Original Article: The needs of patients with severe hypothyroidism referring to the emergency department

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ABSTRACT

Introduction: The current American Thyroid Association (ATA) recommendations support the intravenous administration of a loading dose of levothyroxine and an empiric glucocorticoid as part of the initial therapy despite the lack of adequate evidence. SH may ultimately direct patients to the intensive care unit (ICU) for organ support and specialized care.

Material and Methods: The following baseline data were available at the time of ICU admission: demographics, the modified Charlson score, the Simplified Acute Physiology Score II (SAPS II), the SOFA score, the presence of an underlying thyroid condition, precipitating factors, clinical symptoms, and laboratory results.

Results: Cardiovascular SOFA =2 patients had lower heart rates, higher arterial lactate, and a higher risk of aspiration pneumonia and cardiac arrest prior to ICU admission than those without hemodynamic impairment. Conversely, patients who did not have cardiovascular failure experienced hypercapnia more frequently. In the population as a whole with SH, the median TSH, FT4, and FT3 levels were 51pmol/L, respectively. Notably, there were no differences in thyroid hormone levels, SH etiology, or triggers between patients with and without hemodynamic impairment.

Conclusion: The overall ICU and 6-month post-admission mortality rates were 26% and 39%, respectively, based on 82 patients with SH admitted to ICUs. Age, hemodynamic and respiratory failure, but not neurological failure, were factors that were strongly linked to fatal outcomes. This extremely high mortality for a treatable condition necessitates early diagnosis, prompt levothyroxine administration, and careful cardiac and hemodynamic monitoring. More information is still required to more precisely define the ideal dosage and route of administration for this critical treatment.

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Introduction

Thyroxine (T4) and triiodothyronine (T3) deficiency is linked to the chronic disease known as hypothyroidism. Infertility, cardiovascular disease, as well as neurological and musculoskeletal symptoms, are all effects of untreated or ineffectively treated hypothyroidism [1-3]. Worldwide, environmental iodine deficiency is the most frequent cause of thyroid disorders, including hypothyroidism, whereas in areas with adequate iodine intake, autoimmune thyroiditis (Hashimoto's disease) is the most frequent cause of primary hypothyroidism [4-6].

People's hypothyroidism's full ramifications are not yet fully understood or appreciated. According to European prevalence estimates, up to 5% of the population may have hypothyroidism, and up to 5% may have thyroid failure that has not yet been diagnosed. Up to one-third of patients who receive care are not given it is necessary [7-9].

Therefore, the financial impact of undiagnosed, untreated, or inadequately treated hypothyroidism is not negligible, especially when considering the expenses related to maternal and congenital hypothyroidism, as well as when hypothyroid patients have coexisting conditions like diabetes mellitus [10]. In addition to lowering quality of life, having more sick days, and even increasing mortality, hypothyroidism is also linked to these factors.

The cornerstone medication for treating hypothyroidism is levothyroxine, which is also one of the drugs listed by the World Health Organization as being absolutely essential for the provision of basic healthcare [11-13].

Pathological hypothyroidism is associated with low levels of the thyroid hormone circulating in the blood .Although the prevalence of overt hypothyroidism is estimated to be 1-2 percent in the general population, hypothyroidism can cause a wide range of severity from subclinical hypothyroidism to exceptional life-threatening myxedema coma (MC)[14-16]. The most common etiologies are autoimmune thyroiditis, iodine deficiency, post-thyroidectomy or pharmacological, and central due to pituitary or hypothalamic disorders [17].

Ord coined the term "myxedema" in 1877 to refer to a severe disorder in previously healthy women that was characterized by neurocognitive impairment, profound hypothermia, dry skin, swelling, and other clinical features. After a thyroidectomy, a connection was discovered between the description of cretinism and the symptoms that were seen. However, since that time, the exact prevalence worldwide has remained unknown, and current understanding of severe hypothyroidism (SH) mainly comes from case reports and small series [18-20].

From the observations made previously, it is clear that SH can present in a wide range of ways, including mild to severe coma, seizures, hypothermia, bradycardia, heart failure, and pericardial effusion that result in multiorgan failure and death [21-23]. As a result, the clinical diagnosis of SH requires a low index of suspicion and should be further supported by tests for free thyroxine (FT4) and thyroid-stimulating hormone (TSH).

