Clinical THYROIDOLOGY



# A Large Nationwide Survey of Patients Hospitalized with Thyroid Storm Has Been Used to Develop a Different Approach to Characterizing the Disease

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# Background

Thyroid storm occurs in association with a broad spectrum of nonthyroidal conditions. It can appear in patients without previous hyperthyroidism, but it can also appear after decades of hyperthyroidism, particularly in patients who have not been consistent in taking their antithyroid drugs. Severe stress is often cited as a connection between these various diseases, but the mechanisms involved in thyroid storm remain mysterious; its rarity and the difficulty of establishing just which patients should be given the diagnosis add to the problem. Advances in surgical management and in the care of critical illness are believed to have reduced mortality from thyroid storm. This Japanwide retrospective survey represents a substantial step forward in the systematic study of this nebulous condition. All Japanese university hospitals, all special thyroid or emergency hospitals, and all hospitals over 500 beds were surveyed, along with a randomized size-scaled selection of smaller hospitals with fewer beds. Approximately 20% of all Japanese hospitals were contacted in 2009, and about half responded to the question of whether or not they had seen any suspected storm cases among the patients with thyrotoxicosis who were admitted to their hospitals in the past 5 years. Based on the 541 reports of possible cases, patient-specific data were requested and analyzed, which resulted in 356 patients deemed to have storm occurring in 2004 to 2008. Data from 133 control patients who had thyrotoxicosis but did not have thyroid storm were also collected from the authors' clinics for several months for comparison.

## Methods

The authors initially developed diagnostic criteria

by reviewing case reports (22 from PubMed, 1992 to 2005; 77 from the Japanese Ichushi database, 1983 to 2005; as well as data from 7 unpublished cases) and comparing them with the 133 control patients with thyrotoxicosis who did not have storm. The authors slightly revised the criteria after reviewing the data from the 356 new cases. "Definite" storm cases were defined as patients who had an elevated  $FT_3$  or  $FT_4$  at the time storm developed, and who had one of two sets of features.

(A) Patients who had specific Central Nervous System (CNS) manifestations (restlessness, delirium, psychosis/mental aberrations, somnolence/lethargy, convulsions, or a score of 14 or less on the Glasgow Coma Scale or of 1 or more on the Japan Coma Scale) needed to have only one of 4 additional conditions: either a temperature of 38°C or higher; tachycardia of 130 beats per minute or higher; severe congestive heart failure (CHF; New York Heart Association Class IV or Killip class III, with pulmonary edema, moist rales over more than half the lung field, or cardiogenic shock); or gastrointestinal (GI)/hepatic manifestations (diarrhea, nausea/vomiting, or a bilirubin above 3 mg/dl). (Interestingly, abdominal pain was not a criterion, although perforation of the GI tract was the direct cause of death in 2 cases).

(B) Patients without CNS manifestations (other than anxiety or agitation) had to have the requisite high  $FT_3/FT_4$ , plus at least 3 of the 4 additional conditions listed under A. "Suspected" storm cases were defined as patients having at least two of the four conditions listed under A, plus a high  $FT_3/FT_4$ ; or else they could have all the criteria for "definite" storm, but the requirement for a concurrent serum  $FT_3/FT_4$  value

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was forgiven if other data confirming the existence of thyrotoxicosis was present.

The authors compared the results of their "fever/ tachycardia/GI/CHF with or without CNS" scoring method with the modified Wartofsky scoring system that sums up the numerical severity for each of five parameters—CNS manifestations, GI dysfunction, tachycardia, temperature, and CHF—plus gives an additional 10 points for atrial fibrillation or a precipitating event (1). (The total numerical score gives an estimate of the likelihood of storm: unlikely, impending, likely, or highly likely). Most of the "suspected" cases had a Wartofsky score in the "likely" range, and most of the "definite" cases were scored as "highly likely," although there were some remarkably discrepant cases.

