Review Article

Endocrinopathies – A Trouble Maker In Critically Ill Patients

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Abstract

Endocrinopathies may develop in intensive care unit patients and are not uncommon. These disorders pose unique challenges to the attending clinicians as they present non-specifically. Timely diagnosis and appropriate treatment of the endocrine failures can improve the outcome in critically ill patients. In this review article, endocrine disorders involving the thyroid, anterior pituitary and adrenal glands have been discussed.

Keywords : Endocrinopathies, Critically Ill, Thyroid storm, Pituitary apoplexy, Adrenal insufficiency

Introduction

Endocrine emergencies are the common problems encountered by the treating physician in Intensive Care Unit (ICU). These disorders may either pre - exist or develop during the course of hospitalization. Critical illness like myocardial infarction, sepsis, and trauma are characterized by striking alterations in the hypothalamic – pituitary – peripheral hormone axis.

The clinical presentation of the endocrinopathies may be difficult to recognise in ICU especially if the manifestations of the underlying disorder predominate. A high index of suspicion is needed to recognise the endocrine emergencies in critically ill patients, which can significantly influence the outcome and prognosis in these patients. Although, with wider availabilities of newer diagnostic modalities and improvement in treatment that have vastly helped in diagnosing and treating these endocrine emergencies, the morbidity and mortality is still very high due to failure in recognising these disorders early and treating them efficiently. Recognition and safe treatment of several conditions such as acute adrenal insufficiency, thyroid crisis, hypoglycemia and hyperglycemic crisis may be lifesaving.

This review article focuses on important endocrine emergencies involving the thyroid and adrenal glands, which are common in ICU. Emergencies involving the pituatry gland are also included. Hyperglycemic crisis and hypoglycemia which are common in critically ill patients have been extensively discussed elsewhere and it is not covered here because of space limitations.

Other issues that are related to intensive care, such as fluid and electrolyte imbalance like hypocalcemia, hypercalcemia and hyponatremia may have an underlying endocrine cause and may be treated accordingly with recognition of the disorder; Fluid and electrolyte replacement without correction of the underlying disorder results in insufficient improvement in clinical status of the patient and these disorders are also not discussed here.

The Thyroid Gland

Nonthyroidal Illness Syndrome

It is very difficult to interpret thyroid function test in the ICU because thyroid hormone concentrations are affected by a wide variety of nonthyroidal illness, including sepsis, myocardial infarction, major surgery, and severe malnutrition.[1] In addition, commonly used drugs in ICU including dopamine, corticosteroids, amiodarone, and iodinated radio-contrast agents can also affect thyroid physiology. In the ICU, physicians frequently encounter nonthyroidal illness syndrome (NTIS), previously known as sick euthyroid syndrome.[2] The diagnosis is based on clinical suspicion as well as documenting low serum T3 levels. In more severe illness, T4 production also becomes suppressed and the prognosis becomes poor if total T4 is <4ug/dl. TSH level is typically normal to low.[3]

The mechanisms underlying NTIS are poorly understood, and data on the beneficial effect of thyroid hormone replacement on outcome of the critically ill patients are so far controversial.[4] Similarly, routine thyroid function testing should not be performed without a definite clinical indication in critically ill patients.

Distinguishing primary thyroid disease from NTIS can be difficult in ICU and TSH is the most useful investigation with normal levels excluding primary disease.

Hypothyroid patients should continue their usual thyroxine replacement in the ICU. Thyroid function generally returns to normal as the acute illness resolves.

Thyroid Storm / Thyrotoxic Crisis

Thyroid storm is a rare and potentially life - threatening state that can occur with untreated or partially treated hyperthyroidism. The precipitating factors for thyroid storm in ICU may include surgery (particularly thyroidectomy), sepsis, myocardial infarction, diabetic ketoacidosis, cerebrovascular disease, trauma, pulmonary thrombo-embolism, or following discontinuation of anti-thyroid medications. The drugs like high doses of iodine-containing compounds (for example, radiographic contrast media), new institution of amiodarone therapy, and salicylates have been implicated in triggering thyroid storm.[5]

Thyroid storm is characterized by an exaggerated response to elevated levels of circulating thyroid hormones. Cardinal features includes fever (>38.5˚C), tachycardia, central nervous system dysfunction (agitation, delirium, psychosis, stupor or coma) and gastrointestinal symptoms (nausea, vomiting, abdominal pain). More severe cardiac manifestations may include arrhythmias, heart failure and shock.[6] It is very difficult to differentiate the clinical symptomatology of thyroid storm from other medical emergencies such as neuroleptic malignant syndrome, malignant hyperthermia and pheochromocytoma.

