Original Article

A Lower Prevalence of Central Nervous System and Higher Prevalence of Cardiac Symptoms Characterises Indian Patients with Thyrotoxic Storm: A Retrospective Analysis

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Abstract

Introduction: Thyroid storm is an uncommon but life-threatening presentation of thyrotoxicosis with a mortality rate of 10%. Our objective was to study the demographics, clinical and biochemical characteristics, and outcomes of inpatients diagnosed with thyroid storm in the Indian context. **Methods:** This retrospective study was conducted by analysing the institutional electronic medical records (EMR) of all patients admitted with thyroid storm from 2004 to 2020 with a Burch–Wartofsky score (BWS) of ≥45. **Results:** Thirty-five patients with a BWS ≥45 were included, of whom 71.4% were women, with a mean age of 44.9 ± 10.2 years. 43% did not have any prior history of thyrotoxicosis. Graves' disease was the most common underlying aetiology (71.4%), followed by toxic multinodular goitre (14.3%). Cardiovascular (94.3%) and gastrointestinal-hepatic dysfunction (88.6%) were the most common clinical manifestations. Features of Central nervous system (CNS) dysfunction were seen in only 42.3% of patients diagnosed with a thyroid storm. The Japanese Thyroid Association (JTA) criteria diagnosed only 26 patients (74.3%) with "definite" thyroid storm. The mortality rate was 8.6%, and all three patients expired within 48 hours of admission. **Conclusion:** Nearly one in every two patients with thyroid storm had previously undiagnosed thyrotoxicosis. Toxic multinodular goitre is a notable aetiology in Indians. Features of CNS dysfunction, considered relatively specific for thyroid storm, were less prominent in our series. The JTA criteria might alter the classification of some patients diagnosed with a thyroid storm, when compared to the BWS score due to fewer CNS features among Indian patients.

Keywords: Burch–wartofsky score, hyperthyroidism, japanese thyroid association criteria, thyroid storm

Introduction

Thyroid storm is an uncommon, life-threatening presentation of thyrotoxicosis that is characterised by exaggerated clinical features and the presence of multiorgan dysfunction. Untreated or poorly managed thyroid storm is almost universally fatal (80-100%), and even with treatment, mortality rates of up to 50% have been reported.[1] Retrospective nationwide surveys in the USA[2] and Japan[3,4] have estimated an incidence of 4.8-5.6 cases/100,000 hospitalised Americans per year and 0.2/100,000 hospitalised Japanese per year with thyrotoxicosis. Among American and Japanese patients hospitalised with thyrotoxicosis, thyroid storm was diagnosed in 16.2%[2] and 5.4%[4] of the cases, respectively.

There is neither a linear correlation between the clinical features of thyrotoxicosis and the derangement of thyroid function tests, nor a specific investigation to separately identify thyrotoxic patients with thyroid storm.[4,5] The involvement of nearly every major organ system and the ensuing multitude of non-specific symptoms and signs only serve to further obscure the diagnosis. The clinical point scale developed in 1993 by Burch and Wartofsky (BWS)[5] [Table 1] for the early identification and treatment of thyroid storm remains the most utilised to date. In 2012, the Japanese Thyroid

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Association (JTA) proposed new diagnostic criteria for thyroid storm after their nationwide surveys [Table 2].[4] Unlike the BWS, the JTA criteria give greater weight to features of central nervous system (CNS) dysfunction over other organ systems, as the former is more specific.[4,6]

Although case reports of thyroid storm from India have been published,[7,8] larger studies are required to determine the clinical and biochemical profiles of these patients and identify factors associated with adverse outcomes.

Materials and Methods

Study design

All patients admitted under the Department of Endocrinology, Diabetes and Metabolism from June 2004 to January 2020 were included in the study. The electronic medical records (EMR) of patients who were diagnosed with "thyroid storm," "impending thyroid storm" or "thyrotoxicosis with congestive heart failure" at admission were retrieved, and the Burch–Wartofsky score (BWS) was calculated after reviewing the full course during admission. Only patients with a BWS ≥45 (highly suggestive of thyroid storm) after chart review were included in the study [Table 1]. The demographic details, history, clinical examination findings and investigations (including thyroid stimulating hormone (TSH), T4 and free T4, as well as antithyroid and TSH receptor antibodies), as well as details of their treatment, course and outcomes were obtained from their EMR. An attempt was also made to contact the patients who were lost to follow-up by telephone, and after consent they were interviewed regarding their current health status, and the results were documented.

