Original Article

Effect of ordering thyroid-stimulating hormone levels on subsequent clinical management of internal medicine in-patients admitted with delirium

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Background: Thyroid-stimulating hormone (TSH) is commonly ordered to investigate delirium. Previous studies have recommended against the routine testing of thyroid function in in-patients due to low clinical yield and excess use of resources. This has not been investigated in in-patients admitted for delirium specifically. We aimed to investigate the clinical yield of thyroid function testing in in-patients admitted for delirium.

Methods: This was a retrospective study of 84 patients admitted to hospital with delirium identified as one of their in-hospital issues. Both patients with and without TSH tested in-hospital were included. The primary outcome was a composite of the proportion of patients with TSH tested who had further thyroid-related testing or medications ordered during their hospital stay. Secondary outcomes included number and types of thyroid-related symptoms documented during admission. Multivariate regression was performed to determine factors associated with ordering TSH and with the primary outcome.

Results: TSH was ordered in 65 (77.4%) patients and the result was within reference range in 53 (81.5%) cases. Thyroid disease was identified as the etiology of delirium in zero cases. Only 3 (4.6%) patients had additional thyroid-related testing or medications ordered. Multivariate regression demonstrated a significant association between known hypothyroidism (P=0.001) and pre-existing prescription for levothyroxine (P=0.028) with the primary outcome. The average number of thyroid-related symptoms reported per patient was 1.095. Thirty-one (36.9%) patients had zero symptoms of thyroid disease documented. There was no significant difference in number of symptoms reported between patients who had and did not have TSH testing during admission (P=0.325).

Conclusions: Thyroid function testing does not often result in a change in clinical management in the investigation of delirium in in-patients. Routine TSH testing in delirium without thyroid-related symptoms or when another cause of delirium is apparent may use resources excessively with low clinical yield.

Keywords: Thyroid; thyroid-stimulating hormone (TSH); delirium

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Introduction

Delirium is common in hospitalized older adults (1,2). Among patients requiring medical admission, a recent meta-analysis estimated that 15% have delirium on presentation, while an added 9% develop delirium in hospital (1,2). The pathophysiology of delirium is complex, with metabolic derangements contributing to delirium through a variety of mechanisms (1,3). Thyroid dysfunction is one of many potential underlying metabolic triggers for altered mental status (4).

Thyroid-stimulating hormone (TSH) is a first-line test used to work-up thyroid pathology and is commonly included in the routine work-up for delirium (1,5). However, the routine ordering of TSH in medical in-patients regardless of clinical suspicion of thyroid pathology is not recommended due to low clinical yield and excessive use of resources (6,7). This message is reiterated in guidelines from the American Thyroid Association and American Association of Clinical Endocrinologists (5). This has been supported by the finding that although over 20% of medical in-patients undergo thyroid testing, only 1–2.5% of these same patients will have undiagnosed thyroid disorders (6,8). TSH abnormalities in most in-patients tend to be secondary to nonthyroidal illness syndrome (NTIS), which is a change in serum thyroid hormone levels in response to severe illness as opposed to primary thyroid dysfunction (7,9). These abnormalities generally do not prompt a change in patient care given that they are mild and normalize spontaneously (6,7).

Aside from the financial burden that ordering unnecessary lab tests places on our health care system, indiscriminate testing that is not linked to clinical suspicion generates false negative and positive results, which both have consequences for patients (10). These types of results can make determining the true underlying cause of a patient's pathology more difficult (10). Despite the widespread use of TSH in the workup of undifferentiated delirium in patients admitted to internal medicine, there are no studies to our knowledge that have assessed the rate at which TSH orders have altered patient management. This study aims to quantify how often ordering TSH levels alters patient care in those presenting with delirium. These results could inform quality improvement initiatives to reduce unnecessary thyroid function testing in admitted in-patients. Downstream benefits would include reducing healthcare costs, and minimizing the harms to patients associated with over-testing. We present this article in accordance with the STROBE reporting checklist (available at https://aot.amegroups.com/article/view/10.21037/aot-23-15/rc).

