

Coma in Thyroid Storm: Review of Aggregated English-Language Case Reports

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Context: Coma is a serious manifestation of thyroid storm (TS) about which little is known.

Objective: To describe the features, duration, treatment response, and prognosis of coma in the setting of TS.

Design: Aggregate analysis of individual English-language case reports of coma in the setting of TS from 1935 to January 2019.

Setting: Hospitals.

Patients: Sixty-five cases were identified, 29 from case reports and 36 from case series.

Interventions: Antithyroid drugs, corticosteroids, beta-blockers, iodine, intubation, plasmapheresis, antibiotics, thyroidectomy, radioiodine, dialysis, and L-carnitine.

Main Outcome Measures: Awakening and death rates overall and in relation to administered treatments, day of coma presentation, and time from coma onset; symptoms associated with coma; TS and coma scales; thyroid and cerebrospinal laboratory tests; electroencephalogram; brain imaging; and autopsy results.

Results: Mortality was 38% in the setting of TS-related coma, 11% during the years 1978 to 2019 compared with 70% for 1935 to 1977. Both awakening and death commonly occurred within the first 2 days of coma onset. Reduction in total and free T4 values, and possibly also total T3 value, correlated with awakening from coma. Lower death rates were associated with use of antithyroid drugs, corticosteroids, beta-blockers, and intubation. Plasmapheresis was associated with awakening in 67% of cases but not with lower death rates.

Conclusions: Prognosis of coma associated with TS remains poor. Current guidelines for the early use of plasmapheresis in unresolving TS are advocated and should be considered urgently at the point of confusion or delirium in an effort to abort coma.

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Freeform/Key Words: thyroid storm, coma, unconscious, thyrotoxicosis, plasmapheresis

Thyroid storm (TS) is a rare condition characterized by an extreme, decompensated, life-threatening state of thyrotoxicosis. Diagnostic criteria for TS include, among other features, central nervous system (CNS) effects ranging from agitation to delirium, psychosis, or

Abbreviations: BW, Burch-Wartofsky; CNS, central nervous system; EEG, electroencephalogram; ICU, intensive care unit; LP, lumbar puncture; TFT, thyroid function test; TS, thyroid storm.

extreme lethargy to seizure or coma [1, 2]. Coma or even altered mentation has been reported to indicate a more serious outcome of TS [2–6]. Despite this, little is known regarding specific features or the effect of treatments on TS-related coma. For better understanding of this condition, a review of the English-language literature was performed to itemize individually reported cases with coexistent coma and TS, which were then evaluated in aggregate to describe the features, duration, treatment response, and prognosis of coma in the setting of TS.

1. Methods

The English-language literature was reviewed for reports of thyrotoxicosis with coma. This included single case reports and clinical series containing individual case details or reports. Title or abstract words *TS*, *thyrotoxicosis*, *hyperthyroidism*, *coma*, *plasmapheresis*, and *plasma exchange* with text words *thyroid*, *coma*, and *unconscious* were searched in PubMed. Cases were included if they reported diagnosis of both TS and coma or if they had coma and thyrotoxicosis likely meeting Burch-Wartofsky (BW) TS criteria in an independent review and calculation. Coma was as defined by the reporting authors. Specifically, for the report to be included, the reporting authors must have described the patient as having coma, unconsciousness, or unresponsiveness. Confusion, delirium, stupor, and obtundation were not sufficient for inclusion. Cases clinically diagnosed as status epilepticus were excluded. Consistent coma description without internal contradiction within the report was required for inclusion. Reports were reviewed for details pertinent to the thyroid state and coma, all of which were entered into a REDCap database for storage and aggregate analysis [7]. English-language abstracts were included even if the primary article was not in English. BW TS score was calculated from data available for each case [1]. Specifically, a minimum score of 30 was assigned to all coma cases; when detail permitted, additional points were assigned for atrial fibrillation, heart rate, heart failure, temperature, and gastrointestinal dysfunction.

For cases in which treatment details were given, the absence of a particular therapy/intervention was interpreted as indicating that it was not administered. For cases in which no details were given (*e.g.*, no treatment details for any individual cases within some small series), the cases were excluded from the specific analysis.

Statistical analysis was performed using JMP Pro v. 13 software (SAS Institute, Cary, NC). Continuous data were reported as mean \pm SD or 95% CIs and categorical data as count and proportions. χ^2 or Fisher's exact test was used to compare categorical data. The Student *t* test or Wilcoxon two-sample test was used to determine significance for continuous data as appropriate. All tests were two-sided. A *P* value <0.05 was considered significant.

2. Results

Sixty-five cases of thyrotoxicosis with coma were reported in English-language articles over 84 years between 1935 and 2019. Thirty-six cases were individually reported within small case series [3, 8–16], and 29 were reported as individual case reports [17–45]. The case series (1935 to 2011; median year, 1969) were published earlier than the individual cases (1951 to 2018; median year, 2000). Patients ranged in age from 3.5 to 87 years, with a mean age of 46 (SD, 20) years; 75% of the patients were female. Two patients had more than one episode of coma [32]; in one case, the patient recovered from TS-related coma but later died during the second episode of coma [22].

