ACTHR	*MC2R*	18p11.2
Familial glucocorticoid deficiency type 2 (11)	MRAP	*MRAP*	21q22.11
Triple A (Allgrove) syndrome (12)	ALADIN	*AAAS*	12q13.13
SERKAL syndrome (13)	WNT4	*WNT4*	1p36.12
IMAGe syndrome (14)	CDKN1C	*CDKN1C*	11p15.4
IMAGe-like syndrome (15)	POLE1	*POLE1*	12q24.33
MIRAGE syndrome (16)	SAMD9	*SAMD9*	7q21.2
Adrenal gland destruction			
Autoimmune	Variable	Variable	–
Metabolic lipid disorders			
Adrenoleukodystrophy (17)	ABCD1	*ABCD1*	Xq28
Wolman disease (18)	Lysosomal acid lipase	*LIPA*	10q23.31
Zellweger spectrum syndrome (19)	PEX family proteins	*PEX* gene family	Multiple
Sphingolipidosis (20)	SGPL1	*SGPL1*	10q22.1
Infections	–	–	–
Bilateral adrenal hemorrhage	–	–	–
Metastatic tumors	–	–	–
Other (sarcoidosis, amyloidosis)	–	–	–
Steroidogenetic defects			
Congenital adrenal hyperplasia (CAH)			
21-hydroxylase deficiency (21)	CYP21A2	*CYP21A2*	6p21.33
11-β-hydroxylase deficiency (22)	CYP11B1	*CYP11B1*	8q24.3
3-β-hydroxysteroid dehydrogenase deficiency (23)	3β-HSD	*HSD3B1*, *HSD3B2*	1p12
17-α-hydroxylase/17,20-lyase deficiency (24)	CYP17A1	*CYP17A1*	10q24.32
Cholesterol desmolase deficiency (25)	CYP11A1	*CYP11A1*	15q24.1
Mitochondrial deletion syndromes (26)	Variable	Variable	mtDNA
Smith-Lemli-Opitz syndrome	DHCR7	*DHCR7*	11q13.4
Sphingolipidosis	SGPL1	*SGPL1*	10q22.1
Drugs	–	–	–

*, gene loci confirmed using the HUGO Gene Nomenclature Committee at the European Bioinformatics Institute (27). ACTH, adrenocorticotropic hormone; MIRAGE, major findings of myelodysplasia, infection, restriction of growth, adrenal hypoplasia, genital phenotypes, and enteropathy; SERKAL, SEx Reversion, Kidneys, Adrenal and Lung dysgenesis; IMAGe, intrauterine growth restriction, metaphyseal dysplasia, adrenal hypoplasia congenita, genital anomalies; SGPL1, sphingosine-1-phosphate lyase-1; HUGO, Human Genome Organisation.

Table 2 The search strategy summary

Items	Specification
Date of search	Multiple dates
Databases and other sources searched	PubMed, MedlinePlus, Science Direct, and Google Scholar
Search terms used	Primary adrenal insufficiency, Addison's disease, steroidogenesis, autoimmunity, pediatric, stress dose
Timeframe	Up to November 2021, especially focusing on articles published last 3 years
Inclusion criteria	Clinical trial
	Meta-analysis
	Randomized controlled trial
	Review
	Systematic review
	Language: English
Exclusion criteria	Study was published in a language other than English
	Observational study design
Selection process	All authors equally conducted the selection, reviewed and agreed with the selected article

cause of PAI, especially XL-AHC; in one study, 12/95 patients with PAI of unknown etiology were found to have *DAX1* mutations. The most commonly characterized pathologic gene contained an amino-terminal stop variant, with p.W235 and p.E256 identified in 50% of cases (32). Clinically, these patients present with adrenal insufficiency that often presents in early infancy but may instead appear during childhood after a stressful stimulus is encountered (bimodal distribution) (33). All children with *DAX-1* mutation will require mineralocorticoid replacement and any who survive to puberty will develop hypogonadotropic hypogonadism (34). The typical phenotype at puberty is PAI with hypogonadotropic hypogonadism, with *DAX1* mutations accounting for two-thirds of all patients with PAI and hypogonadotropic hypogonadism in adolescence (19,34). Due to the variable age of presentation and many atypical phenotypes of subjects with *DAX-1* mutations, clinicians should consider genetic testing any children with PAI of unknown etiology who later develop hypogonadotropic hypogonadism (35).

