Autoimmune Thyroiditis in an Adolescent Girl on Lithium

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Chief Complaint and Presenting Problem

T. was a 14-year-old adolescent girl with a history of prediabetes and hypothyroidism admitted to a residential treatment center (RTC) with symptoms of depression and recurrent suicidal ideation.

History of Present Illness

At the time of admission, T. reported depressive symptoms that had been worsening over the preceding two months. During that time, she had had difficulties in maintaining her daily activities as she was feeling sad, tired, and had problems concentrating. She was also struggling with falling and staying asleep and had reduced appetite, although she had gained up to 20 pounds over the six months before her admission. In that context, she had felt herself perseverating on the idea that she was causing a lot of problems to her mother and that life was not worth living.

T. experienced onset of depression at age 12 years, soon after her stepfather was deported and her mother began a subsequent escalation in use of alcohol. At that time, T. exhibited low mood, fatigue, concentration difficulties, insomnia, and suicidal ideation, which led to her first psychiatric hospitalization. During her first admission she was started on sertraline, which was titrated up to 100 mg. T. did not experience any benefit from this medication, so she was switched to duloxetine 60 mg with partial improvement of the depressive symptoms.

During the year that followed her first admission, T. had six other inpatient psychiatric hospitalizations for high risk of suicide. On two occasions, she was hospitalized after a suicide attempt by medication overdose.

Five months before residential admission, T. reported having had episodes during which she experienced an elated mood and an increased sense of self-confidence. During these episodes, which lasted 2–3 days, T. was more sociable and participated in activities that were unusual for her, such as cooking and painting. Although symptoms were noticeable to T.'s peers, they had not yet resulted in any clear functional impact. With suspicion of bipolar disorder, she was started on aripiprazole 10 mg by her outpatient psychiatrist.

In addition to her mood symptoms, T. also reported intrusive memories, recurrent flashbacks, and nightmares related to a history of sexual abuse. T. was first victimized when she was 6 years old by a family member who was 11 years old at the time. In addition, she reported sexual molestation by a family member at age 12 and being raped at age 13. She was diagnosed with posttraumatic stress disorder (PTSD) a few days before RTC admission, and was started

on melatonin 3 mg at bedtime for insomnia and prazosin 1 mg at night with some improvement of nightmares.

Over the year before RCT admission, T. had also experienced increased anxiety, especially in social situations. She often worried about being judged, avoided meeting new people, and was extremely anxious when she had to talk in front of people. She had a history of truancy, and claimed she had missed more than 20 days of school over the prior year because of an intense fear of being embarrassed in class. Four weeks before RTC admission, she was started on buspirone 10 mg twice a day and lorazepam 0.5 mg every morning for anxiety symptoms by her outpatient psychiatrist. Buspirone was stopped for a lack of efficacy immediately before her transfer to residential care.

In this context, T. reported self-harming behaviors beginning at age 12 years; she acknowledged cutting herself once every few weeks in response to stress. She also reported smoking cigarettes occasionally to reduce her anxiety. T. denied a history of using alcohol, marijuana, or any other illicit substances.

Upon presentation, T. did not endorse obsessive compulsive, agoraphobia, panic, or generalized anxiety symptoms. There was no history of oppositional defiant, conduct, autism spectrum, or eating disorder symptoms.

Developmental History

T. was the product of an uneventful pregnancy with full prenatal care and no *in utero* exposure to medications or illicit substances. T. was born full term through vaginal delivery and was not underweight; there were no peri- or postnatal complications.

T.'s acquisition of speech and motor milestones was reached at appropriate ages.

Educational History

T. was in the ninth grade when she was admitted to the RTC. Over the preceding year, her school had been providing increased resource room support, given her psychiatric impairments. Despite the support, T.'s academic performance had declined from average to below average grades.

She did not have a history of suspensions or expulsions from school because of disciplinary issues.

Social History

T. was the oldest of four siblings, with two sisters who were 12 and 10 years old, and one half-brother who was 7 years old at the time of admission. Her parents divorced when she was 4 years old,

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and she did not have further contact with her father. Her stepfather came into her life close to the time her parents divorced. She reported him to be a supportive figure; however, he was deported for immigration reasons when she was 13 years old. After her stepfather's deportation, T.'s mother began heavily abusing alcohol. At the time of admission, T. was living with her three siblings, mother, and maternal grandfather.