A. Preexisting Conditions

No differences were noted in the characteristics of the study population or the TS manifestations relative to the origin of the data, whether from case reports or case series (Tables 1 and 2).

Preexisting hyperthyroidism was reported in 21 cases (32%), preexisting goiter in 27 cases (42%), and both goiter and hyperthyroidism in 15 cases (23%). Except for two cases involving

Table 1. Characteristics of Study Population

Feature	Number of Individual Cases		
	From Whole Series	From Case Reports	From Case Series
n	65	29	36
Publication year, range	1935–2018 (median, 1984)	1951–2019 (median, 2000)	1935–2011 (median, 1969)
Age, range, y	3.5–87 mean (SD): 46 (20)	3.5–87 mean (SD): 48 (21)	10–74 mean (SD): 44 (19)
Female/Male ^a	49 (75)/16 (25)	22 (76)/7 (24)	27 (75)/9 (26)
Preexisting hyperthyroidism	21 (32)	9 (31)	12 (33)
Preexisting goiter	27 (42)	12 (41)	15 (42)
Preexisting goiter and hyperthyroidism	15 (23)	6 (21)	9 (25)
Preexisting weight loss	19 (29)	8 (28)	11 (31)
Emaciated	5 (7.7)	4 (14)	1 (2.8)
Cardiac history	7 (11)	3 (10)	4 (11)
History of atrial fibrillation	4 (6.2)	3 (10)	1 (2.8)
History of stroke or brain atrophy	4 (6.2)	3 (10)	1 (2.8)
New or known diabetes	8 (12)	3 (10)	5 (14)
Pregnancy	2 (3)	2 (6.9)	0
Death reported on case report	25 (38)	4 (14)	21 (58)

Data are presented as n (%) unless otherwise noted.

^aFemale/Male ratio may exceed 100% because of rounding.

noncompliance [23, 24] and one case each in which iodine withdrawal or thyroidectomy was cited as the precipitant for the TS [3], the reports generally lacked detail on whether treatment was given for hyperthyroidism or its duration or efficacy before the TS event.

In 19 cases (29%), patients reportedly lost weight before the TS event, and four were described as emaciated at presentation. New or known diabetes was present in eight cases (12%). Preexisting heart condition (excluding atrial fibrillation) was present in seven cases (11%). Past brain event or abnormality was present in four and history of atrial fibrillation in four (6.2% for each).

Table 2. Systemic Findings Associated With Thyroid Storm in Patients With Coma

	Total (n = 65)	From Case Reports (n = 29)	From Case Series (n = 36)	<i>P</i>
Tachycardia >120 bpm	57 (88)	27 (93)	30 (83)	1.000
Fever >100.5°F	54 (83)	21 (72)	33 (92)	0.0689
Hypertension	19 (29)	9 (31)	10 (28)	0.7907
Heart failure	20 (30)	8 (28)	12 (33)	0.7877
Atrial fibrillation	15 (23)	8 (28)	7 (19)	0.7621
Liver dysfunction	15 (23)	10 (34)	5 (14)	0.4454
Renal dysfunction	13 (20)	6 (21)	7 (19)	0.1013
RR >20/min	9 (14)	7 (24)	2 (6)	1.000
Hypotension or shock	8 (12)	6 (21)	2 (6)	0.2529
Hyperglycemia	8 (12)	6 (21)	2 (6)	1.000
Hypoglycemia	5 (8)	5 (17)	0	1.000
Other arrhythmia	3 (5)	2 (7)	1 (3)	1.000
DIC	3 (5)	3 (10)	0	1.000

Data are presented as n (%) unless otherwise noted. The *P* value shows the comparison for the parameter based on report type, either case reports or from case series. Other arrhythmia = atrial flutter or ventricular fibrillation. Abbreviations: bpm, beats per min; DIC, disseminated intravascular coagulation; RR, respiratory rate.

Overall, no preexisting condition stood out as a predominant feature in most cases of TS-related coma.

B. Precipitant of TS With Coma

More than one event precipitating the TS-related coma was identified in 21 cases [3, 8, 14–16, 21–24, 33, 35, 36, 38]. No precipitating event could be identified in eight cases [10, 11, 30, 40, 42, 43, 45], and 10 cases had no information on the TS-precipitating event. In some cases, it was not possible to separate precipitating events from consequences of the TS, such as seizure or stroke [15, 20, 24, 26, 35].