SF1 (NR5A1)

SF1 is a protein of the nuclear receptor superfamily that is implicated in both adrenal and gonadal differentiation Most identified mutations of this gene are heterozygous and arose from *de novo* mutation during spermatogenesis; in rare cases, female carriers may pass this mutation to their male child in a sex-limited dominant manner (19). Adrenal insufficiency is very rare in patients with SF1 deficiency, with the primary presenting symptoms being more related to disordered sexual differentiation, ovarian failure, or male factor infertility (32). Males will most often display testicular dysfunction but may also manifest hypospadias (5–7%) or rarely 46,XY sex development (DSD). A broad spectrum of 46,XY DSD phenotypes have been described in association with SF1 deficiency; the most common is ambiguous genitalia without Mullerian structures with and normal adrenal function (34). In females, the primary manifestation is 46XX sex reversal; early-onset PAI is still rare but more common than in 46,XY and may present before 14 months with salt-losing adrenal failure and seizures (36). Heterozygous females may also present with hypertension and ambiguous genitalia during early adulthood (37). Streak gonads may be observed in conjunction with phenotypically normal external female genitalia (31). Although homozygotic mutations are not generally identified in humans, mouse models have shown that complete loss of SF1 function results in agenesis of adrenal glands and gonads leading to severe adrenal insufficiency and neonatal death (38).

Adrenocorticotropic hormone (ACTH) resistance syndromes

Familial glucocorticoid deficiency (FGD)

Mutations in the *MC2R* or the *MRAP* are the etiology of FGD (39). About 25% of FGD cases are due to mutation of *MC2R*, which acts as the endogenous receptor for ACTH; these cases are categorized as FGD-1. Affected individuals mostly present in the neonatal period with hypoglycemic seizures, hyperpigmentation, and signs of immunosuppressed status (40).

A more recently identified second gene, *MRAP* encodes a small single transmembrane domain protein that is essential for proper targeting and transport of the ACTH receptor (MC2R) to the cell membrane (41). Due to this interconnected functionality, mutation or loss of *MRAP* presents similarly to *MC2R* deficiency and is responsible for 20% of identified cases of hereditary unresponsiveness to ACTH (42). Clinically, lack of

appropriate MRAP activity will manifest in the first months of life as an FGD-like condition with electrolyte imbalances, hypoglycemia, and other signs of PAI (32). Generally, only glucocorticoids are affected in FGD as the renin-angiotensin-aldosterone system is intact, but some volume-depleted patients may have elevation of aldosterone (43). Symptomatically distinguishing defects in *MRAP* from defects in *MC2R* is difficult, but patients with *MRAP* mutations may have onset of symptoms later in life than the classic first 6 months associated with *MC2R* mutations. This has led to the concept of FGD type 1 and 2, with type 2 being similar to other etiologies of FGD but with later onset and lack of extra-adrenal features such as cryptorchidism and testis adenoma (34,44). However, 56% of patients will present with hypoglycemia leading to convulsions; in severe cases respiratory distress will also be noted. Other etiologies of PAI cause these symptoms significantly less often (32). Despite an average higher age at presentation for *MRAP* deficiency, patients may still manifest severe salt loss, adrenal insufficiency, and hyperpigmentation within the first months of life (36).

In addition to *MC2R* and *MRAP*, FGD has been associated with mutations in *MCM4* (the mini chromosome maintenance-deficient 4 homolog gene), NNT (nicotinamide nucleotide transhydrogenase), *TXNRD2* (thioredoxin reductase 2), *GPX1* (glutathione Peroxidase 1), and *PRDX3* (peroxiredoxin 3) (41).

Allgrove syndrome

One form of ACTH resistance syndrome is Allgrove syndrome, also termed "Triple A" syndrome (45). This syndrome is due to autosomal recessive mutation of the *AAAS* gene on chromosome 12q13, resulting in a truncated protein product (46). *AAAS* codes for the protein ALADIN, a nucleoporin that is primarily expressed within the pituitary, adrenals, and pancreas (47). The pathogenesis of Allgrove syndrome is multifactorial and has not been clearly elucidated, but likely is related to impaired oxidative stress response within affected cells (48). The age of presentation for various features of Allgrove syndrome is highly variable, with glucocorticoid deficiency appearing at any time from 6 to 19 years of age. Achalasia similarly may present early in infancy or in adulthood (49). A recent genetic analysis of 70 Chinese children with adrenal insufficiency determined that 2/70 of these children had a mutation within the *AAAS* gene, highlighting Allgrove syndrome as an important component of the PAI differential (50).

