Critically ill patients: histopathological evidence of thyroid dysfunction

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Research Article

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Abstract

**Background:** Critical illness is characterized by severe biphasic physical and metabolic stress as a result of systemic inflammatory response syndrome and multiple organ dysfunction syndrome, and is frequently associated with non-thyroidal illness. The purpose of this study is to better understand the cytomorphological basis of NTI by performing histopathological examinations of the thyroid gland on autopsies of patients who died from critical illness.

**Methods:** Histopathological examination of the thyroid gland of 58 critically ill patients was performed in our hospital. The cases included 24 cases of burn injury, 24 cases of traumatic brain injury, and 10 cases of cerebral stroke. Thyroid samples obtained during a medicolegal autopsy were preserved in 10% formol saline and stained with hematoxylin and eosin. The sections were visualized under light microscopy.

**Results:** Out of the 58 cases examined, 21 patients showed normal thyroid findings, and the rest of the cases had unusual thyroid findings in the histopathological study. The principal finding was the distortion of thyroid follicular architecture. Other findings include mononuclear cell infiltration, clumping of thyroglobulin, and exhaustion of thyroid follicles.

**Conclusion:** Critical illness produces metabolically damaging effects on the thyroid gland, which functionally corresponds to the state of low T3 syndrome. These effects worsen over time and warrant intervention through hormone replacement therapy.

1. **Introduction**

Critical illness is the ultimate form of profound physical and metabolic stress and is characterized by unrivalled and well-orchestrated endocrine and metabolic adaptations. This state can be attributed to a variety of insults like polytrauma, stroke, burns, complicated surgery, and severe medical illnesses. Even when the initial trigger of critical illness has been resolved, these patients enter a chronic state of critical illness, through distinct endocrine and metabolic alterations that can produce subpar clinical outcomes (1).

Multiple organ dysfunction syndrome (MODS) is the leading cause of mortality in critically ill patients, constituting more than 75% of deaths in adult surgical intensive care units. Systemic inflammatory response syndrome (SIRS) is the early stage of MODS (2, 3). This progression of SIRS to MODS in critically ill patients has been technically proved by the nuclear magnetic resonance-based metabonomic approach (3). SIRS in critical illness produces a biphasic inflammatory, immune, hormonal, and metabolic response, leading to MODS. The acute and chronic phases of critical illness are triggered by cytokine mediators, which cause circulatory changes and tissue hypoxia, as well as irreversible cell damage (4).

"Nonthyroidal illness (NTI) syndrome" also known as low T3 syndrome or "sick euthyroid syndrome" is often noted in acute and chronic critical illnesses (5). Patients typically present with a constellation of low or normal plasma thyroxine (T4), low plasma triiodothyronine (T3), and increased plasma reverse T3.
(rT3) concentrations in the absence of a rise in thyrotropin (TSH) (6). Prior studies have described NTI as a syndrome with different faces based on both its origin and impact on the outcome, mainly due to the different neuroendocrine paradigms of SIRS and MODS proposed in acute and prolonged critical illness conditions. The development of NTI and its severity is strongly associated with increased all-cause mortality, periods of survival following illness, and underlying pathology or injury. NTI has also been proposed as a prognostic factor for worse outcomes in various critical illnesses (5–9).

Since functional adaptations are often accompanied by cytomorphological changes, this led us to scrutinize the thyroid gland of critically ill patients. Our study aims to determine the histopathological changes in the thyroid gland of critically ill patients as an effort to provide key novel insights regarding the pathophysiology and significance of the endocrine thyroid response in critical illness. Here we investigated the correlation between the morphological changes in the thyroid gland and the different types of critical illness.

We postulated that the thyroid gland would be involved in patients with a critical illness, as evidenced by functional abnormalities and biochemical derangements seen in these patients (5–9). Our study is the first original report to describe the histopathology of the thyroid gland in the acute phase of critically ill patients.

2. Materials And Methods

2.1. Study design and subjects

This cross-sectional, observational study was conducted to determine the histopathological changes in the thyroid of critically ill patients on autopsy. A total of 58 thyroid samples were collected during the autopsy over 6 months. However, cases of trauma to the neck, poisoning, decomposed bodies, and cases with a known history of thyroid dysfunction were excluded from the study.

2.2. Methods

Patient details like age, sex, date and time of incidence, date and time of admission, and date and time of death were noted from hospital records and inquest papers. The total body surface area of the burn (TBSA-B) in case of burn injury was calculated at the time of autopsy using Wallace's rule of nine.

Thyroid tissues of 1 cm³ were collected using standard dissection techniques. All the samples were preserved in buffered 10% formol saline and sent for paraffin block preparation and hematoxylin and eosin (H&E) staining to the Department of Pathology. The sections thus obtained were visualized under light microscopy for cytomorphological studies.

2.3. Ethical considerations

Written informed consent was sought from the family member of the deceased prior to data and sample collection. The study was approved by the Institutional Ethics Committee at Nilratan Sircar Medical
3. Results

3.1. Patient characteristics

Fifty-eight cases were investigated on autopsy in this study. The study comprised 24 cases of burn injury (BI), 24 cases of traumatic brain injury (TBI), and 10 cases of cerebral stroke. There were 27 females and 31 males with an age range of 4–85 years. The mean survival period of 4.5 days in BI, 11.2 days in TBI, and 4 days in cerebral stroke.