T. reported being in a romantic relationship with a 14-year-old female, whom she met on a social networking site.

T. had previously been charged with truancy, but denied any other legal charges. She denied experiencing interpersonal violence, or running away from home.

Family History

Mother was diagnosed with bipolar I disorder and alcohol use disorder. Both of T.'s maternal grandparents had histories of major depressive disorder. Maternal half-brother had been diagnosed with attention-deficit/hyperactivity disorder.

Paternal psychiatric history was unknown.

There was no known family history of autoimmune disorders.

Medical History

T. was diagnosed with hypothyroidism and prediabetes three months before admission to the RTC. She had been started on immediate release metformin, and subsequently switched to extended release formulation for diarrhea and stomach cramps, to control glucose levels. T. was also started on levothyroxine by her family physician for her hypothyroidism.

Laboratory Values

Before admission, T.'s thyroid stimulating hormone (TSH) was within normal range (TSH 4.56 UIU/mL; reference range: 0.40–5.10 UIU/mL) while hemoglobin A1c (Hgb A1c) was above normal (Hgb A1c 6.3%; reference range: 4.5–5.6%).

Mental Status Examination

T. was an age-appropriate appearing 14-year-old Caucasian female. She displayed good self-care but had marked psychomotor retardation. She was anxious during the initial part of the interview. Rapport was difficult to establish, but improved as the interview progressed. There were no unusual movements in her extremities or facial muscles. Her speech was low in tone, rate, and volume. She displayed a dysphoric mood with congruent affect. Her thought process was logical and goal directed. She endorsed intrusive memories and flashbacks consistent with PTSD. She denied having symptoms of psychosis, including auditory or visual hallucinations or delusions. She denied active suicidal thoughts, but T. did report passive suicidal thoughts (i.e., "Why am I here?"). She denied homicidal ideation. T.'s immediate, recent, and remote memories were intact. Her concentration was mildly impaired, as she seemed anxious. She displayed adequate insight and judgment.

Treatment Course

At admission, T. reported symptoms of cold intolerance, reduced appetite, and fatigue that were suggestive of residual hypothyroidism, so levothyroxine was increased to 37.5 µg. As T. denied major changes in mood after previous levothyroxine titrations, levomethylfolate 15 mg was added as an augmenting agent.

T. also denied significant improvement of depressive symptoms with duloxetine, so it was discontinued early in the treatment course. As medications in the selective serotonin reuptake inhibitor class are indicated for treatment of major depression in youth, and are beneficial for PTSD in adolescents, fluoxetine was initiated at 10 mg, and gradually increased to 40 mg daily.

For better control of anxiety throughout the day, lorazepam was switched to clonazepam 0.25 mg in the morning and 0.125 mg at bedtime. To promote sleep, melatonin was increased to 6 mg in the evening. To address PTSD-related nightmares, prazosin was increased to 3 mg at bedtime and a morning dose of 1 mg was added later.

Despite the changes in medication, T. continued to exhibit residual depressive symptoms. Given T.'s history of hypomanic symptoms, the treatment team decided to start lithium. Lithium was started at 300 mg twice a day, and gradually titrated up to 900 mg per day. At 900 mg daily, T.'s lithium level was 1.21 mmol/L, but she developed diarrhea. The dose was reduced to 750 mg a day, and eventually re-established at 900 mg a day once the diarrhea had subsided.

After initial improvement, three weeks after lithium initiation, T. exhibited an abrupt decline in mood. In addition to worsening depressive symptoms, she experienced blurred vision, weight gain, and psychomotor retardation. Repeat lithium levels were in therapeutic range. As depressive symptoms and blurred vision persisted, thyroid functions were re-evaluated. Free thyroid hormones (T3 and T4) were within normal limits, but TSH and thyroid auto-antibodies (thyroid peroxidase antibodies and antithyroglobulin antibody) were above the normal ranges.

Clinical symptoms and laboratory results were suggestive of autoimmune thyroiditis; thus, levothyroxine was increased to 75 µg per day. Lithium was maintained according to treatment guidelines.