Thyroid hormone replacement therapy has significantly improved the prognosis, with in-hospital mortality reaching 30–40% in the most recent series. The cornerstone of the therapeutic management of SH is, in fact, levothyroxine. The current American Thyroid Association (ATA) recommendations support the intravenous administration of a loading dose of levothyroxine and an empiric glucocorticoid as part of the initial therapy despite the lack of adequate evidence. SH may ultimately direct patients to the intensive care unit (ICU) for organ support and specialized care [24-26]. Data on these critically ill patients admitted to the ICU

are currently scarce [27-29]. The clinical characteristics, treatment, and outcomes of a sizable cohort of SH patients who were treated in French ICUs are reported here [30].

Material and Methods

populace for study

The patients in this study were SH patients who had been admitted to 32 ICUs between 2000 and 2017 . The local investigator in each participating ICU screened all consecutive patients with at least one of the following International Classification of Diseases 10 diagnoses: E03.5 (Myxedema coma) and E03.9 (Hypothyroidism, unspecified). ICU reports were then sent anonymously to two researchers, who independently chose patients meeting inclusion criteria. After consultation with a third researcher (MS), disagreements were settled by consensus. Adults over the age of 18 who were admitted to the ICU with at least one organ failure and/or a Sequential Organ-Failure Assessment (SOFA) score of 1 were eligible.

Data gathering

The following baseline data were available at the time of ICU admission: demographics, the modified Charlson score, the Simplified Acute Physiology Score II (SAPS II), the SOFA score, the presence of an underlying thyroid condition, precipitating factors, clinical symptoms, and laboratory results. The use of inotropic medications, invasive mechanical ventilation, renal replacement therapy, and vasopressors were tracked as follow-up parameters. The composite diagnosis score for myxedema coma proposed by Popovenic et al. which was used in our cohort takes into account changes in the cardiovascular, gastrointestinal, respiratory, and metabolic systems as well as the presence or absence of a precipitating event. Additionally reported were the specific thyroid management (thyroid hormone replacement therapy) and corticosteroid use in the ICU. Finally, survival at ICU discharge and 6-month survival status following ICU admission were noted (via medical charts or phone contact).

Analyses using statistics

The STROBE statement's advice for cohort studies was followed in this study. The Wilcoxon test or the Student's t test, as appropriate, were used to compare continuous variables that were expressed as median (interquartile range). Two-tailed tests were used to compare categorical variables. Bivariate analyses were performed on patient demographic, clinical, management, and laboratory data to determine whether they were related to in-ICU mortality and the presence of circulatory failure. Then, to look into factors connected to ICU and 6-month mortality, factors achieving p 0.10 in bivariate analyses were entered into logistic regression models. Multiple backward-stepwise logistic-regression analyses were conducted, and the Akaike information criterion was used to select the final regression model. Each variable's variance inflation was calculated to test for multicollinearity, which was ruled out if it was less than 4 and 0.2. The model did not take into account variables with one another. Finally, Kaplan-Meier survival curves were calculated for the age (binary), cardiovascular, and ventilation components of the SOFA score, and compared with Mantel-Cox log-rank tests. No assumptions were made for missing data. A p-value lower than 0.05 was considered statistically significant. R 4 (R Foundation for Statistical Computing, Vienna, Austria) software was used to compute the analyses.

Results

447 adult patients with TSH and/or FT4 concentrations outside the reference range and at least one organ failure were admitted to 32 ICUs over the course of the 18-year study period. 82 of the individuals in this group had their SH diagnoses confirmed. Table 1 lists their key

characteristics. In a nutshell, they had a SAPS II of 55 (45-70) and were 70 (59-78) years old. Thyroiditis (29%) and thyroid surgery (19%) were the two main causes of hypothyroidism, with no clear cause identified in about one-fourth of patients. Additionally, 44 (54%) patients had their hypothyroidism diagnosed for the first time while in the intensive care unit. Levothyroxine discontinuation (28%) and hypothyroidism caused by amiodarone (11%), as well as sepsis (15%), were the most common causes of SH. During the winter months, the hospital admitted 33 patients, or 40% of the total. Intriguingly, multiple systemic manifestations of SH were found upon admission to the ICU (Fig 1).

