UDC: 616.45 - 008.64 - 07 – 08

PRIMARY ADRENAL INSUFFICIENCY IN A CHILD: A CLINICAL CASE, DIFFERENTIAL DIAGNOSIS, AND THE ROLE OF GENETIC TESTING



Khalimova Zamira Yusufovna, Alimuhamedova Gulkuh Aybekovna, Mekhmanova Surayyo Otabekovna
Republican Specialized Scientific-and-Practical Medical Centre of Endocrinology named after academician Yo.Kh.Turakulov, Republic of Uzbekistan, Tashkent

БОЛАДА БИРЛАМЧИ БУЙРАК УСТИ БЕЗИ ЕТИШМОВЧИЛИГИ: КЛИНИК ҲОЛАТ, ДИФФЕРЕНЦИАЛ ДИАГНОСТИКА ВА ГЕНЕТИК ТЕКШИРУВНИНГ АҲАМИЯТИ

Халимова Замира Юсуфовна, Алимухамедова Гульрух Айбековна, Мехманова Сурайё Отабековна
Академик Ё.Х.Туракулов номидаги Республика ихтисослаштирилган эндокринология илмий-амалий тиббиёт маркази, Ўзбекистон Республикаси, Тошкент ш.

ПЕРВИЧНАЯ НАДПОЧЕЧНИКОВАЯ НЕДОСТАТОЧНОСТЬ У РЕБЕНКА: КЛИНИЧЕСКИЙ СЛУЧАЙ, ДИФФЕРЕНЦИАЛЬНАЯ ДИАГНОСТИКА И РОЛЬ ГЕНЕТИЧЕСКОГО ТЕСТИРОВАНИЯ

Халимова Замира Юсуфовна, Алимухамедова Гульрух Айбековна, Мехманова Сурайё Отабековна
Республиканский специализированный научно-практический медицинский центр эндокринологии имени акад. Ё.Х. Туракулова, Республика Узбекистан, г. Ташкент

e-mail: surayka329@gmail.com

Резюме. *Бирламчи буйрак усти бези етишмовчилиги (PAI) кам учрайдиган, аммо жиддий эндокрин касаллик бўлиб, ўз вақтида аниқлаш ва даволашни талаб қилади. Ушбу мақолада 4 ёшли қизалоқда PAI клиник ҳолати тасвирланган бўлиб, унда кучсизлик, вазн йўқотиш, терида гиперпигментация, артериал гипотензия ва музмембраналарида доимий кандидоз кузатилган. Комплекс текширув натижалари кортизол даражасининг пасайгани, адренокортикотроп гормон (ACTH) даражасининг ошгани, шунингдек, бир вақтнинг ўзида гипопаратиреоз ва кандидоз мавжудлигини кўрсатди. Клиник белгиларга асосланиб, аутоиммун полиэндокрин синдроми 1-тури (APS-1) деб тахмин қилинди. Бироқ, молекуляр-генетик таҳлил AIRE ген мутациясини аниқламади, бу эса ушбу ҳолатни ноанъанавий қилади. Касалликнинг эҳтимолий бошқа генетик ва аутоиммун механизмлари муҳокама қилиниб, кенгайтирилган молекуляр таҳлил ўтказиш зарурияти таъкидланди. Ушбу клиник ҳолат PAI этиологиясини аниқлаш ва беморни бошқариш стратегияларини оптималлаштириш учун лаборатория, инструментал ва генетик усулларни ўз ичига олган комплекс диагностик ёндашувнинг аҳамиятини кўрсатади.*

Калит сўзлар: *бирламчи буйрак усти бези етишмовчилиги; Аддисон касаллиги; аутоиммун полигландуляр синдром 1-тури; AIRE.*

Abstract. *Primary adrenal insufficiency (PAI) is a rare but serious endocrine disorder requiring timely diagnosis and treatment. This article presents a clinical case of PAI in a 4-year-old girl, manifested by weakness, weight loss, skin hyperpigmentation, arterial hypotension, and chronic mucosal candidiasis. A comprehensive examination revealed decreased cortisol levels, elevated adrenocorticotropic hormone (ACTH), as well as concomitant hypoparathyroidism and candidiasis. Based on the clinical presentation, autoimmune polyendocrine syndrome type 1 (APS-1) was suspected. However, molecular genetic testing did not detect mutations in the AIRE gene, making this case atypical. Possible alternative genetic and autoimmune mechanisms of disease development are discussed, along with the need for further expanded molecular analysis. This clinical case highlights the importance of a comprehensive diagnostic approach, including laboratory, instrumental, and genetic methods, for the accurate determination of PAI etiology and optimization of patient management strategies.*