Highlight box

Key findings

- This retrospective study identified thyroid disease as the cause of delirium in zero cases, and ordering thyroid-stimulating hormone (TSH) resulted in a change in clinical management in only 3 (4.6%) patients.
- Symptoms of thyroid dysfunction were scarcely documented, and there was no statistically significant difference in number of symptoms reported between patients who had and did not have TSH tested during admission.

What is known and what is new?

- Routine ordering of thyroid function tests in all in-patients is not recommended due to low clinical yield.
- This study suggests that routine ordering of TSH in patients with delirium may also be of low clinical yield, despite TSH being a first-line test in the investigation of delirium.

What is the implication, and what should change now?

- Larger studies with prospective methodology are needed to confirm these preliminary results.
- These results could inform quality improvement initiatives aimed at reducing TSH testing in delirium when pre-test probability of thyroid disease is low.

Methods

We performed a retrospective chart review of patients ≥18 years old admitted to the internal medicine service at St. Joseph's Healthcare in Hamilton, Ontario between January 1st, 2019 and December 31st, 2019 with an admission diagnosis of delirium. Patients were identified using the electronic medical record (EMR) and included if the terms 'delirium', 'confusion', 'altered mental status' or 'altered level of consciousness' were included in their electronic admission diagnosis, hospital problem list, or discharge diagnosis. Both patients with and without TSH testing performed during the in-patient encounter were included. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Hamilton Integrated Research Ethics Board (No. 13732) and individual consent for this retrospective analysis was waived.

Demographic data, thyroid function testing during hospitalization, and patient medications were extracted from the EMR and confirmed by manual review. These

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Table 1 Baseline characteristics and demographics

Characteristics and demographics	Value (N=84)
Mean age (years)	77.2 (15.5)
Male	37 (44.0)
Hospital length of stay (days)	23.5 (58.7)
Known hypothyroidism	18 (21.4)
Known hyperthyroidism	1 (1.2)
Prescription for thyroid replacement	16 (19.0)
Prescription for anti-thyroid medication	1 (1.2)
Prescription for lithium	3 (3.6)
Prescription for amiodarone	0 (0)

Data are presented as n (%) or mean (SD). SD, standard deviation.

data included patient age, sex, hospital length of stay, medical history of hypothyroidism or hyperthyroidism, and prescriptions for thyroid hormone replacement, anti-thyroid medications, lithium, or amiodarone at admission to hospital. Documented symptoms of thyroid-related disease were extracted by manual review. Symptoms of hypothyroidism extracted were cold intolerance, fatigue, weight gain, constipation, hair loss, brittle hair, dry skin, menorrhagia, delayed reflexes, and bradycardia. Symptoms of hyperthyroidism extracted were heat intolerance, irritability, weight loss, diarrhea, oily hair/skin, irregular menses, brisk reflexes, tachycardia, tremor, and ocular symptoms. Thyroid-related biochemical testing and imaging were extracted from the EMR and confirmed by manual review. Presence of testing during hospital admission including TSH, free T4, free T3, thyroid antibodies (anti-thyroid peroxidase, anti-thyrotropin receptor antibodies), thyroid ultrasound, computed tomography (CT) of the thyroid, or thyroid uptake and scan were collected.

The primary outcome of interest was the proportion of cases where TSH testing led to a direct change in clinical management of the patient hospitalized for delirium. This was defined broadly as a composite of the presence of further thyroid-related testing performed (anti-thyroid antibodies, ultrasound or CT of the thyroid, or nuclear imaging) or new or altered prescriptions for thyroid hormone replacement, anti-thyroid therapy, lithium, or amiodarone during the hospital stay or at discharge. Secondary outcomes included the percentage of symptoms related to thyroid disease documented during hospitalization, the average number of thyroid-related symptoms reported, and the proportion of patients with zero symptoms of thyroid disease documented.

