REVIEW

DOI: 10.4274/jcrpe.galenos.2024.2024-6-24-S

J Clin Res Pediatr Endocrinol 2025;17(Suppl 1):66-71

The Causes and Diagnosis of Non-congenital Adrenal Hyperplasia Primary Adrenal Insufficiency in Children

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Abstract

Primary adrenal insufficiency (PAI) is a critical condition that requires prompt diagnosis and initiation of treatment. Diagnosis can be challenging due to various underlying causes, including defects in adrenal gland development, resistance to adrenocorticotropic hormone, autoimmune causes, and metabolic problems. A specific diagnosis is essential for developing a treatment plan and identifying other possible accompanying pathologies. Biochemical studies, genetic analyses, and imaging techniques are helpful in establishing a specific diagnosis. This evidence-based guideline includes the specific diagnoses that cause PAI and their clinical and genetic features. It also provides evidence-based steps to follow when making a diagnosis.

Keywords: Primary adrenal insufficiency, diagnosis, children, adolescent

Introduction

Primary adrenal insufficiency (PAI) is a rare but life-threatening condition that requires urgent diagnosis and treatment. It is characterized by inappropriate synthesis of glucocorticoids and/or mineralocorticoids and/or adrenal androgens (1). Unlike adults, congenital causes due to genetic disorders are predominant in the etiology of childhood PAI (2,3). Although most of these diseases start in the neonatal period and infancy, the diagnosis of mild or non-classical forms can occur at later ages or in adulthood (4). The most common cause of PAI is congenital adrenal hyperplasia (CAH) (5,6). Non-CAH, as a sub-group of PAIs, can be categorized into four groups: i) defects in adrenal gland development; ii) resistance to adrenocorticotropic hormone (ACTH) and similar conditions; iii) autoimmune causes; and iv) metabolic causes.

In childhood, PAI may rarely develop due to physical conditions, such as adrenal hemorrhage, infiltration (e.g., neuroblastoma), and some viral (e.g., Epstein-Barr virus, cytomegalovirus, human immunodeficiency virus) and bacterial infections (e.g., tuberculosis) (5,7,8). In addition, medications that disrupt cortisol synthesis, such as ketoconazole, aminoglutethimide, and etomidate, and medications that accelerate glucocorticoid metabolism, such as phenytoin, phenobarbital, and rifampicin, are involved in the etiology of PAI (9).

This evidence-based review with good practice points was developed by the Adrenal Working Subgroup of the Turkish Society for Pediatric Endocrinology and Diabetes. We developed this evidence-based review for "The Causes and Diagnosis of Non-CAH Primary Adrenal Insufficiency in Children".

Cite this article as: Atar M, Akın L. The causes and diagnosis of non-congenital adrenal hyperplasia primary adrenal insufficiency in children. J Clin Res Pediatr Endocrinol. 2025;17(Suppl 1):66-71

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Conflict of interest: None declared
Received: 27.06.2024
Accepted: 31.10.2024
Epub: 23.12.2024
Publication date: 10.01.2025

Clinical Findings and Etiological Clues

Clinical signs of cortisol deficiency include fatigue, weakness, weight loss, arthralgia, orthostatic hypotension, hyponatremia, hypoglycemia, hypercalcemia, direct hyperbilirubinemia, lymphocytosis, and eosinophilia (6). Clinical signs of mineralocorticoid deficiency include growth retardation, nausea, vomiting, abdominal pain, dizziness, hypotension, dehydration, and hypovolemic shock (8). Neonates have the highest predisposition to present with mineralocorticoid deficiency (10). Typically, aldosterone production in newborns is higher than in childhood (11). This may be due to the relative mineralocorticoid resistance in the kidneys during the neonatal period, unpredictable fluid intake, and/or low sodium content of the breast milk (12). Related to aldosterone deficiency, hyponatremia, and hyperkalemia can be biochemically detected within the first two weeks of life (4). Mineralocorticoid deficiency is always associated with adrenocortical dysfunction (6).

