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Review Article

Complications of Elevated Antidiuretic Hormone (ADH) and Cortisol Levels

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Abstract: This review is focused on the prevailing question of physiological and clinical consequences of chronic elevation of cortisol and ADH levels, concentrating on their individual and collective foe. Water retention and hyponatremia due to increased ADH, such as seen in syndrome of inappropriate antidiuretic hormone (SIADH) secretion, may lead to acute neurologic symptoms including seizures and coma1 or chronic complications like osteoporosis, cognitive impairment2 and gait impairment. Systemic disorders including hypertension, insulin resistance, visceral obesity, muscles atrophy and bone loss mood disorders and immune suppression, which have been associated with increased cortisol levels identified in endogenous Cushing's syndrome patients or in long-term GC therapy. The diagnostic challenge of differentiating SIADH from adrenal insufficiency and other electrolyte abnormalities, especially in patients who are ill or have undergone surgery, also is addressed by the study. Similarly, the interrelationship of cortisol and ADH regulation are described, stressing upon complex neuroendocrine feedback mechanisms. Decline of morbidity and improvement of the final outcome may be achieved by early diagnosis and correct therapy for these hormonal disorders.

Keywords: *anti diuretic hormone , cortisol , hypercortisolism.*

1. Introduction

The pathophysiology and systemic sequelae of prolonged ADH excess, a hallmark of SIADH, and chronic endogenous or exogenous hypercortisolism (Cushing's syndrome) are described in this article. Elevations in cortisol and ADH affect multiple other systems. Hyponatremia and dysregulated control of water homeostasis, and possible neurologic catastrophe are associated with ADH causing the syndrome of inappropriate antidiuretic hormone secretion (SIADH). Meanwhile, endogenous (e.g., Cushing's disease, adrenal neoplasms) or exogenous (aerogenic glucocorticoids treatment) chronic exposure to high levels of corticosterone disturbs the delicate harmony between immune system, skeleton, metabolism, cardiovascular system and neuropsychiatry [1]. Focusing on the problems associated with consistently high concentrations of cortisol and ADH, they share a biological basis and clinical implications for their diagnosis and treatment, providing an up-to-date comprehensive review.

1.1 SIADH and Elevated ADH:

There is excessive, unregulated ADH production or increased renal ADH responsiveness resulting in water retention without significant solute gain and with dilutional hyponatremia and either euvolemia or mild hypervolemia [2]. Whereas chronic hyponatremia is associated with mild neurologic deterioration, gait disturbance, cognitive deficits and osteoporosis among others [3], acute hyponatremia can lead to CE causing headache, nausea, seizures, disorientation or coma even death [3]. There are several an etiologies that account for this phenomena including CNS diseases, cancers (specifically small cell lung cancer), drugs, surgical stress and rare genetic abnormalities as well [2]. Fluid limitation, addressing the underlying causes, cautious correction to avoid osmotic demyelination, and use of vasopressin receptor antagonists as needed are the cornerstones of therapy [4].

1.2 Elevated Cortisol / Cushing's Syndrome:

Generalized metabolic and structural organ damage occurs due to longstanding hypercortisolism, irrespective of aetiology (pituitary adenomas [Cushing's disease], ectopic ACTH release, adrenal tum ours, chronic glucocorticoid treatment) [5]. Hypertension, insulin resistance or overt type 2 diabetes, dyslipidemia, visceral obesity, coagulopathy, increased cardiovascular and thromboembolic events, immune suppression with increased risk of infection, osteoporosis and pathological fractures, myopathy, neuropsychiatric disturbances (depression, cognitive decline), and delayed wound healing are complications [6].

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Mineralocorticoid effects of cortisol in ectopic ACTH release can also result in electrolyte derangement (hypokalemia, hypernatremia) and rare yet life-threatening complications such as ileus and gastrointestinal perforation [7].

1.3 Interrelationship and Clinical Implications:

In some clinical conditions, ADH dynamics may be indirectly influenced by too high levels of glucocorticoids. Blockade of CRH and vasopressin due to cortisol might alleviate hyponatremia in SIADH. Yet this effect could be less profound in states with high ADH secretion [8]. For these reasons diagnostic alertness is essential to distinguish associated syndromes such as SIADH, cerebral salt-wasting and secondary adrenal failure especially, in post-operative or neurosurgical patients [4].

2. Results

2.1 SIADH and Elevated ADH

SIADH may result from a number of causes due to inappropriate release of ADH and enhanced renal sensitivity, including idiopathic/genetic syndromes, lung disease [8], drugs, cancer (particularly small cell lung cancer), surgery, CNS diseases [9]. Dilutional hyponatremia occurs primarily as a result of water retention. Although chronic hyponatremia may lead to cognitive impairment, gait disturbances, osteoporosis and even higher mortality rates, acute hyponatremia can induce cerebral edema, convulsions or coma with fatal outcome [10].

