ORIGINAL ARTICLE

Hypothyroidism and Adrenal Insufficiency in Sepsis and Hemorrhagic Shock

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Hypothesis: We hypothesized that hypothyroidism and adrenal insufficiency frequently occur together in critically ill patients.

Design: A prospective observational study.

Setting: Surgical intensive care unit of a university-affiliated tertiary referral center.

Patients: Sixty-six consecutive patients with severe sepsis, septic shock, and hemorrhagic shock who required pulmonary artery catheterization for resuscitation were studied.

Interventions: Thyrotropin and baseline cortisol levels were obtained at 3 AM followed by intravenous injection of 250 µg of cosyntropin, a synthetic adrenocorticotropic hormone derivative. A second measurement of the cortisol level was performed 1 hour later.

Main Outcome Measures: Incidence of hypothyroidism and adrenal insufficiency and mortality.

Results: Mean (SD) age was 62 (19) years. The mean (SD) Acute Physiology and Chronic Health Evaluation II score was 21 (5). Twenty-seven patients (40.9%) had severe sepsis, 31 (46.9%) had septic shock, and 8 (12.1%) had hemorrhagic shock. Five patients (7.6%) had hypothyroidism alone and 35 (53.0%) had only adrenal insufficiency. Eight patients (12.1%) had both hypothyroidism and adrenal insufficiency. All patients with endocrine abnormalities were treated. Mortality for the total group was 15 (22.7%) of 66 patients.

Conclusion: There is a 12% incidence of simultaneous hypothyroidism and adrenal insufficiency in our study and the routine testing for both may be indicated in this population of critically ill patients.

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Multiple endocrine derangements have been described in critically ill patients. These include abnormalities in the levels of thyroid,[1-3] adrenocortical,[4] growth,[5] and sex hormones.[6] The clinical significance of various changes in the thyroid hormone levels and the appropriateness of endocrine intervention is controversial.[7-9] Maldonado et al[10] showed that a high level of thyrotropin (TSH) is a significant independent predictor of nonsurvival in critically ill patients. Subclinical hypothyroidism, defined as increased TSH concentrations associated with normal free thyroxine (T_4) and free triiodothyronine (T_3) concentrations, have been shown to have significant negative effects on cardiac function[11,12] that are reversible when euthyroidism is restored.[12]

Adrenal insufficiency can be caused by sepsis, surgery, bleeding, and head trauma. In a recent study Zaloga and Marik[4] have reported incidences of adrenal insufficiency in critically ill patients ranging from 0% to 95%. This wide range, in part, results from a lack of a standard definition of adrenal insufficiency. Some of the definitions used by different investigators are as follows: (1) maximal cortisol concentration less than 18.0 to 20 µg/dL after a 250-µg dose of cosyntropin,[13,14] (2) change in cortisol or in delta cortisol response of less than 7 µg/dL,[15] or (3) delta cortisol response of 9.0 µg/dL or less[16] after cosyntropin stimulation, and (4) random cortisol level of less than 25 µg/dL in a highly stressed patient.[17] Studies using corticosteroids in the treatment of adrenal insufficiency in critically ill patients have demonstrated decreased mortality.[16,18]

Hypothyroidism, in addition to adrenal insufficiency, may contribute to the hemodynamic instability of critically ill patients in the surgical intensive care unit. Since treating patients with glucocorticoids has been reported to lower total T_3,

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Table 1. Demographics of Study Population*

Variable	Result
Total No. of patients	66
Age, y	62 (19)
Sex, M/F patients	41/25
Condition, No. of patients	
Severe sepsis	27
Septic shock	31
Hemorrhagic shock	8
Trauma	15
TRISS score (n = 6)	0.80 (0.27)
ISS score (n = 11)	25.91 (12.65)
APACHE II score	21 (5)
ARDS at time of enrollment, No. of patients	9
Organ dysfunctions at time of enrollment, No.	2.1 (1.1)

Abbreviations: APACHE II, Acute Physiology and Chronic Health Evaluation II; ARDS, acute respiratory distress syndrome; ISS, Injury Severity Score; TRISS, Trauma and Injury Severity Score.

*Data are given as the mean (SD) unless otherwise indicated.

total T_4, and TSH levels,[19,20] concurrent TSH testing at the time of adrenal testing may be indicated to prevent masking of hypothyroidism once glucocorticoid treatment is initiated. The purpose of this study is to assess the incidence of concurrent hypothyroidism and adrenal insufficiency in a population of critically ill patients with severe sepsis, septic shock, and hemorrhagic shock.