Brief Formulation

T. was a 14-year-old adolescent girl with a history of prediabetes and hypothyroidism admitted to an RTC for severe depression and suicidal thoughts. On admission, T. exhibited symptoms of a major depressive episode and an exacerbation of a recently established diagnosis of hypothyroidism. Given past hypomania symptoms, T. was a candidate for a bipolar disorder diagnosis. However, hypomanic symptoms were never present for four consecutive days; hence, she did not meet full criteria for bipolar II disorder.

From a biological perspective, T. had a genetic predisposition to affective disorder, given bipolar disorder and major depressive disorder on the maternal pedigree. In addition, hypothyroidism was also significantly contributing to her depressive symptoms.

From a psychosocial perspective, T.'s loss of stepfather and sexual trauma suffered at age 13 could have precipitated the onset of mood and PTSD symptoms. A lack of healthy maternal role modeling and coping strategies rendered T. more vulnerable to the emotional consequences of these losses.

Multiaxial Diagnoses

Axis I: Other specified bipolar and related disorder
PTSD

Axis II: None

Axis III: Autoimmune thyroiditis

Prediabetes

Axis IV: Problems with primary support group

Axis V: GAF 35-40 at admission; GAF 60 at discharge

Discussion

This case illustrates the complexities and challenges of establishing a diagnosis and planning treatment of mood disorders in children and adolescents in the context of hypothyroidism.

Hypothyroidism is an endocrine condition defined by the body's lack of thyroid hormones. It represents the most common thyroid disorder in children and adolescents. Clinical manifestations are nonspecific, and include symptoms such as depressed mood, fatigue, weight gain, reduced sexual desire, or poor concentration that can be difficult to disentangle from a primary mood disorder.

Moreover, hypothyroidism and mood disorder can co-occur. In these circumstances, pharmacological management can be complex because of potential interactions between psychotropic medications and thyroid function. This is particularly relevant for lithium therapy, a first-line treatment for bipolar disorder in adults (Yatham et al. 2013) and pediatric patients older than 12 years of age (Amitai et al. 2014 and McClellan et al. 2007).

Lithium has been shown to be generally well tolerated in the pediatric population, and can be utilized without the risk of extrapyramidal symptoms, weight gain, or metabolic problems associated with atypical antipsychotic medications (Findling et al. 2015). This profile is particularly relevant in patients with hypothyroidism, who can experience weight gain and hypercholesterolemia as a result of their thyroid dysfunction. Although there are many benefits to lithium treatment, lithium use can also be challenging, given a narrow therapeutic window and renal, cardiac, and neurological adverse effects. Thyroid abnormalities, including goiter, hypothyroidism, autoimmune thyroiditis, and hyperthyroidism, are all potential lithium-related adverse effects that have been widely described (Kibirige et al. 2013).

Several mechanisms have been suggested to explain how lithium may cause hypothyroidism. First, lithium has been reported to directly interfere with the thyroid gland by inhibiting a specific enzyme that regulates thyroid cell proliferation (Rao et al. 2005). In addition, there are reports showing that lithium interferes with the thyroid gland's ability to reuptake iodine (Kibirige et al. 2013) and to concentrate iodine into iodinated thyroglobulin molecules (Mouaffak et al. 2006). Other studies have shown that lithium can alter the thyroid gland's ability to release thyroid hormone by blocking the gland's microtubules (Bhattacharyya and Wolff 1976) and reducing its sensitivity to TSH (Mouaffak et al. 2006). Finally, lithium can also alter the levels of thyroid hormones by decreasing the amount of free T4 that is deiodized through the hepatic system into the active form of T3 (Kibirige et al. 2013).

Autoimmune processes have also been proposed as a mechanism by which patients who take lithium are prone to thyroid abnormalities. A 1986 study demonstrated fluctuation of thyroid antibody levels in patients treated with lithium (Lazarus and McGregor 1986). However, lithium's induction of thyroid autoimmunity remains controversial, since other studies have reported increased thyroid antibody titers in patients with bipolar disorder, regardless of lithium treatment (Oomen et al. 1996). Adding to the controversy, Bocchetta et al. (2007) did not find differences in thyroid antibody levels between 150 patients prescribed lithium for 15 years and the general population.