3.2. Pathological findings

Out of the total 58 patients examined, 91.6% of BI patients, 70% of cerebral stroke patients, and 37.5% of TBI patients reported abnormal histologic findings (Table 1). The Chi-square test performed on this data showed significant results in the histopathological changes noted in TBI, BI, and cerebral stroke patients (p < 0.05).

<table>
<thead>
<tr>
<th>Type of critical illness</th>
<th>Frequency of abnormal histologic findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Burn Injury</td>
<td>91.6%</td>
</tr>
<tr>
<td>Cerebral Stroke</td>
<td>70%</td>
</tr>
<tr>
<td>Traumatic Brain Injury</td>
<td>37.5%</td>
</tr>
<tr>
<td>Frequency of abnormal histologic findings</td>
<td></td>
</tr>
</tbody>
</table>

The histological changes are summarised in Table 2.

<table>
<thead>
<tr>
<th>Histologic findings</th>
<th>Frequency in BI patients (n = 24)</th>
<th>Frequency in TBI patients (n = 24)</th>
<th>Frequency in cerebral stroke patients (n = 10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Distortion of thyroid follicular architecture</td>
<td>70.8%</td>
<td>16.6%</td>
<td>70%</td>
</tr>
<tr>
<td>Mononuclear cell infiltration</td>
<td>66.7%</td>
<td>25%</td>
<td>40%</td>
</tr>
<tr>
<td>Exhaustion of thyroid follicles</td>
<td>8.4%</td>
<td>12.5%</td>
<td>40%</td>
</tr>
<tr>
<td>Clumping of thyroglobulin</td>
<td>29.2%</td>
<td>NIL</td>
<td>NIL</td>
</tr>
<tr>
<td>Frequency of various histopathological changes in thyroid</td>
<td></td>
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</tbody>
</table>
Distortion of thyroid follicular architecture was the most common finding (n = 28), followed by mononuclear cell infiltration (n = 26) (Table 2) (Fig. 1). Both focal and diffuse types of distortion were observed. The majority of BI cases (70.8%) and cerebral stroke patients (70%) showed distortion, while it was evident in only 16.6% of TBI patients. In the interfollicular space, there was focal and diffuse mononuclear lymphocytic cell infiltration, which was more prevalent in BI patients (66.7%) and cerebral stroke patients (40%). However, only 12.5% of TBI cases reported mononuclear cell infiltration.

Exhaustion of thyroid follicles and clumping of thyroglobulin were some minor findings reported on histopathological examination (Fig. 2). Exhaustion of thyroid follicles occurs as a result of over-secretion of the thyroid hormone from the follicles, resulting in a pale and rather empty appearance of thyroid follicles. Clumping of thyroglobulin on the other hand is due to the transformation of homogenously distributed thyroglobulin into small globules, giving rise to prominent empty spaces within the follicles.

4. Discussion

Critical illness is a life-threatening condition that requires pharmacological and/or mechanical support of vital organ functions, without which death would be imminent. A state of critical illness can be provoked by extensive burn injuries, sepsis, severe trauma, acute or chronic medical illness, or a complex surgery. An evolutionary and conserved hormonal stress response is supposed to be produced immediately following the onset of the triggering events (10). The strain produced as a result of critical illness is the perfect embodiment of severe and prolonged stress, manifested as a stress-related decompensation syndrome mediated through various endocrine, neural, bioenergetic, and immune systems (11). All of these changes, which are mediated by SIRS and MODS, occur over two distinct phases of critical illness: the acute phase, which lasts from hours to days, and the chronic phase, which lasts from seven to ten days (12).

In our study, we conducted autopsies of critically ill patients who suffered extensive burn injury, traumatic brain injury, or severe cerebral stroke. All these patients succumbed during the acute phase of their critical illness.

Biochemical studies of the thyroid profile of critically ill patients reveal that numerous complex alterations occur in the hypothalamic-pituitary-thyroid (HPT) axis, resulting in euthyroid sick syndrome or low T3 syndrome. During the acute phase, the circulating T3 levels drop and the rT3 levels increase. The magnitude of these changes reflects the severity of the illness (12). These biochemical findings are very much in accordance with the histopathological findings noted in our study. In the majority of cases of BI, TBI, and cerebral stroke in their acute phases, irreversible histological changes are observed. The distorted appearance is primarily due to the disruption of the basement membrane and the alteration in follicular shape and size, rendering the thyroid follicles incapable of producing thyroid hormones. These changes become more diffuse and progressive with prolonged illness as a result of the continuous insult produced by the stress response, leading to even deteriorating circulating levels of T3 as observed in the
chronic phase of critical illness (13). A previous study also found a link between the histopathology of the euthyroid sick syndrome and reduced follicular size in chronically ill patients (14).

