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ORIGINAL ARTICLE

# PEDIATRIC NON-CONGENITAL ADRENAL HYPERPLASIA RELATED PRIMARY ADRENAL INSUFFICIENCY: A SINGLE-CENTER 20-YEAR CASE SERIES

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## ABSTRACT

**Introduction:** Primary adrenal insufficiency (PAI) in children is rare and life-threatening, with nonspecific clinical presentations that often delay diagnosis. Non-congenital adrenal hyperplasia (non-CAH) etiologies are less frequent and include autoimmune and monogenic disorders.

**Objective:** Review pediatric non-CAH PAI cases over a 20-year period in a tertiary care hospital.

**Methods:** Retrospective analysis of children diagnosed with non-CAH PAI between January 2004 and December 2024. Data were collected from medical records and analyzed descriptively.

**Results:** Six patients were identified (5 males, 1 female; median age 10.9 years). Etiologies included autoimmune adrenalitis (n=3), Triple A (Allgrove) syndrome (n=2), and X-linked adrenoleukodystrophy (ALD, n=1). Clinical presentation was variable: hyperpigmentation (83%), vomiting (83%), fatigue (33%), seizures (33%); two patients required ICU (Intensive Care Unit) admission. Biochemical findings included hyponatremia in 57% and hyperkalemia in 29%; all patients presented markedly elevated ACTH and low cortisol. All received hydrocortisone; five also required fludrocortisone. Genetic confirmation was achieved in ALD and one Triple A patient. Four patients (67%) had neurodevelopmental comorbidities.

**Discussion:** Non-CAH PAI in childhood often presents with nonspecific symptoms, while classic features such as hyperpigmentation may be absent. Autoimmune adrenalitis was the most common etiology, whereas genetic disorders, namely ALD and Triple A syndrome, accounted for a substantial proportion of cases. Laboratory hallmarks include hyponatremia, elevated ACTH, and low cortisol. Clinical and biochemical findings, together with molecular analysis, allow precise etiologic diagnosis, guiding prognosis, treatment optimization, and family screening. Clinicians should maintain a high index of suspicion to prevent adrenal crisis.

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Primary Adrenal Insufficiency, Addison Disease, Adrenal Insufficiency, Adrenal Gland Diseases, Adrenoleukodystrophy, Triple A syndrome.

## Introduction

Adrenal insufficiency (AI) is a life-threatening condition characterized by deficient or insufficient production of adrenal steroids, glucocorticoids and/or mineralocorticoids, or reduced response to these hormones.[1] If AI is caused by dysfunctional or unresponsive adrenal cortex, it is classified as primary AI (PAI), traditionally known as Addison's disease. On the other hand, if it is caused by dysfunction of the pituitary gland and/or hypothalamus, it is termed secondary AI.[2,3]

PAI is a rare disease, with an estimated prevalence of 10-15 per 100,000 in western countries. The reported number of cases has substantially increased over time, while remaining relatively uncommon in children.[2,4,5]

It often presents with nonspecific and insidious symptoms such as fatigue, malaise, abdominal pain, weight loss, nausea, and vomiting.[1,5] Because this condition is rare and lacks distinct early symptoms, it is often overlooked in the initial differential diagnosis, which can delay its identification. As a result, many patients present initially in the emergency department with an acute and potentially life-threatening adrenal crisis, increasing the risk of severe morbidity or mortality.[2,5]

In western societies, autoimmune adrenalitis accounts for approximately 80% of primary adrenal insufficiency cases in adults, whereas infectious or malignant causes are less common. Autoimmune adrenalitis can arise isolated (40%) or in combination with other autoimmune disorders as part of autoimmune polyglandular syndromes (APS) (60%).[1,2]

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**Table 1. Etiologies and characteristics of non-congenital adrenal hyperplasia primary adrenal insufficiency patients**