Statistical analysis

Descriptive statistics were used to analyze the data set. The percentage of patients with known hypothyroidism, hyperthyroidism, and existing prescriptions for thyroid hormone replacement, anti-thyroid medication, lithium, or amiodarone were calculated. The percentage of patients with thyroid-related testing performed including TSH, free T4, free T3, thyroid antibodies, ultrasound or CT of the thyroid, and nuclear imaging were calculated. The mean and standard deviation of thyroid related biochemical testing were calculated. The primary outcome was determined by calculating the percentage of patients with TSH tested during hospitalization who had at least one of the above thyroid related tests or medications completed during admission or organized at discharge from hospital.

Additionally, an unpaired *t*-test was performed to compare the total number of positive symptoms of thyroid dysfunction documented between patients who had TSH tested and who did not have TSH tested during hospital admission. Multivariate regression was used to determine factors associated with ordering TSH. Independent variables included age, sex, hospital length of stay, known history of hypothyroidism, pre-existing prescription for levothyroxine, number of positive symptoms of thyroid dysfunction reported. Multivariate regression was also performed to determine factors associated with the primary outcome of change in patient management. Independent variables analyzed included age, sex, known hypothyroidism, pre-existing prescription for levothyroxine, TSH value, and number of positive symptoms.

Results

A total of 84 patient charts were reviewed and included in the study. All patients were ≥18 years old with 'delirium' or an equivalent term included in their hospital problem list and as such zero patients were excluded from the study. Demographic data and prior history of thyroid-related disease or medications are shown in *Table 1*. Of note, 19 (22.6%) of patients had a known history of either hypothyroidism or hyperthyroidism and 17 (20.2%) of patients were taking thyroid replacement or anti-thyroid medications at admission. Three (3.57%) patients were taking lithium at admission and no patients were on

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Table 2 Symptoms of thyroid dysfunction documented at hospital admission

Symptom	Present at admission (N=84)	Not documented (N=84)
Hypothyroid, n (%)		
Cold intolerance	0 (0)	83 (98.8)
Fatigue	7 (8.3)	72 (85.7)
Weight gain	0 (0)	78 (92.9)
Constipation	7 (8.3)	53 (63.1)
Hair loss	0 (0)	84 (100)
Brittle hair	0 (0)	84 (100)
Dry skin	2 (2.4)	80 (95.2)
Brittle nails	0 (0)	84 (100)
Menorrhagia	0 (0)	84 (100)
Delayed reflexes	1 (1.2)	77 (91.7)
Bradycardia	3 (3.6)	9 (10.7)
Depression	4 (4.7)	74 (88.1)
Hyperthyroid, n (%)		
Heat intolerance	0 (0)	84 (100)
Irritability	16 (19.0)	64 (76.2)
Weight loss	7 (8.3)	76 (90.5)
Diarrhea	9 (10.7)	45 (53.6)
Oily hair/skin	0 (0)	82 (97.7)
Irregular menses	0 (0)	84 (100)
Brisk reflexes	2 (2.4)	77 (91.7)
Tachycardia	16 (19.0)	7 (8.3)
Tremor	11 (13.1)	63 (75.0)
Ocular symptoms	3 (3.6)	73 (86.9)
At least 1 symptom, n (%)	53 (63.1)	–

amiodarone.