SERKAL (SEx Reversion, Kidneys, Adrenal and Lung dysgenesis) syndrome

Wnt family member 4 (WNT4) is an essential WNT ligand for proper development of adrenocortical cells, as well as organogenesis of the lung and kidney. Inadequate WNT4 function results in overactivity of protein kinase A during fetal development; double inactivation of WNT4 (autosomal recessive) will result in fetal nonviability (38). Fetuses with characterized WNT4 double inactivation will undergo spontaneous abortion with autopsy revealing lack or underdevelopment of lungs, kidneys, and adrenal glands, as well as sex reversal in 46,XX fetuses (34). This is termed SERKAL syndrome (female sex reversal and dysgenesis of kidneys, adrenals, and lungs), may also result in Mullerian aplasia or hyperandrogenism, and has only been characterized within one family and two fetuses (36).

IMAGe and IMAGe-like syndromes

IMAGe syndrome is caused by mutations in *CDKN1C* (cyclin-dependent kinase inhibitor 1C), a key negative cell cycle regulator gene (19). IMAGe syndrome is an acronym for the major findings of intrauterine growth retardation (IUGR), metaphyseal dysplasia, adrenal hypoplasia congenita, and genital anomalies in males (51). This syndrome may be diagnosed at a wide range of ages across the lifespan, from prenatal to teenage years, but is most commonly identified at birth (52).

Logan *et al.* recently described biallelic loss of function variants in *POLE1* (polymerase epsilon-1) in 15 individuals from 12 families; these individuals had similar phenotypic features of IMAGe syndrome, distinctive facial features, and immunodeficiency characterized by lymphocyte depletion (53). *POLE1* is a key DNA-leading strand polymerase, and its loss of function disrupts DNA replication (19).

MIRAGE (major findings of myelodysplasia, infection, restriction of growth, adrenal hypoplasia, genital phenotypes, and enteropathy) syndrome

MIRAGE syndrome is a recently described complex disorder characterized by myelodysplasia, infections, restriction of growth, adrenal hypoplasia, genital anomalies, and enteropathy (16). Affected individuals also have developmental delay, dysmorphism, chronic lung disease, central nervous system abnormalities, thrombocytopenia/anemia, and high mortality rate (54). Most mortality occurs early in the life span due to infection (55).

MIRAGE syndrome is caused by a gain-of-function variant in the growth repressor, *SAMD9* gene located on the long arm of chromosome 7 (7q21.2) (56).