Infection was either treated or thought to be likely in 20 cases [3, 8, 10, 12–14, 19, 22, 23, 32], with all other potential precipitating causes reported much less frequently. Six episodes followed an operation (including curettage in two, cesarean section, hysterectomy, thyroid cancer metastasis biopsy, and thyroidectomy) [3, 8, 13, 21, 36, 38]. Iodine exposure from amiodarone was reported in two cases [16, 31] and from CT contrast medium in three cases [15, 34, 38]. There were five cases each of thyroid hormone overdose [14], dehydration [16, 18, 27, 33, 39], and hypoglycemia [22, 29, 32, 35]. Diabetic ketoacidosis or hyperosmotic diabetic coma was reported in four cases [3, 8, 18], and there were three cases each of cardiac events [25, 28, 33], obstetric-related events [13, 21, 36], and trauma [15, 37, 44] or following use of radioactive iodine [3, 35, 41]. Confusion or delirium was reported to precede coma in 38 of 57 cases (67%).

Precipitants of TS-related coma varied, commonly including possible infection. Most cases of coma were preceded by delirium or confusion.

C. Systemic Manifestations of TS During Coma

The most common systemic findings associated with the TS-related coma state were tachycardia (88%) and fever (83%). Cardiovascular abnormalities, including heart failure, hypertension, and atrial fibrillation, were the second-most common events, followed by liver or kidney dysfunction (Table 2). Temperature $\geq 101^\circ\text{F}$ was reported in 45 cases (69%), and temperature $\geq 104^\circ\text{F}$ was seen in 18 cases. Heart rate >140 beats per minute was reported in 39 cases (60%). Comorbidities that can also affect the level of consciousness were present in some cases, including hypotension, hypoglycemia, or hepatic failure. Systemic findings associated with TS-related coma were not different between patients reported in case reports and those reported in case series.

The minimum BW score ranged from 30 to 120 points, with a mean (SD) score of 69 (19) points for cases with adequate detail to make the calculation. Not all reports described the thyrotoxic state with coma as a “TS” [9, 14, 15, 18, 23, 24, 29, 33, 44]. Calculation of the BW score of 13 such cases revealed a range of 30 to 110 points, with a mean (SD) score of 59 (23) points, despite having incomplete data for specific calculation of all BW categories in one of the reports (specifically, fever or tachycardia was present in all cases but not in sufficient detail to assign a BW score) [14].

In summary, systemic manifestations associated with TS-related coma were typical of severe hyperthyroidism.

D. Neurologic Findings Associated With Coma in TS

Only eight cases reported Glasgow [46] or other coma scales [15, 23, 27, 31, 32, 34, 37, 38]. In these cases, Glasgow coma scale mean and median values were 7.3 and 7.5, respectively, with a range of 3 to 12. Most reports did not provide sufficient detail for independent calculation of the Glasgow coma scale.

Positive Babinski sign was reported in five cases [20, 25, 30, 40, 42] and clonus in two [40, 42]. Seizure and stroke presented together in two patients [24], including one pediatric patient [35]. Four others had seizure alone [29], three of whom were pediatric patients [15,

45]. Three patients had a stroke [14, 20, 26]. None of these patients had known preexisting structural brain disease.

Neurologic testing in association with TS-related coma may have included electroencephalogram (EEG), lumbar puncture (LP), or brain CT or MRI. EEG was performed in 11 cases [11, 15, 20, 37], seven of which reported diffuse slowing [19, 30, 33, 38, 39, 42, 45]. LP was performed in 15 cases [11, 15, 19, 20, 22, 29, 30, 37, 38, 40, 42, 43, 45]. Low cerebrospinal fluid glucose level was reported in two cases (as 18 and 27 mg/dL) [22, 45].

Eleven patients had abnormal results from either head CT or brain MRI [20, 22, 24, 26, 32, 34, 35, 37], three of whom had a preexisting structural abnormality [25, 27, 30]. Head CT was reported in 18 cases and was read as normal in 11 cases (65%). Brain MRI was reported in only seven cases [33, 38] and had abnormal results in five, including reversible lesion of the splenium in the corpus callosum [37], diffuse atrophy [34], chronic lacunar infarcts in bilateral pons [30], and stroke [35]. There are no reports of functional MRI or fluorodeoxyglucose positron emission tomography in TS-related coma.

Two patients merit special comment because each had two bouts of coma, the second of whom had been under prolonged treatment after the TS. Harada *et al.* [32] reported a patient with a stroke on day 24 followed by a second bout of coma. Homma *et al.* [22] reported a patient with seizure and a second coma associated with posterior leukoencephalopathy syndrome diagnosed at 29 days, followed by death within 2 days.

In summary, only a small proportion of patients with TS-related coma had detailed descriptions of the coma or associated brain testing or imaging. When performed, EEG commonly showed diffuse slowing, and LP cerebrospinal fluid was mostly normal. Brain MRI was performed in too few patients to draw conclusions on TS-related coma associations.

