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Case Report

Hypothalamo-pituitary-adrenal axis dysfunction presenting as a life threatening acute medical emergency: A case study

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ABSTRACT

Hypothalamo-pituitary-adrenal axis dysfunction can present clinically as one of the few endocrinological emergencies found in daily clinical practice. The HPA axis primarily deals with stress response, energy metabolism, immune function and neuropsychiatric function. Unfortunately the clinical presentation of HPA axis dysfunction is non-specific and often progresses insidiously resulting in late diagnosis, or in severe cases present with acute circulatory collapse. Here we present a case where a 60 year-old lady who presented with shock, altered mental status, bradycardia and hypoglycemia, was found to have HPA axis dysfunction and was managed effectively with glucocorticoids along with other supportive management.

1. Introduction

Human beings react to different environmental challenges by activating a coordinated response by the brain and the body known as the stress response. This is largely regulated by the hypothalamic pituitary adrenal axis. Its normal functioning ensures an appropriate response to any environmental challenge thus representing an essential system for our survival. Disruption of this HPA axis can lead to dysregulated stress response resulting in various symptoms and can often be life threatening.

2. Case Summary

A 60-year-old lady with a background of hypertension was being planned for surgery for bilateral lower limb chronic venous ulcers. Two days prior to surgery the lady developed anorexia, weakness, apathy along with gradually progressive alteration in mental status (delirium, psychosis). On the day of the planned surgery the patient presented to the Emergency Department of our hospital with altered mental status. She was delirious, not oriented to time, place or person along with features of acute maniac psychosis. Temperature was 98.6° F, she was in shock with a blood pressure of 60/30 mmHg but without reflex tachycardia (pulse rate 72 beats/min, regular in rhythm, feeble) and room air saturation of 99%. Physical examination showed no other significant abnormalities. Initial Laboratory findings showed hypoglycaemia (random blood glucose of 65 gm/dl), hyponatremia (Sr. Sodium levels of 119.3 mEq/L), normal Sr. Potassium level of 4.31 mEq/L, anaemia (Haemoglobin of 7.9 g/dL), total leukocyte count of 10,900/cumm and normal lactate values of 1.02. Urinary ketones were positive but there was no metabolic acidosis. Initially the patient was started on supportive management with IV crystalloids, hypertonic saline, IV Dextrose and vasopressors (Inj. Noradrenaline). Then she was shifted to intensive care unit for further monitoring and management.

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Subsequently she was unable to maintain parameters inspite of intensive monitoring and management, also developed recurrent episodes of bradycardia, hypoglycaemia and hypothermia. Finally she was intubated and mechanically ventilated due to refractory hypotension and worsening of mental status.On revisiting the history it was found that she had persistent unexplained fatigue which was present for some duration. Considering her status of hyponatraemia, delirium, recurrent hypoglycaemia, hypotension and hypothermia a provisional diagnosis of hypothalamic pituitary adrenal axis dysfunction was considered and labs for evaluation of endocrine insufficiency were sent. Non-contrast CT of brain did not show any significant abnormality and CSF study was done to rule out infective causes of altered mental status which was also within normal limits. Echocardiography was of normal study. Blood reports showed that 8 a.m. serum Cortisol level was low (7.83mcg/dl), normal ACTH 23.8 pg/ml (reference range 7.2-63.3 pg/ml), raised TSH 12.62 uIU/ml, normal FT3 2.9 pg/ml, normal FT4 0.95 ng/dl, though anti-TPO was negative and normal Sr. FSH 25.55 mIU/ml (postmenopausal). Other causes of shock and altered mental status were ruled out. After exclusion of infection the patient was started on Injection Hydrocortisone (100 mg intravenous bolus dose followed by 50 mg every 6 hours). Following the administration of injection Hydrocortisone the hyponatraemia, hypotension and delirium improved dramatically and the patient was weaned off mechanical ventilation within 1-2 days. She was also started on oral thyroid hormone replacement. MRI brain (focussing on Pituitary gland) also did not show any significant abnormality, no pituitary lesions or adjacent lesions. She was finally discharged on oral hydrocortisone replacement.

3. Discussion

Adrenal insufficiency is broadly classified into primary, secondary, and tertiary types based on whether Cortisol deficiency results from a defect in the adrenal gland, pituitary gland, or hypothalamus, respectively. Secondary and tertiary adrenal insufficiency together are referred to as Central Adrenal Insufficiency.

Primary adrenal insufficiency, also known as Addison's disease, is characterized by decreased production of aldosterone and cortisol due to impaired adrenal gland function. This condition most commonly arises from autoimmune adrenalitis. Other causes include infections such as tuberculosis, systemic fungal infections (e.g., AIDS-related infections), adrenal metastases from cancers originating in the lungs, breast, or kidneys, lymphoma affecting the adrenals, adrenoleukodystrophy, adrenal hemorrhage, non-functional primary adrenocortical carcinoma (Jagtap, 2014)[1] or bilateral adrenalectomy.

Secondary adrenal insufficiency occurs due to decreased adrenocorticotropic hormone (ACTH) production or function, resulting in reduced adrenal gland stimulation. This condition is typically caused by pituitary tumors or metastases to the pituitary gland, other cranial tumors like craniopharyngioma, meningioma, or germinoma, central nervous system infections, pituitary surgery or radiation therapy, primary or secondary hypophysitis, head trauma, pituitary apoplexy (Sheehan syndrome), or pituitary infarction secondary to conditions such as sarcoidosis or histiocytosis. Empty sella syndrome can also contribute to secondary adrenal insufficiency.