TSH levels, total and free thyroxine levels (T4 and fT4) were measured using a chemiluminescence method with the Siemens Atellica automated assay analyser (Siemens Healthineers, Erlangen, Germany), with a reported measurement range of 0.008-150 mIU/L and 0.1-12 ng/dL for TSH and fT4,[9] respectively. The intra-assay coefficient of variation reported was 3.8% for TSH, 4.5% for T4 and 3.6% for fT4. TSH receptor antibodies (TrAb) were detected and measured by electrochemiluminescence technology using the Roche Cobas 602 instrument (Roche Diagnostics, Mannheim, Germany). All patients who were included were found to have a suppressed TSH and an elevated free thyroxine (fT4) level. The assay for TrAb antibodies has been available in our institution since 2017, and hence, only six patients (17.1%) were tested for the same.

Statistical analysis

Data obtained from the hospital EMR was entered into Microsoft Excel. An analysis was performed using Statistical Package for Social Sciences (IBM Corp, SPSS Version 21). Continuous variables were reported with mean and median values along with standard deviation (SD) and inter-quartile range, and categorical variables were reported as numbers with percentages (%).

Table 1: Burch–Wartofsky Score (BWS) for the Diagnosis of Thyroid Storm

Thermoregulatory Dysfunction		
Temperature (ºF/ºC)	99-99.9/37.2-37.7	5
	100-100.9/37.8-38.2	10
	101-101.9/38.3-38.8	15
	102-102.9/38.9-39.4	20
	103-103.9/39.4-39.9	25
	≥ 104/≥ 40	30
Central Nervous System Effects		
Mild	Agitation	10
Moderate	Delirium, psychosis or extreme lethargy	20
Severe	Seizure or coma	30
Gastrointestinal-hepatic Dysfunction		
Moderate	Diarrhoea, nausea/vomiting or abdominal pain	10
Severe	Unexplained jaundice	20
Cardiovascular Dysfunction		
Tachycardia	99-109	5
	110-119	10
	120-129	15
	130-139	20
	≥ 140	25
Atrial fibrillation		10
Heart Failure		
Mild	Pedal oedema	5
Moderate	Bibasilar rales	10
Severe	Pulmonary oedema	15
Precipitant History		
Negative		0
Positive		10
Interpretation		
<25	Unlikely to represent thyroid storm	
25-44	Suggestive of impending thyroid storm	
≥ 45	Highly suggestive of thyroid storm	

Reference: Burch HB, *et al*. Am. 1993 Jun; 22 (2):263-77.

Ethical aspects

This study was approved by the Institutional Review Board of the study centre and all procedures followed were in accordance with the Helsinki Declaration of 1964, as revised in 2000. Due to the retrospective nature of the study, consent was waived. Patient confidentiality was maintained using password-protected software and restricted users.

Results

A total of 73 patients were identified with an initial diagnosis of thyroid storm, impending thyroid storm or thyrotoxicosis with cardiac failure during the study period. Following the calculation of their BWS after chart review, 35 patients (47.9%) had a BWS ≥45 and were included in the study. Among the remaining 38, 22 of these patients (30.1%) met the criteria for impending thyroid storm (a BWS of 25-44), and 16 (21.9%) did not meet

Table 2: Japanese Thyroid Association (JTA) Diagnostic Criteria for Thyroid Storm

Prerequisite:

Presence of thyrotoxicosis with elevated levels of free triiodothyronine (FT3) or free thyroxine (fT4)

Symptoms:

1. Central nervous system (CNS) manifestations: Restlessness, delirium, mental aberration or psychosis, somnolence or lethargy, coma (≥1 on the Japanese Coma scale or <14 on the Glasgow Coma Scale
2. Fever: ≥38° C
3. Tachycardia: ≥130 beats per minute or heart rate ≥130 in atrial fibrillation.
4. Congestive heart failure (CHF): Pulmonary oedema, moist rales over more than half of the lung field, cardiogenic shock, or Class IV by the New York Heart Association or ≥ Class III in the Killip classification
5. Gastrointestinal (GI)/hepatic manifestations: nausea, vomiting, diarrhoea or a total bilirubin level ≥3.0 mg/dL

Interpretation:

Diagnosis	Combination of Features	Requirements for Diagnosis
"Definite" thyroid storm (TS1)	First combination	Thyrotoxicosis plus at least one CNS manifestation and one of the following: fever, tachycardia, CHF or GI/hepatic manifestation.
	Alternate combination	Thyrotoxicosis and at least three of the following: fever, tachycardia, CHF or GI/hepatic manifestation.
"Suspected" thyroid storm (TS2)	First combination	Thyrotoxicosis and a combination of two of the following: fever, tachycardia, CHF or GI/hepatic manifestation.
	Alternate combination	Meets the diagnostic criteria for TS1, except that serum fT3 or fT4 levels are not available

Exclusions and Provisions:

Cases are excluded if other underlying diseases are clearly causing fever, impaired consciousness, heart failure and liver disorders. As some of these disorders trigger thyroid storm, the symptom should be regarded as being due to a thyroid storm that is caused by these precipitating factors (clinical judgement in this matter is required).

Reference: Akamizu T, *et al*. Thyroid. 2012 Jul; 22 (7):661-79

the criteria. Notably, one patient had met the first combination of features for the diagnosis of "definite thyroid storm" (TS1) under the JTA criteria but did not have a BWS ≥45. Eighteen of the 35 patients included (51.4%) had a BWS ≥45 at presentation and were documented to have thyroid storm. For the remaining 17 patients who were found to have a BWS ≥45 during the course of admission, 13 of 35 (37.2%) were classified as impending thyroid storm and 4 (11.4%) were documented to have thyrotoxicosis with congestive cardiac failure at presentation.

Twenty-seven patients of 35 (77.1%) were from Southern India, considering that this is an endocrine emergency and the location of the institution. The mean age was 44.9 ± 10.2 years, with a female preponderance (71.4%). The baseline characteristics and laboratory investigations are summarised in Table 3 and Table 4, respectively. Of note, hypokalaemia at presentation was seen in 14 patients (40%). Graves' disease was the predominant etiological cause, seen in 25 patients of 35 (71.4%). Five patients (14.3%) were diagnosed as having toxic multinodular goitre (TMNG), and one patient each (2.9%) was diagnosed with Hashimoto's thyroiditis and Hashitoxicosis, with destruction of the thyroid gland leading to the excessive release of pre-formed hormones and thyrotoxicosis. The underlying aetiology could not be established in 3 (8.6%) patients who had expired.

Cardiovascular dysfunction (tachycardia, with or without concomitant atrial fibrillation) was the most common clinical feature, seen in all but 2 (94.3%) of the patients. This was followed by symptoms of gastrointestinal dysfunction, seen in 31 (88.6%) patients. The clinical features are summarised in Table 5. Notably, only 42.3% of patients exhibited CNS manifestations, and none had severe CNS

Table 3: Baseline Characteristics of Patients with Thyroid Storm

Characteristics	Actual Values
Mean age in years (SD)	44.91±10.17
Female gender (%, *n*=35)	25 (71.4%)
Geographical Distribution (%, *n*=35)	
Southern India	27 (77.1%)
Eastern India	7 (20%)
Central India	1 (2.9%)
Diagnosis at Admission (%, *n*=35)	
Thyroid Storm	18 (51.4%)
Impending Thyroid Storm	13 (37.1%)
Thyrotoxicosis with Congestive Cardiac Failure	4 (11.4%)
Index Presentation (%, *n*=35)	15 (42.9%)
Recurrent thyroid storm (%, *n*=35)	4 (11.4%)
Primary Aetiology (%, *n*=35)	
Graves' Disease	25 (71.4%)
Toxic Multinodular Goitre	5 (14.29%)
Thyroiditis	1 (2.85%)
Hashitoxicosis	1 (2.85%)
Undetermined	3 (8.6%)
Outcome (%, *n*=35)	
Expired	3 (8.6%)
Lost to follow-up	16 (45.7%)
Radioactive iodine ablation	9 (25.7%)
Thyroidectomy	2 (5.7%)
Remission with antithyroid medications	3 (8.6%)
Undecided during follow-up	2 (5.7%)