E. Thyroid Tests With Coma and Recovery

At least one thyroid function test (TFT) was reported in 43 cases (Table 3). A range of TFTs was reported. Most cases reported either total T4 [13–15, 21, 24, 25, 37–43, 45] or free T4 [15, 16, 19, 20, 22–24, 26–28, 30, 31, 33–36, 47]. The highest blood levels were noted in the acute levothyroxine overdose cases, with total T4 level of 600 µg/dL in a patient with preexisting chronic renal failure, an outlier that highly influenced the mean total T4 and T3 values [14]. Cross-sectional analysis of available TFTs showed major reduction in mean total and free T4 and total T3 levels at awakening compared with coma onset. Only a few cases reported longitudinal TFTs both at onset of coma and at awakening in the same patient [15, 30, 31, 34, 38–40, 42, 45]. These cases showed substantial reduction in total and free T4 levels at the time of awakening from coma. Protein-bound iodine was reported in five cases [12, 13, 29] and high radioiodine uptake in six cases [12, 13, 18, 39].

Table 3. Thyroid Function Tests at Coma Onset and at Awakening

Test	Cross-Sectional	Mean [CI]	P	Long	Mean [CI]	P
Total T4, µ/dL	Coma onset (n = 23)	77 [26, 128]	0.0083	5	67 [−0.7, 135]	0.0216
	Awakening (n = 5)	15 [−94, 124]			15 [−53, 82]	
Free T4, ng/dL	Coma onset (n = 18)	5.8 [5.0, 6.5]	0.0009	4	5.9 [4.0, 7.8]	0.0432
	Awakening (n = 4)	2.9 [1.5, 4.2]			3.2 [1.5, 5.0]	
Total T3, ng/dL	Coma onset (n = 18)	2295 [−4897, 5132]	0.0020	4	376 [195, 557]	0.1124
	Awakening (n = 4)	118 [−347, 4939]			110 [−71, 291]	
Free T3, pg/dL	Coma onset (n = 12)	1547 [980, 2116]	0.1390	3	1426 [−67.2, 2920]	0.3493
	Awakening (n = 3)	621 [−516, 1757]			621 [−873, 2114]	
No TFTs	(n = 22)					

Cross-sectional average thyroid hormone levels at coma onset and awakening. Most cases did not have measurement at both times. Long = mean of longitudinal TFTs performed in the same patient at coma onset and at awakening. Abbreviation: CI, 95% confidence interval.

To summarize, available cross-sectional TFT data suggest an association between awakening and major improvement in total and free T4 and total T3 levels. Limited longitudinal data showed an association between awakening and improvement in only total and free T4 levels.