| No | Sex | Age at diagnosis (year) | Time to diagnosis (days) | Clinical presentation | ICU admission at diagnosis | Additional pathologies and imaging findings | Serum cortisol (µg/dL) | Serum ACTH (pg/mL) | Serum VLCFA | Etiology | Gene mutation and variant | Treatment |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | M | 9.8 | 303 | Hyperpigmentation, vomiting, dehydration and hyponatremia | No | - | <1 | >3500 | N | Autoimmune | - | HC, FC |
| 2 | M | 16.6 | 50 | Hyperpigmentation, vomiting, fatigue, followed by cardiogenic shock | Yes | ASD, ADHD, epilepsy | - | 1210 | N | Autoimmune | - | HC, FC |
| 3 | M | 15.3 | 69 | Hyperpigmentation | No | ADHD, autoimmune thyroiditis | 2.3 | >2000 | - | Autoimmune | - | HC, FC |
| 4 | M | 7.8 | 139 | Hyperpigmentation, vomiting, fatigue, headache | No | Short stature, alopecia | 8.1 | 3688 | High | ALD | Hemizygous mutation c.2010dupG p.(L671fs*63) in ABCD1 gene | HC, FC, DHA, carnitine |
| 5 | F | 7 | - | Vomiting, hypoglycemia-associated seizures | No | DLD, hypothyroidism | - | >1250 | - | Triple A syndrome | Awaiting genetic testing | HC |
| 6 | M | 12 | - | Hyperpigmentation, vomiting, status epilepticus secondary to severe hyponatremia | Yes | DLD, cognitive impairment, epilepsy, right temporal lobe oligodendroglioma | <0.2 | 3792 | - | Triple A syndrome | Variant c.399+5G>A in apparent homozygosity in AAAS gene | HC, FC |

ACTH: adrenocorticotropic hormone, ADHD: attention-deficit/hyperactivity disorder, ALD: adrenoleukodystrophy, AI: adrenal insufficiency, ASD: autism spectrum disorder, DLD: developmental language disorder, DHA: docosahexaenoic acid, FC: fludrocortisone, F: female, HC: hydrocortisone, ICU: intensive care unit, M: male, N: normal levels, No: patient number, VLCFA: very long chain fatty acids, -: data not available/missing data

In children, PAI usually results from inherited or sporadic monogenic causes. Congenital adrenal hyperplasia (CAH) is the most common cause of PAI in pediatric age (70-85%), with an estimated prevalence of 1/10,000-18,000, and 21-Hydroxylase deficiency is the most common cause of CAH.[3,4,6] Non-CAH PAI cases are less common, and their exact frequencies remain unclear. However, studies report that non-CAH etiologies account for approximately 10–30% of childhood PAI, with autoimmune adrenal insufficiency usually being the most frequent cause, [3–5,7] A 2023 Finnish study found that non-CAH PAI occurs at a rate of 0.3–0.4 per 100,000 person-years in those under 15, with higher rates in males.[8]

The aim of this study was to review the etiology, clinical presentation, laboratory findings, genetic analysis, and treatment features of non-CAH PAI pediatric patients that were followed in a pediatric endocrinology unit of a tertiary care hospital over a 20 year period.

**Methods**

We conducted a retrospective study and reviewed all the patients with non-CAH PAI managed in the pediatric endocrinology unit of a Portuguese tertiary care hospital, between January 2004 and December 2024. All the information was retrieved from clinical records and electronic files. Data were analyzed by descriptive statistical methods.

**Results and Discussion**

A total of six patients were diagnosed with non-CAH PAI over a 20-year period. Regarding etiology, three patients presented autoimmune adrenalitis, two had Allgrove syndrome (Triple A syndrome) and one was diagnosed with X-linked adrenoleukodystrophy (ALD).

Five patients (83%) were male, and one was female. The median age at diagnosis was 10.9 years (IQR 7.6-15.6 years) and there was a maximum 10 month delay between symptom onset and final diagnosis.

Clinical presentation was heterogeneous. Five patients (83%) presented with mucocutaneous hyperpigmentation, which was the sole sign in one case; five patients (83%) experienced nausea and vomiting; and two patients (33%) reported fatigue. The patient with isolated hyperpigmentation was already under pediatric endocrinology follow-up for autoimmune thyroiditis, which enabled an earlier diagnosis. Two patients experienced seizures, with hypoglycemia identified as the cause in one case. Two patients required Intensive Care Unit (ICU) admission: one patient developed status epilepticus secondary to severe hyponatremia following neurosurgical removal of a brain tumor; another developed cardiogenic shock in the context of an Influenza A infection.

At diagnosis, hyponatremia was documented in at least four patients (67%), with sodium levels as low as 113 mEq/L; two patients also developed hyperkalemia, reaching up to 6.7 mEq/L. Mean plasma ACTH level was markedly elevated (2573.3 ± 1226.8 pg/mL), while mean serum cortisol level was significantly decreased (2.9 ± 3.6 µg/dL).

All patients were treated with hydrocortisone at diagnosis, and five (83%) also received oral fludrocortisone treatment.

Autoimmune adrenalitis patients (n=3) presented with mucocutaneous hyperpigmentation and all had positive adrenal autoantibodies. One patient also had a coexisting autoimmune thyroiditis, while the other two had no additional autoimmune conditions identified.