METHODS

This is a prospective observational study carried out in the surgical intensive care unit of the Queen's Medical Center, Honolulu, Hawaii, a university-affiliated tertiary medical center. The study was approved by the Queen's Medical Center institutional review board. Informed consent was obtained from all patients or their families. The study population consisted of 66 admitted patients having the diagnosis of severe sepsis, septic shock, as previously defined by consensus conference,[21] or hemorrhagic shock who underwent pulmonary artery catheter insertion for cardiovascular optimization and fluid management. Hemorrhagic shock was defined as blood requirement of 12 U or more of packed red blood cells within 12 hours with total fluid requirement of more than 6 L in 6 hours[22] and hypotension, defined as a systolic blood pressure less than 90 mm Hg or a 40-mm Hg or more decrease from baseline. Patients were excluded if they had known adrenal or thyroid insufficiency or glucocorticoid or levothyroxine sodium use within the last year. Also excluded were children (<18 years old) and patients with severe irreversible head injury, uncontrolled neoplastic disease, or do-not-resuscitate orders.

Within 24 hours of pulmonary artery catheter insertion, blood samples were obtained at 3 AM for measurement of TSH and baseline cortisol concentrations. This was immediately followed by intravenous injection of 250 µg of cosyntropin (Cortrosyn; Organon Inc, West Orange, NJ). Cortisol levels were again obtained 1 hour after cosyntropin stimulation. Thyroid and adrenal testing was repeated as clinically indicated during the course of the surgical intensive care unit stay. The cortisol concentration was measured using paramagnetic particle, competitive binding, chemiluminescent immunoassay (Beckman Access Immunoassay system; Beckman Coulter Inc, Fullerton, Calif). The TSH level was measured using 2-step paramagnetic particle, chemiluminescent enzyme immunoassay (Beckman Access Immunoassay system; Beckman Coulter Inc).

Table 2. Endocrine Abnormality Associated With Severe Sepsis/Septic Shock and Hemorrhagic Shock*

Endocrine Abnormality	Severe Sepsis/Septic Shock (n = 58)	Hemorrhagic Shock (n = 8)
Hypothyroidism only	5	0
Adrenal insufficiency only	30	5
Both	6	2
Neither	17	1

*Data are given as the number of patients.

The reference range for TSH level in our laboratory is 0.24 to 3.80 mU/L. Hypothyroidism was defined as TSH concentration greater than 3.80 mU/L. Adrenal insufficiency was defined as a baseline cortisol level of less than 18 µg/dL, and/or cortisol response of less than 7 µg/dL after 250-µg cosyntropin stimulation.[15] Organ dysfunction, as previously defined,[23] and Acute Physiology and Chronic Health Evaluation (APACHE) II[24] scores were determined for all patients within 24 hours of enrollment in the study. Injury Severity Score and Trauma and Injury Severity Score were assessed for trauma victims in the study.

RESULTS

A total of 66 consecutive patients were studied. Patient demographics are listed in **Table 1**. Of the 58 patients with severe sepsis and septic shock, 10 (17.3%) were trauma patients. All 10 patients sustained blunt trauma with multiple injuries. Of the 66 patients, 5 patients (7.6%) had only hypothyroidism and 35 patients (53.0%) had only adrenal insufficiency. Eight patients (12.1%) had hypothyroidism and adrenal insufficiency and 18 patients (27.3%) had neither. There was no statistically significant differences in age or APACHE II scores between the groups with the different endocrine abnormalities. The distribution of these patients among the severe sepsis/septic shock and hemorrhagic shock groups is given in **Table 2**. Overall mortality was 22.7% (15 of 66 patients) and mortalities of the different groups are listed in **Table 3**. The mean (SD) TSH level of the patients with hypothyroidism was 8.5 (6.2) mU/L. Of the 43 patients with adrenal insufficiency, 7 patients (16.2%) had low baseline cortisol levels with normal response to stimulation, 18 (41.8%) had normal baseline cortisol levels but an inadequate response to stimulation, and 18 (41.8%) had a low baseline and an inadequate response to stimulation. Eosinophilia was noted in 6 (14.0%) of 43 patients with adrenal insufficiency.