Regardless of the underlying cause, most guidelines agree that patients with thyroid problems do not need to discontinue lithium treatment, as long as thyroid function is monitored and controlled (McClellan et al. 2007). Guidelines recommend physical

examination of the thyroid gland and laboratory tests for serum TSH and antithyroid peroxidase titers before initiation of lithium treatment. Patients who do not have symptoms of thyroid dysfunction during treatment with lithium should have thyroid functions monitored every 6–12 months (Barbesino 2010). For adolescent patients, some authors have suggested that thyroid function should be monitored every 2–3 months (LaFranchi 2016).

In T.'s case, pretreatment thyroid antibody levels were not available, and so it is unclear whether autoimmune thyroiditis was present before the treatment or a result of it. The case illustrates the importance of careful evaluation of patients before initiating lithium therapy, and the need for monitoring thyroid functions during treatment. Close monitoring is especially important for patients with a history of autoimmune disorders, or for those who develop symptoms suggestive of thyroid disease during treatment.

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References

- Amitai M, Zivony A, Kronenberg S, Saar S, Sever J, Apter A, Shoval G, Golubchik P, Weizman A, Zalsman G. Short-term effects of lithium on white blood cell counts and on levels of serum thyroid-stimulating hormone and creatinine in adolescent inpatients: A retrospective naturalistic study. *J Child Adolesc Psychopharmacol* 24:494–500, 2014.
- Barbesino G. Drugs affecting thyroid function. *Thyroid* 20:763, 2010.
- Bhattacharyya B, Wolff J. Stabilization of microtubules by lithium ion. *Biochem Biophys Res Commun* 73:383–390, 1976.
- Bocchetta A, Cocco F, Velluzzi F, Del Zompo M, Mariotti S, Loviselli A. Fifteen-year follow-up of thyroid function in lithium patients. *J Endocrinol Invest* 30:363–366, 2007.
- Findling RL, Robb A, McNamara NK, Pavuluri MN, Kafantaris V, Scheffer R, Frazier JA, Rynn M, DelBello M, Kowatch RA, Rowles BM, Lingler J, Anand R, Clemons TE, Taylor-Zapata P. Lithium in the acute treatment of bipolar I disorder: A double blind, placebo controlled study. *Pediatrics* 136:885–894, 2015.
- Kibirige D, Luzinda K, Ssekitooleko R. Spectrum of lithium induced thyroid abnormalities: A current perspective. *Thyroid Res* 6:3, 2013.
- LaFranchi S. Acquired hypothyroidism in childhood and adolescence. UpToDate, 2016. Available at www.uptodate.com/contents/acquired-hypothyroidism-in-childhood-and-adolescence Accessed October 5, 2016.
- Lazarus JH, McGregor AM, Ludgate M, Drake C, Creagh FM, Kingswood CJ. Effect of lithium carbonate therapy on thyroid immune status in manic depressive patients. *J Affect Disord* 11:155–160, 1986.

- McClellan J, Kowatch R, Findling R. Practice parameter for the assessment and treatment of children and adolescents with bipolar disorder. *J Am Acad Child Adolesc Psychiatry* 46:107–125, 2007.
- Mouaffak F, Gourevitch R, Baup N, Loo H, Olie JP. Interrelations between lithium therapy, auto-immune thyroiditis, and TSH. *Pharmacopsychiatry* 32:77–78, 2006.
- Oomen HA, Schipperijn AJ, Drexhage HA. The prevalence of affective disorder and in particular of a rapid cycling of bipolar disorder in patients with abnormal thyroid function tests. *Clin Endocrinol* 45:215–222, 1996.
- Rao AS, Kremenevskaja N, Resch J, Brabant G. Lithium stimulates proliferation in cultured thyrocytes by activating Wnt/B-catenin signaling. *Eur J Endocrinol* 153:929–938, 2005.
- Yatham LN, Kennedy SH, Parikh SV, Schaffer A, Beaulieu S, Alda M, O'Donovan C, MacQueen G, McIntyre RS, Sharma V, Ravindran A, Young LT, Milev R, Bond DJ, Frey BN, Goldstein BI, Lafer B, Birmaher B, Ha K, Nolen WA, Berk M. Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) collaborative update of CANMAT guidelines for the management of patients with bipolar disorder: Update 2013. *Bipolar Disord* 15:1–44, 2013.

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