Case Report **IJCR (2019) 4:103**

International Journal of Case Reports
(ISSN:2572-8776)

Psychosis Due to Hypothyroidism: Are Antipsychotics Indicated?

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ABSTRACT

Objective: To present a case of thyroid-related psychosis and review the literature to assess evidence regarding the use of antipsychotic medications in patients who develop this condition.

Data Sources: The OVID database was utilized to search for the terms “myxedema madness” and the combination of the terms “psychosis” and “thyroid.” The database was searched from 1946 until July 2018 and was limited to English language articles.

Study Selection: A total of 25 articles were included in this study. These included 27 distinct case reports.

Data Extraction: The abstracts of identified articles were reviewed. If an abstract was unavailable or inconclusive, the full article was reviewed. If there was no case report, or if the case was not clearly related to hypothyroidism, it was excluded. Authors assessed and identified cases included. Studies were excluded if recovery time was unreported; if cases included patients with pre-existing, chronic mental illness or intellectual disability, or if thyroid replacement medication was not initially administered.

Results: Data suggested that there may be no benefit to treating thyroid-related psychosis with scheduled dosing of antipsychotics in addition to thyroid replacement. The review also suggested that male patients with thyroid-related psychosis seemed to respond more rapidly to thyroid replacement than female patients.

Conclusions: Scheduled dose antipsychotic therapy was not observed to hasten recovery. Males with thyroid-related psychosis were observed to respond more quickly to thyroid replacement than females among the identified cases identified. Consideration should be given to initial trials of thyroid replacement alone in cases of thyroid-related psychosis.

Keywords: Hypothyroidism, Myxedema, Psychosis,Hallucinations, Levothyroxine, Endocrine

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How to cite this article:
Deborah L. Sanchez, Adam J. Fusick, William B. Hudson, Theresa A. Schwitalla, Maria C. Catalano, Susan K. Schultz, Glenn Catalano. Psychosis Due to Hypothyroidism: Are Antipsychotics Indicated?. International Journal of Case Reports, 2019 4:103

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Website: https://escipub.com/

1. Introduction

Myxedema psychosis is a variant of thyroid deficiency that often presents with bizarre hallucinations or perceptual changes [1]. While delusions and hallucinations often occur as the disease progresses, currently no known correlation exists between the degree of thyroid dysfunction and the development of psychiatric symptoms [1].

The initial evaluation of a patient with suspected hypothyroidism and psychiatric symptoms typically involves measurement of the thyroid stimulating hormone (TSH) level, the most sensitive test for detecting hypothyroidism [2]. The free thyroxine (T4) level is often used in combination with TSH to evaluate hypothyroidism [2]. Identifying the cause and initiating thyroid replacement is the cornerstone of the treatment of hypothyroidism. It has been noted that the hallucinations and delusions that characterize myxedema psychosis usually remit about one week after beginning thyroid replacement therapy [3].

The treatment of myxedema psychosis can be complicated. Treatment centers around thyroid replacement, but care must be taken to consider the patient's cardiac status and age as well as addressing other potential metabolic disturbances [4]. Clinical consensus suggests that for patients under the age of 50 without underlying cardiac disease, levothyroxine can be started at 1.6 μg/kg/day [4]. Patients over age 50 or with a complicated cardiac history should be initiated at lower doses as not to exacerbate pre-existing cardiac symptoms [4]. If thyroid replacement is started too aggressively, clinicians risk worsening the patient's psychosis [5]. Conversely, premature discontinuation of thyroid medications may lead to symptom re-emergence and delay in effective thyroid management can result in symptoms failing to remit [2]. It has been suggested that the addition of antipsychotic medications may lead to an earlier remission of psychotic symptoms although confirmatory data are lacking due to the infrequency of the condition, precluding clinical trials [5].

We now present a patient with longstanding thyroid illness who developed psychotic symptoms after prolonged non-adherence to thyroid supplementation.

2. Case Report

The patient was a 64-year-old Caucasian male who was brought to the Emergency Department (ED) for assessment due to altered mental status as well as three days of nausea, vomiting, fatigue, and headaches. He endorsed seeing visions of ghosts for approximately one year and reported new onset visual hallucinations of "gorillas and snakes" for two weeks. He noted that these visions were "not real," however, he noted that he "would like to kill the snakes." On examination, he denied experiencing hallucinations, but his family reported that he had recently been observed speaking to people who had been dead for years.