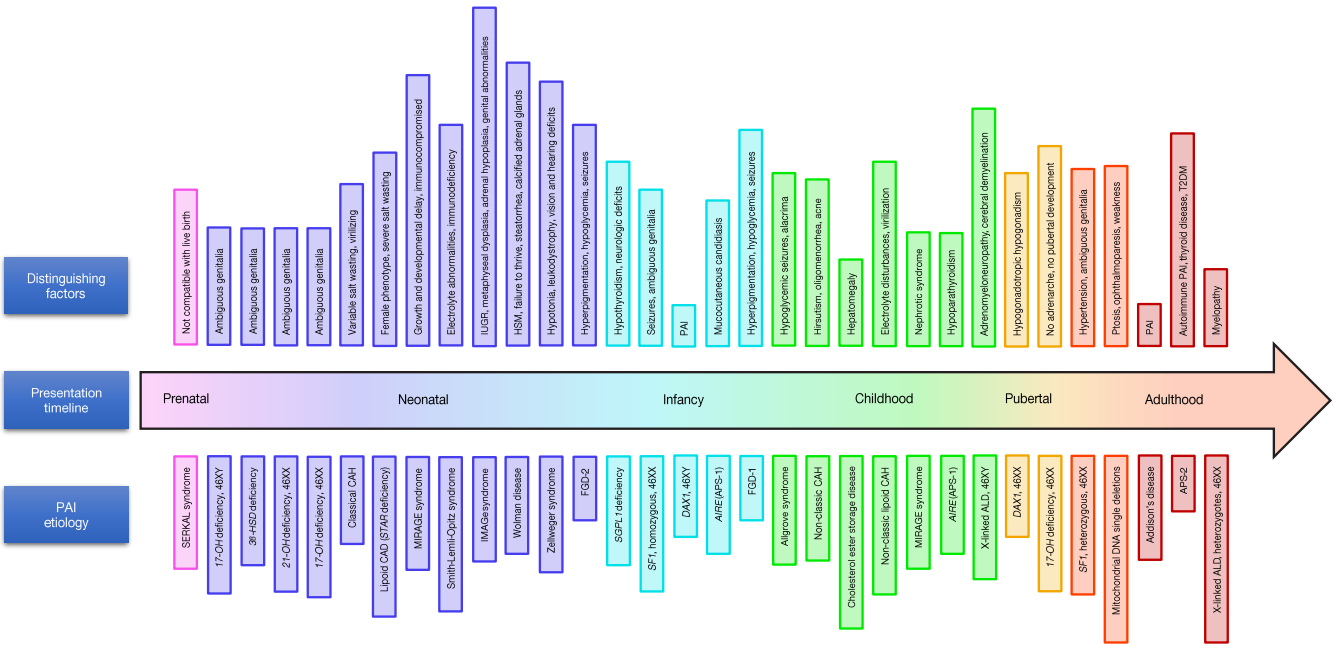

Figure 1 Genetic etiologies of PAI and distinguishing signs and symptoms by age of manifestation. PAI, primary adrenal insufficiency; IUGR, intrauterine growth retardation; HSM, hepatosplenomegaly; T2DM, diabetes mellitus; OH, hydroxylase; SERKAL, SEx Reversion, Kidneys, Adrenal and Lung dysgenesis; HSD, hydroxysteroid dehydrogenase; CAH, congenital adrenal hyperplasia; STAR, steroidogenic acute regulatory protein; MIRAGE, major findings of myelodysplasia, infection, restriction of growth, adrenal hypoplasia, genital phenotypes, and enteropathy; IMAGe, intrauterine growth restriction, metaphyseal dysplasia, adrenal hypoplasia congenita, genital anomalies; FGD, familial glucocorticoid deficiency; SGPL1, sphingosine-1-phosphate lyase; SF1, steroidogenic factor 1; AIRE, autoimmune regulator; CAH, congenital adrenal hyperplasia; ALD, adrenoleukodystrophy; APS1, autoimmune polyglandular syndrome type 1.

Adrenal gland destruction

Autoimmune PAI (Addison's disease)

Autoimmune adrenalitis is the most common cause of PAI in older children and adults, accounting for 68–94% of cases (57). More than 80% of patients have circulating serum autoantibodies to the 21-hydroxylase, the key steroidogenic enzyme (29). The presentation of Addison's disease occurs at a mean age of 30; although autoimmune PAI may occur in isolation, over 50% of cases have other autoimmune disorders as part of APS-1 or APS-2 (58).

Genetic etiologies of PAI and distinguishing signs and symptoms by age of manifestation are shown in *Figure 1*. Mutation of the autoimmune regulator (*AIRE*) gene on chromosome 21q22.3 results in the disorder APS-1, also referred as autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED). The *AIRE* gene is responsible for appropriate clonal selection of T-cells within the thymus, and loss of this function results in proliferation of auto-sensitized immune cells. The estimated prevalence of APS-1 is about 1 in 80,000 in general population, equally affecting males and females (59,60) but is higher in certain ethnic groups, such as Iranian Jews (1/9,000) (61), Sardinians (1/14,000) (62), and Finns (1/25,000) (63,64). APS-1 is defined by the presence of at least two of the three major components of the disease: chronic mucocutaneous candidiasis, acquired hypoparathyroidism, and autoimmune Addison's disease. APS-1 typically presents first with chronic mucocutaneous candidiasis by 5 years of age—with 50% presenting before 2 years of age—hypoparathyroidism by 8 to 10 years of age, and Addison's disease by 12 years of age (65). However, the clinical presentation of APS-1 is highly variable even within the same family and this phenomenon may result in delayed diagnosis (63). While 80–90% of European patients present with one or more major components of APS-1 at the onset of disease, the majority of American APS-1 patients initially show organ-specific nonendocrine symptoms (urticarial eruption, hepatitis, gastritis) early in life and significant delay in the development of classical

components of APS-1 (66). In addition, almost all patients have anti-interferon-alpha and anti-interferon omega autoantibodies before the appearance of clinical symptoms of APS-1. These observations have led to changes in criteria for diagnosis of APS-1 (67):

One of the three following criteria is required for a definitive diagnosis:

(I) Presence of at least two of the three major components: chronic mucocutaneous candidiasis, hypoparathyroidism, autoimmune adrenal insufficiency;
(II) One of the major components if a sibling has a confirmed diagnosis of APS-1;
(III) APS-1 mutations in both *AIRE* genes.