#### Results

As expected, the levels of TSH,  $FT_4$  and  $FT_3$  did not differ between control patients with hyperthyroidism and the 356 patients with definite or suspected storm. There were 38 deaths in total. Mortality in the 282 classified as definite storm was the same as in the 74 classified as suspected storm: about 10%. A cause of death was identified in 77% of patients; the most common cause in both definite and suspected storm was multiple organ failure (24%), followed by CHF (21%), respiratory failure (8%), arrhythmia (8%), disseminated intravascular coagulation (DIC; 5%), and GI perforation (5%). Multiple-logistic-regression analysis indicated that patients who had multiple organ failure had a 10-fold increase in the risk of death, while those who either had shock or DIC had a 4-fold increase in the risk of death; again, there was no difference between definite and suspected cases. Triggering factors for storm were identified in 70%; the five commonest triggers were irregular use or discontinuation of antithyroid drugs (34%), infection (24%), and diabetic ketoacidosis, severe emotional stress, or trauma (3% each). Thyrotoxicosis had been present for less than a month before storm developed in about 45 patients, but storm also developed in patients in whom thyrotoxicosis had been present for decades. The mortality rate for patients with a bilirubin over 3 mg/ml was 32%, with multiple organ failure 24%, and with severe CHF 21%. Atrial fibrillation occurred in 38% of all patients with storm, but was present in almost 53% of fatal cases.

#### Conclusions

Simple regression analysis suggested that CNS manifestations and/or CHF might be associated with increased mortality, but multiple regression analysis did not confirm an association. Patients with multiple organ failure were 10 times as likely to die, and those with shock or DIC had a 4-fold increased risk of death. Perhaps a future prospective study using the diagnostic criteria outlined could help us make clinical decisions earlier, although the variety of possible associated diseases probably would hinder establishing standard clinical protocols.

#### ANALYSIS AND COMMENTARY • • • • •

When one encounters a noncompliant patient with Graves' disease who has marked tachycardia, diaphoresis, and nausea and diarrhea or who has a severe respiratory infection, signs of sepsis, heart failure, or mental changes, the safest thing to do is hospitalize the patient and provide empiric therapy. Not uncommonly, the patient will turn out to be "a tropical depression" and not a full blown "storm," but making a decision on hospitalization based on a point score or on the number of organ systems that show abnormalities remains a long way in the future.

The current study excluded any cases in which an underlying disease appeared to be responsible for fever (e.g., pneumonia), impaired consciousness

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(e.g., psychiatric or cerebrovascular disorders), heart failure (e.g., acute myocardial infarction), or liver failure (e.g., viral hepatitis or acute liver failure). However, such diseases clearly can trigger thyroid storm. The updated Wartofsky approach (1) indicates that when it is not possible to distinguish whether a finding is due to an intercurrent illness or to thyrotoxicosis, the higher point score is given so as to favor empiric therapy. In addition to the stringency of the selection criteria in the current study, its spectrum of cases may differ from those in other parts of the world, since Japan has a high level of dietary iodine intake, while toxic nodular goiter is rare. The authors required documentation of serum FT<sub>3</sub>/FT<sub>4</sub> levels to prove thyrotoxicosis, but severe illnesses are well known to reduce T<sub>3</sub> levels, and patients with thyroid storm who are already receiving antithyroid drugs could have been excluded. It is interesting that a single cutoff value of a temperature over 38°C (which isn't that uncommon in patients with garden-variety Graves' disease) was useful, while only the most severe grade of CHF was useful in distinguishing cases of storm, and that atrial fibrillation, abdominal pain, and agitation were not useful. Finally, the division of cases into definite and suspected seems to have been relatively unrewarding, since both groups had the same mortality rate. This ambitious and exciting study extends hope not only for prospective studies, but also for studies on organ-specific toxicities of thyroid hormones and for cooperative clinical studies to analyze the tsunami of cytokines and chemokines that doubtless occur in these unusual patients.

- Stephen W. Spaulding, MD

## REFERENCES

 Wartofsky L. Thyrotoxic storm. In: Braverman L, Utiger R, eds. Werner and Ingbar's The thyroid: a fundamental and clinical text. 9th ed. Philadelphia: Williams & Wilkins, 2005:651-7.