Hyponatremia (sodium level <136 mEq/L) was noted in 6 patients with adrenal insufficiency, 1 patient with hypothyroidism, and 2 patients with both abnormalities. Hyperkalemia (potassium level >5.0 mEq/L) was found in 2 patients with adrenal insufficiency and 1 patient with hypothyroidism. Hypokalemia (potassium level <3.6 mEq/L) was noted in 5 patients with adrenal insufficiency and 1 patient with hypothyroidism. None of

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Table 3. Mortality by Endocrine Abnormality

Endocrine Abnormality	No. of Survivors	No. of Nonsurvivors	Total No. of Patients	Mortality,%
Hypothyroid	4	1	**5**	20.0
Adrenal insufficiency	27	8	**35**	22.9
Both	5	3	**8**	37.5
Neither	15	3	**18**	16.7

the patients were hypothermic (body temperature <35°C) or hypoglycemic.

All patients found to have hypothyroidism and/or adrenal insufficiency were treated with thyroxine and/or hydrocortisone. Thirty-one of 36 patients with adrenal insufficiency required vasopressor support at the time of diagnosis. After 24 hours of hydrocortisone treatment, they had, on average, a 43% decrease in vasopressor requirement. Two patients initially diagnosed as having only hypothyroidism were noted to have increased hemodynamic instability 4 days after initiation of levothyroxine therapy. They were both tested and found to have new development of adrenal insufficiency.

COMMENT

Both overt and subclinical hypothyroidism has long been recognized to have important clinical effects on cardiac function.[11] Patients with subclinical hypothyroidism may demonstrate left ventricular diastolic dysfunction from delayed relaxation, and systolic dysfunction on effort resulting in poor exercise capacity.[12] These patients also have an increased risk for atherosclerosis, myocardial infarction, and cardiovascular death. Hypothyroidism has also been associated with increased heart rate, atrial arrhythmias, and increased left ventricular mass with marginal concentric remodeling.[11] These abnormalities are reversible when treated with levothyroxine to restore euthyroidism.[12]

The TSH concentration elevations in our study differ from the well-recognized thyroid abnormality in critically ill patients known as the nonthyroidal illness syndrome or the euthyroid sick syndrome. In the euthyroid sick syndrome the first and most consistent thyroid hormone abnormality is a decrease in T_3 level. With increased severity and duration of illness, the T_4 level is decreased as well, owing in part to a decrease in T_4 production. Thyrotropin levels in these patients are typically within or below the reference range during the acute phase of critical illness and only rise to above normal levels during recovery.[1,25,26] Our study measured the serum TSH level during the acute phase of the critical illness, when TSH concentration elevation most likely reflects true hypothyroidism. Although T_4 levels were not obtained in this study, the serum TSH concentration is believed to be the single best test to discern patients with true abnormal thyroid function who require treatment from those with euthyroid sick syndrome.[3]

Studies on the treatment of critically ill patients using T_3 and T_4 level replacements have yielded conflicting results and the appropriateness of treatment remains controversial.[7-9,26] Brent and Hershman[27] randomized intensive care unit patients to receive intravenous thyroxine vs placebo for 2 weeks and found that the 12 treated patients had normal serum T_4 levels but that mortality in both groups was similar. Becker et al[28] administered T_3 to severely burned patients and showed that free T_3 indices were normalized but there was no reduction in mortality. These[27,28] and other similar studies[7-9,26] do not specify whether TSH levels were elevated in the treated patients. Recently, Inan et al[29] found that thyroid hormone supplementation in septic rats resulted in lowered mortality. Most animal studies have shown no clear benefit or harm from triiodothyronine or thyroxine treatment[7,26] but there is a lack of data on treating subjects with elevated TSH levels and whether this influences outcome.

Adrenal insufficiency is increasingly recognized to be common in critically ill patients. Annane et al[30] found that in patients with septic shock, 54% had adrenal insufficiency. If we applied their criteria (cortisol response of <9.0 µg/dL to cosyntropin stimulation), 36 (54.5%) of our 66 patients would have adrenal insufficiency. Briegel et al[18] randomized 40 critically ill patients with sepsis and hypotension requiring vasopressor support to receive stress-dose hydrocortisone or placebo and found that the group receiving hydrocortisone required less time on vasopressor therapy. Bollaert et al[31] randomized patients in septic shock to treatment with hydrocortisone vs placebo and found that the treated patients had improved reversal of shock and improved 28-day mortality. Keh et al[32] demonstrated that in patients with septic shock, hydrocortisone treatment restored hemodynamic stability and attenuated the systemic inflammatory response. A prospective randomized trial with 300 patients in France with refractory septic shock and adrenal insufficiency demonstrated a significant survival benefit when treated with corticosteroids.[16]