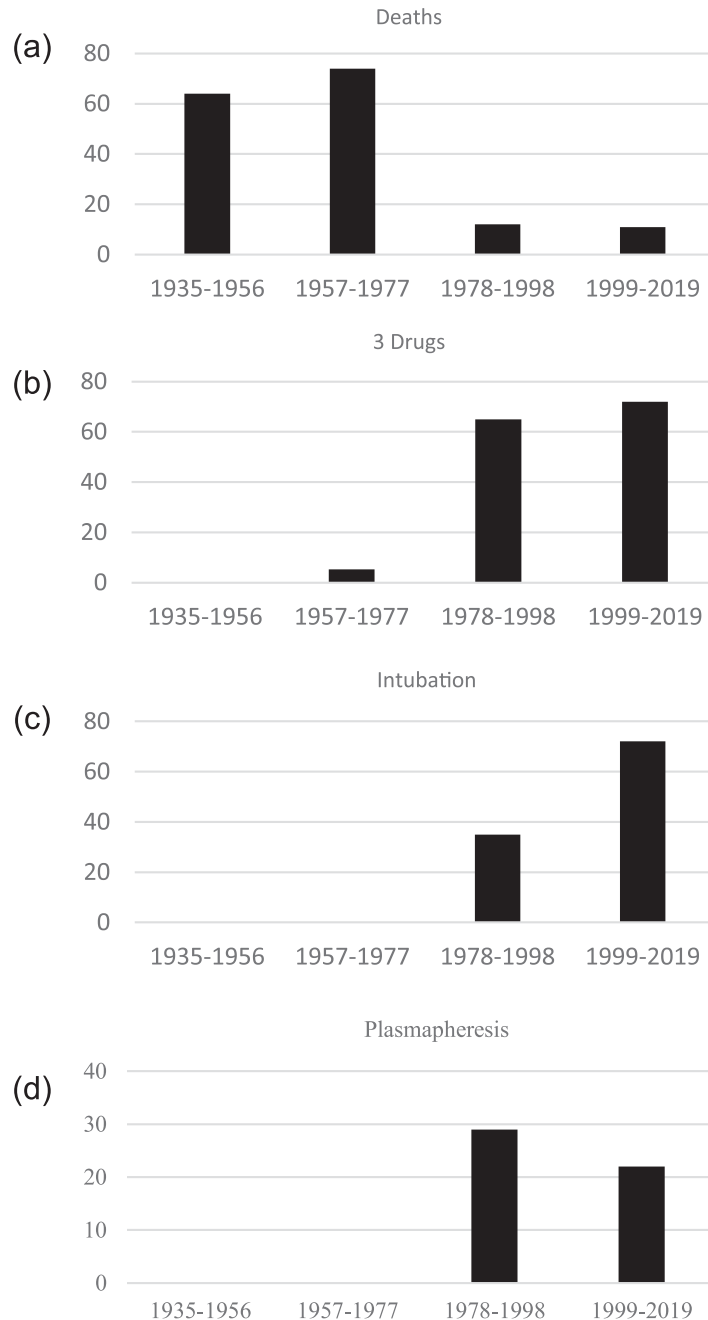


Figure 1. Percentage of events associated with coma in the setting of thyroid storm as reported in the English-language literature from 1935 to 2019, divided by 21-y quartiles. (a) Deaths: 1935–1956, 64% (7/11); 1957–1977, 74% (14/19); 1978–1998, 12% (2/17); 1999–2019, 11% (2/18); $P < 0.0001$. Death rate: 1935–1976, 70% (21/30) and 1978–2019, 11% (4/35). (b) Three-drug therapy involving antithyroid drugs, corticosteroids, and beta-blockers: 1935–1956, 0; 1957–1977, 5.3% (1/19); 1978–1998, 65% (11/17); 1999–2019, 72% (13/18); $P < 0.0001$. (c) Intubation: 1935–1956, 0; 1957–1977, 0; 1978–1998, 35% (6/17); 1999–2019, 72%; (13/18); $P < 0.0001$. (d) Plasmapheresis: 1935–1956, 0; 1957–1977, 0; 1978–1998, 29% (5/17); 1999–2019, 22% (4/18); $P = 0.0874$.

Table 4. Relationship of Coma Presentation Time to Awakening and Death

Coma Onset Relative to Hospital Presentation	Group, n (% Total)	Survived Coma Days to Awakening n (% of Presentation Group)	Died, n (%)	Coma Days to Death, n
Coma at presentation [15, 17–19, 24, 27, 28, 35, 40, 42, 44, 45]	13 (30)	N = 12 (92) <1 d: 3 (25) 1–2 d: 6 (50) >2 d: 1 (8) No data: 2 (17)	1 (7.7)	<1 d: 1
Coma onset day 1 or 2 off/after hospitalization [8, 11, 14, 21, 23, 25, 26, 29, 30, 33, 37, 39, 41, 43]	17 (39)	N = 13 total (76) ^a <1 d: 3 (23) 1–2 d: 1 (8) >2 d: 8 (62) No data: 1 (8)	4 (24) ^a	2 d: 1 ^a 5 d: 1 >14 d: 1 Unclear: 1
Coma onset day 3 or later after hospitalization [9–12, 14, 20, 32, 34, 36, 38]	14 (32)	N = 9 (57) ^b <1 d: 1 1–2 d: 1 >2 d: 7	6 (43) ^b	<1 d: 3 1–2 d: 2 >14 d: 1 ^b
Total	44 (100)	34 (77)	11 (25)	

$P = 0.1138$ for death by coma day of presentation.

^aThe patient had coma day 1, recovered, and then had recurrent coma associated with posterior leukoencephalopathy syndrome nearly 1 mo later, with death day 2 on the second episode [22]. This case is listed in both the awakening and death columns.

^bThe patient awoke from coma but then died later from another cause [38]. This case is listed in both the awakening and death columns.

F. Death or Awakening From Coma

The overall death rate for the group was 38% (25/65). The death rate was 58% in the group extracted from the case series compared with 14% in the group of single cases. Death rates were significantly different over time, with lower mortality (11% to 12%) in the last two quartiles of the study report time (covering the period from 1978 to 2019) [Fig. 1(a)].

Table 4 shows the data for the 44 cases reporting details on the relationship between time of coma onset relative to days to awakening or death. Coma was present in 13 patients (30%) at hospital presentation [15, 17–19, 24, 27, 28, 35, 40, 42, 44, 45], in 17 (39%) within the first 2 days of hospitalization [8, 11, 14, 21–23, 25, 26, 29, 30, 33, 37, 41, 43], and in 14 (32%) from day 3 or later of hospitalization. For those presenting with coma, three were found unconscious [40, 42, 45] and one had a witnessed collapse [19]. Of the 17 patients who developed coma within the first 2 days of hospitalization, many were described as developing the condition rapidly or over minutes [8, 21, 29] to hours [8, 11, 25, 26, 30, 41, 43]. Eight percent (1/13) of patients who presented with coma, 24% (4/17) who developed coma within 2 days of hospitalization, and 43% (6/14) who developed coma on day 3 of hospitalization or later died ($P = 0.1138$).

The duration from coma onset to death was not clearly reported in 12 of 25 deaths. For 10 cases, coma ended in death within <1 day in four cases (40%), 1 to 2 days in three cases (30%), 3 to 7 days in 1 case (10%), and >14 days in two cases (20%). One death followed resolution of coma [38], and one death followed a second bout of coma nearly 1 month after hospital presentation [22].

For the 40 patients who did not die and for whom there were data, the duration of coma to awakening was <1 day in seven patients (22%), 1 to 2 days in nine patients (22.5%), and >2 days in 18 patients. Specifically, the duration of coma to awakening was >14 days in five patients [14, 16, 20, 31, 37].