Probable diagnostic criteria

(I) Presence of one of the three major components: chronic mucocutaneous candidiasis, hypoparathyroidism, autoimmune adrenal insufficiency (before 30 years of age) and at least one of the minor components (chronic diarrhea, keratitis, periodic rash with fever, severe constipation, autoimmune hepatitis, vitiligo, alopecia, enamel hypoplasia);
(II) Any component and presence of anti-interferon antibodies;
(III) Any component and antibodies against aromatic L-amino acid decarboxylase, tryptophan hydroxylase, tyrosine hydroxylase or NACHT leucine-rich repeat protein.

Approximately 50% of autoimmune PAI is associated with APS-2, also known as Schmidt's syndrome (68). APS-2 is defined by autoimmune PAI in conjunction with autoimmune thyroid disease and/or type 1 diabetes mellitus (T1DM) (68,69). Other autoimmune conditions such as vitiligo, chronic atrophic gastritis with or without pernicious anemia, chronic autoimmune hepatitis, alopecia, and myasthenia gravis may also present at the time of diagnosis or develop with time in patients with APS-2. The prevalence of disease is estimated as one in 20,000 in the general population (70) with the peak incidence at the 3rd and the 4th decade of life. It is three times more common in females than males (71).

APS-2 is a polygenic disease and does not have a simple inheritance pattern (72). The genetics of APS-2 are controlled by the major histocompatibility (MHC) complex human leukocyte antigen (HLA) haplotypes including DR3-DQ2, DR4-DQ8, DRB1-0301, and DRB1-0404 which confer disease risk to multiple autoimmune disorders. Moreover, genes within the MHC region and some of genes responsible for T-cell signaling including C*TLA4*, the *PTPN22* have been linked to APS-2 and isolated autoimmune PAI (29).

Other causes of adrenal gland destruction

Metabolic lipid disorders [X-linked adrenoleukodystrophy (ALD), Wolman syndrome, Zellweger syndrome], sphingolipidosis, multiple infection agents (mycobacterial, bacterial, viral, and fungal), amyloidosis, sarcoidosis, adrenal metastases (e.g., lung, breast, colon, lymphomas), or hemorrhage can cause adrenal gland destruction and lead to PAI (28).

X-linked ALD

X-linked ALD is characterized by defective peroxisomal beta oxidation of saturated unbranched very long-chain fatty acids (VLCFA) that results accumulation of saturated VLCFA (≥22 carbons) in tissues and body fluids, particularly, in adrenal cortex and central nervous system causing PAI and progressive cerebral inflammatory demyelination, respectively (73). Additionally, the accumulation of VLCFA in Leydig cells causes testicular dysfunction (74), and in hair cells results in thin and sparse hair (75). ALD is a progressive neurodegenerative disease. The responsible gene for ALD is the *ABCD1* [ATP-binding cassette *(ABC)* transporter subfamily D member 1] gene that encodes the peroxisomal ABC half-transporter ABCD1 (formerly adrenoleukodystrophy protein, ALDP), and is mapped to chromosome Xq28 (76). The estimated incidence of ALD is 1:16,800 (77). Although VLCFA levels in plasma are already elevated at birth, there is a wide variation of clinical outcomes from the rapidly progressive and if untreated fatal cerebral demyelination, cerebral ALD, in boys between 5–12 years, to milder forms of adrenomyeloneuropathy in boys and adult men, or isolated adrenal insufficiency (78). In isolated adrenal insufficiency, neurological symptoms of ALD may present years later. Therefore, in any boy with PAI, but no adrenal autoantibodies, VLCFA measurement should be included in the assessment (32).

Adrenal insufficiency affects >80% of ALD patients. The exact mechanism of adrenal insufficiency is poorly understood. It is thought that the chronic accumulation of cholesterol with saturated VLCFA in the adrenal cortex leads to cell dysfunction and cell death (79).

Neonatal ALD is a variant of Zellweger syndrome spectrum, characterized by hypotonia, leukodystrophy, and vision and sensorineural hearing deficiencies. Adrenal insufficiency and renal calcifications can present later in

childhood (80).

Women who are heterozygous carriers of ALD may develop signs of myelopathy as they get older (from 18% before 40 years of age to 80% by 60 years of age). They may also develop adrenal insufficiency (<1%) (81).

