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Clinical characteristics and outcomes of myxedema coma: Analysis of a national inpatient database in Japan

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ABSTRACT

Background: Myxedema coma is a life-threatening and emergency presentation of hypothyroidism. However, the clinical features and outcomes of this condition have been poorly defined because of its rarity.

Methods: We conducted a retrospective observational study of patients diagnosed with myxedema coma from July 2010 through March 2013 using a national inpatient database in Japan. We investigated characteristics, comorbidities, treatments, and in-hospital mortality of patients with myxedema coma.

Results: We identified 149 patients diagnosed with myxedema coma out of approximately 19 million inpatients in the database. The mean (standard deviation) age was 77 (12) years, and two-thirds of the patients were female. The overall proportion of in-hospital mortality among cases was 29.5%. The number of patients was highest in the winter season. Patients treated with steroids, catecholamines, or mechanical ventilation showed higher in-hospital mortality than those without. Variations in type and dosage of thyroid hormone replacement were not associated with in-hospital mortality. The most common comorbidity was cardiovascular diseases (40.3%). The estimated incidence of myxedema coma was 1.08 per million people per year in Japan. Multivariable logistic regression analysis revealed that higher age and use of catecholamines (with or without steroids) were significantly associated with higher in-hospital mortality.

Conclusions: The present study identified the clinical characteristics and outcomes of patients with myxedema coma using a large-scale database. Myxedema coma mortality was independently associated with age and severe conditions requiring treatment with catecholamines.

Introduction

Myxedema coma, an emergency presentation of hypothyroidism, is well-known to be a life-threatening condition.[1] The occurrence of this disease is rare, with an estimated incidence of 0.22 per million per year in a previous European study.[2]

Owing to its rarity, the clinical features associated with enhanced survival of this disease remain unclear. Currently, the initial thyroid hormone replacement of intravenous L-thyroxine (LT4) is regarded as the standard therapy for myxedema coma induced by long-standing severe hypothyroidism.[3] L-triiodothyronine (LT3) can be administered simultaneously, depending on coexistent cardiac risk factors.[3–6] However, any recommendations for the treatment of myxedema coma have merely been based on expert opinions and case reports.[3–6] In Japan, patients with myxedema coma are treated with enteral LT4, with or without LT3, through a nasogastric tube, while, in many other countries, these treatments are more frequently given intravenously.

In previous small case-series studies, the mortality rates of myxedema coma were 36% (4 of 11 patients), 52% (12 of 23 patients), and 25% (2 of 8 patients).[2,7,8] However, the factors associated with mortality due to myxedema coma remain uncertain.

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The aims of the present study were (i) to describe the patient characteristics and current clinical treatment practice patterns for myxedema coma, including thyroid hormone replacement therapy; and (ii) to examine the factors affecting in-hospital mortality due to myxedema coma, using a national inpatient database in Japan.

Methods

Data source

The Diagnosis Procedure Combination (DPC) database is a discharge abstract and national administrative claims database for acute-care inpatients in Japan, the details of which have been described elsewhere.[9–12] Briefly, 1042 hospitals participated in the database and provided data for 6.85 million inpatient admissions in 2012. The attending physicians are required to record the diagnosis of the disease accurately because the diagnostic records are linked to the payment system. The database includes the following data: dates of admission and discharge; patient age and sex; primary and secondary diagnoses, comorbidities at admission, and complications after admission; procedures; medications and devices used; consciousness level at admission, measured with the Japan Coma Scale (JCS); and in-hospital mortality. Diagnoses are recorded using International Classification of Diseases, Tenth Revision (ICD-10) codes and text data in Japanese. The JCS scores are defined as follows[13]: 0, alert consciousness; 1–3, wakefulness without any stimuli; 10–30, arousal by some stimuli; 100–300, coma. JCS and Glasgow Coma Scale assessments are well-correlated.[14] The database does not contain any laboratory data, including serum thyroid hormone levels prior to or during treatment.

Written informed consent was not required because of the anonymous nature of the data. The Institutional Review Board at The University of Tokyo approved the study.

Patient selection and data

From the DPC database, we retrospectively extracted the records for all patients diagnosed with myxedema coma (ICD code: E03.5) from July 1, 2010 through March 31, 2013. We excluded patients with suspected diagnosis of myxedema coma.