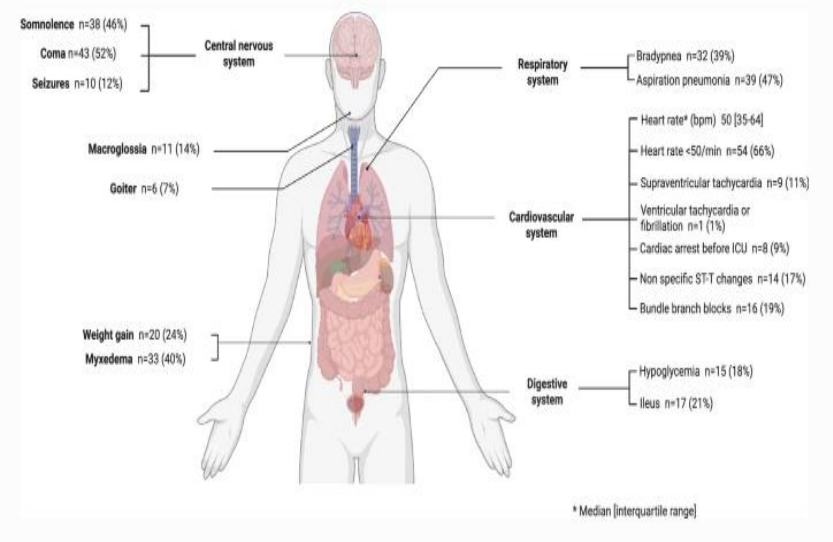

Figure 1: Main clinical presentation of severe hypothyroidism in critically-ill patients

First, 43 patients (52%) were reported to have central nervous system involvement, such as a Glasgow coma scale of 9, while 38 (46%) and 10 (12%) patients, respectively, were reported to have somnolence and seizures. 54 patients (66%) had frequent hypothermia, with a median in-ICU lowest temperature of 34 °C . Other notable features included aspiration pneumonia in 39 patients (48%) and bradypnea in 32 patients (39%) as well as ileus in 17 patients (21%) and hypoglycemia in 15 patients (18%). Importantly, 47 (57 percent) of the patients reported hemodynamic impairment, which is defined as SOFA cardiovascular component = 2, while 41 (50 percent) and 8 (10 percent) of the patients reported bradycardia and cardiac arrest upon ICU admission, respectively. However, there was no discernible difference between ICU survivors and nonsurvivors when comparing the population's composite diagnosis score of myxedema coma, which was 65 (50-75). Cardiovascular SOFA =2 patients had lower heart rates, higher arterial lactate, and a higher risk of aspiration pneumonia and cardiac arrest prior to ICU admission than those without hemodynamic impairment. Conversely, patients who did not have cardiovascular failure experienced hypercapnia more frequently. In the population as a whole with SH, the median TSH, FT4, and FT3 levels were 51pmol/L, respectively. Notably, there were no differences in thyroid hormone levels, SH etiology, or triggers between patients with and without hemodynamic impairment.

ICU nonsurvivors required significantly more frequent use of vasopressors, inotropic support, invasive mechanical ventilation, and renal replacement therapy than ICU survivors did. Of note, 9 (11%) patients required isoprenaline or

temporary transvenous ventricular pacing, and two received pericardial drainage.

43 percent of patients receiving specific treatment for hypothyroidism received levothyroxine with a loading dose of 300 g to replace their thyroid hormone. Levothyroxine exposure intervals were not related to ICU survival following hospital or ICU admission. Finally, 52 (63%) of the patients had thyroid hormone replacement therapy in addition to corticosteroids. Critically ill SH patients had a 26% ICU mortality rate. Mortality reached 39% among the 72 patients for whom a 6-month survival status was available. The average age of ICU nonsurvivors was higher, and their SAPS II and SOFA scores were higher as well. Additionally, ICU survival was lower in patients with hemodynamic failure and aspiration pneumonia.

Similar to ICU survivors, ICU nonsurvivors had significantly lower hemoglobin levels and higher arterial lactate .s. Cardiogenic shock was reported more frequently during the ICU stay in nonsurvivors, and a higher dose of vasopressors and dobutamine was used as a result (Fig 2).