Keywords: *primary adrenal insufficiency; Addison's disease; autoimmune polyendocrine syndrome type 1; AIRE.*

Introduction. Primary adrenal insufficiency (PAI), also known as Addison's disease, is a rare but potentially life-threatening endocrine disorder associated with the destruction of the adrenal cortex and insufficient secretion of corticosteroids and mineralocorticoids. The prevalence of PAI in the general population ranges from 4 to 6 cases per 100,000 individuals, with the main causes including autoimmune processes, infections, genetic mutations, and metabolic disorders [1].

In developed countries, the most common cause of PAI is autoimmune adrenalitis, which occurs in 60–80% of cases as part of autoimmune polyendocrine syndrome type 1 (APS-1) or as an isolated condition [2]. One of the key genes involved in the pathogenesis of PAI is AIRE (Auto-

immune Regulator). This gene plays a crucial role in the development of APS-1, a syndrome associated with thymic dysfunction and impaired central immune tolerance, leading to autoimmune destruction of the adrenal glands. Mutations in AIRE result in defective central immunological tolerance and the development of an autoimmune response against endocrine organs, including the adrenal glands [3].

Genetic research plays an essential role in diagnosing hereditary forms of PAI, not only confirming the etiology of the disease but also predicting the potential development of other autoimmune pathologies. AIRE mutations serve as a diagnostic marker for APS-1 and indicate an increased risk of hypoparathyroidism, chronic mucocutaneous candidiasis, and other autoimmune disorders [4].

This article presents a clinical case of primary adrenal insufficiency in a child associated with AIRE mutation and highlights the role of modern genetic research in diagnosing and managing patients with hereditary forms of this condition.

Case Description. Medical History. A 4-year-old girl was admitted to the pediatric department with complaints of weakness, loss of appetite, frequent episodes of vomiting, weight loss (approximately 2 kg over the past three months), and white plaques on the oral mucosa. The parents also reported increased irritability and drowsiness. The patient was born full-term with normal anthropometric parameters. Routine vaccinations were administered according to schedule. There was no family history of endocrine or autoimmune diseases.

Physical Examination. Upon admission, the patient was in a moderately severe condition. She appeared lethargic, with pale skin and areas of hyperpigmentation in the elbow and knee regions. White plaques on the oral mucosa, easily removed with a spatula, were indicative of candidiasis. Blood pressure was reduced (85/50 mmHg), and heart rate was elevated (110 bpm). Mild epigastric tenderness was noted on palpation. No signs of bone deformities or tetany were present.

Laboratory and Instrumental Findings. *Complete blood count*: Hemoglobin: 132 g/L; Leukocytes: 12×10^9/L

Biochemical blood analysis:

Serum glucose: 3.8 mmol/L (reference range: 3.3–5.5 mmol/L)

Serum cortisol: 356 nmol/L (reference range: 140–600 nmol/L)

Increased ACTH: 168 pg/mL (reference range: 7.2–63.3 pg/mL)

Anti-TPO antibodies: 9.5 IU/mL (reference range: <34 IU/mL)

TSH: 1.4 mIU/L (reference range: 0.4–5.0 mIU/L)

Decreased calcium: 1.8 mmol/L (reference range: 2.2–2.6 mmol/L)

Increased phosphorus: 2.0 mmol/L (reference range: 1.0–1.5 mmol/L)

Decreased parathyroid hormone: 8 pg/mL (reference range: 15–65 pg/mL)

Microbiological analysis. Oral mucosa swab: Candida albicans detected

Instrumental investigations:

Renal and bladder ultrasound: Pronounced pyramidal pattern bilaterally

Adrenal ultrasound: Increased echogenicity of both adrenal glands

ECG: Sinus tachycardia, prolonged QT interval (hypocalcemia)

Echocardiography: No structural heart abnormalities, functional murmur present

Neurological consultation: Febrile seizure episode noted, EEG recommended

Cardiology consultation: Functional murmur, no signs of organic heart disease

Based on the clinical presentation and laboratory and instrumental findings, the following diagnosis was established:

Primary adrenal insufficiency (Addison's disease). Chronic mucosal candidiasis. Hypoparathyroidism. Given the presence of adrenal insufficiency in combination with hypoparathyroidism and candidiasis, autoimmune polyendocrine syndrome type 1 (APS-1) was suspected. Genetic testing was performed, but no AIRE gene mutation was detected.