Patients with PAI may present with adrenal crisis, causing signs of acute cardiovascular decompensation, such as hypotension, tachycardia, and shock (1). In contrast, chronic PAI may present with non-specific symptoms, such as malaise, fatigue, weakness, anorexia, and weight loss. Absence or delayed adrenarche suggests a deficiency of adrenal sex steroids (13). Hyperpigmentation (on the skin, areola, genitalia, axillae, nail beds, joints, and scars) does not occur in secondary adrenal insufficiency but is present in 90 % of patients with PAI. However, it may not be detected in infancy until the sixth week or in the first episode of the disease (9).

The age at onset of adrenal insufficiency is an important clue in the diagnosis (4). A family history of similar cases is instructive, and a history of sudden death or death secondary to gastroenteritis or infection suggests potential missed cases. The presence of comorbid findings, such as intrauterine growth retardation, steroid-resistant nephrotic syndrome, hypogonadotropic hypogonadism, and enteropathy, and detailed examination of history and physical examination are essential in providing guidance to the specific diagnosis (Table 1) (6,9).

Making a specific diagnosis of PAI is essential in determining the need for mineralocorticoid use and diagnosing and monitoring other related non-adrenal pathologies (4,6). Sanger sequencing or targeted next-generation sequencing techniques can help with a genetic diagnosis if a specific cause is suspected. In cases where the alleged mutation cannot be detected, next-generation sequencing and panel, whole exome analysis, or whole genome analysis are used as further investigations (14). Reaching a specific genetic diagnosis is also important for providing genetic counseling for families (5,15,16).

Adrenal imaging modalities that can be used as an aid in the diagnosis of PAI include ultrasound, radiography, magnetic resonance imaging, and computed tomography. They have limited indications for diagnostic use in childhood. In CAH and congenital lipoid adrenal hyperplasia, the adrenal glands are usually large but may be normal on adrenal imaging. In Cytochrome P450scc deficiency, adrenal glands may be small. In diagnosing PAI, they help to investigate etiological causes, such as hemorrhage, tuberculosis, and tumor infiltration. Calcifications are present in adrenal glands in Wolman's disease, tuberculosis, and sphingosine-1-phosphate lyase (SGPL1) deficiency. (17,18).

The clinical conditions associated with PAI and adrenal crisis have been adequately defined following previous studies and clinical experience (Table 1). Since the clinical presentation of chronic adrenal insufficiency in childhood may be insidious, there may be a delay in diagnosis. However, delayed diagnosis leads to high mortality, especially in case of adrenal crisis. Therefore, the indication for testing for adrenal insufficiency should be at an optimum level, avoiding delays in testing (1,19).

Good practice point:

1. Patients with clinical findings compatible with glucocorticoid or mineralocorticoid deficiency should be investigated for adrenal insufficiency. Blood samples should be reserved for biochemical tests, and waiting for test results should not delay treatment (1⊕⊕⊕O).

Diagnostic Tests for Primary Adrenal Insufficiency

Serum and salivary cortisol: The most accessible assessment to confirm the diagnosis of PAI is low basal cortisol levels compared to high ACTH levels. ACTH levels above 300 pg/mL are sufficient for maximal cortisol response (1,20). However, the kit and reference ranges should be taken into consideration. Failure to reach adequate levels of cortisol synthesis despite elevated ACTH indicates that the adrenal cortex cannot adequately respond to ACTH stimulation and provides strong evidence for PAI.

In early PAI cases, adequate cortisol response to elevated ACTH may be found, and elevated ACTH may be the first

Table 1. Hereditary causes of primary adrenal insufficiency (non-CAH)