To summarize, both awakening and death occurred most commonly within the first 2 days of coma onset. Mortality appeared to be higher in patients who developed coma after

Table 5. Treatment Given for Thyroid Storm and Coma

	Treatment, n (% of Population)	Death, n (% of Treatment Group)	Death % of Without Treatment Group (n)	<i>P</i>
Antithyroid drug	36 (68)	6 (17)	52% (11/21)	0.0070
Corticosteroid	34 (64)	4 (12)	52% (11/21)	0.0017
Beta-blocker	34 (64)	4 (12)	52% (11/21)	0.0017
Three drugs	25 (47)	3 (12)	55% (22/40)	0.0006
Iodine	32 (60)	8 (25)	30% (7/23)	0.7621
Four drugs	19 (36)	2 (11)	50% (23/46)	0.0043
Intubation during coma	19 (26)	3 (16)	48% (22/46)	0.0239
Antibiotic	14 (26)	4 (29)	21% (6/28)	0.7071
Plasmapheresis	9 (17)	1 (11)	32% (15/47)	0.4210
Thyroidectomy	9 (17)	1 (11)	33% (16/48)	0.2540
Radioiodine	4 (7.5)	1 (25)	29% (15/52)	1.000
Dialysis	3 (5.7)	1 (33)	38% (23/61)	1.000
L-carnitine	2 (3.8)	1 (50)	29% (15/51)	0.5167
Other	17 (32)	6 (35)	23% (3/13)	0.6908

Subgroup analysis of cases for which treatment information is available. Data are shown for all available cases and then further subdivided by those who died with the treatment vs the percentage of those who died without the treatment. “Three drugs” indicate the patient received antithyroid drug, corticosteroid, and beta-blocker; “four drugs” indicates the patient received antithyroid drug, corticosteroid, beta-blocker, and iodine. The *P* statistic represents Fisher exact test for the presence or absence of the treatment vs the presence or absence of death.

hospitalization than in those who presented with coma, though this did not achieve statistical significance.

G. Treatment of TS With Coma

Data on the cases for which treatment information is available are shown on [Table 5](#). No treatment information was available on 12 cases. The most common forms of treatment were antithyroid drugs (68% of cases), corticosteroids (64% of cases), beta-blockers (64% of cases), and iodine (60% of cases). All four drug classes were used in 29% of cases, and all three drug classes except iodine were used in 38% of cases. Death rates were lower in patients who were treated with antithyroid drugs, corticosteroids, beta-blockers, all three of these drugs, all four drugs, and intubation. Treatment with iodine alone was not associated with improved outcome related to death. Intubation was reported in 26% of cases, all after 1978.

One or more sessions of plasmapheresis were performed in nine cases [16, 23, 26, 38, 40, 41], including three cases with thyroid hormone overdose [14]. It was performed within 1 or 2 days of onset of coma in five cases, within 3 days in one, within 4 days in two, and within 10 days in one. Plasmapheresis was associated with awakening in six of nine cases (67%) in which it was used [14, 23, 38, 40, 41]. In four of the six cases, the plasmapheresis-attributed awakening was also associated with normalization of either T3 or T4 value. In one case, the TFTs were said to be normal the day after awakening. One patient who was treated with plasmapheresis after 10 days of coma and who had awakening associated with the treatment, later died, but not from TS [38]. Plasmapheresis was not associated with a reduced death rate ($P = 0.4210$) ([Table 5](#)). One patient was treated with whole blood exchange transfusion, which was also associated with awakening [13, 48].

To summarize, patients with TS-related coma treated with antithyroid drugs, corticosteroids, beta-blockers, and intubation had lower death rates. Plasmapheresis was performed in a limited number of patients, in whom it was often followed by awakening but not by lower death rates.

3. Discussion

This report, based on an analysis of aggregated English-literature case reports, describes the characteristics and treatment of 65 patients with coexistent TS and coma, the largest series to

date on this specific population. Fifty-one percent of the patients (24/47) either died or awoke within 2 days of coma onset. The overall mortality rate of the group was 39%, lower for those described in case reports (14%) than for those described in case series (58%), probably because the case reports were from a later median time period than the case series. Specifically, the mortality rate was also lower during the last two quartiles (42 years) of the study period (1978 to 2019), when it was 12% and 11%, compared with 64% and 74% for the first two 21-year quartiles (1935 to 1977). Mortality appeared to be higher in patients who developed coma after hospitalization than in those who presented with coma, though this did not reach statistical significance. Factors associated with coma in TS were similar in cases extracted from individual reports or case series. Reduction in total and free T4 values, and possibly also total T3 level, correlated with awakening from coma. Death rates were lowest for patients treated with antithyroid drugs, corticosteroids, beta-blockers, and intubation. Plasmapheresis was credited with awakening in a high percentage of cases in which it was used, but it was not associated with lower death rates.

