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Subclinical Hypothyroidism, Its Manifestations and Management a Case Report

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Abstract

Introduction: Thyroid states can be associated with psychiatric manifestations, be it hypothyroid, hyperthyroid or even euthyroid. The effect of depression is significant in subclinical hypothyroidism. Sometimes, its signs and symptoms are indistinguishable from Major Depressive Disorder. Our immunological system and early embryologic origins also play a role in the coexistence of other comorbidities like Pernicious Anemia. **Case:** A 35-year-old Hispanic female presented with significant low mood, somnolence, weight gain, increased hunger, cold intolerance and epigastric pain. It is important to note the variety of clinical manifestations of our hypothyroidism patient to understand its associations and help us with a better approach to treatment. **Discussion:** Standard approaches to treatment of Subclinical Hypothyroidism will depend mostly on laboratory findings such as TSH levels and free T4. Individualized therapy chosen for our patientwas based on his mood symptoms, laboratory findings and coexistence of Pernicious Anemia. The use of daily 0.025 mg of levothyroxine, 10 mg of escitalopram oxalate and weekly injections of cyanocobalamin were treatments of choice. **Conclusion:** During follow up of our patient, we can conclude that Levothyroxine and Escitalopram Oxalate was able to improve hypothyroidism symptoms, reduce thyroglobulin and peroxidase antibodies and improve mood symptoms including cognitive functions. In addition to this, weekly cyanocobalamin injectionswere integrated into the management. As parietal cell antibodies decreased, gastrointestinal symptoms also disappeared. By addressing the concerns of our patient, we improved quality of care, and this reflected on the patient's wellbeing being the physical and psychological.

Keywords

Cyanocobalamin, Escitalopram Oxalate, Hashimoto's Thyroiditis, Levothyroxine, Pernicious Anemia, Polyglandular Syndrome

1. Introduction

The term subclinical hypothyroidism is given to patients with early stage of hypothyroidism with mild aberrations in thyroid function tests. Sometimes the condition might resolve on its own or remain as a progressive disease until full-scale hypothyroidism develops [1]. Subclinical hypothyroidism is caused by the same disorders that affect individuals with hypothyroidism. One of the most important causes is Hashimoto's thyroiditis, which is an autoimmune disease which anti-thyroid peroxidase and anti-thyroglobulin antibodies cause inflammation and damage of the thyroid gland. In addition, other causes of subclinical hypothyroidism include radioactive iodine, medications such as amiodarone or lithium, thyroid removal surgery, and heavy exposure to radiation of the head or neck [2].

Symptoms of subclinical hypothyroidism include weakness, fatigue, dry skin, cold intolerance, non-pitting edema, constipation, weight gain, bradycardia, abnormal menstrual periods, muscle cramps, delayed reflexes, cardiac dysfunction, hyperlipidemia, among others. Most of the time, the only signs or symptoms present in patients are depressive episodes, which can mask the underlying problem [3]. Subclinical hypothyroidism is diagnosed when lab values of thyroxine are within normal ranges and (TSH) thyroid stimulating hormone is increased above normal range.

The constant interplay between thyroid hormone action and the immune system can influence the variations of symptoms in which a patient develops. Because of this, it is important to have a thorough examination followed by blood tests to rule out immunological coexistence [4]. Levothyroxine is the treatment of choice for subclinical hypothyroidism. It is a synthetic thyroid hormone taken orally and is well tolerated by patients. Furthermore, the prognosis of subclinical hypothyroidism is satisfactory. A Wickham study said that there was no cardiac mortality in patients who were followed in a 20-year period [5].

2. Case Presentation

A 35-year-old Hispanic housewife presented to her primary care provider with complaints of depression, excessive drowsiness, decreased memory, fatigue, exhaustion, somnolence, cold intolerance, constipation, increased hunger and weight gain. Her previous medical history was unremarkable without previous major depressive episodes, hospitalizations and she denied intake of any prescribed or over-the-counter medications. She denied any previous or active history of tobacco, alcohol, illicit substance or allergies to medications. She denied the existence of diabetes, hypertension or obesity in family history, but there was confirmed diagnosis of hypothyroidism in father, mother, and one sibling.

2.1. Clinical Findings

When questioned about her depression on 2/26/2020, she says it began four months prior to her first clinic visit. In reference to that, she reported low mood,

poor self-esteem, anhedonia, fatigue, sleep disturbances, poor concentration, no suicidal ideation, increased appetite and postprandial epigastric pain. Table 1 describes the severity rating scales of depression and proposed treatment actions. Our patient scored 17 on health questionnaire (PHQ 9), thus apresumptive diagnosis of moderate severe major depressive episode was made.