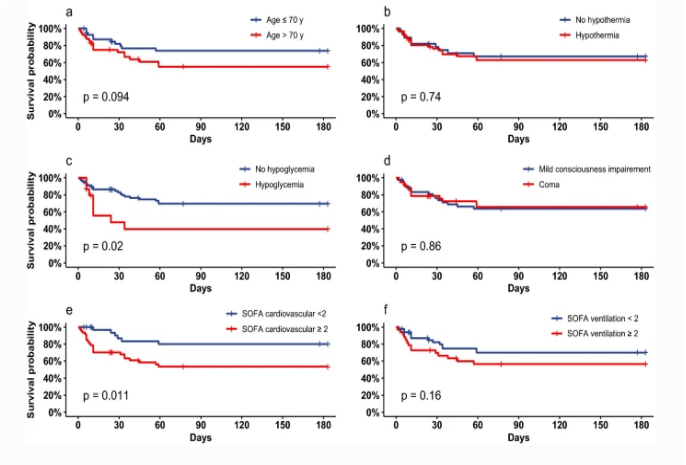

Figure 2: Six-month survival according to A age, B hypothermia, C hypoglycemia, D coma, E cardiovascular component of the SOFA score, and F ventilation component of the SOFA score

Age > 70 years, hemodynamic failure, and ventilation impairment were independently associated with in-ICU mortality after being entered into the logistic regression model along with age, the SOFA score's hemodynamic and ventilation components, and hypoglycemia. The same results were obtained when the logistic regression model used 6-month survival as the dependent variable.

Discussion

Here, we present data on the largest multicenter cohort of SH patients admitted to the ICU [31-33]. A significant in-ICU and 6-month mortality of 26% and 39%, respectively, is related to SH, an incredibly uncommon thyroid emergency. Despite the fact that the clinical presentation may include a number of recognized symptoms of hypothyroidism, hemodynamic and respiratory failures due to SH at the time of ICU admission were strongly linked to a higher risk of mortality [34].

Levothyroxine was consistently given in place of the thyroid hormone, despite variations in the administration method and loading dose. Furthermore, steroids were frequently added to this treatment [35].

The two main determinants of hypothyroidism resulting in SH were thyroiditis and thyroidectomy. In iodine-sufficient regions of the world, autoimmune thyroiditis is thought to be the primary cause of hypothyroidism, which

affects middle-aged women more frequently than men. In our population, a 3:1 gender ratio favoring women and an average age of 70 (59-78) years was noted. It's possible that worse clinical manifestations are linked to a history of stopping levothyroxine [36-38].

Amiodarone's high iodine content further supports the link between this medication and seriously debilitating thyroid diseases, such as SH or thyroid storm, as it was a significant trigger of SH in our population. As a result, thyroid function should be regularly monitored following the prescription of amiodarone, even though amiodarone-induced hypothyroidism is common and does not always call for amiodarone discontinuation [39].

SH should be identified as soon as possible in order to begin thyroid replacement, monitoring, and treatment of any potentially fatal organ failures that may be connected. Creating trustworthy diagnosis scores may enable the early detection of SH patients. Indeed, the performance of the diagnosis scoring system for myxedema coma put forth by Popoveniuc et al is externally validated by our results, due to the fact that the population's median score was under 60, which is strongly suggestive of myxedema coma. However, this score was not related to outcomes in our population, so using it as a predictive survival model is not possible.

According to our findings, adding to that score additional variables pertaining to the hemodynamic and respiratory status at ICU admission may help to more accurately predict the prognosis of this population. Neurological impairment was a common clinical symptom among our cohort of SH patients, though it came in different severity forms like coma, somnolence, and seizures [40].

Importantly, only half of our patients experienced coma, which is consistent with results from a national database Japanese cohort that reported that only one-third of SH patients had experienced a coma at the time of hospital admission. Myxedema coma, which is frequently used to define SH, may also be misleading because hemodynamic and ventilation failures are frequent clinical manifestations that are, in contrast to coma, associated with worse outcomes.