CNS manifestations are common in TS diagnostic criteria and associated scoring systems [1, 2]. In the BW system, coma or seizure is assigned the maximum CNS section of 30 points, where a total score of 45 or more points is highly suggestive of TS. In the Japanese TS scoring system, a score of 1 or higher on the Japan Coma scale (for which coma has a score of 100 to 300) or 14 or lower on the Glasgow Coma Scale is sufficient CNS manifestation to qualify as TS1 [2].

Coma may occur in the setting of critical illness without thyrotoxicosis, where it has a high associated mortality. In a prospective cohort study of adults who were admitted to 361 intensive care units (ICUs) and who received mechanical ventilation, coma was present in 17%, for whom it was associated with a 36% ICU mortality rate [49]. In a retrospective study of 2189 ICU patients with coma, overall 58% died, including 20% in the “metabolic brain dysfunction” group, for whom TS was not listed specifically as a cause of coma [50].

In contrast, coma was noted in 7.9% of 356 TS cases in a Japanese survey and in 7.4% of 1324 TS cases in a Japanese nationwide database [2, 5]. Review of 16 TS series (Table 6) showed a wide range of individual study rates of coma in TS, death in TS, and death in patients with TS-related coma. Combining the data from 1922 patients with TS, 294 died (15%), 164 had coma (8.5%), and 61 of 164 patients with TS-related coma (37%) died [3–5, 10,

Table 6. Historical Rates of Coma and Death in Thyroid Storm

	TS (n)	TS With Coma (n)	TS Deaths (n)	Coma Deaths (n)
1934, Bayley [56]	51	Not specified	51	Not specified
1935, Zondek [9]	3	2 (67%)	2 (67%)	2 (100%)
1944, Waldenstrom [10]	10	4 (40%)	3 (30%)	3 (75%)
1947 McArthur <i>et al.</i> [57]	36	0	24 (67%)	0
1951, Rives [51]	25	Not specified	10	Not specified
1960 Waldstein <i>et al.</i> [52]	21	4 (19%)	6 (29%)	2 (50%)
1969, Nelson and Becker [12]	21	8 (38%)	16 (76%)	8 (100%)
1969, Mazzaferrri and Skillman [3]	20	4 (20%)	4 (20%)	3 (75%)
1971 Roizen and Becker [53]	8	6 (75%)	3 (38%)	3 (50%)
1972 Ashkar <i>et al.</i> [13]	6	3 (50%)	3 (50%)	2 (67%)
1999, Weber <i>et al.</i> [54]	4	0	0	0
2011, Muller <i>et al.</i> [16]	3	1 (33%)	0	0
2012, Akamizu <i>et al.</i> [22]	356	28 (7.9%)	38 (11%)	Not specified
2015, Swee <i>et al.</i> [55]	28	0	7 (25%)	0
2015, Angell <i>et al.</i> [4]	25	1 (4%)	0	Not specified
2016, Ono <i>et al.</i> [5]	1324	98 (7.4%)	134 (10%)	38 (39%)
Total	1922	164 (8.5%)	294 (15%)	61 (37%)
Present study		65		25(38%)

n = number of patients, not n of coma episodes.

12–14, 16, 51–57]. As shown in Table 6, these results are heavily influenced by the two large Japanese cohorts compared with all other studies, which had 36 or fewer cases. Excluding the data from the two large cohorts, 122 of 242 patients (50%) died, 38 of 242 patients (16%) had coma, and 23 of 38 patients with TS-related coma (61%) died. Comparison of death rates across the individual studies as well as the aggregate data might lead to the conclusion that the mortality rate is higher in patients with coma in TS than in the general population with TS.

The 65 TS coma cases from the current report had a death rate (38%) similar to that of past TS series. However, the current results may provide important timeline discrimination that could not be seen in past reports. Specifically, death rates associated with TS-related coma have been lower in the last 42 years than before then, now in the 11% to 12% range, similar to the overall death rate of TS reported by Ono and Akamizu [2, 5], covering dates starting in 2004. This same period was associated with higher use of combined treatment with antithyroid drugs, beta-blockers, and corticosteroids; intubation; and plasmapheresis [Fig. 1(b)–1(d)].

Treatment of TS-related coma most commonly included antithyroid drugs, corticosteroids, and beta-blockers, and a high percentage of patients received drugs from all three classes, especially during the last 42 years (since 1978) of the study period. The death rate was lower in patients who received all of the three drug classes than in patients who did not receive them; it was not possible to separate out the effect strength of individual drug classes because a majority of patients who received any of the three drug classes also received all three drug classes (up to 25 of 36 patients). In contrast, a statistically beneficial TS-related coma mortality effect of iodine or antibiotic treatment was not shown. The TS-related coma death rate was lower in those who underwent intubation and mechanical respiratory support than in those who did not receive this treatment, demonstrating an unsurprising beneficial effect of modern day supportive medical care. Very small numbers of subjects received other treatments not associated with improved mortality, including dialysis, thyroidectomy, radioactive iodine, and L-carnitine.