Disease	Gene	Associated clinical features
Developmental adrenal gland disorders		
X-linked congenital adrenal hypoplasia (DAX-1)	*NR0B1*	Hypogonadotropic hypogonadism, gonadotropin independent precocious puberty
Adrenal hypoplasia associated with steroidogenic factor-1 defect	*NR5A1*	46, XY DSD and 46, XX DSD, primary ovarian failure, disorders of spermatogenesis
IMAGe syndrome	*CDKNC1*	IUGR, metaphyseal dysplasia, genital anomalies
IMAGEI syndrome	*POLE1*	IUGR, skeletal deformities, immune deficiency, developmental hip dysplasia, atypical facial appearance
Pallister-Hall syndrome	*GLI3*	Hypothalamic hamartoma, hypopituitarism, polydactyly, imperforate anus, bifid epiglottis
MIRAGE syndrome	*SAM9D*	Myelodysplasia, growth retardation, infections, enteropathy, genital anomalies
SeRKAL syndrome	*WNT4*	46, XY DSD, renal dysgenesis, pulmonary hypoplasia
Pena-Shokeir syndrome	*DOK7* *RAPSN*	Fetal akinesia, IUGR, arthrogryposis, facial anomalies, pulmonary hypoplasia, intestinal malrotations, cystic hygroma, cleft palate, cryptorchidism
Meckel-Gruber syndrome	*MKS1*	Cystic renal disease, CNS malformation, polydactyly, hepatic abnormalities
Galloway-Mowat syndrome	*WDR73*	Early onset severe encephalopathy, epilepsy, microcephaly, optic atrophy, hiatal hernia, nephrotic syndrome
Hydrolethalus syndrome	*HYLS1*	Hydrocephalus, absent midline structure of the CNS, micrognathia, polydactyly, pulmonary defects
Resistance to the effect of ACTH and similar disorders		
Familial glucocorticoid deficiency type 1	*MC2R*	Mostly normal MC activity, tall stature, subclinical hypothyroidism, characteristic facial appearance (hypertelorism, medial epicanthus, frontal bossing)
Familial glucocorticoid deficiency type 2	*MRAP*	Normal MC activity
AAA-Triple A syndrome	*AAAS*	Alacrima, achalasia, mental retardation, deafness, hyperkeratosis, autonomic nervous system disorders
DNA repairing defects	*MCM4*	Natural killer cell defects, short stature, microcephaly, recurrent viral infections, chromosomal breaks
Bioinactive ACTH	*POMC*	Symptoms of POMC deficiency accompanied by high ACTH levels
Mitochondrial ROS detoxification defects		
Nicotinamide nucleotide transhydrogenase deficiency	*NNT*	Isolated GC deficiency, subclinical hypothyroidism, insulin-dependent type 1 DM, precocious puberty
Thioredoxin reductase deficiency	*TXNRD2*	Isolated GC deficiency, cardiac defects
Glutathione peroxidase deficiency	*GPX1*	Isolated GC deficiency
Peroxiredoxin deficiency	*PRDX3*	Isolated GC deficiency
Autoimmunity		
Isolated autoimmune adrenalitis	*CLTA-4* *HLA-DR3* *HLA-DR4*	
APS (autoimmune polyglandular syndrome) type 1 (APECED)	*AIRE*	Chronic mucocutaneous candidiasis, hypoparathyroidism, and other autoimmune diseases (autoimmune thyroid diseases, type 1 DM, pernicious anemia, alopecia, vitiligo, hypergonadotropic hypogonadism, hypophysitis)
APS type 2	*CLTA-4* *HLA-DR3* *HLA-DR4*	Autoimmune thyroid disease, type 1 DM, premature ovarian failure, vitiligo, and pernicious anemia
APS type 4	*CLTA-4* *HLA-DR3* *HLA-DR4*	One or more autoimmune diseases (atrophic gastritis, pernicious anemia, celiac disease, myasthenia gravis, hypophysitis, alopecia, vitiligo, hypogonadism)