Physical examination including vitals were unremarkable except an overweight patient with **153 lbs (BMI: 29.92) and 5 feet in height.** On cardiovascular examination, heart rate was normal with regular rhythm and a normal S1 and S2 sounds. In addition, there was absence of murmurs, gallops, and rubs. On inspection, there was absence of goiter, tremors, fasciculations, or pretibial myxedema. The skin had a normal color, texture, temperature, mobility and turgor. Hair inspection had a normal distribution with absence of alopecia, scaliness or lumps. Inspection of nails revealed no nodules, pitting or brittle nails. Neurological examination was normal including external ocular movements, deep tendon reflexes, pupillary reaction, and pupil size bilaterally.

Laboratory workup included a baseline complete blood count (CBC) with differential, and a comprehensive metabolic panel (CMP). Results showed a hemoglobin level of 14 g/dl, Hematocrit 42%, MCV 91 fl, MCH 30.4 pg, MCHC 33.5 g/dl, blood glucose 86 mg/dl. Sodium 138 mmol/L, potassium 3.9 mmol/L, chloride 103 mmol/L, CO_2 20 mmol/L. BUN 13 mg/dl, creatinine 0.70 mg/dl. Further tests were done because of the unique family history and possible associations to hypothyroidism. In addition, a thyroid profile was pursued because the patient was still complaining of cold intolerance, constipation, and epigastric pain. The following symptoms show the initial laboratory values, and post laboratory results after treatment. Table 2 showsthyroid function tests including anti-thyroid peroxidase (anti-TPO), and anti-thyroglobulin (anti-TG) antibodies. Because of absence of goiter or nodules on neck examination, the physician deferred a thyroid ultrasound. Table 3 shows a positive test for anti-parietal cell antibody. Lipid panel, total cholesterol, triglyceride, and high-density lipoprotein were within normal limits.

Table 1. PHQ-9 scores and proposed treatment actions.

PHQ-9 Score	Depression Severity	Proposed Treatment Actions
0 - 4	None-minimal	None
5 - 9	Mild	Watchful waiting, repeat PHQ-9 at follow up
10 - 14	Moderate	Treatment plan, considering counseling, follow-up and/or pharmacotherapy
15 - 19	Moderate Severe	Active treatment with pharmacotherapy and/or psychotherapy
20 - 27	Severe	Immediate initiation of pharmacotherapy and, if severe impairment or poor response to therapy, expedited referral to a mental health specialist for psychotherapy and/or collaborative management

Table 2. Thyroid function tests.

Reference Range and Units	(TSH) Thyroid Stimulating Hormone 0.450 - 4.500 uIU/ML	Free-T4 Thyroxine 0.82 - 1.77 ng/dL	Thyroid Peroxidase Ab 0 - 34 IU/ML	Thyroglobulin Ab 0.00 - 0.9 IU/ml	Free-T3 2.0 - 4.4 pg/mL	Thyroid Stimulating Immunoglobulin (TSI) 0.00 - 0.055 IU/L
2/26/2020	5.010	1.11	96	7.7	3.7	0.09
8/21/2020	3.810	1.26	40	1.9	3.8	Not Reported

Table 3. Laboratory tests for pernicious anemia.

Reference Range and Units	Parietal Cell Ab Screen 0.00 - 20.0 Units	Vitamin B12 232 - 1245 pg/mL
2/26/2020	124.5	Not reported
8/21/2020	0.10	703

2.2. Therapeutic Interventions

After careful analysis, the final diagnosis was subclinical hypothyroidism based on elevated TSH, and normal value in free thyroxine. Moreover, anti-parietal cell antibody was found positive in lab results indicating pernicious anemia. Although the MCV was within normal range, the fact of having a positive antibody screen prompted treatment. Prior to starting treatment, and todetermine the appropriateness of medication dosing regimen, renal and hepatic organ function tests were obtained. Table 4 shows glomerular filtration rate, BUN/Creatine, total bilirubin, alkaline phosphatase, along with AST and ALT enzymes. The patient was prescribed a daily oral dose of levothyroxine 0.025 MG, a (SSRI) escitalopram oxalate tablet 10 mg daily, and cyanocobalamin 1,000 mcg/ML with intramuscular directions every 7 days with a follow up appointment at 6 months for re-evaluation.

2.3. Follow up and Outcomes

Upon return to clinic on 8/21/2020, the patient showed marked improvement in mood, less fatigue, feeling more focused with more energy and attention. The patient also explained that while adhering to the medication regimen, her symptoms of constipation, cold intolerance, and epigastric pain diminished. Table 1 we see that Thyroid Stimulating Hormone (TSH) stabilized and anti-parietal cell antibody returned to normal ranges. In addition, there was significant improvement in the anti-thyroid peroxidase (anti-TPO), anti-thyroglobulin (anti-TG) antibody readings.