Thyroid function tests show suppressed TSH, elevated free T4 and or T3. Other biochemical features include hyperglycaemia, leucocytosis, mild hypercalcaemia, and abnormal liver function tests. Adrenal reserve may be impaired. Blood results cannot discriminate thyroid storm from thyrotoxicosis, as it is a clinical diagnosis.

The aim of treatment includes is summarized in table 1.[7]

- Treatment of the precipitating events,
- Inhibition of thyroid hormone synthesis and release,
- Reduce conversion of T4 to T3,
- Block the peripheral effects of thyroid hormone,
- Supportive therapy includes IV fluids, cooling blanket, antipyretics such as paracetamol and chlorpromazine for hyperthermia, oxygen therapy, and mechanical ventilation for hypoxemia, fluid and electrolyte replacement, and appropriate management of cardiac arrhythmias and heart failure.

Drug	Mechanism of Action	Dosage
Propranolol	Blocks beta-receptor mediated effect of catecholamines. Reduces peripheral conversion of T4 to T3	0.5 to 1.0 mg IV, every 2 to 3 hours, or 40 to 80 mg, PO, every 4 to 8 hours
Propylthiouracil	Blocks thyroid hormone synthesis and release. Prevents peripheral conversion of T4 to T3	200-400 mg PO or rectally every 4-6hours
Carbimazole	Blocks thyroid hormone synthesis and release	20 mg every 6 hours PO or rectally
Inorganic iodine	Blocks the release of preformed hormone	Lugol's solution - four to eight drops, PO, every 6 hours (1 h after anti-thyroid drug administration)
Hydrocortisone	Blocks peripheral conversion of T4 to T3	300 mg IV stat followed by 100 mg three times a day

Table 1 : Drugs used in treatment of thyroid storm

Myxedema Coma

Myxedema coma is an uncommon medical emergency that results from undiagnosed, untreated or inadequately treated hypothyroidism with a very high mortality rate (20-60%).[8] This condition is typically seen in obese elderly females. These patients usually present with hypothermia, altered mental status, and an acute precipitating event. Numerous precipitating factors have been identified, including infection especially pneumonia, myocardial infarction, cardiac failure, stroke, trauma, gastrointestinal blood loss and several drugs (e.g. lithium, amiodarone, sedatives, diuretics and anaesthetic agents). Other clinical features include bradycardia, hypotension, hypoventilation, anorexia, nausea, abdominal pain, and decreased gastrointestinal motility. Clinicians should always consider the possibility of myxedema coma in a patient who presents with a triad of hypothermia, hyponatremia, and hypercapnia with a history of thyroid surgery in the past.

Blood reports frequently show elevated TSH and low free T4 values. Treatment should be started on the basis of clinical suspicion rather than relying on the investigations and is shown in table 2. Cortisol level should be measured before initiating the treatment, as it may precipitate or unmask the underlying adrenal insufficiency.

Key treatment goals are[9]

- Replacement of thyroid hormones,
- Identification of precipitating factors,
- Supportive therapy includes hemodynamic support with isotonic fluids, passive rewarming techniques, correction of electrolyte abnormalities and
- Administration of hydrocorticoids - 100 mg every eighth hourly

Intravenous T3	Initial dose: 10-20 µg First 24 hours: 10 µg q4 h Followed by 1-2 days: 10 µg q6 h
Intravenous or oral T4	Initial dose: 500 µg Followed by: 100 µg every day

Table 2 : Replacement of Thyroid Hormones

Adrenal Gland

Adrenal Insufficiency (AI)

It is one of the common disorders encountered in critically ill patients. The prevalence of AI varies between 10 to 20% and even rates as high as 60-90% has been reported in patients with severe sepsis.[10]

The adrenal suppression in critically ill patients is often reversible with the treatment of the underlying disorders, and is called critical illness-related corticosteroid insufficiency (CIRCI).[11] The patho-physiology of CIRCI is very complex and may arise as a result of dysfunction of the hypothalamic-pituitary-adrenal axis at any level. As a result of systemic inflammatory response elicited commonly by bacterial toxins, there is failure of adrenal glands to produce adequate amount of cortisol or tissue resistance to the effect of cortisol.

Sepsis is the leading cause of AI in critically ill patients. Others causes include disseminated tuberculosis, HIV and fungal infection, immune adrenalitis, intra adrenal hemorrhage secondary to anticoagulant therapy, Waterhouse-Friderichsen syndrome and metastasis.[12] Drugs that interfere with steroid hormone synthesis and metabolism can also cause AI. Therapeutic glucocorticoid use is also the cause of AI in ICU that becomes clinically apparent when the physiologic stress exceeds the anticipated glucocorticoid requirement.