Wolman disease

Wolman disease is an autosomal recessive disorder due to mutations in the *LIPA* gene at locus 10q23.31 on the chromosome 10 (18). The *LIPA* gene codes for lysosomal acid lipase (LAL), which catalyzes the conversion of cholesterol esters and triglycerides to cholesterol, glycerols, and free fatty acids (82). LAL deficiency results in intracellular massive accumulation of cholesterol esters and triglycerides, particularly in liver, spleen, gastrointestinal tract, and adrenal glands. It is very rare with the incidence of less than 1 in 100,000 live births (83). Affected infants present with hepatosplenomegaly, failure to thrive, steatorrhea, and vomiting within the first months of life. Enlarged adrenal glands with calcifications is evident on plain X-rays by 6 months of age (82). If left untreated, Wolman disease is fatal within the first year of life. Cholesterol ester storage disease (CESD) is the moderate form of LAL deficiency, presenting at various times throughout the lifespan with hepatomegaly, hyperlipoproteinemia, and accelerated atherosclerosis. The age of presentation varies with the amount of functional enzyme produced, with the most common presenting symptom being hepatomegaly (84). Adrenal gland calcification is rare in CESD form (85).

Peroxisome biogenesis disorders

Peroxisome biogenesis disorders are a group of autosomal recessive disorders in the Zellweger spectrum (PBD-ZSD) and characterized by impaired peroxisome function due to mutations in any of *PEX* genes (86). The Zellweger spectrum includes Zellweger syndrome (severe form), neonatal ALD (intermediate form), and infantile Refsum disease (mild form). There is a significant overlap of signs and symptoms. Affected infants present with craniofacial anomalies, failure to thrive, hypotonia, seizures, cataracts, and adrenal insufficiency (87).

Sphingolipidoses

Sphingolipidoses are a broad category of disease that result from a deficiency of any enzyme required for the proper degradation or storage of lipids. Sphingosine-1-phosphate lyase (SGPL1) deficiency is a sphingolipidosis that affects the adrenal glands resulting in PAI within 12 months of birth. Other manifestations include nephrotic syndrome, failure of sexual development, ichthyosis, neurological dysfunction, immunodeficiency, and hypothyroidism (36).

Infectious agents

Infectious agents may cause adrenal insufficiency by either colonizing and destroying the adrenal gland directly or by secreting endotoxins that secondarily damage the adrenal gland. One example is the secretion of endotoxins by N. meningitidis, which may cause hemorrhage within the adrenal glands and shock, referred to as Waterhouse-Friderichsen syndrome (88).

Bilateral adrenal hemorrhage

Bilateral adrenal hemorrhage owing to trauma, especially in a newborn after prolonged labor or traumatic delivery, sepsis, antiphospholipid syndrome, and heparin induced thrombocytopenia may cause the loss of adrenal function (28).

Steroidogenic enzyme defects

Congenital adrenal hyperplasia

CAH is a group of autosomal recessive disorders of steroidogenesis characterized by impaired cortisol synthesis with a compensatory increase in ACTH leading to adrenal hyperplasia. The most common cause of CAH is deficiency of 21-hydroxylase (95% of cases) (89) followed by 11-beta-hydroxylase, and 3-beta-hydroxysteroid dehydrogenase enzymes (90). The less often enzyme deficiencies are 17-alpha-hydroxylase/17,20-lyase and cholesterol desmolase. Each enzyme is encoded by a specific gene and mutations causing CAH have been identified. Depending on the severity of enzyme deficiency, CAH can be divided into classical and non-classical (milder and symptoms start later in life) forms. Classical CAH due to 21 hydroxylase deficiency is further divided into salt-wasting and simple virilizing forms (91). In both 21-hydroxylase and 11-beta hydroxylase deficiencies, excess androgen production causes ambiguous genitalia in newborn females and progressive postnatal virilization in both sexes. In 3-beta-hydroxysteroid dehydrogenase deficiency, mineralocorticoid, glucocorticoid, and sex steroids production is decreased resulting in undervirilized males and some virilization in females. CAH due to 17-alpha-hydroxylase/17,20-lyase is characterized by decreased production of adrenal and gonadal steroids; females have no adrenarche and lack of pubertal development, males have ambiguous genitalia (92).