The hemodynamic effects of a thyroid hormone deficiency combine with an increase in systemic vascular resistance and a decrease in cardiac contractility to result in a reduction in cardiac output. Severe bradycardia and arrhythmias linked to abnormal cardiac repolarization and prolonged QT interval may also happen, as well as cardiac tamponade brought on by the buildup of fluid rich in mucopolysaccharides in the pericardium. Additionally, according to a number of reports, thyroid hormone administration may make hemodynamic instability worse(Fig 3).

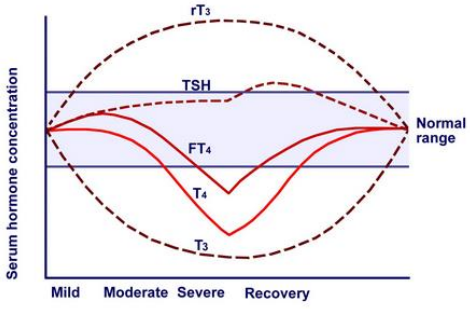

Figure 3: Euthyroid sick syndrome. Relationship between serum thyroid hormone concentrations and severity of nonthyroidal illness (NTI). Abbreviations: reverse triiodothyronine (rT3), thyroid-stimulating hormone (TSH), free thyroxine (FT4), thyroxine (T4), triiodothyronine (T3).

There are several theories put forth to explain the high incidence of respiratory failure in this population. First, aspiration pneumonia was a common occurrence and might be caused by neurological damage. Second, 66 percent of our patients needed invasive mechanical ventilation due to bradypnea, which affected more than one-third of them. The duration of mechanical ventilation may be extended by impaired ventilatory response to hypoxia and hypercapnia, partial obstruction of the upper airway, and neuromuscular and diaphragmatic dysfunction, all of which have already been reported in this context.

Levothyroxine has been the go-to medication for thyroid replacement in SH for a long time, as triiodothyronine (T3) was more likely to cause side effects and hemodynamic instability. Aggressive levothyroxine replacement at the start of SH treatment may increase the risk of myocardial infarction or arrhythmias, so the initial dose and route of administration are still up for debate. Thyroid replacement in the context of SH should be pragmatic and tailored to the patient's age, medical history, and critical illness condition, as demonstrated by the wide variation in dose, route of administration, and loading dose in our population.

Levothyroxine should be administered intravenously at an initial dose of 200–400 g, with lower doses given for very young or older patients, those with a history of coronary disease or arrhythmia, and those without. However, data are still lacking regarding the advantages of combining corticosteroids with thyroid hormone replacement.

According to current recommendations, this treatment should be used in the early stages of SH to possibly treat any autoimmune adrenal insufficiency that may be caused by pituitary or hypothalamic diseases. Our study's advantages include a large cohort that was thoroughly characterized and investigated, a multicenter design, and a follow-up period of six months following ICU admission. It should be noted that there are a number of shortcomings. Its retroactive design is what causes the first problem. Analysis of any potential correlation between clinical evolution and thyroid hormone level kinetics was impossible due to missed follow-up thyroid hormone dosages. Additionally, some lingering confounding variables might have influenced the direction of our findings. Second, 18 years were spent collecting the data. Therefore, we cannot rule out the possibility that the standard of care for critically ill patients has not changed during the course of the study. Third, SH is a rare, poorly understood emergency thyroid disease. However, European and American recommendations regarding the first-line treatment of hypothyroidism remained unchanged during the study period. Therefore, our extremely stringent inclusion criteria may have excluded patients with the most severe form of hypothyroidism and at least one organ failure, underestimating the incidence rate of this rare disease. Finally, 54/82 patients were missing calcemia at ICU admission, making it impossible to determine the incidence of associated hypoparathyroidism in each case.

Conclusion

SH is a rare, life-threatening endocrine emergency that can present in a variety of ways clinically and require ICU admission. Even though half of these severely ill patients are in comas, neurological clinical features may only include seizures or mild changes in consciousness. The overall ICU and 6-month post-admission mortality rates were 26% and 39%, respectively, based on 82 patients with SH admitted to ICUs. Age, hemodynamic and respiratory failure, but not neurological failure, were factors that were strongly linked to fatal outcomes. This extremely high mortality for a

treatable condition necessitates early diagnosis, prompt levothyroxine administration, and careful cardiac and hemodynamic monitoring. More information is still required to more precisely define the ideal dosage and route of administration for this critical treatment.

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