A comment on the mortality rate timeline reported in this series on TS-related coma compared with that of a population with TS, relative to beta-blocker treatment, is merited. A relationship between the availability of propranolol and the outcome of TS was noted by Mazzaferri and Skillman [3] in their 1969 series involving 22 episodes of TS in 20 patients; they observed that before 1960, patients did not get adrenergic blockade, whereas all but one received adrenergic blockade after 1960. The TS mortality rate was 43% before the use of beta blockade and 7% after beta-blockers were added to the treatment regimen [3]. This contrasts with the current report, which showed a 74% TS-related coma death rate in the 21-year quartile extending to 1978, suggesting that beta blockade availability starting in 1964 was insufficient to significantly affect outcomes in TS-related coma.

No improvement in the death rate was seen with plasmapheresis in this series, in which only nine patients underwent the treatment; however, plasmapheresis was associated with awakening in six (67%). Others have also observed the association of awakening with plasmapheresis treatment [58]. Plasmapheresis has been recommended as treatment of TS-related coma on the basis of a few individual reports [16, 38, 48] and also for TS not clinically improving within 24 to 48 hours in the guidelines of the Japan Thyroid Association TS and American Society for Apheresis [6, 59].

What is it about TS that causes or increases susceptibility to coma? The time course of coma onset in patients with massive levothyroxine overdose may help answer this question [14]. Here, classic symptoms of thyrotoxicosis occurred within 3 days, but coma onset did not occur until 7 to 10 days after massive thyroid hormone ingestion, suggesting that the thyrotoxic state may take time to affect (*i.e.*, deplete or accumulate) a process or substance related to brain function. Likewise, awakening from coma associated with reduction in high T4 levels may support the direct or indirect effect of high thyroid levels on brain function. This was demonstrated in a high percentage of patients treated with plasmapheresis, which may have also removed other CNS effectors (*e.g.*, autoimmune, catecholamine, cytokine) beyond

thyroid hormones. Systemic findings expected to affect brain function, including hypotension (12%) and hypoglycemia (8%), were noted in a minority of TS-related coma cases; once reversed, they should have resolved coma, but did not. Renal dysfunction requiring dialysis was present in only three patients (4.7%). Hepatic failure–related encephalopathy was not typical of most reports describing abnormal liver tests. Most TS-related coma cases have not had a structural brain abnormality, or if they did, it was attributed to concomitant stroke. EEG most often showed diffuse slowing, a nonspecific finding typical of coma. Autopsy was performed in 16 of the 25 coma-related deaths reported here, but brain findings were specifically described in only three, two with cerebral edema [12] and one with “leptomeningitis chronica” [10]. Others have described focal brain edema in the limbic system, attributed to limbic encephalitis, associated with altered mental status and drowsiness followed by seizure in the setting of TS, but not with coma [60]. Finally, past CNS events may convey a susceptibility to TS-related coma or recurrent coma.

Other possible mechanisms may include alterations in brain hemodynamics, energy metabolism [61, 62], neurotransmitters [63], or brain network connectivity [64]. Relative to these mechanisms, no data specific to TS-related coma exist, but rather only hypothesis might be extrapolated from studies in hyperthyroid animals and humans.

The limitations of this study include the retrospective design and nonuniform and potentially incomplete information across cases. All parameters were as defined by the original reporting authors and may not have been consistent across the study. The denominator was less than the total n of the study cases for many of the evaluated parameters. It was impossible to ensure that the absence of a reported detail indicated the feature was not present, only that it was not reported. Time to awakening from coma was limited by descriptions that may have lacked details relative to the degree of mental status abnormality. The analysis does not include control groups of TS cases without coma or critical illness coma cases without TS. Nevertheless, this report demonstrates the utility of REDCap-indexed analysis of aggregated case reports as a rich source of primary human clinical data, providing a foundation upon which to build an evidence base [65].

4. Conclusions

Prognosis of TS-related coma remains poor but has improved with modern day treatments, including antithyroid drugs, beta-blockers, corticosteroids, and intubation. Both awakening and death occurred most commonly within the first 2 days of coma onset. Plasmapheresis was associated with awakening from coma in a high percentage of cases in which it was used. Current Japan Thyroid Association TS guidelines for the early use of plasmapheresis in unresolved TS are recommended and we also suggest its urgent use for TS-related coma and also at the onset of confusion or delirium to abort coma. Modern day neuroimaging investigations or treatments, which have been reported in other types of coma, have not yet been reported in TS-related coma. Future investigations or investigational treatments of TS-related coma may enhance understanding of coma-related mechanisms and target improved outcomes for this patient population; these interventions include fMRI or PET, therapeutic hypothermia, and more detailed neurologic autopsy, focusing on brain regions relevant to awakesness. Future case reports on TS-related coma should record longitudinal Glasgow coma scale subparameters, as well as details on duration of coma in response to specific therapies and thyroid hormone levels at awakening.

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