Triple A (Allgrove) syndrome patients (n=2) had a history of vomiting and seizures, and one had hyperpigmentation. Vomiting was difficult to relate to adrenal insufficiency, given the association with achalasia. One of the patients presented with congenital alacrimia and later developed adrenal insufficiency, diagnosed in the context of hypoglycemia-associated seizures; achalasia was identified three years later. The second patient was diagnosed with achalasia at the age of nine, requiring feeding via nasogastric tube and subsequently gastrostomy. Adrenal insufficiency was identified three years later, following an episode of status epilepticus attributed to severe hyponatremia in the postoperative period after surgery for refractory epilepsy. He was confirmed to have a homozygous pathogenic variant in the AAAS gene through molecular testing, while genetic testing results for the girl are still pending.

The ALD patient (n=1) presented with hyperpigmentation, vomiting, fatigue and headache. He had elevated very long-chain fatty acid (VLCFA) levels, MRI evidence of cerebral white matter involvement, and genetic confirmation of ABCD1 mutation.

Interestingly, four patients (67%) had neuro-developmental comorbidities, namely attention - deficit/ hyperactivity disorder (ADHD) and developmental language disorder. Epilepsy was an additional diagnosis in two patients, one with autoimmune adrenalitis and the other with Allgrove syndrome.

**Discussion**

PAI in childhood is a relatively rare but potentially life-threatening condition that should be considered in any acutely or chronically ill patient presenting with non-specific symptoms such as fatigue, severe weakness, weight loss, dehydration, hypotension, recurrent nausea or vomiting, abdominal pain and skin hyperpigmentation.[2,3,6,9]

Delayed diagnosis can lead to adrenal crisis and significant morbidity or mortality, highlighting the need for increased clinical awareness. A high index of suspicion is essential for timely diagnosis, particularly when symptoms develop subacutely or chronically.[6]

In our cohort of six non-CAH PAI cases, autoimmune adrenalitis was the most common cause (50%), aligning with previous reports. Several studies from Western countries, including Portugal, have shown that autoimmune causes are the leading etiology of non-CAH PAI in children, accounting for approximately 30–55% of cases.[5–8] These findings align with a previous Portuguese 34-year cohort in which six cases of non-CAH PAI were identified.[6]

Other causes of childhood PAI include both genetic and non-genetic conditions. Rare genetic disorders, mostly monogenic, include adrenal gland developmental anomalies, ACTH resistance, Triple A syndrome, glucocorticoid resistance, aldosterone synthesis or action defects, and metabolic disorders like ALD. Non-genetic causes include adrenal hemorrhage, infections,

infiltrative diseases, and bilateral adrenalectomy.[2,8]

In our cohort, Triple A syndrome was identified in 33% of patients, while ALD accounted for 17% of cases. The proportion of ALD cases observed in our series is identical to that reported in a previous Portuguese cohort published in 2019, and differs from the higher proportions reported in several Turkish, Indian, and Chinese cohorts, where ALD represents the most common non-CAH etiology (36.3%–44.9%).[3,4,6,10] These findings suggest that regional, ethnic, and genetic factors may influence the distribution of PAI etiologies. The reported frequency of Triple A syndrome varies widely across international cohorts, ranging from 0% to 22.7%.[3–8,11] The higher proportion of Triple A syndrome observed in our cohort may be influenced by cohort size and the tertiary referral nature of our center, rather than reflecting true population-level differences.

The median age at diagnosis of non-CAH PAI in our cohort was 10.9 years (IQR 7.6-15.6 years). Published series report a broad age range at diagnosis, from early childhood to adolescence, with median values between 3.5 and 12.3 years.[3,5,8,10,11]

Across published cohorts, the most common presenting feature of non-CAH PAI in children is skin hyperpigmentation, reported in 50–90% of cases.[3–6,10,11] Fatigue, weakness, or failure to thrive are also frequent (20–67%); and gastrointestinal complaints such as anorexia, nausea, and vomiting may affect up to 89% of patients and often preceded diagnosis by weeks to months.[3–6,10,11] Additional findings include hypoglycemia (~40%), features of adrenal crisis (22–33%) and associated complications such as seizures (~30%).[3,4,10] Among our patients, clinical presentations largely matched what has been previously reported: 83% experienced mucocutaneous hyperpigmentation, which sometimes appeared alone; nausea and vomiting were reported in 83% of cases, while fatigue was present in 33%. Two patients presented with seizures, one in the context of hypoglycemia and the other in the context of hyponatremia; and two required intensive care admission due to severe acute presentations.