The signs and symptoms of hypothyroidism and adrenal insufficiency are nonspecific and difficult to detect in critically ill patients. Hypothyroidism is associated with lethargy, hypoglycemia, hypothermia, cold intolerance, mental status changes, prolonged deep tendon reflexes, and respiratory depression as well as electrocardiographic changes.[33] In our study, no patient had hypothermia and 1 patient with hypothyroidism had bradycardia. Patients in septic and hemorrhagic shock are frequently intubated, ventilated, and sedated; they also are receiving vasopressor and inotropic support and total parenteral nutrition. They often have mental, pulmonary, cardiovascular, renal, and hepatic dysfunction that

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can easily mask the presence of hypothyroidism as well as adrenal insufficiency. Symptoms such as hypotension, hypoglycemia, tachycardia, hypovolemia, or hyponatremia; decreased myocardial contractility; and decreased vascular tone may be attributed to underlying diseases and treatments rather than to hormonal failure. In our study, hyponatremia occurred in 8 (18.6%) of 43 patients with adrenal insufficiency and 3 (23.0%) of 13 patients with hypothyroidism. All of our patients received enteral and/or parenteral nutritional support or glucose-containing intravenous fluids. No patient was hypoglycemic.

Eosinophilia, defined as an eosinophil count greater than 3% of the total white blood cell count, has been reported as a marker of adrenal insufficiency.[15,34] In this study, 6 (14.0%) of our 43 patients with adrenal insufficiency had eosinophilia. Therefore testing for adrenal insufficiency should be considered in hemodynamically unstable patients with eosinophilia.[15,34]

Treatment of hypothyroidism with thyroxine has been reported to precipitate addisonian crisis in patients who also have adrenal insufficiency.[15,35-37] This may be due to an increase in metabolic rate induced by thyroid replacement therapy resulting in overt manifestations of adrenal insufficiency. In our study, 2 patients with hypothyroidism developed hemodynamic instability and were diagnosed as having adrenal insufficiency after 4 days of thyroxine therapy. Both patients initially had normal adrenal function test results. Corticosteroids have been shown to suppress TSH levels into the reference range in patients with hypothyroidism.[19,38,39] It is possible that in patients treated for adrenal insufficiency, concomitant hypothyroidism may remain undiagnosed if therapy with corticosteroids are started before TSH levels are measured.

In our study, patients with severe sepsis, septic shock, and hemorrhagic shock had a 12.0% incidence of concurrent hypothyroidism and adrenal insufficiency. It has been reported that 25% of patients with Addison disease have hypothyroidism.[37] In our study, 8 (18.6%) of the 43 patients with adrenal insufficiency also had hypothyroidism.

One limitation of our study is that the levels of T_3 and T_4 were not tested in patients with elevated TSH concentrations. Except on rare occasions, serum TSH concentration provides a precise and specific barometer of the patient's thyroid status[40] and is believed to be the single best test to differentiate between patients with true abnormal thyroid function and those with euthyroid sick syndrome.[3] Patients with the euthyroid sick syndrome typically have TSH levels within or below the reference range during the acute phase of their critical illness and only have above-normal levels of TSH during the recovery phase.[1,25,26] Although we measured TSH levels during the acute phase of the critical illness, when TSH elevation most likely reflects true hypothyroidism, T_3 and T_4 levels would have allowed us to differentiate between patients with clinical and subclinical hypothyroidism.

Another limitation is that this is not a prospective randomized trial with treatment outcomes. Surks et al[41] recently published a review of 195 studies on subclinical thyroid disease and concluded that there is insufficient data to support routine treatment. Our study population consists of critically ill, hemodynamically unstable patients. No clear adverse outcomes have resulted from treatment with triiodothyronine and thyroxine in this population.[7-9,26-28] Because of the severity of their illnesses, and the known adverse cardiovascular effects of subclinical hypothyroidism,[11,12] all patients with endocrine abnormalities were treated. Our mortality rate of 22.7% compares favorably with other studies of severe sepsis, septic shock,[42,43] and hemorrhagic shock.[44] Treatment of adrenal insufficiency has been shown to improve outcomes but the treatment of subclinical hypothyroidism will need further study. The current evidence suggests that treatment of hypothyroidism and adrenal insufficiency may improve the outcome of these critically ill patients.

To avoid missing the diagnosis of hypothyroidism or precipitating addisonian crisis in patients with adrenal insufficiency, the routine testing for both abnormalities in this population of patients may be warranted. There seems to be a close association between adrenal and thyroid dysfunction. Treatment of hypothyroidism may unmask adrenal insufficiency,[15] although it is possible that adrenal insufficiency developed later in the intensive care unit course. Repeated checks of both hormonal functions in patients who remain unstable or develop instability may be warranted as well.

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