



Escitalopram related edema in a patient with Hashimoto's thyroiditis

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ABSTRACT

Advanced Practice Providers recognize and treat the most common side effects patients bring to our attention with the use of antidepressants, including insomnia, weight gain, emotional flattening, and sexual side effects. (<https://www.psychcongress.com/article/top-5-side-effects-psychotropics-and-how-manage-them>). We are, however, less intuitive and competent at picking up the high risk and rare, problem prone side effects our patients may experience related to the medications we prescribe, particularly in the more medically complex patients. In addition, the medically complex patient may mask a psychiatric concern as the psychiatric provider finds themselves caught up in the ambiguity of numerous somatic symptoms a patient presents with versus the psychiatric concerns that bear our attention. Autoimmune disorders often blur this line all too well affecting both psychiatric and physical well-being.

Introduction

Hashimoto's thyroiditis is one of the most commonly seen autoimmune disorders of the thyroid with a prevalence rate of 2% affecting primarily women (Ayhan, Uguz, Askin, & Gonen, 2014). It is commonly thought that both active Hashimoto's and the euthyroid stage of Hashimoto's can lead to psychological stress and decreased quality of life. This can present as increased cases of depression and anxiety (Ayhan et al., 2014; Yalcin et al., 2017). Cross-sectional controlled studies found higher rates of depression and anxiety in those with euthyroid Hashimoto's without a thyroid replacement compared to control subjects with worse health-related quality of life (Yalcin et al., 2017). Ayhan, Uguz, Askin & Gonen found in their comparative study that those with Hashimoto's had a prevalence of roughly 30% and 33% of having both major depression and any depressive disorder as compared to 6% in the control group. Therefore, patients with a comorbid diagnosis of Hashimoto's or other thyroid disorders should be monitored carefully. This case report of a patient with comorbid Hashimoto's thyroiditis and depression calls to attention a rare SSRI associated side effect, new onset edema.

A review of literature was done using PubMed with the following search terms: edema, SSRI, escitalopram, antidepressant. A deliberate link was avoided in searching the relationship to the Hashimoto's which can be a common cause of edema for reasons demonstrated in the case study below. Literature review showed four cases of new onset peripheral edema directly related to the SSRI class of antidepressants (Hosseini & Ahmadi, 2012; Masdrakis, Oulis, Kouzoupis, Masdrakis, & Soldatos, 2009 and Ravi, Ravishankar, & Andrande, 2014). Only two cases were found specific to escitalopram itself (Masdrakis et al., 2009; Ravi et al., 2014), one case specific to citalopram though it was given concurrently with risperidone (Hosseini & Ahmadi, 2012) and one case

specific to paroxetine (Uguz, 2014). Edema occurs due to an excess of fluid trapped in the tissue of the body secondary to capillary leakage. It is most often associated with medication, pregnancy or underlying diseases, typically believed to be autoimmune, cardiac, hepatic or renal in nature. (<https://www.mayoclinic.org/diseases-conditions/edema/symptoms-causes/syc-20366493>). Fortunately, treatment is simple in all cases and merely involves removing the offending agent. One case (Dadic-Hero et al., 2011) was found to demonstrate angioedema associated with sertraline and when the SSRI was reintroduced, escitalopram provoked urticaria. There was one SNRI case found related to duloxetine causing periorbital edema 2 days after treatment initiation, again with resolution of edema following discontinuation of drug (Oulis et al., 2008).

The majority of case reports found in literature have shown new onset edema as an adverse effect related to the antipsychotic class (Roy, Astreika, Dunn, & Sappati Biyyani, 2009; Yang, & Cheng, 2012). Looking at dermatologic side effects of psychotropics as a whole, Mitkov, Trowbridge, Lockbridge, and Caplan (2014) contend that antidepressants in general are responsible for 29% of all cutaneous reactions.

This case report presents an unusual side effect in a middle-aged woman diagnosed with major depression and generalized anxiety disorder with a multigenerational family history of Hashimoto's thyroiditis. She is known to be sensitive to thyroid medicine with traditional modalities such as levothyroxine causing adrenal fatigue, or HPA dysregulation known as hypothalamus-pituitary-adrenal axis dysregulation. This is a major part of the endocrine influencing immune response, emotions, and energy metabolism among other functions. It can be tested by a dexamethasone test to assess cortisol levels. Patient will commonly refer to themselves as having adrenal fatigue as this patient does if they test positive (Du & Pang, 2015).

