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CLINICAL-IMMUNOLOGICAL PREDICTORS OF EARLY DIAGNOSIS AND TREATMENT OF PRIMARY CHRONIC ADRENAL INSUFFICIENCY

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Abstract
Primary chronic adrenal insufficiency (PAI) is an uncommon but high-impact endocrine disorder in which progressive adrenal cortex failure leads to chronic glucocorticoid and—often—mineralocorticoid deficiency. Delayed recognition remains a major clinical problem because early symptoms are non-specific and diagnosis is frequently made only after adrenal crisis. This article reviews clinical and immunological predictors that can enable earlier diagnosis and more timely, individualized treatment. On the clinical side, persistent fatigue, weight loss, orthostatic hypotension, salt craving, hyperpigmentation, recurrent gastrointestinal symptoms, and characteristic biochemical signals (hyponatremia, hyperkalemia, elevated ACTH, elevated plasma renin activity, low/normal morning cortisol, and impaired response to ACTH stimulation) form a pattern that should prompt targeted testing.

Keywords: Primary adrenal insufficiency; autoimmune Addison's disease; 21-hydroxylase autoantibodies; ACTH stimulation test.

INTRODUCTION

Primary chronic adrenal insufficiency (PAI), traditionally referred to as Addison's disease when autoimmune in origin, results from inadequate production of adrenal cortex hormones—chiefly cortisol and, in many cases, aldosterone. Despite being treatable, PAI remains clinically dangerous because symptoms often develop gradually and mimic common conditions such as chronic fatigue, gastrointestinal disorders, depression, or nonspecific "asthenia." Consequently, a significant proportion of patients are diagnosed only after decompensation, sometimes during

life-threatening adrenal crisis. Contemporary guidelines emphasize maintaining a low threshold for diagnostic testing in patients with suggestive symptoms or predisposing risk factors, precisely because the cost of missing early disease can be catastrophic. [1]

MATERIALS AND METHODS

The phrase “clinical-immunological predictors” is useful because PAI—especially autoimmune PAI—progresses through a continuum. Before overt failure, many patients pass through a phase of subclinical adrenal impairment in which immune activity is present, but basal cortisol may still appear “borderline” and symptoms are vague. In this window, immunological markers can identify people at risk, while clinical and biochemical markers can reveal early decompensation. Autoimmune adrenalitis is commonly associated with other autoimmune endocrinopathies (e.g., thyroid disease, type 1 diabetes) and therefore offers a practical opportunity for targeted screening rather than waiting for crisis-level presentations. The Endocrine Society guideline explicitly recommends diagnostic evaluation in symptomatic individuals and suggests a low diagnostic threshold in high-risk settings. [1]

RESULTS AND DISCUSSION

Early PAI is rarely announced with a dramatic sign; it is usually a pattern that becomes obvious only when clinicians actively connect the dots. Common early features include persistent fatigue, loss of stamina, anorexia, weight loss, nausea, abdominal discomfort, dizziness on standing, salt craving, and low blood pressure. In autoimmune PAI, hyperpigmentation can appear as ACTH rises (via melanocortin signaling), providing an especially helpful clinical clue when present. Yet none of these findings is specific; the predictive value comes from co-occurrence and persistence, particularly when symptoms worsen under stress (infection, surgery, pregnancy) or when patients repeatedly present with unexplained hypotension or electrolyte abnormalities.

Biochemistry provides stronger predictors. Hyponatremia and hyperkalemia, especially when combined with hypotension and volume depletion, should prompt urgent evaluation for PAI, because mineralocorticoid deficiency is a key differentiator from secondary adrenal insufficiency. A contemporary clinical summary notes that diagnosis is supported by low cortisol (and often low aldosterone), high renin, and a blunted cortisol response to ACTH stimulation. [5] Importantly, normal electrolytes do not exclude early disease, particularly in partial

deficiency, but the appearance of salt wasting physiology often signals that the disease is no longer “early” and crisis risk is increasing.

From a predictive standpoint, three routine hormonal measures are especially informative:

- Morning serum cortisol (8–9 am): low values raise suspicion; intermediate values warrant dynamic testing.
- Plasma ACTH: elevated ACTH in the context of low/low-normal cortisol strongly suggests primary (not secondary) adrenal failure.
- Plasma renin activity (or direct renin) with aldosterone: rising renin reflects early mineralocorticoid insufficiency and can precede overt electrolyte changes.

Clinical guidelines prioritize ACTH (cosyntropin) stimulation testing for confirmation when feasible, because it directly measures adrenal reserve. [1] In practice, clinicians should adopt a “do not wait for perfect classic signs” mindset: early PAI is most safely detected when suggestive symptoms trigger timely cortisol/ACTH assessment and follow-up dynamic testing.

CONCLUSION

Primary chronic adrenal insufficiency is a high-risk condition mainly because it is frequently recognized late, after prolonged non-specific symptoms or during adrenal crisis. A clinical-immunological predictor approach offers a realistic way to shorten diagnostic delay. Clinically, persistent fatigue, weight loss, orthostatic hypotension, salt craving, hyperpigmentation, and suggestive laboratory patterns should trigger early endocrine testing rather than repeated symptomatic treatment. Biochemically, the combined signal of low/low-normal morning cortisol with elevated ACTH, rising renin, and impaired cosyntropin response is highly informative for early detection and staging.

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