The symptoms and signs of CIRCI include fever, asthenia, confusion, delirium, coma, nausea, vomiting, intolerance to enteral nutrition associated with hypotension that is refractory to fluid resuscitation and decreased sensitivity to catecholamines. The hallmark of this condition is hypotension that is refractory to volume expansion and responds poorly to vasopressors. The blood biochemistry usually shows hypoglycaemia, hyponatremia, hyperkalemia and metabolic acidosis.[11] A high index of suspicion is needed to recognise adrenal insufficiency in ICU and biochemical diagnosis should not delay treatment.

The diagnosis relies on delta cortisol (change in baseline cortisol at 60 min of < 9 µg/dL) after cosyntropin (250 µg) administration and a random plasma cortisol of < 10 µg/dL in patients with putative symptoms and signs of CIRCI.[11]

Fluids and glucocorticoid replacement are the mainstays of treatment.[12] Current guidelines recommend use of 100 mg of intravenous hydrocortisone after collecting blood for cortisol and adrenocorticotropic hormone (ACTH) followed by a daily schedule of 300 mg in divided doses. This can be discontinued after satisfactory resolution of the underlying condition.

The Pituitary Gland

Pituitary Apoplexy

Pituitary apoplexy is characterized by a sudden onset of headache, visual symptoms, altered mental status, and features of hypopituitarism due to acute hemorrhage or infarction into an existing pituitary adenoma, and rarely in normal pituitary gland.[13] The risk factors include hypertension, major surgery (particularly involving cardiac bypass), anticoagulants, trauma, dynamic pituitary function testing, and various drugs (e.g. oestrogens, bromocriptine, and aspirin).[14] The clinical presentation ranges from relatively mild symptoms to adrenal crisis due to dysfunction of the hypothalamic-pituitary-adrenal axis. If pituitary apoplexy is suspected, hydrocortisone 100 mg intravenously three times a day should be administered without delay and continued until the crisis is over after collecting blood for cortisol, prolactin, follicle stimulating hormone, luteinising hormone, oestradiol (in females), testosterone (in males), free thyroxine, thyroid stimulating hormone, insulin-like growth factor-1, and ACTH. Following stabilization, early neurosurgical opinion should be obtained for surgical decompression and tumour resection as it improves neuro-ophthalmic outcome.

Diabetes Insipidus (DI)

Central DI (impaired synthesis and release of vasopressin) is commonly encountered in ICU rather than nephrogenic DI (renal insensitivity to circulating vasopressin). It commonly develops in patients following transsphenoidal pituitary surgery, traumatic and hypoxic brain injury, intracranial hypertension, infections like encephalitis and meningitis and brain death.[15] As this disease is characterized by polyuria, patients usually develop dehydration, hypotension and hypernatremia as they are unable to access water. Symptoms of DI may not appear until sodium level exceeds 155-160 mEq/L or serum osmolality exceeds 330 mOsm/kg. Symptoms include confusion, lethargy, coma, and seizures Criteria to diagnose DI includes urine output >200 ml/hr or 3 ml/kg/hr, urine specific gravity <1.005, urine osmolality <150 mOsm/kg and serum sodium>145 mEq/L after excluding other causes for polyuria in ICU (Diuretics, large resuscitation, mannitol, hyperglycemia and cerebral salt wasting).

Treatment of DI includes[16]

- Calculating and replacing free water loss using ½ NS; No more than 50% of the water deficit is replaced in the first 24 hours
- Monitoring and replacing urine losses hourly with an appropriate fluid
- If patient is euvolemic, DDAVP can be given. Initial dose is 0.4 to 1µg SC or IV. Subsequent doses titrated according to the urine output and serum sodium
- Monitoring electrolytes at least 4th hourly
- Sodium should not rise or fall greater than 0.5 mEq/h

Conclusion

Endocrine disorders occurring in ICU patients are common and are often unappreciated in this setting. If left untreated, these disorders are associated with increased morbidity and mortality. Some endocrinopathies like non thyroid illness may not require specific treatment. Thyroid storm, myxedema coma, addisonian crisis, pituitary apoplexy, and diabetes insipidus can present with nonspecific symptoms. A high index of suspicion is needed to recognise them in ICU especially when the primary disorder is unresponsive to standard therapy. Aggressive management of the patient improves the outcome.

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