The patient had a medical history significant for resection of a pituitary adenoma 26 years earlier. The resection resulted in vision loss to the right eye and a panhypopituitary state. His outpatient medications were hydrocortisone 20 mg qAM and 10 mg qHS and levothyroxine 0.125 mg daily. However, there were concerns regarding medication compliance. Under his family's supervision, the patient restarted his medications two days prior to his ED presentation. Further medical history included hypertension, hyperlipidemia, basal cell carcinoma (resected five years prior to encounter), and pulmonary lung nodules. Laboratory studies were non-contributory, except for a serum sodium of 121 mEq/L, a TSH level of 5.678 mIU/L, and free T4 levels of 0.6 ng/dL (normal values range from 0.7 to 1.3 ng/dL).

The patient was admitted to the Medicine Service, and his hydrocortisone was increased to 25mg bid. Later, the patient was given a 100mg rescue dose of hydrocortisone, and his standing dose was decreased to 15mg qAM and

10mg qHS. His levothyroxine dose was maintained at 0.125mg daily. Risperidone was ordered 0.5mg q12 hours as needed for agitation,but was not given during the hospitalization. His admission mental status examination revealed a completely oriented individual, with no fluctuations in his level of consciousness. With fluid restriction, the patient's serum sodium corrected to 137 mEq/L over the course of five days. On the evening of Hospital Day #3, the patient was found pacing in his room, complaining that someone was trying to enter his 7th floor window. Other than that event, there were no other episodes of paranoia, delusions, or hallucinations noted. The patient was discharged on Hospital Day #6. At the time of discharge, the patient was alert and fully oriented. He denied experiencing hallucinations or delusions. He did not appear to be attending to internal stimuli. His family felt that he was "back to normal."

3. Methods

An OVID search was performed searching for the term "myxedema madness" and a combination of the terms and "psychosis" and "thyroid". The search covered from 1946 until July 2018. Articles were limited to those using the English language. Studies were excluded upon abstract review if there was no case report present or cases were not truly hypothyroidism. If the abstract review was inconclusive, a full-text review was performed. Duplicate articles were removed. Two authors then independently assessed and identified the remaining full texts for inclusion in the systematic review.

Authors independently extracted data from full text articles using a standardized form created by the authors. Information from the articles was obtained via electronic review. The data included: study identification (authors, date of publication, study title), patient demographics (sex, age, race, past psychiatric history, past medical history), patient presentation (psychiatric symptoms, physical symptoms, psychiatric symptoms after treatment, physical symptoms after treatment), pertinent labs and other relevant information. The primary outcome assessed was recovery time, in days, of psychotic symptoms after treatment with thyroid replacement medication. Studies were excluded if recovery time was not reported, involved a patient with pre-existing, chronic mental illness or intellectual disability, or if thyroid replacement medication was not initially administered for treatment. The decision to exclude cases that delayed initial treatment with thyroid agents was made based on literature stating that delay in effective hypothyroid treatment may result in prolonged symptom time course or presentations that may even fail to remit completely [2].

4. Results and Discussion

This case describes a 64-year-old man who developed psychotic symptoms after a prolonged amount of time in a hypothyroid state. He developed auditory and visual hallucinations that had been present for an extended period of time, but that had worsened within the two weeks prior to admission. The patient's symptoms resolved within five days of re-initiation of levothyroxine and without antipsychotic medications.

Case reports were identified from the Ovid literature search and the articles that discussed cases of hypothyroid-induced psychosis were reviewed. The demographic data and clinical presentations of these cases can be seen in Table 1 [5-29]. Treatments and time to response for each of the cases can be seen in Table 2. Some case reports that were excluded due to either the patient having a pre-existing psychotic illness, or not initially being treated with thyroid medication, or if the recovery time was not noted in the report. The decision to exclude cases that delayed initial treatment with thyroid supplementation was made based on literature stating that delay in effective hypothyroid treatment may result in prolonged symptom time course or presentations that may even fail to remit completely [30].