We examined patients' age, sex, JCS score at admission, and requirement for mechanical ventilation. Age was categorized into ≤69, 70–79, 80–89, and ≥90 years, because this grouping was clinically practical based on previous studies showing that elderly patients with hypothyroidism were more likely to experience myxedema coma.[2,7,8] We also examined the practice patterns for treating myxedema coma in terms of variation in type and dosage of thyroid hormone replacement therapy (enteral LT4 alone; enteral LT4 combined with LT3; others, comprising no replacement of thyroid hormones or in-hospital preparation of thyroid hormones), and use of steroids (hydrocortisone, prednisolone, methylprednisolone, dexamethasone, and betamethasone) and catecholamines (dopamine, noradrenaline, adrenaline, dobutamine, and isoprenaline). Intravenous administration of thyroid hormones is considered an optimal therapy for patients with myxedema coma, who are unable to take medication orally.[3–6] In Japan, however, injectable forms of thyroid hormones are not commercially available.[15] Instead, crushed thyroid hormone tablets are enterally administered through a nasogastric tube. Otherwise, injected or suppository forms of thyroid hormones prepared in individual hospitals are used. However, in the DPC database, we could not confirm whether in-hospital preparations of thyroid hormones were used. Therefore, we categorized these unknown patients as "others". The maximal per-day dosage of LT4 was categorized into <100, 100–199, and ≥200 μg, and the maximal per-day dosage of LT3 was categorized into <20, 20–49, and ≥50 μg. Duration of LT3 treatment was categorized into <7 and ≥ 7 days. Use of steroids and catecholamines was categorized into (i) none, (ii) use of steroids alone, and (iii) use of catecholamines with or without steroids. Duration of steroid and catecholamine treatments were categorized into <7, 7–13, and ≥14 days.

Season at admission was divided into spring (March through May), summer (June through August), autumn (September through November), and winter (December through February). We identified the following comorbidities at admission: cardiovascular diseases, neuromuscular and psychiatric diseases, diabetes mellitus, pneumonia, chronic renal diseases, infections, chronic lung diseases, cerebrovascular diseases, adrenal insufficiency, gastrointestinal and hepatic diseases, trauma, and malignancy. We also identified patients who were newly diagnosed with acute myocardial infarction, angina pectoris, or arrhythmias after admission.

Statistical analyses

We assumed that all patients with myxedema coma were hospitalized. We estimated the incidence of myxedema coma based on bed volume stratification in all acute-care hospitals in Japan and the numbers of beds and myxedema coma patients in the DPC hospitals in 2012. The estimated numbers of myxedema coma patients (Y) were calculated using the following equation:

$$Y = \sum_{i=1}^{k} N_i \frac{X_i}{n_i}$$

where N is the number of beds in all acute-care hospitals in Japan, n is the number of beds in the DPC hospitals, and X is the observed number of myxedema coma patients in the DPC hospitals in 2012.[16] Because of the rarity of the disease, we calculated their 95% confidence intervals (CI; T_L, T_U) using the method for weighted sums of Poisson parameters.[16] The CIs were calculated using the equation:

$$T_L = Y + (V/X)^{1/2}(X_L - X) \text{ and } T_U = Y + (V/X)^{1/2}(X_U - X)$$

where $X = \sum X_i$, $V = \sum \left(\frac{N_i}{n_i}\right)^2 X_i$, and the corresponding confidence limits X_L and X_U were calculated using the chi-square method.[16] The annual incidence of myxedema coma (number per population per year) was calculated by dividing the estimated number of myxedema coma patients (Y) by the population of Japan in 2012.

In-hospital mortality was compared between the groups using chi-square tests. A multivariable logistic regression analysis was performed to evaluate factors associated with in-hospital mortality. In the multivariable regression model, we included clinically important independent variables (age as a continuous variable, sex, and variation of thyroid hormone replacement) regardless of statistical significance, and candidate independent variables possibly associated with in-hospital mortality ($P < 0.10$ in the chi-square tests). When the ratio of the number of non-survivors to the number of candidate independent variables was small, we selected the more clinically important variables to avoid using too many independent variables with an insufficient sample size. In the category of variation of thyroid hormone replacement, we only included patients who received enteral administration of LT4 alone or LT4 combined with LT3.

All tests were two-tailed, and values of $P < 0.05$ were considered statistically significant. All statistical analyses were performed using the SPSS statistical package, version 22.0 (IBM Corp., Armonk, NY, USA).

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