Non-CAH PAI typically shows biochemical evidence of combined glucocorticoid and mineralocorticoid deficiency – low cortisol with elevated ACTH – along with hyponatremia, hyperkalemia, and hypoglycemia, which is more common in children.[2] Across studies, hyponatremia is the most frequent laboratory abnormality, reported in 55–89% of cases.[5,6,11] Hyperkalemia occurs in 22–50% and hypoglycemia varies widely (7–50%), with lower rates likely reflecting glucose given before sampling.[3,5,6,11] In our cohort, 57% of patients had hyponatremia at diagnosis and 29% had hyperkalemia; mean plasma ACTH was markedly elevated and mean serum cortisol was significantly decreased. These findings align with published data, confirming hyponatremia and elevated ACTH as hallmarks of non-CAH PAI.

The main etiologies of non-CAH PAI identified in our cohort – autoimmune adrenalitis, Triple A syndrome, and adrenoleukodystrophy – will be discussed in more detail:

Autoimmune adrenalitis may occur in isolation or as part of an autoimmune polyendocrine syndrome (APS).[2] APS type 1 (APS-1) is a rare autosomal recessive disorder characterized by a triad of PAI, chronic mucocutaneous candidiasis, and hypoparathyroidism, and may also include alopecia, primary hypogonadism, nail and dental enamel dystrophy, and vitiligo. APS type 2 (APS-2), also known as Schmidt's syndrome, is defined by the coexistence of PAI, autoimmune thyroid disease, and type 1 diabetes mellitus. It typically manifests in older children or adolescents.[9] In our cohort, two patients had isolated autoimmune PAI, and one had concurrent autoimmune thyroiditis disease, without type 1 diabetes mellitus. The diagnosis of autoimmune PAI is confirmed by the presence of anti-adrenal antibodies in the serum,[2] and all three patients had detectable anti-adrenal antibodies. Notably, all were male, consistent with some pediatric series reporting a male predominance, in contrast to the female predominance seen in adults.[4–8,11]

Triple A syndrome, also known as Allgrove syndrome, is a rare autosomal recessive multisystem disorder, with an estimated prevalence of approximately 1 in 1,000,000, likely significantly underdiagnosed.[13] It results from mutations in the AAAS gene, located on chromosome 12q13, which encodes the nucleoporin protein ALADIN.[3,13] It is classically characterized by a triad of alacrimia, achalasia, and PAI as well as neurological and dermatological manifestations. Additional findings, such as short stature and facial dysmorphisms may also be present. Fatigue, hyperpigmentation and hypoglycemia are frequently reported symptoms at presentation.[1,3,11,13] In our cohort, both patients presented with vomiting and seizures, but only one had hyperpigmentation. Both patients were diagnosed with developmental language disorder, and only one demonstrated broader cognitive impairment. No dermatological abnormalities or characteristic facial dysmorphisms were documented in their medical records.

Adrenoleukodystrophy (ALD) is an extremely rare X-linked metabolic disorder with an estimated prevalence of 1:20,000 newborn males. It is caused by mutations in the ABCD1 gene, which encodes a peroxisomal transporter membrane protein necessary for very-long-chain fatty acids (VLCFA) (>24 carbon atoms) degradation.[1,3,8,9,12] Consequently, there is accumulation of VLCFA in the plasma and several tissues in the body, particularly in the adrenal glands and the central nervous system, leading to a proinflammatory state and cell death.[3,9] The clinical picture comprises adrenal insufficiency and neurological impairment due to white-matter demyelination.[1] Adrenal insufficiency may precede neurological symptoms and is the sole manifestation in approximately 15% of cases.[1] As an X-linked disorder, the disease primarily affects males.[9] Diagnosis is established through elevated VLCFA plasma levels and confirmed by genetic testing; this diagnosis should be investigated in any male child presenting with PAI without identified etiology even if neurological signs and symptoms are absent.[3,5,9] Our patients was male, showed elevated plasma VLCFA levels, and had a pathogenic variant identified in the ABCD1 gene. Neuroimaging revealed white matter involvement. ALD causes glucocorticoid deficiency, with mineralocorticoid deficiency appearing in 0–37.5% of cases, as seen in our patient.[3,4,7]

Overall, PAI in childhood is rare and often presents with

nonspecific symptoms such as fatigue, weight loss and gastrointestinal distress, while classic features such as hyperpigmentation may be absent. In children older than four years, autoimmune etiologies are the most frequent cause of non-CAH PAI. Clinical and laboratory findings, with or without molecular analysis, can identify the underlying etiology in most cases, and establishing a precise genetic diagnosis is valuable for prognosis, treatment optimization, and early detection of at-risk relatives. Prompt recognition, appropriate hormone replacement, and patient and family education on stress management are essential to prevent adrenal crises and improve long-term outcomes.

Limitations of this study include its single-center, retrospective design, which may restrict generalizability, yet the findings underscore the importance of maintaining a high index of suspicion and a structured diagnostic approach in pediatric PAI.

**Compliance with Ethical Standards**
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