2.2 Chronic Hypercortisolism (Cushing's Syndrome)

There are several systemic issues that are related to chronically elevated levels of cortisol. Metabolic syndrome with hypertension, visceral obesity, dyslipidemia insulin resistance and manifest type 2 diabetes; musculoskeletal complications of progressive osteoporosis and fractures or sarcopenia; neuropsychiatric hyperpnea during sleep apneas resulting in headaches and mood lability involving depression, anxiety cognitive deficits; immune suppression and increased susceptibility to severe infections requiring modifiable intubation risk factor precautions; elevated thromboembolic effects predisposing to cardiovascular morbidity/mortality that significantly increase the burden of death prolongs ventilatory requirements [11]. Indeed, in recent echocardiographic studies, myocardial fibrosis related to hypercortisolism was shown to impair left ventricular function independently of metabolic disturbances suggesting direct cardiomyopathic effects despite remission [12]. Dr. Ivancevich's: In the setting of type 2 diabetes, microvascular problems related to cortisol are also interesting. High levels of cortisol are associated with higher prevalence of diabetes complications, such as diabetic nephropathy, retinopathy and neuropathy suggesting a possible role for cortisol as a predictive metabolic marker to monitor response to diabetes therapy [13].

3. Discussion

3.1 Pathophysiology and Clinical Spectrum

Hyponatremia and its neurological sequelae occur due to increased ADH, impacting cognition and bone metabolism over time. Due to its multifactorial genesis a strict differential diagnosis is essential, especially as cerebral salt wasting or postoperative cortisol deficiency could alter treatment [9]. In contrast, elevated cortisol inhibits anabolic functions in muscle and bone and enhances energy release via gluconeogenesis and insulin resistance. Common dermatological, cardiovascular, musculoskeletal and neuropsychiatric manifestations can be accounted for by the downregulating action of cortisol on inflammation and the ensuing systemic endothelial dysfunction [14].

3.2 Interplay Between ADH and Cortisol Excess

Cortisol's inhibitory effect on vasopressin (ADH) release might alter the magnitude of hyponatremia in SIADH-related contexts, but seldom prevents difficulties in more extreme or prolonged ADH excess states, despite a lack of direct interplay investigations. There is a need to differentiate overlapping symptoms, such as SIADH, cerebral salt wasting and adrenal insufficiency (especially in the perioperative or neurologically impaired populations) [9].

3.3 Long-term Consequences and Remission

Some of these detrimental cardiovascular changes appear to be long-lasting, like myocardial fibrosis and impaired left ventricular mechanics, which may not totally recover despite biochemical remission of hypercortisolism, especially in patients with a prolonged course of illness [12]. Long-term risks include persisting metabolic risk, negative impact on life quality and also mortality [15]. After remission, continued evaluation is essential with a focus on cardiovascular, metabolic, cognitive and bone health.

4. Conclusion

Water homeostasis, electrolytes, metabolism, musculoskeletal health, psychological wellbeing, immunity and cardiovascular function are at risk in the presence of both high levels ADH and cortisol release that cause individual yet frequently coexisting symptomatology. The morbidity and the mortality coupled to either entity, underscore the need for early

recognition, comprehensive treatment and long term follow up in spite of distinct etiologies.

Recommendations

1. **Early and Accurate Diagnosis**

Whenever patients with neuropsychiatric complaints present with metabolic syndrome features or unexplained hyponatremia, a high level of clinical suspicion for the two conditions should be considered in a differential diagnosis. Appropriate to clinical context: Aggressive hormonal evaluation-history-blood Na-osmolarity-urine Na-Cortisol-ACTH Acute very far away.

2. **Differential Diagnosis is Crucial**

Especially in hospitalized, surgical or neurologically impaired patients, overlapping conditions like SIADH versus adrenal insufficiency or cerebral salt wasting syndrome must be meticulously distinguished. However, improper fluid therapy and the use of steroid drugs may be ascribed to a wrong diagnosis.

3. **Individualized Treatment Strategies**

Therapy is primarily symptom directed, but the cause of SIADH should be addressed (e.g., cancer, pituitary adenoma, ectopic ACTH secretion, drug-related SIADH). For SIADH, fluid restriction and vasopressin receptor antagonists or hypertonic saline may be used; in Cushing's syndrome, cortisol suppression via surgery or medications is important.

4. **Monitor for Long-Term Complications**

Such patients may experience long-term effects such as osteoporosis, metabolic syndrome, CVD or cognitive impairment even after biochemically successful correction of ADH or cortisol excess. Children should have long-term follow-up with endocrinology, bone health assessment and mental health treatment is strongly recommended.

5. **Multidisciplinary Management**

Especially in complex or refractory cases, a multidisciplinary approach involving endocrinologists, neurologists, cardiologists, nephrologists and mental health professionals may be beneficial.

6. **Patient Education and Lifestyle Interventions**

Complications can be minimized if patients are warned of the potential adverse effects of some medications (e.g. SSRI, antipsychotics and glucocorticoids) and encouraged to adopt a healthier lifestyle by reducing salt, exercising or decreasing cardiovascular risk).

7. **Research and Guideline Development**

The interaction of ADH and cortisol on pathophysiological aspects, especially in overlapping disorders, needs further clinical evaluation. Standard practices in dual hormone dysregulation should follow the evidence based clinical guideline.

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