Congenital lipoid adrenal hyperplasia—deficiency of steroidogenic acute regulatory protein (StAR) is a rare, severe form of CAH and most common in Japan and Korea (89). The *STAR* gene is affected in this disorder preventing the initial conversion of cholesterol into pregnenolone, entirely disabling the adrenal steroid

Table 3 Signs and symptoms of adrenal insufficiency and crisis

Adrenal insufficiency
Signs
Hyperpigmentation of sun exposed areas, skin creases, mucous membranes, groin, axillae, scars
Hypotension with worsening postural hypotension
Dehydration
Failure to thrive
Hypoglycemia
Apnea (newborn)
Symptoms
General malaise
Fatigue
Headache
Weakness
Dizziness with standing
Weight loss
Anorexia
Abdominal pain, nausea, vomiting, diarrhea
Salt craving
Icterus (newborn)
Adrenal crisis
Signs
Hypotension
Tachycardia
Reduced or altered consciousness
Dehydration (hypovolemia)
Apnea (newborn)
Symptoms
Severe weakness
Altered behavior, confusion or extreme fatigue
Abdominal pain, vomiting
History of febrile illness or stress

synthesis pathway. Due to loss of androgen production, both 46,XY, and 46,XX infants will present with a female phenotype; corticosteroid production loss results in severe salt-wasting presenting in the first month of life (93). A non-classic form of lipoid CAH exists, corresponding to only partial deficiency of *STAR* protein activity which presents at a median of 4 years of age. In addition to virilization, non-classic lipoid CAH will manifest with electrolyte imbalances—due to decreased mineralocorticoid production—and PAI (94).

More detailed information on CAH can be found in numerous review articles that have already been published (95,96).

Mitochondrial DNA deletion syndromes are characterized by mitochondrial respiratory chain deficiency that result in a spectrum of overlapping phenotypes, including Kearns-Sayre syndrome (KSS), Pearson syndrome, and progressive external ophthalmoplegia (PEO) (97). Although neuromuscular symptoms are prominent, endocrine dysfunction, particularly diabetes, is common. Other endocrine dysfunctions include short stature, hypothyroidism, hypogonadism, and adrenal insufficiency (98).

Smith-Lemli-Opitz syndrome

Smith-Lemli-Opitz syndrome is a rare disorder due to a deficiency of the 7-dehydrocholesterol reductase enzyme (DHCR7), which converts 7-dehydrocholesterol into cholesterol. This leads to an accumulation of 7-dehydrocholesterol and a deficiency of all adrenal steroids (99). All patients will present with intellectual disability, as well as electrolyte abnormalities, adrenal insufficiency, hypoparathyroidism, hypothyroidism, and various manifestations of immunodeficiency (100).

Diagnosis and treatment

Clinical presentation of PAI is the result of glucocorticoid and mineralocorticoid deficiency. Signs and symptoms include weakness, fatigue, musculoskeletal pain, weight loss, hypotension, abdominal pain, and hyperpigmentation of the skin and mucous membranes (*Table 3*). As melanocyte-stimulating hormone (MSH) is made simultaneously with ACTH, overproduction of ACTH by the pituitary in response to PAI also increases circulating levels of MSH (101). The characteristic hyperpigmentation is a result of the increased stimulation of the melanocortin 1 receptor (encoded by *MC1R*) by MSH (102,103). In children, this can be most noticeable in areas that typically do not get significant sun exposure, such as the axilla, palms, and groin. Patients may present in acute adrenal crisis if their condition is not previously known or poorly managed.

Diagnosis of PAI is based on low morning serum cortisol concentrations and confirmed by low stimulated

Table 4 Treatment of primary adrenal insufficiency in children and adolescents (73,75,77)

Medications/condition	Dose/comments
Maintenance dosing	
Hydrocortisone	8 mg/m^2/day in 3 divided doses
Fludrocortisone	100 µg daily
Sodium chloride (for infants less than 6 months of age)	1–2 g/day in divided doses given in feedings
Hydrocortisone stress dosing	
Febrile illness	
Temperature >38 ℃	Double maintenance dose
Temperature >39 ℃	Triple maintenance dose
If unable to tolerate oral intake	Intramuscular or subcutaneous hydrocortisone to be given:
	Infants: 25 mg
	School age children: 50 mg
	Adolescents: 100 mg
Surgery	
Minor surgery	25–75 mg/day in divided doses for 1–2 days, then returning to maintenance dosing
Major surgery or trauma	50 mg/m^2 IV bolus, followed by 50–100 mg/m^2/day in divided doses given every 6 hours. Appropriate IV fluids with dextrose and NaCl should also be given
	Return to oral dosing as clinically able
Adrenal crisis	
Hydrocortisone	50–100 mg/m^2 bolus; followed by 50–100 mg/m^2/day in divided doses given every 6 hours
0.9% normal saline (for shock/hypovolemia)	20 mL/kg bolus, repeated to max 60 mL/kg in 1 hour
10% Dextrose (for hypoglycemia)	5–10 mL/kg administered slowly at a rate of 2–3 mL/min

IV, intravenous.