Documentation of symptoms of hypothyroidism or hyperthyroidism is outlined in *Table 2*. Symptoms of thyroid disease were not documented in a large proportion of cases. Hair loss, brittle hair, brittle nails, menorrhagia, heat intolerance, and irregular menses were documented in zero patient charts while cold intolerance, weight gain, dry skin, delayed reflexes, weight loss, oily hair/skin, and brisk reflexes were not documented in >90% of patients. The mean number of symptoms reported/documented per patient was 1.095 with 31 (36.9%) patients having zero documented symptoms of thyroid dysfunction recorded in the chart. The symptoms of hypothyroidism that were most frequently present at admission included fatigue (8.3%), constipation (8.3%), and depression (4.7%). Symptoms of hyperthyroidism that were most frequently present at admission were irritability (19.0%), tachycardia (19.0%), and tremor (13.1%). Mean number of symptoms reported was 1.015 (N=65) for patients who had TSH tested during admission and 1.368 (N=19) for patients who did not have TSH tested during admission. There was no significant difference in total number of positive symptoms reported between patients who had TSH tested and those who did not (P=0.325, *Table 3*). Multivariate regression found no significant association between age, sex, hospital length of stay, known hypothyroidism, pre-existing prescription for levothyroxine, and number of positive symptoms with whether or not TSH was ordered during admission (*Table 4*).

Thyroid related biochemical and imaging studies performed, in addition to changes to medical therapy as it relates to thyroid disease is shown in *Table 5*. Of the 84 patients reviewed, TSH was ordered in 65 (77.4%) patients with a result within the reference range being reported in 53 (81.5%) cases. Free T4 was subsequently ordered in 14 (21.5%) patients and the result was abnormal in 2 (14.3%) cases. Free T3 was ordered in 1 (1.5%) patient and the result was abnormal (100%). Subsequent thyroid antibodies, CT of the thyroid, and nuclear imaging were ordered in zero (0%) patients. Ultrasound of the thyroid was ordered in 1 (1.5%) patient. No patients were provided with new prescriptions for thyroid hormone replacement or anti-thyroid medications at discharge. Two out of 16 patients (11.8%) with prior prescriptions for thyroid hormone replacement had their dose altered at discharge while one out of 3 patients (33.3%) with a prior prescription for lithium had their dose adjusted, though this was for reasons unrelated to thyroid disease.

In terms of the primary outcome, of the 65 patients with TSH tested during hospital admission, only 3 (4.6%) experienced any change in their subsequent management as a result of thyroid function testing. This included two patients with their dose of levothyroxine altered and one patient for which a thyroid ultrasound was ordered. The patient with the adjustment to their lithium dose was excluded as this was due to reasons unrelated to thyroid disease. In the three cases above, thyroid related dysfunction was not identified as the cause of the patient's delirium presentation. Additionally, in all cases reviewed in

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Table 3 Unpaired *t*-test comparing number of symptoms of thyroid dysfunction between patients with and without TSH testing during hospital admission

Statistic	TSH measured during admission	TSH not measured during admission
Sample size	65	19
Mean number of symptoms documented	1.015	1.368
Variance	1.109	2.023
Degrees of freedom	24	
T statistic (two-tailed)	2.064	
P value (two-tailed)	0.325	

TSH, thyroid-stimulating hormone.

Table 4 Multivariate regression of effect of clinical and demographic variables on ordering of TSH during hospital admission

Independent variable	Coefficient (standard error)	P value
Age	–0.006 (0.003)	0.061
Sex	–0.135 (0.098)	0.170
Hospital length of stay	0.000 (0.001)	0.868
Known hypothyroidism	0.234 (0.296)	0.432
Pre-existing prescription for levothyroxine	–0.244 (0.312)	0.435
Number of symptoms of thyroid dysfunction	0.030 (0.042)	0.479
Constant	0.748	0.009*
R squared	0.114	
F-ratio	1.653	
N	84	

*, P<0.05. TSH, thyroid-stimulating hormone.

this study, thyroid dysfunction was identified as the etiology of delirium in zero cases. Multivariate regression found a significant association between a prior known history of hypothyroidism (P=0.001) and pre-existing prescription for levothyroxine (P=0.028) with the primary composite outcome of change in patient management. Age, sex, TSH value, and number of positive symptoms reported were not significantly associated with change in management (*Table 6*).