Table 1. Continued

Disease	Gene	Associated clinical features
Metabolic causes		
Disorders of cholesterol synthesis/metabolism		
Smith-Lemni Opitz syndrome	*DHCR7*	IUBG, mental retardation, microcephaly, atypical facial appearance, polydactyly, urogenital anomalies, syndactyly between 2nd and 3rd toes
Abetalipoproteinemia	*MTP*	Ataxia, retinopathy, acanthocytes in peripheral smear, fat malabsorption
Familial hypercholesterolemia	*LDLR*	Xanthomas, coronary artery disease, corneal arcus
Wolman disease	*LIPA*	Subcapsular punctate calcifications in the adrenal glands, growth retardation, malnutrition secondary to malabsorption, xanthomatous changes in the hematopoietic system and intestines, lungs, brain
Peroxisomal diseases		
X-linked adrenoleukodystrophy	*ABCD1*	Progressive neurodegeneration, cognitive and behavioral changes, progressive hearing and vision loss, dementia, spasticity, seizures
Zellweger spectrum disorders	*PEX*	Hypotonia, seizures, encephalopathy, hepatic failure
Endoplasmic reticulum defects		
Sphingosine-1-phosphate lyase 1 deficiency	*SGPL1*	Steroid-resistant nephrotic syndrome, ichthyosis, neurological disorders, hypothyroidism, undescended testis
Mitochondrial diseases		
Kearns Sayre syndrome	MtDNA deletions, *MTTL1*	Progressive external ophthalmoplegia, ptosis, cardiac conduction defects
GFER-associated mitochondrial encephalopathy	*GFER*	Encephalomyelopathy, congenital cataract, hypotonia, hearing loss, lactic acidosis, respiratory failure
Mitochondrial DNA polymerase deficiency	*POLG*	Infantile epilepsy, metabolic strokes, chronic ataxia, neuropathy, ophthalmoplegia, type 1 DM, hypothyroidism
MELAS syndrome	Various mitochondrial genes	Mitochondrial myopathy, encephalopathy, lactic acidosis, stroke-like attacks
Pearson syndrome	Various mitochondrial genes	Low birth weight, growth retardation, sideroblastic anemia, exocrine pancreatic dysfunction
Mitochondrial complex 1 deficiency	*NDUFAF5*	IUGR, agenesis of the corpus callosum, abnormal hair, congenital left diaphragmatic hernia, lactic acidosis
Impaired synthesis and action of aldosterone		
Aldosterone synthase deficiency	*CYP11B2*	Isolated mineralocorticoid deficiency
Mineralocorticoid resistance	*NR3C2*	Isolated mineralocorticoid deficiency

ROS: reactive oxygen species, ACTH: adrenocorticotropic hormone, POMC: proopiomelanocortin, DM: diabetes mellitus, IUGR: intrauterine growth retardation, CAH: congenital adrenal hyperplasia, GC: glucocorticoid, CNS: central nervous system, DSD: disorders of sex development

finding (1). In infancy, basal serum cortisol level may not be reliable due to variations in circadian rhythm, sleep patterns, intrauterine growth retardation, maternal stress level, and corticosteroid-binding globulin levels (4,21). Threshold cortisol values indicating adequate cortisol levels may vary depending on the laboratory device and method used (22). The diagnosis of adrenal insufficiency should be confirmed with dynamic tests in the presence of low morning serum cortisol levels and normal or low serum cortisol levels in times of stress.

Circadian rhythm may not develop until the age of three years. There is no definite consensus regarding the serum cortisol level sufficient to exclude the diagnosis of PAI. Still, a cortisol level above 17.3-20 mcg/dL is considered sufficient in children without stress (23,24). Recently, the ability to evaluate serum cortisol with methods including liquid chromatography/tandem mass spectrometry (LC-MS/MS) has become valuable in preventing drug, diet, and other steroid hormone interactions in immune methods. Another essential advantage of LC-MS/MS over immunoassays is the ability to evaluate multiple steroids in a single analysis, up to 15 or more in some methods, thus significantly expanding the identification of different forms and underlying causes of adrenal insufficiency (25).

A different method for assessing cortisol synthesis capacity is salivary cortisol. Since salivary cortisol is 10-50 times less abundant than serum cortisol levels, it should be evaluated with sensitive measurement methods. This method is less invasive because it does not require blood sampling. In contrast to serum cortisol, salivary cortisol assessed by LC-

MS/MS is not affected by changes in corticosteroid-binding globulin levels (26). Salivary cortisol levels during Synachen test measured by LC-MS/MS method have been shown to correlate with serum cortisol levels when the cut-off values are set at 18 mcg/dL for serum cortisol and 500 ng/dL for salivary cortisol, respectively, for adrenal sufficiency with 100% sensitivity and specificity (27) Although serum and salivary cortisol levels can be used for PAI assessment, exact cut-off values still need to be determined. However, the diagnosis based on serum and salivary cortisol levels is only valid in acute situations where it is not possible to wait for the Synacthen (cosyntropin or tetracosactide) test (1).