Table 4: Laboratory Investigations at Presentation

Investigation	Mean	Standard deviation
Haemoglobin (Hb) [in g/dL]	11.26	2.1
Total Leukocyte Count [in cells/mm^3]	8809	3433
Absolute Neutrophil Count [in cells/mm^3]	5731	3121
Sodium (Na) [in mmol/L]	138.6	5.04
Potassium (K) [in mmol/L]	3.75	0.8
Total bilirubin [in mg/dL]	1.82	2.05
Aspartate aminotransferase (AST) [in U/L]	83.8	212.8
Alanine aminotransferase (ALT) [in U/L]	54.61	110.02
Alkaline phosphatase (ALP) [in U/L]	126.7	42.95
Creatinine (Cr) [in mg%]	0.7	0.44
Thyroid stimulating hormone (TSH) [in µIU/ml]	0.009	0.007
Total thyroxine (T4) [in µg/dL]	23.26	6.97
Free thyroxine (fT4) [in ng/dL]	6.98	3.26

Table 5: Clinical Features and Diagnostic Criteria

Clinical Feature	Number (n=35)
Thermoregulatory dysfunction	22 (62.9%)
Central Nervous System Effects	15 (42.3%)
Mild	9 (25.7%)
Moderate	6 (16.6%)
Severe	0
Gastrointestinal-hepatic Dysfunction	31 (88.6%)
Moderate	26 (74.3%)
Severe	5 (14.3%)
Cardiovascular Dysfunction	33 (94.3%)
Tachycardia	31 (88.6%)
Atrial fibrillation	14 (40%)
Heart Failure	21 (60%)
Mild	9 25.7%)
Moderate	11 (31.4%)
Severe	1 (2.9%)
Positive Precipitant History	21 (60%)
Non-compliance with medications	18 (51.4%)
Additional precipitants	13 (37.14%)
Mean Burch–Wartofsky Score	55.71±13.24
Japanese Thyroid Association (JTA) Criteria	
"Definite" Thyroid Storm (TS1)	26 (74.3%)
First Combination	15 (42.9%)
Alternate Combination	11 (31.4%)
"Suspected" Thyroid Storm (TS2)	7 (20%)
Not met TS1/TS2 criteria	2 (5.7%)

manifestations (defined as seizures or coma). Among the 35 patients with a BWS ≥45, only 26 (74.3%) met the JTA criteria for definite thyroid storm (TS1). Two (5.7%) patients did not satisfy either the TS1 or TS2 (suspected thyroid storm) criteria.

Thyroid storm was the index presentation of thyrotoxicosis in almost half of the patients (15/35; 43%). Among the remaining 20 (57%) patients with a prior history of thyroid disease, 18 patients had discontinued their antithyroid medications, with the remaining two having developed thyroid storm despite being compliant. Among the 18/20 (90%) patients who had discontinued treatment, two had performed so for medical reasons (namely, medication-induced bone marrow suppression and following the period post-radioactive iodine ablation). Apart from non-compliance with medications, additional precipitating factors were identified in only 13 (37.1%, n = 35) of all patients. 10 patients (76.9%; n = 13) were diagnosed with concurrent infections, and the rest included radioactive iodine ablation, iodinated contrast, and symptomatic nephrolithiasis (each affecting one patient).

Details of pharmacological treatment during admission are summarised in Table 6. Thioamides were used in all but three patients. Propylthiouracil (PTU), the preferred drug for the management of thyroid storm over methimazole (due to its additional inhibition of conversion of T4 to the more potent T3), was used in most patients (22/35, or 62.8%). Carbimazole was used in 10 (28.6%; n = 35) patients. One patient was diagnosed with viral hepatitis that precluded the use of thioamides, and the second patient was initially managed without thioamides as the initial aetiology was suspected to be contrast-induced thyrotoxicosis. On follow-up, this patient was later diagnosed with Graves' disease. The third patient had been diagnosed with thioamide-induced bone marrow suppression, and, on admission for thyroid storm was treated with lithium to block the release of thyroid hormones.