cortisol during a corticotropin stimulation test. PAI is highly likely if serum cortisol is <140 nmol/L (5 µg/dL) and ACTH concentration that is elevated greater than 2 times above the upper reference limit for the specific assay (104). The gold standard for PAI diagnosis is the corticotropin stimulation test (cosyntropin or ACTH test) and should be performed to unless basal results are absolute. Commonly used, the short corticotropin test measures cortisol levels before and 30 and/or 60 minutes after IV or IM administration of cosyntropin. A dose of 250 µg is utilized in children ≥2 years of age; in children less than 2 years of age a dose of 125 µg is used and in infants a weight-adjusted dose of 15 µg/kg is recommended (104). While the cutoff used to make the diagnosis is assay-specific, a peak stimulated cortisol level exceeding 500 nmol/L (18 µg/dL) is widely accepted as evidence of sufficient adrenocortical response.

Children with PAI require glucocorticoid and mineralocorticoid replacement. Hydrocortisone is preferred in children with PA to minimize linear growth retardation and pubertal delay often common in more potent, longer acting glucocorticoids. Dosing of corticosteroids is based on physiological basal secretion of cortisol at 6–9 mg/m^2/day (105,106). Recommended starting dose is 8 mg/m^2/day in two to four divided doses with maintenance dosing typically between 6–12 mg/m^2/day (104,107). Improved adherence and ease of administration comes with fewer daily doses. First morning dose should be higher than subsequent doses with last dose administered 4–6 hours before bedtime to mimic physiological cortisol secretion (108). Longer acting glucocorticoids such as prednisone or prednisolone at 5.0–7.5 or 0.25–0.5 mg/day in divided doses, respectively, are alternative treatment options in older adolescent patients. Mineralocorticoid replacement is accomplished by giving fludrocortisone at 50 to 200 µg/day with typical dose at 100 µg/day. Infants who require mineralocorticoid replacement will need sodium chloride supplementation due to insufficient sodium intake through breast milk or formula at a dose of 17–34 mEq/day in several divided doses with feedings (*Table 4*).

Patients should be closely monitored for signs of inadequate or excessive glucocorticoid and mineralocorticoid replacement. Decreased growth velocity, excessive weight gain and other signs and symptoms of Cushing syndrome may indicate excessive glucocorticoid treatment. Likewise, poor weight gain, fatigue and hyperpigmentation may suggest need for increased glucocorticoid treatment. Inadequate mineralocorticoid replacement may present with salt craving, poor weight gain, dehydration, and hyponatremia with hyperkalemia and elevated renin. Hypertension, edema, and low renin concentration may suggest excessive mineralocorticoid replacement. Infants and young children should be monitored more frequently, monitoring growth

and blood pressure. The latest Endocrine Society Clinical Practice Guidelines recommend to use clinical assessment including growth velocity, body weight, blood pressure, and energy levels to adjust glucocorticoid and mineralocorticoid dosing in children (103).

Stress dosing and management of adrenal crisis

Patients with PAI require increased corticosteroid dosing during illness and stress. Recommended hydrocortisone dose is double or triple the daily maintenance for 24–48 hours or until afebrile for 24 hours before returning to maintenance. Children with low grade fever (<38 ℃) may not need stress dosing. Patients who are vomiting or have diarrhea, who may be unable to take medication orally, will require intramuscular hydrocortisone (*Table 4*).

Adrenal crisis may occur in severe illness, physical or physiological stress, inadequate treatment, or abrupt withdrawal of corticosteroids. Patients with suspected crisis should immediately be treated with Solu-Cortef (hydrocortisone sodium succinate) 100 mg/m^2 intravenous or intramuscular. High dose hydrocortisone should continue at 100 mg/m^2/day intravenously divided every 6 hours. Once patient is able to tolerate oral intake, hydrocortisone should be given at 25–30 mg/m^2/day or triple maintenance dose in three divided doses. Once stress is over, hydrocortisone should be gradually weaned back to daily maintenance dose.

Conclusions

PAI has a number of potential underlying etiologies and can affect a wide spectrum of patients, from pediatrics to geriatrics. Since its first description by Addison, great advancements have been made in the understanding of adrenal gland development and function. While PAI remains a relatively rare condition, it has serious and precipitous implications when it arises. Having a high index of suspicion is the key for early diagnosis of PAI and the prevention of life-threatening adrenal crisis. Corticosteroid and mineralocorticoid replacement is necessary to prevent morbidity and life-threatening adrenal crisis. Adrenal crisis is an endocrine emergency that requires high doses of corticosteroids along with intensive medical monitoring.

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