Discussion

This retrospective analysis of 84 in-patients presenting to the hospital with delirium demonstrated that the ordering of TSH in the work-up of delirium did not identify thyroid dysfunction as the cause of delirium in any of the cases. Furthermore, ordering of TSH altered the clinical course in only three patients (4.6%), with two patients receiving levothyroxine dose adjustments and one patient receiving a thyroid ultrasound. In keeping with this, multivariate regression found a significant association between known hypothyroidism and pre-existing prescription for levothyroxine with a change in management in our study, while age, sex, TSH value, and number of positive symptoms were not significantly associated.

Symptoms of thyroid dysfunction were infrequently reported in a large proportion of the cases. Specifically, the mean number of symptoms reported per patient was 1.095 with 36.9% of patients having zero documented symptoms. Additionally, the most frequently reported symptoms of thyroid dysfunction were irritability (19%) and tachycardia (19%), both of which are non-specific. Furthermore, we found no significant difference in number of positive

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Table 5 Thyroid-related laboratory tests, imaging studies, and medications ordered during hospital admission

Investigations and management	Value
TSH	
TSH ordered	65/84 (77.4)
TSH abnormal	12/65 (18.5)
TSH value (mIU/L)	2.38 (3.28)
Free T4	
Free T4 ordered	14/65 (21.5)
Free T4 abnormal	2/14 (14.3)
Free T4 value (pmol/L)	11.15 (2.62)
Free T3	
Free T3 ordered	1/65 (1.5)
Free T3 abnormal	1/1 (100.0)
Free T3 value (pmol/L)	2.15 (N/A)
Other investigations	
Thyroid antibodies ordered	0/65 (0)
Ultrasound thyroid ordered	1/65 (1.5)
Thyroid CT ordered	0/65 (0)
Nuclear imaging ordered	0/65 (0)
Medications	
New prescription for thyroid replacement	0/60 (0)
Altered prescription for thyroid replacement	2/16 (11.8)
New prescription for anti-thyroid medication)	0/64 (0)
Altered prescription for anti-thyroid medication	0/1 (0)
Altered prescription for lithium	1/3 (33.3)

Data are presented as n/N (%) or mean (SD). TSH, thyroid-stimulating hormone; CT, computed tomography; SD, standard deviation.

symptoms reported between patients who had TSH tested during admission and those who did not. These results suggest that indiscriminate ordering of TSH in patients presenting with delirium is of low clinical yield, not often guided by symptomatology, and may not be an effective use of resources.

While the exact prevalence of thyroid dysfunction being the predominant etiology in patients presenting with delirium is unknown, common precipitating factors include infections, electrolyte derangements, and medications (1,11). Khurana *et al.* [2011] found that sepsis was the most common identified cause of delirium in a study of 400 admitted patients at a medical center in India, with endocrine disease identified in 14% of cases (11). The proportion of this group with delirium due to thyroid disease was not explicitly stated (11). In keeping with a low overall prevalence of thyroid dysfunction causing delirium, our study did not identify thyroid dysfunction as the cause of delirium in any of the cases reviewed.

The current literature suggests that the failure of thyroid function testing to alter a patient's clinical course is not exclusive to the present study. Adlan *et al.* [2011] assessed the utility of thyroid testing in acutely ill in-patients at a hospital in the United Kingdom and found that clinicians did not act on abnormal thyroid function test results in 74.5% of cases reviewed (12). Additionally, only 45.5% of patients with abnormal results received follow-up after discharge from hospital (12). The authors postulate that the pattern of thyroid function test abnormalities seen in in-patients is often difficult to interpret, possibly contributing to the low clinical impact of abnormal results (12). Indeed, even when NTIS is diagnosed, it remains unclear whether this warrants specific treatment (13,14). These results are reflected in the current study which demonstrated an alteration in clinical course in only 25% of patients with abnormal TSH results. The proportion of patients with abnormal thyroid function testing who received follow-up at discharge is unknown.