Beta-adrenergic blockers, used to counteract the sympathetic overdrive caused by thyrotoxicosis, were administered to nearly all patients, apart from three patients with comorbid asthma who received calcium channel blockers (verapamil) instead. The usage of iodine agents to inhibit thyroid hormone release (by the Wolff–Chaikoff effect) was documented in only 11/35 (31.4%) patients. As only 18 patients were diagnosed at the initial point with thyroid storm, this might explain the low usage of iodine-containing agents (as well as their availability) to treat thyroid storm in our study. This hypothesis is further supported by the observation that 8 of the 11 (72.7%) patients, who received iodine-containing agents, were documented to have thyroid storm in their records. Nearly three-fourths (26/35) of patients were administered glucocorticoids, which are used to inhibit the peripheral conversion of T4 to T3. Cholestyramine was not administered to any of the patients in our study.

Three patients (8.6%) died during their hospital stay, with the causes of death being multiorgan dysfunction in two (5.7%) patients and refractory arrhythmias causing arrest in one (2.9%). All of them worsened rapidly and died within 48 hours of admission, with two requiring mechanical ventilation. Apart from five patients who were lost to follow-up after discharge, the remaining 27 patients had at least one revisit after their initial admission. 11 patients did not subsequently follow up for definitive management. Among the 16 patients on regular follow-up, definitive treatment for hyperthyroidism was documented in 11 patients in the form of either radioiodine ablation (9) or by thyroidectomy (2), with a median interval

Table 6: Drugs Utilised in Patients with Thyroid Storm

Agent	Percentage (n=35%)
Propylthiouracil	22 (62.9%)
Carbimazole	10 (28.6%)
Lithium	1 (2.9%)
Beta blockers	32 (91.4%)
Calcium channel blockers	3 (8.6%)
Iodine	11 (31.4%)
Glucocorticoids	26 (74.3%)

of 189 days (6.21 months) since the index presentation. Three patients had attained remission with antithyroid medication alone. Four patients presented with recurrent thyroid storm, and the median interval was 2.2 years. Three of these patients had been diagnosed with TMNG, with one having failed radioactive iodine ablation twice and the other two being non-compliant with their medications. The fourth patient, with Graves' disease, had also defaulted on treatment.

Discussion

Thyroid storm was first described in 1928 by Lahey as "the crisis of exophthalmic goitre" and was universally fatal.[10] With the development of clinical scores for early diagnosis and treatment, the mortality of thyroid storm has decreased substantially from nearly 100% without treatment to 10-30% in recent studies.[1,4,6,1-14] The most common causes of death are multiorgan failure, congestive heart failure and respiratory failure.[4] Advancing age (>60 years), CNS dysfunction at admission, inadequate treatment (not administering antithyroid drugs or beta blockers) and patients requiring mechanical ventilation or plasma exchange with haemodialysis have been identified as predictors of mortality.[14]

To our knowledge, this is the first study detailing the clinical profiles and outcomes of patients presenting with thyroid storm in an Indian context. The mean age (44.9 ± 10.2 years) and female preponderance (71.4%) in our sample are in concordance with previous studies in other countries.[2,4,6] About half of the patients were documented at admission to have thyroid storm with a BWS ≥ 45, and the remaining cases met the criteria for thyroid storm only after the recalculation of their scores following their inpatient course. This mirrors the findings of Angell *et al*.,[6] who noted that only 14.8% of patients satisfying the diagnostic criteria for thyroid storm were initially diagnosed with a thyroid disorder at admission. More than 40% of our cases presented with no prior history of thyrotoxicosis, a concerning feature reported by others,[6,11] with the risk of delayed diagnosis and treatment.