Tertiary adrenal insufficiency refers to decreased hypothalamic stimulation of the pituitary to secrete ACTH resulting from long-term exogenous glucocorticoid use.

In adrenal insufficiency, serum cortisol levels are critical for diagnosis. A morning serum cortisol level below 3 μg/dL (80 nmol/L) is indicative of adrenal insufficiency, while levels above 18 μg/dL (500 nmol/L) suggest a normal functioning hypothalamic-pituitary-adrenal (HPA) axis. But serum cortisol greater than 3 μg/dL (80 nmol/L) and less than 18 μg/dL (500 nmol/L) gives indeterminate result which requires further evaluation with Cosyntropin stimulation test, where a baseline cortisol level is measured before and after administering synthetic ACTH. A normal response is characterized by peak cortisol levels exceeding 18 to 20 μg/dL (497 to 552 nmol/L) after stimulation; a lower response indicates adrenal insufficiency.

Once cortisol deficiency is confirmed, the next step involves determining the underlying cause of adrenal insufficiency. Plasma adrenocorticotropic hormone (ACTH) levels are crucial in distinguishing between primary adrenal insufficiency (Addison's disease) and central adrenal insufficiency (secondary or tertiary adrenal insufficiency) (Bornstein SR, 2016).[2] For primary adrenal insufficiency (Addison's disease), elevated ACTH levels are typically observed, often exceeding two-fold the upper limit of the reference range and occasionally reaching or surpassing 4000 pg/mL. Conversely, in central adrenal insufficiency (secondary or tertiary), ACTH levels are generally lower, typically falling within the lower half of the reference range, which is insufficient given the cortisol deficiency. When ACTH levels are within the upper half of the reference range, distinguishing between primary and central adrenal insufficiency can be challenging. Additional evaluation with plasma aldosterone and renin levels helps clarify the diagnosis and guide appropriate treatment strategies for patients suspected of adrenal insufficiency. (Lynnette K Nieman, Determining the etiology of adrenal insufficiency in adults. UpToDate., 2024).[3,4]

In the above case scenario as the patient was considered to be in adrenal crisis as suggested clinically, a basal serum cortisol level of < 18 mcg/dl (7.83mcg/dl in our patient) suggests the diagnosis of adrenal insufficiency. Along with

that an ACTH level in the lower half of the reference range indicates central adrenal insufficiency. The normal MRI scan (Husebye ES, 2020) of the pituitary paired with other normal (Husebye ES, 2020)[5] or raised pituitary hormones suggest Isolated ACTH deficiency.

Parenteral glucocorticoid therapy is essential for managing acute adrenal crisis, with hydrocortisone being the preferred medication. The initial treatment typically involves administering 100 mg of hydrocortisone intravenously as a bolus, followed by 50 mg every 6 hours or 200 mg over a 24-hour period via continuous infusion. Additionally, patients experiencing adrenal crisis require fluid resuscitation with isotonic fluids such as saline (0.9% saline or 5% dextrose in 0.9% saline) to address hyponatremia and hypovolemia. Dextrose-containing fluids are beneficial for correcting associated hypoglycaemia. Once the patient stabilizes, hydrocortisone is gradually tapered over 1-3 days and transitioned to an oral maintenance regimen as soon as the patient can tolerate oral medications. The typical total daily dose for maintenance therapy ranges from 15-25 mg, administered in 2-3 divided doses per day (Lynnette K Nieman, Treatment of adrenal insufficiency in adults. UpToDate., 2024). However, tissue resistance to glucocorticoids during acute systemic inflammatory conditions, such as co-existing sepsis (Karen Dendoncker, 2017)[6] and acute respiratory distress syndrome (ARDS) (Barnes, 2009), can cause a significant challenge in treatment. This resistance is largely attributed to the interaction between the glucocorticoid receptor (GR) and nuclear factor-kappaB (NF-kB), which can be dysregulated in inflammatory states.

4. Conclusion

Isolated adrenocorticotropic hormone (ACTH) deficiency causing secondary adrenal insufficiency was the aetiology behind the HPA axis dysfunction which resulted in all the symptoms in our patient. Isolated ACTH deficiency is a rare endocrine disorder characterized by a specific reduction in ACTH production from the pituitary gland, leading to secondary adrenal insufficiency. This condition can result from various causes, including autoimmune processes, congenital factors, or physical trauma, and is often associated with other endocrine disorders like primary hypothyroidism. Patients typically present with nonspecific symptoms of adrenal insufficiency, such as fatigue, anorexia, weight loss, nausea and vomiting, hypoglycaemia, hypotension (Okauchi, 2019).[7] These symptoms can be mistaken for mental health disorders due to their general nature, complicating diagnosis (Atsuko Ikenouchi, 2022).[8,9] Diagnosis is confirmed through low serum ACTH and cortisol levels. Early recognition and treatment are crucial to prevent adrenal crisis, which can be life-threatening.

Thus adrenal crisis should be suspected in patients who exhibit sudden vascular collapse without an obvious cause. Examination of basal Cortisol level and ACTH tests are recommended to diagnose adrenal insufficiency. However, treatment with glucocorticoid should be started in patients with severe symptoms of adrenal insufficiency or adrenal crisis, without waiting for the results of a confirmatory test. Hence a patient presenting with constellation of symptoms including altered mental status, hypotension, hypoglycaemia, hypothermia in varying combinations a high degree of suspicion for HPA axis dysfunction should be considered.

5. Consent

Informed consent was obtained from the patient for publication of this case report.

6. Source of Funding

None.

7. Conflicts of Interest

The authors declare there is no conflicts of interest regarding publication of this article.

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