Overall, a total of 25 studies with 27 case reports were identified for review after meeting inclusion

and exclusion criteria. One study included two case reports on two separate admissions of a single female patient [28]. In reviewing Table 1, the female to male ratio of these cases is 2:1 (18 case reports in female patients and 9 cases in male patients). The age range of all cases reviewed was 13 to 67 years of age. The mean age of female patients was 43.59 years and the mean age of male patients was 36.67 years of age. Table 2 summarizes the treatments the patients received and their time to response. Of the 27 cases, eight cases (29.6%) were initially treated with thyroid replacement (TR) medication alone. In these cases, the average recovery time was 4.44 days. Another eight cases (29.6%) were treated initially with TR medication and as needed doses of antipsychotic agents. For these cases, the average recovery time was 6.25 days. The last eleven cases (40.7%) were initially treated with both TR medication and scheduled antipsychotics. This group had an average recovery time of 17.27 days.

Table 1: Patient Characteristics and Presenting Symptoms

Study	Sex	Age	Psychiatric History	Presenting Psychiatric Symptoms	TSH (mIU/L)	Presence of Clinical Symptoms of Hypothyroidism
5	F	33	None	Mutism, paranoia	0.6	Yes
6	F	NS	None	Delusions, VH	60.29	NS
7	F	29	Depression	"Psychosis", suicidal ideation	20.7	No
8	M	13	NS	AH, depressed mood, intrusive thoughts, suicidal ideation	188	NS
9	M	25	NS	Agitation	97	NS
	M	42	NS	Hallucinations	29	NS
10	M	67	None	Paranoia, VH	>75	Yes
11	F	48	Schizoaffective Disorder: Depressed type	Paranoia, self-neglect	30	Yes
12	F	44	None	Delusions	>100	Yes
13	F	48	None	Disorganized thinking. Hyper-religiosity, paranoia,	93.77	Yes
14	F	23	Anxiety secondary to medical illness	Agitation, broadcasting thoughts, paranoia	<0.01	Yes
15	F	34	None	Agitations, delusions, distractibility, grandiosity, TH, VH	>100	Yes
16	M	61	None	Agitation, depressed mood, somatic hallucinations, VH	0.12	Yes
17	F	29	None	Anxiety, paranoia, 'psychotic behavior'	>100	No
18	F	41	None	AH, decreased sleep, delusions, expansive mood, pressured speech, VH	18.79	Yes
19	F	38	None	AH, delusions, depressed mood, psychomotor agitation, VH	10	Yes
20	M	31	None	Agitation, flight of ideas, hallucinations, paranoia	306	No
21	F	51	None	Delusions, disorganized thinking, response to internal stimuli	176.8	Yes
22	F	62	None	Decreased sleep, delusions, nonproductive hyperbulia, psychomotor agitation, tachylalia	62.9	Yes
23	M	32	None	Agitation, AH	98.7	Yes
24	M	47	None	Depressed mood, VH	47.2	Yes
25	F	30	1.5 years psychotic symptoms	AH, delusions, paranoia, psychomotor retardation	63.71	Yes
26	F	47	None	Agitation, AH, bizarre behavior, decreased sleep, delusions, 'inappropriate talk', VH	63.7	Yes
27	F	53	None	AH, paranoia, VH	NS	Yes
28	F	65	None	Confusion, depression, hallucinations, mutism, paranoia	100.34	No
	F	65	None	Capgras syndrome, catatonic features, psychosis, paranoia	61.4	Yes
29	M	12	None	AH, VH	> 100	Yes

AH = auditory hallucinations; F = female; M = male; NS = not stated; TH = tactile hallucinations; VH = visual hallucinations.

Among these cases, there appeared to be gender differences in the treatment outcomes of hypothyroid psychosis. Among male patients who received thyroid replacement, the mean time to response was 2.9 days (with or without prn antipsychotics) while female patients demonstrated a slower response with a mean of 7.2 days. Among patients who received both TR and scheduled antipsychotic medications, women continued to lag in recovery time with a mean of 19.4 days compared to 7.5 days for male patients. The availability of only limited case report information precludes an assessment of statistical significance and the predominance of female patients in the overall sample suggests that other unmeasured confounders affecting the base rates of psychosis may be influencing our observations.