Treatment and Outcome. The patient received the following inpatient treatment: Fludrocortisone (Cortineff) 0.1 mg – ¼ tablet once daily after meals; Hydrocortisone (Cortef) 10 mg – ½ tablet in the morning and ¼ tablet in the evening after meals; Vitamin A (Aevit) – 1 capsule once daily; Ascorutin – ½ tablet twice daily; Suxamed – 100 mL IV infusion; Vitamin D (Aquadetrim Plus) – 3 drops once daily after meals; Sodium valproate (Convulex drops) – as prescribed.

During treatment, the patient showed positive clinical dynamics. She was discharged in stable condition with continued outpatient follow-up and therapy.

Discussion. The presented clinical case of primary adrenal insufficiency (PAI) in a 4-year-old girl exhibits the typical manifestations of the disease, including chronic fatigue, weight loss, skin hyperpigmentation, arterial hypotension, and mucosal candidiasis. Laboratory tests confirmed cortisol deficiency with compensatory elevated ACTH levels, indicating a primary etiology of the disease.

The clinical picture led to the suspicion of autoimmune polyendocrine syndrome type 1 (APS-1), as the patient exhibited a combination of adrenal insufficiency, hypoparathyroidism, and chronic candidiasis. The literature suggests that AIRE gene mutations serve as the primary genetic marker of APS-1 [1,4]. However, in this case, genetic testing did not reveal AIRE mutations, suggesting the possibility of an atypical form of PAI or another autoimmune endocrinopathy.

A comparison of this case with similar reports in the literature indicates that AIRE mutations are the primary diagnostic criterion in most APS-1 patients [5]. However, rare cases exist where PAI occurs within other autoimmune or genetic syndromes, such as X-linked immune dysregulation syndrome (IPEX) or APS variants associated with other genetic defects [2].

The patient's laboratory findings also deserve particular attention. Unlike the classical presentation of Addison's disease, the serum cortisol level was within the normal range, which could be attributed to its diurnal variations or stress-related fluctuations at the time of admission. However, elevated ACTH levels and concurrent autoimmune disorders support the diagnosis of primary adrenal insufficiency.

An unusual feature of this case is the absence of a hereditary predisposition, which has also been described in the literature. Cases of sporadic mutations and polygenic

interactions contributing to APS-1 development have been reported, even in the absence of identified AIRE mutations [3].

Thus, this clinical case underscores the importance of a comprehensive diagnostic approach to PAI, incorporating laboratory, instrumental, and genetic investigations. The absence of an AIRE mutation does not rule out the autoimmune nature of the disease, necessitating further molecular-genetic analysis to identify other possible causes of endocrine dysfunction.

Conclusion. Primary adrenal insufficiency remains a challenging condition to diagnose, particularly in pediatric practice. This case highlights the importance of early recognition of clinical symptoms, laboratory testing, and genetic diagnostics. While AIRE mutations are the most common cause of APS-1, their absence in this case suggests the possibility of alternative genetic and autoimmune mechanisms underlying the disease. This emphasizes the need for further investigation into alternative molecular markers and comprehensive genetic screening for patients suspected of having autoimmune polyendocrine syndromes.

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Халимова З.Ю., Алимухамедова Г.А., Мехманова С.О.

Резюме. *Первичная надпочечниковая недостаточность (ПНН) — редкое, но серьезное эндокринное заболевание, требующее своевременной диагностики и лечения. В данной статье представлен клинический случай ПНН у 4-летней девочки, проявившийся слабостью, потерей веса, гиперпигментацией кожи, артериальной гипотонией и хроническим кандидозом слизистых оболочек. Комплексное обследование выявило снижение уровня кортизола, повышение адренокортикотропного гормона (АКТГ), а также сопутствующие гипопаратиреоз и кандидоз. На основании клинической картины был заподозрен аутоиммунный полиэндокринный синдром 1 типа (АПС-1). Однако молекулярно-генетическое тестирование не выявило мутаций в гене AIRE, что делает данный случай атипичным. Обсуждаются возможные альтернативные генетические и аутоиммунные механизмы развития заболевания, а также необходимость расширенного молекулярного анализа. Этот клинический случай подчеркивает важность комплексного диагностического подхода, включающего лабораторные, инструментальные и генетические методы, для точного определения этиологии ПНН и оптимизации стратегий ведения пациентов.*

Ключевые слова: *первичная надпочечниковая недостаточность; болезнь Аддисона; аутоиммунный полигландулярный синдром 1 типа; AIRE.*