Although Graves's disease was the most common aetiology (71.4%) in our study as well,[2,4,6,11] TMNG comprised 14.3% of the cases in our series. Although TMNG with hyperthyroidism is less common, it is more prevalent in iodine-deficient areas, where it may even supplant Graves' disease as the most common aetiology of hyperthyroidism in such regions.[15,16] Nearly 200 million Indians are at risk of iodine deficiency disorders, despite increasing efforts towards universal salt iodisation.[17] This may partially explain the greater number of cases in our study as compared to other series from developed countries[18] with lower levels of iodine deficiency. Among the four patients who were admitted with a second episode of thyroid storm, the majority (75%) had been diagnosed with TMNG. Thus, these patients may benefit from early definitive therapy when compared to patients with Graves' disease.

Hypokalaemia was present in 40% of patients at admission, necessitating frequent potassium monitoring and judicious correction. Notably, less than half of our patients had features of CNS dysfunction (42.3%), with none having developed severe features (namely, seizures or coma), a finding also reported by Swee *et al*.[11] One-fourth (9/35, 25.7%) of patients with a BWS ≥45 did not meet the definite thyroid storm (TS1) criteria proposed by the JTA and two did not meet the criteria for suspected thyroid storm (TS2) as well. Other studies comparing the two criteria[6,11] have reported good concordance between both criteria. These observations in our study are likely explained by the paucity of CNS involvement in our study patients. A BWS ≥45 has also been shown previously to be more sensitive than the JTA criteria[6] in diagnosing thyroid storm over those with compensated thyrotoxicosis, but the final decision to treat a patient must rest on clinical judgement. Although early and aggressive treatment of thyroid storm is advocated, in the absence of a gold standard test, the adverse effects of treatment must also be considered. Inpatient treatment for thyroid storm in our institution was comparable to those reported by other studies.[6,14] Almost all patients previously diagnosed with hyperthyroidism and presenting with thyroid storm (90%) had discontinued their oral antithyroid medications, with infections being the most common additional risk factor, a pattern reported by others.[4,11] The mortality rate for thyroid storm patients admitted to our hospital was 8.6%. All three patients deteriorated rapidly[11] (within two days of admission), with two patients requiring mechanical ventilation, a known predictor of mortality.[12,14] The mortality rate may have been skewed by the younger patient population and lower incidence of CNS dysfunction.[14] Less than half of the patients who were discharged underwent definitive management of hyperthyroidism at our institution. The administration of large doses of iodine during treatment of thyroid storm precludes the early use of radioactive iodine ablation. Similarly, elective thyroidectomy is offered after a euthyroid state has been achieved with medications to minimise the risk of precipitating a second episode of thyroid storm[5] during surgery.

The limitations of the study include its retrospective nature, with selection bias, the recalculation of the BWS from previous reports loss to follow-up as well as absence of TSH receptor antibody in a significant number of patients. The small sample size precluded further analysis including predictors of mortality. The rarity of thyroid storm and the likelihood

of missed diagnoses only compound this issue, rendering prospective studies difficult to conduct.[4] A large multicenter study across India may help further characterise such patients and identify predictors of morbidity and mortality in the Indian context.

Conclusion

Although rare and despite progress in diagnosis and management, thyroid storm is a potentially lethal presentation of thyrotoxicosis. Graves' disease is the most common underlying aetiology; however, toxic multinodular goitre is prominent in this series. Notably, features of CNS dysfunction were less common and less severe than reported elsewhere.[4,6,11] The JTA criteria may identify fewer patients with thyroid storm in this setting when compared to the BWS. Only half of the patients were correctly identified and documented to have thyroid storm at admission, emphasising the necessity of a high index of suspicion. Untreated toxic multinodular goitre is more likely to present with recurrent thyroid storm when compared to Graves' disease. Definitive therapy in the form of radioactive iodine ablation or thyroidectomy is required to prevent recurrence as well as complications arising from untreated Graves' disease.

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Authors' contribution

Lath, Devraj: Data curation (equal), formal analysis (lead), investigation (equal), validation (equal), writing-original draft (lead).

Nandipati, Venkata Sandeep: Data curation (equal), formal analysis (supporting), investigation (equal), validation (equal), writing-original draft (supporting).

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Conflicts of interest

There are no conflicts of interest.

Data Availability statement

Original data generated and analyzed during this study are included in this published article.

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