Synacthen (synthetic ACTH) tests: Tetracosactide or cosyntropin (Synacthen) is a synthetic peptide containing 39 amino acids with the same amino acid sequence as the N-terminal 24 amino acids of ACTH (28). In the high-dose Synacthen test, adrenal insufficiency is diagnosed by evaluating cortisol levels taken at 30 and 60 minutes following intravenous administration of the Synacthen. A peak cortisol level above 18-20 mcg/dL is considered as sufficient response (1,29). At the same time, a 2-3-fold increase in the cortisol level from basal cortisol or a rise of 7 mcg/dL at 30 or 60 minutes of the test is also considered a sufficient response (1,6,30). The one mcg Synacthen test is recommended for diagnosing PAI only in case of difficulty in accessing the 250 mcg Synacthen test (1).

Mineralocorticoid levels: Increased plasma renin concentration or plasma renin activity (PRA) and concomitant low aldosterone levels before deteriorating electrolyte levels are essential for mineralocorticoid deficiency (31). However, interpretation of the data obtained from these tests requires consideration of many variables, including sample storage and processing conditions, dietary salt intake, physical activity, sex steroids, and the patient's position (supine or prone position) at the time of sample collection (6). PRA measurement is based on the level of angiotensin 1 produced during the renin-catalyzed conversion of angiotensinogen to angiotensin 1. Therefore, PRA is affected by conditions that alter both renin and angiotensinogen levels.

Plasma angiotensinogen levels increase in pregnancy, glucocorticoid and estrogen exposure, and decrease in liver diseases (32). Renin is synthesized as prorenin, an inactive zymogen. To prevent the conversion of prorenin to renin during measurement, it is recommended to centrifuge and freeze the sample, especially in laboratories where the sample cannot be studied rapidly (33). In addition, if the sample is kept at a high temperature, renin will continue to form angiotensin 1 from angiotensinogen and cause angiotensin 1 level to be higher than normal in PRA measurement (32). Whether the patient is supine or standing at the time of sampling and the change in the amount of daily sodium consumption cause fluctuations in renin levels (34). Since PRA levels vary for these reasons, it is recommended to be measured twice a day while the patient takes 100-200 mEq of sodium daily for precise evaluation (34). The most objective way of the assessment is to have the first measurement in the morning after spending the night in the supine position and the second measurement after spending four hours standing (8).

Methods are described at Part 1 (Clinical, Biochemical and Molecular Characteristics of Congenital Adrenal Hyperplasia Due to 21-hydroxylase Deficiency) of this supplement (35).

Good practice points:

1. A diagnosis of PAI can be made if the cortisol level taken between 06:00-10:00 a.m. is below five mcg/dL and the ACTH value is above two times the normal value for the kit used (1⊕⊕⊕O).

2. The "gold standard" method for diagnosing PAI is the high-dose Synacthen test. It should be administered at 250 mcg in patients over two years of age, 125 mcg in patients under two years of age, and 15 mcg/kg in infants. The test can be performed at any time of the day (2⊕⊕OO).

3. One mcg low-dose Synacthen test is recommended for diagnosing PAI only in case of difficulty in accessing the 250 mcg Synacthen test (2⊕⊕OO).

4. In patients with suspected PAI, plasma renin or PRA should be evaluated simultaneously for concomitant mineralocorticoid deficiency (1⊕⊕⊕O).

Footnotes

Authorship Contributions

Concept: Müge Atar, Leyla Akın, Design: Müge Atar, Leyla Akın, Literature Search: Müge Atar, Leyla Akın, Writing: Müge Atar, Leyla Akın.

Financial Disclosure: The authors declared that this study received no financial support.

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