The spectrum of critical illness-related decompensation encompasses the systemic inflammatory response syndrome (SIRS) which affects multiple organs, and the thyroid gland is no exception. SIRS is at the heart of critical illness, redefining homeostasis as the balance of forces generating pro- and anti-inflammatory responses (15). Organ dysfunction results when the body is no longer capable of maintaining homeostasis. In the case of neurocritical patients suffering from TBI and cerebral stroke, a neurogenically originating inflammatory response syndrome develops, which sometimes causes systematic inflammation. As part of neurological pathology, multiorgan and tissue damage in some of the polytraumatized patients could increase by the mediators in the circulation (16). Mononuclear cell infiltration evident in our study can be attributed to SIRS that occurs as a result of the existing morbidities. SIRS in turn triggers multiorgan dysfunction, including thyroid dysfunction syndrome, and this continuum of severity in turn affects the prognosis of the patients.

SIRS, in general, is an exaggerated stress-induced defence response that results in a dysregulated cytokine storm, paving the way for a massive inflammatory cascade that eventually leads to irreversible end-organ dysfunction and even death (17). Though all 3 types of insults (BI, TBI, and cerebral stroke) are massive stress inducers and are associated with SIRS, MODS, and the euthyroid sick syndrome profile, our results are more prominent among the BI and cerebral stroke patients, as studied in the acute phase of critical illness with a mean survival period of 4.2 and 4 days, respectively. However, TBI patients, even with a slightly higher mean survival period of 11.2 days, didn't essentially produce a similar grade of histologic findings. In the case of a cerebral stroke, a rather appropriate explanation for the extensive destruction of the thyroid gland would be the pre-existing stressful health conditions like hypertension, diabetes mellitus, and hyperlipidemia that might have an additive role as stress inducers. A multitude of studies has indicated that the decrease in T3 levels is the most common abnormality in hemorrhagic stroke patients. In acute hemorrhagic stroke patients, the decrease in T3 and T4 is linked with high mortality rates. Hence T3 and T4 levels are even considered useful predictors of poor prognosis in acute hemorrhagic stroke patients, as they are in patients with TBI and BI (18–22).

A correlation analysis between thyroid function parameters, and neurological and functional outcomes in TBI patients revealed that decreasing T3 levels were associated with the worst neurological and functional outcomes in terms of functional independence measure (FIM). The correlation study also reported a 14.4% mortality rate in post-TBI patients with decreasing T3 (23), which shows considerable correspondence with the frequency of various histologic findings noted in TBI patients in our study. The lesser frequency of thyroid damage in TBI may be due to the absence of other pre-existing comorbidities as encountered in cerebral stroke patients or due to restricted systemic involvement. The greater the systemic involvement or stress more is the chances of obtaining histological changes in the thyroid.

Our study helps modulate the mode of treatment in this condition of low T3 syndrome in the setting of critical illness. Since irreversible histopathologic changes are produced in the thyroid gland, plasma
iodine overload or exogenous administration of TSH in severely ill patients with prominent damage to the thyroid gland beyond compensation fails to improve thyroid function (24). Administration of thyroxine also has potentially damaging effects once the patient has entered a period of established MODS where the cells are in a stage of dormancy to improve their chances of survival (4). Hormone replacement therapy (HRT) is suggested as part of the early management of critically ill patients. Several studies have also found that HRT can improve survival rates in neurocritical and BI patients (25, 26). However, understanding the degree and timing of intervention remains crucial.

5. Conclusion

SIRS and later MODS essentially lead to irreversible structural changes in the thyroid gland due to the destruction of thyroid architecture. This finding is linked to the functional state of the euthyroid sick syndrome, which is seen in critically ill patients. However, the degree of damage to the thyroid is more in burn injury and cerebral stroke patients compared to TBI.

Early management with hormonal replacement therapy might be beneficial.

Abbreviations

MODS: Multiple organ dysfunction syndrome

SIRS: Systemic inflammatory response syndrome

NTI: Nonthyroidal illness

T3: Triiodothyronine

T4: Thyroxine

TSH: Thyroid stimulating hormone

TBSA-B: Total body surface area of burn

H&E: Hematoxylin and eosin

BI: Burn injury

TBI: Traumatic brain injury

FIM: Functional independence measure

HRT: Hormone replacement therapy

Declarations
**Funding**

No funds, grants, or other support were received.

**Ethical approval and consent to participate**

The study was approved by the Institutional Ethics Committee at Nilratan Sircar Medical College and Hospital. Written informed consent was sought from the family member of the deceased prior to data and sample collection.

**Consent for publication**

Not applicable

**Competing interests**

The authors have no relevant financial or proprietary interests in any material discussed in this article.

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**Authors’ contributions**

All authors made substantial contributions to the conception of the work. DS drafted the work and SC, AR, and SD revised it critically for important intellectual content. All authors approved the version to be published.

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**Figures**
Figure 1

Thyroid tissue showing moderate mononuclear cell infiltration and distortion (arrow) (H&E × 400 magnification)
Figure 2

Thyroid tissue showing features of secretory exhaustion (black arrow) and clumping of thyroglobulin (red arrow) (H&E × 100 magnification)