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She initially declined all antidepressant therapies until a euthyroid state could be achieved. Once euthyroid, she opted to start an antidepressant, escitalopram, which had been proposed at the beginning of her treatment. In three months' time, while mood improved, she developed new onset bilateral 3+ pitting edema to lower extremities with no other known cause including her Hashimoto's.

Case description

A 42-year-old woman who initially presented for psychiatric care for depression and anxiety in March 2017 in context of psychosocial stress. She had no previous psychiatric history prior to her initial intake evaluation. She was diagnosed with moderate major depression and generalized anxiety. Her consent was obtained for this case report and all identifying information has been removed. Her medical history was pertinent for untreated Hashimoto's thyroiditis since 2006 due to adrenal fatigue with levothyroxine. She also has a history of Raynaud's syndrome, hypertension, benign heart murmur, peptic ulcer disease and is post hysterectomy. She has no known allergies. Her medications, both over-the-counter and prescribed are: Armour thyroid 7.5 mg daily, biotin 10,000 µg daily, Dexilant 30 mg daily, fish oil 1200 mg daily, glucosamine chondroitin 1500 mg daily, magnesium 250 mg daily, Premarin 0.625 mg twice daily, selenium 200 µg daily, vitamin B12 5000 µg daily and vitamin D3 5000 units daily. She denies intake of caffeine, nicotine, alcohol and illicit substances.

At the time of the psychiatric evaluation she also going to be seen by a new endocrinologist, however her first appointment was six weeks away. At the time of initial presentation, per lab reports available, her TSH was 0.99 mIU/L (0.4–4.0 mIU/L), free t4 was 1.0 ng/dL (0.7–1.53 ng/dL), thyroglobulin antibodies were 1.0 IU/ml (< 4.0 IU/ml) and thyroid peroxidase antibodies were 74 IU/ml (< 35 IU/ml). Her presenting psychiatric symptoms were difficulty concentrating, increased stress, and irritability. She initially elected to begin supportive therapy until a euthyroid state could be achieved due to her historical sensitivity to medications. She was seen one month later for follow-up therapy and thyroid peroxidase antibodies were 166 IU/ml (< 35 IU/ml). She was seen two weeks later for therapy at which point endocrine has now begun care, and she was placed initially on Tirosint 13 every 4 days with a goal of reaching daily dosing. She continued to receive regular therapy and endocrine care achieving a euthyroid state with TSH 1.52 in November of 2017. Thyroid peroxidase antibodies were not drawn at that time. Due to job dissatisfaction and workplace role strain, she now elected to start an SSRI. Escitalopram was chosen as discussed earlier on in her course of care and started patient at 10 mg daily. Two days later, the patient called with side effects following the first dose of headache, nausea and sweating, and decision was made to decrease the dose to 5 mg daily in November 2017. Mood and physical symptoms were beginning to improve with thyroid treatment with concomitant antidepressant therapy evidenced by steady drop in PHQ-9 scores [9/27 March 2017 to 2/27 February 2018]. PHQ-9 ([Patient Health Questionnaire, 1999](#)) is an objective measure of depression using patient's self-rating of symptoms. Clinical relevance begins with score of 5 or higher with scores between 5 and 9 correlating to mild depression.

The patient was seen one month later for routine follow-up care feeling she was tolerating the escitalopram better at the 5 mg dose, reporting an improvement in her mood. Given the improvement in mood and lack of side effects, she was willing to attempt to increase her escitalopram dose back to 10 mg daily. She was switched by her endocrinologist from Tirosint 13 to Armour Thyroid 7.5 mg on Mondays and Thursdays in mid-November 2017.

The patient presented for routine follow-up two months later, reporting good mood with bright affect. She was experiencing night sweats and diffuse new onset pitting 3+ bilateral edema. She stated she had stopped her Armour Thyroid for two weeks in an attempt to assess correlation with the edema and found it made no difference. She was having trouble wearing her normal shoes and boots. She was advised to

follow up with endocrinology to have labs checked to ensure her Hashimoto's was not definitively playing a role in the edema to allow conclusive determination it was her SSRI; however, no labs beyond November of 2017 were available. At that time her endocrinologist was made aware of her two-week trial off the Armour thyroid. Brief review of literature at that the time showed 3 cases of new onset SSRI related edema ([Ravi et al., 2014](#); [Dadic-Hero et al., 2011](#); [Masdrakis et al., 2009](#)). The cases ranged in age from 40 to 70, all women. Along with the aforementioned edema, symptoms included in one of the patients: whole body rash, flushing, severe itching and diarrhea with re-introduction. Testing in every single patient came back negative for other causes including renal and cardiac. The edema in all cases resolves with removal of the SSRI. Given that her edema resolved with adjustment of the escitalopram and not with stopping her Armour Thyroid for two weeks adds to the evidence that despite edema being linked to autoimmune diseases, her edema is thus felt to be independent of her Hashimoto's and related to the antidepressant therapy.