While thyroid function testing in medical in-patients has been previously examined, to our knowledge this is the first study to assess the yield of thyroid function testing in patients admitted to hospital with delirium specifically. Other strengths of the study include a broad definition of changes to clinical management (i.e., laboratory investigations, imaging, and change to medications), and collection of a wide range of documented symptoms of thyroid dysfunction. Despite encapsulating a large definition of possible impacts on clinical management, this study still demonstrates that ordering of TSH rarely altered the course of patient's in-hospital management. Collection of the documented symptoms of thyroid dysfunction demonstrates that these symptoms are rarely present and scarcely documented in the patient chart, reflecting that ordering of thyroid function tests may not be guided by clinical symptoms or signs on physical examination. In support of this, we found no significant difference in the mean number of positive symptoms of thyroid dysfunction between patients who had TSH tested and those who did not.

There are several limitations of this study. Firstly,

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Table 6 Multivariate regression of effect of clinical and demographic data on change in management associated with TSH testing during hospital admission

Independent variable	Coefficient (standard error)	P value
Age	−0.002 (0.002)	0.418
Sex	−0.017 (0.053)	0.757
Known hypothyroidism	−0.502 (0.140)	0.001*
Pre-existing prescription for levothyroxine	0.342 (0.151)	0.028*
Number of symptoms of thyroid dysfunction	−0.004 (0.026)	0.880
TSH value (mIU/L)	0.000 (0.008)	0.952
Constant	0.304	0.092
R squared	0.246	
F-ratio	3.151	
N	65	

*, P<0.05. TSH, thyroid-stimulating hormone.

patients were only included in the study if delirium or a related term was listed in the patient's problem list, admission diagnosis or discharge diagnosis. These sections of the patient's chart often do not provide a comprehensive overview of all the clinical problems associated with a patient's admission. For example, if the underlying cause of delirium was apparent, this underlying cause may have been the diagnosis listed instead of delirium, and this patient would not have been included in the study. It is possible that TSH ordering may have been less frequent in these patients since the etiology of delirium was already apparent, which would have impacted our results. Secondly, only 84 patients were reviewed in this study which is a relatively small sample size. A larger sample size may have detected a more meaningful impact on patient management of TSH testing. Lastly, given that our chart review terminated at the end of the hospital stay, thyroid-related investigations and treatments initiated in the community post-discharge would not have been captured.

Future studies should further investigate the clinical yield and cost-effectiveness of ordering TSH in patients presenting to the hospital with delirium with larger patient populations in a prospective manner. Given that TSH testing is relatively inexpensive, cost-effectiveness studies may ultimately demonstrate a net benefit even if the proportion of cases where testing impacts management is low. Furthermore, determining what symptoms warrant ordering a thyroid work up in these patients would be useful to guide more appropriate use of healthcare resources. For example, common hyperthyroid symptoms warranting further investigation may include heat intolerance, diaphoresis, tremor, palpitations, and diarrhea (15). Similarly, common hypothyroid symptoms may include generalized fatigue, cold intolerance, dry skin, constipation, and muscle weakness (16). Future quality improvement initiatives could be focused at encouraging clinicians to inquire about and document symptoms of thyroid dysfunction in patients presenting with delirium.

Conclusions

Our study provides preliminary evidence to suggest that the routine ordering of TSH for all patients presenting to the hospital with delirium regardless of clinical suspicion of thyroid disease has a low impact on subsequent patient management. Thyroid dysfunction is an uncommon cause of delirium in these patients. Further research should examine if certain clinical features are more likely to be associated with thyroid dysfunction in delirium and the costs associated with thyroid function testing in this population. This could guide quality improvement initiatives to reduce over-testing of thyroid function in the context of delirium.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://aot.amegroups.com/article/view/10.21037/aot-23-15/rc

Data Sharing Statement: Available at https://aot.amegroups.com/article/view/10.21037/aot-23-15/dss

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://aot.amegroups.com/article/view/10.21037/aot-23-15/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Hamilton Integrated Research Ethics Board (No. 13732) and individual consent for this retrospective analysis was waived.

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