Table 2: Patient Treatment and Response Time

Reference	Sex	Treatment	Antipsychotic Administration	Time to Response (Days)
7	F	Levothyroxine	NONE	3
9	M	Triidothyronine	NONE	2
	M	Triidothyronine	NONE	1.5
23	M	Levothyroxine, sodium bicarbonate	NONE	3
24	M	Levothyroxine	NONE	2
27	F	Levothyroxine	NONE	10
29	M	Thyroxine	NONE	7
5	F	Levothyroxine, haloperidol	PRN	12
11	F	Levothyroxine, haloperidol	PRN	15
12	F	Levothyroxine, olanzapine	PRN	4
13	F	Levothyroxine, haloperidol, lorazepam	PRN	2
16	M	Levothyroxine, cabergoline, hydrocortisone, testosterone	PRN	2
17	F	Levothyroxine, risperidone, IV potassium chloride	PRN	7
20	M	Levothyroxine, haloperidol, hydrocortisone	PRN	3
21	F	Levothyroxine, haloperidol, diphenhydramine	PRN	5
6	F	Levothyroxine, haloperidol	SCHEDULED	10
8	M	Levothyroxine, fluoxetine, clonazepam	SCHEDULED	10
10	M	Thyroxine, haloperidol	SCHEDULED	5
14	F	Levothyroxine, lorazepam, risperidone	SCHEDULED	30
15	F	Levothyroxine, triiodothyronine, quetiapine	SCHEDULED	30
18	F	Levothyroxine, valproate, quetiapine	SCHEDULED	21
19	F	PTU, risperidone	SCHEDULED	42
22	F	Levothyroxine, thyroxine, lorazepam, haloperidol, levomepromazine,	SCHEDULED	7
25	F	Thyroxine, risperidone	SCHEDULED	14
26	F	Thyroxine, haloperidol	SCHEDULED	7
28	F	Levothyroxine	NONE	7
	F	Levothyroxine, olanzapine	SCHEDULED	14

F = female; IV = intravenous; M = male; PTU= Propylthiouracil; PRN = given as needed

Our patient responded quickly to thyroid replacement therapy alone and did not require antipsychotic medications, consistent with the other cases reviewed. Our case was also interesting in view of the patient's mildly elevated TSH, yet he clearly displayed an episode of psychosis that resolved with TR. This raises the possibility that panhypopituitarism also contributed to his overall presentation as well as his recovery in the context of comprehensive hospital care including hydrocortisone. Hypopituiatrism has been associated with psychosis in case reports and may have placed our patient at greater risk for his psychotic presentation [31,32]. Further, panhypopituitarism frequently leads to a

deficiency in TSH [33]. For that reason, a better assessment of thyroid status in this case would be the free T4 level, which was low in our patient. This is consistent with the patient's reported noncompliance with TR. This observation is also in line with recent reports that highlight the key role of thyroid regulation in the modulation of psychiatric symptoms. Cohen et al have made a compelling case for careful control of thyroid status, particularly in populations at greater risk for thyroid dysregulation such as the elderly and those who are pregnant or post-partum [34]. Cohen et al recommended TSH levels should remain below 2.5 mIU/L in high risk patients. This is in contrast to the traditional 4.0-4.5 mIU/L range that is used as the target level for TR. We suggest that our case was a similarly vulnerable patient who was at risk for mental status changes in the context of non-compliance with hypothyroidism treatment and concomitant hyponatremia. While hyponatremia also likely contributed to the overall clinical presentation, it is noteworthy that our patients did not display some common CNS effects of hyponatremia such as impaired consciousness, seizures, or gait disturbance [35].

Regarding the time required to observe a response relative to choice of treatment, it has been suggested that initiation of antipsychotics may lead to an earlier remission of psychotic symptoms and that the use of standing dose antipsychotics may be appropriate in the elderly as their psychotic symptomatology seems to respond more slowly to thyroid replacement therapy [5]. These recommendations were not entirely supported the reviewed cases. One possible explanation for these disparate findings is that our data comes exclusively from existing case reports. Case reports, in general, tend to be limited in number and focus on highlighting rarer and often extreme versions of an established illness. Because of the bias toward more severe presentations, it is possible that based on the providers' judgement, antipsychotic medications were warranted in these patients.

6. Conclusion

Possible issues with this review include that it is based solely on case reports, which may not be generalizable to the general population. Also, there were fewer case reports involving males likely relating to the higher incidence of hypothyroidism in women [36], which may also impact generalizability. Finally, it is possible that more severe cases that required scheduled antipsychotics have added vulnerabilities that contribute to greater psychosis severity and a longer illness course. Given the rare nature of myxedema psychosis, controlled clinical trials are not likely to be feasible, however pharmacoepidemiologic research examining antipsychotic prescribing in the context of thyroid disease may be a source of data to guide future practice.

Disclosures: The authors report no proprietary or commercial interest in any product mentioned or concept discussed in this article.

Sources of Funding and Material Support:

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Declarations of Interest:

None

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