In this case, the patient was instructed to stop her escitalopram and come off the SSRI completely in order to see if the medication was the root cause of the edema. She called the office one week later to report 5-pound water weight loss and decrease in edema. She did report being off SSRI her blood pressure was elevated along with an increase in irritability, impulsivity, and agitation. She was instructed to remain off medication another full week to further decrease edema prior to starting a new antidepressant. She called office one week later with no further weight loss to report resolution of edema. She was placed on vortioxetine, a multi-modal agent, at a dose of 2.5 mg without side effects reported. TSH in May revealed level of 2.05 at which time her endocrinologist removed the Armour thyroid for a period of two months, resuming it in July at 7.5 mg again daily this time. Her TSH and free T4 level at that time were 2.24 and 1.0 respectively. She has remained edema free off the SSRI and both on and off the Armour thyroid. It should be noted that throughout this process the patient remained concordant to all treatments by all specialties as prescribed except where noted.

Discussion

This case report highlights the need to look at our patients critically from at least two perspectives. There is a multi-system perspective to consider as she lives with Hashimoto's/thyroid disease and depression often go together hand-in-hand. This case report is an example of how practitioners are discouraged from relying on a TSH level alone to ensure that the depressed patients are euthyroid. Consultation (referral/conferral) is needed with an endocrinologist collaborating with a complex presentation. In patients with thyroid disease, our baseline lab work should include TSH, free t4, and thyroglobulin antibodies with any positive results being sent to the primary care physician and endocrinology. This case was limited by not having updated full thyroid panel studies, specifically thyroid peroxidase antibodies from 2018, which may have been helpful. Second, how when a patient calls our attention to a rare side effect easily explained by another system we must listen.

We normally think of edema related to vascular disease, cardiac disease, and autoimmune diseases; however, edema could be a side effect of steroids, calcium-channel blockers, NSAIDs or in psychiatry, an antipsychotic. Normally, practitioners would not consider the SSRI as the first cause of edema. In a patient with +3 pitting lower extremity edema, it is easy to brush aside concerns that they may bring to a provider and order a cardiology consult; particularly in a young woman to ensure a more serious issue is not missed. In our patient, with the history of Hashimoto's, it is easy to insist repeatedly that she get labs and see her endocrinologist over and over until she does given the role of edema in autoimmune disorders. Given that she was able to remain edema free off the SSRI despite adjustments in her thyroid management, one has to conclude that despite close ties to edema in

autoimmune disorders, she truly had SSRI induced edema. We are taught from day one to treat the symptoms we see for what they are and typically nothing more, nothing less. As the saying goes, “when you hear hoofbeats, look for horses, not zebras.”

This is also to be considered if a provider were to look at the Ladder of Inference theory, a seven-rung ladder that takes one through the critical thinking process from reality and facts to the action taken based on information they have critically examining each piece of information and evidence obtained along each step of the way. The Ladder of Inference theory was utilized here as we examined our patient physically, went through every laboratory value, every medication to ensure we had all the facts and with each fact could interpret the correct meaning, draw a proper conclusion and thus, take appropriate action (*The Ladder of Inference*, 2018). The psychiatric provider who was faced with this patient and looked up side effects of escitalopram in common desktop sources at hand using Epocrates (*Escitalopram*, 2018) and Stahl's Essential Psychopharmacology (*Stahl*, 2008) as examples, they would not find edema listed as a side effect and feel reassured that it was not their drug as the source of the patient's discomfort. It takes the expert clinician to recognize this is associated to more than a vascular issue, more than underlying cardiac disease, more than the patient's autoimmune disorder and know to take the extra time with that patient and discover they have the patient with the rare presentation. They would have known this by working through the ladder of inference.

When practitioners stop, listen and take the time to put the whole puzzle together we can meet the needs of patient immediately in one visit by listening to what our patient is really telling us. In a busy world with a push to see as many patients as we possibly can in an hour, the art of listening between the lines is easily lost. It is that art that I challenge us as Advanced Practice Providers to return to in order to enable a return to best practice. The wise words of Roujeau and Stern (1994) serve us well: “Prompt differentiation of severe adverse cutaneous reactions from less serious skin disorders may be difficult. Rapid recognition of severe reactions is essential.” (p. 1272).

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