3. Discussion

Literature explains that subclinical hypothyroidism (SCH), presents a normal thyroid hormone level but an elevated serum thyroid-stimulating hormone (TSH). SCH tends to occur in 3% to 8% of the general population, and similarly

Table 4. Laboratory tests.

Reference Range and Units	EGFR >59 mL/min/1.73	BUN/Creatinine Ratio 9 - 23	Total bilirubin 0.00 - 1.2 mg/dL	Alkaline Phosphatase 39 - 117 IU/L	AST 0 - 40 IU/L	ALT 0 - 32 IU/L
2/26/2020	105	12	0.5	73	16	12
8/21/2020	106	14	0.7	84	21	23

to our case reportit is more common in women than men, and the higher the age, the more common it becomes [1]. Causes of subclinical hypothyroidism include radioactive iodine exposure, head or neck surgery, and use of medications such as methimazole, propylthiouracil, lithium, oramiodarone. When questioning our patient, she denied previous exposure to radiation, iodine deficiency or excess, intake of the involved medications, or neck and head surgery.

Literature tells us that SCH can be present with antithyroid microsomal antibodies (antithyroid peroxidase), or antithyroglobulinantibodies [6]. Similarly, another author favors the idea of autoimmunity by telling us that the most common association isanti-thyroid peroxidase antibodies found in Hashimoto's thyroiditis [7]. Our patient has positive antibodies to thyroglobulin and peroxidase confirming the relationship to Hashimoto's thyroiditis. Moreover, studying the different antibodies that could appear, could one determine which of these is more specific to rule in a diagnosis? It is said that 50% of cases of Hashimoto's are missed because of negative peroxidase antibodies. The same can be said with thyroglobulin antibodies. A high level of these antibodies may suggest that a person has an autoimmune disorder but cannot tell us specifically the causality. From these facts, we can determine that both peroxidase and thyroglobulin antibodies are sensitive but less specific if measured individually but could help us narrow down our diagnosis of SCH if both test positive.

Some authors say that a mutation in the TSH receptor or signaling pathway may have been culprits in hereditary subclinical hypothyroidism [8]. We can see this in a pediatric case of two siblings affected by fatigue, mood changes, low concentration, and weight gain. Consequently, a molecular analysis for TSH receptor showed a heterozygous missense mutation in both siblings [9]. Literature helps us understand the importance of how a mutated TSH receptor affects hypothyroid patients and their families but does not change the final guidelines on treatment.TSH levels will always remain the first and most sensitive test to screen any thyroid dysfunctions and monitor replacement therapy. Literature continues to explain that there can be two groups of SCH, depending on their TSH readings. One group with TSH levels (4.0 - 10.0 mIU/l), and another group with TSH levels above (>10 mIU/l). Authors in literature recommend a standard approach in using levothyroxine in patients with a TSH of more than 10.0 mIU/L while individualized therapy in those with TSH of less than 10.0 mIU/L [1].

Common manifestations in patients with SCH include weakness, lethargy, dry

skin, coarse hair, cold intolerance, constipation, weight gain, muscle cramps, bradycardia, hoarseness, delayed reflexes, among others. Its risks frequently include coronary artery disease, dyslipidemia, liver disease, mayor depressive disorder, and infertility. In addition, a SCH can manifest with decreased strength inproximal muscle groups in both upper and lower limbs, elevated CPK, periorbital puffiness and dryness, coarse skin, extreme psychomotor retardation, and bilateral ptosis [10]. While our patient did present with similar symptoms such as depression, excessive drowsiness, decreased memory, fatigue, exhaustion, somnolence, cold intolerance, constipation, increased hunger and weight gain, the lipid profile and neurological examination were normal including external ocular movements, and deep tendon reflexes.

A retrospective chart analysis of 200 patients conducted at Endocrine and Diabetes Unit at Jinnah Postgraduate Medical Centre found that the most common symptoms in SCH patients were: lethargy (56%), goiter (49.2%), palpitation (46.9%), muscle weakness (42.7%) and weight gain (39.2%) [7]. This study, however, does not tell us if these patients had other comorbidities that could explain similarities in symptoms. Our patient experienced lethargy and weight again. We cannot conclude that the weight gain was a direct cause of a lagging metabolism, or simply because of increased intake of meals in adepressed state. Likewise, being lethargic could also mean a slow metabolic state or a symptom of pernicious anemia. It is said that mayor depressive disorder is also commonly found in patients with SCH. Studies show that the depression is higher in patients with subclinical hypothyroidism with a frequency of (56%) and (20%) in those without SCH [11]. In this case study, our patient was diagnosed with moderate severe major depression based on a PHQ-9 of 17 and not a depressive state attributable to another medical condition.

Polyglandular syndrome characterized by consecutive or concurrent deficiencies in the function of several endocrine glands that have a direct causal relationship. Etiology is autoimmune and can include hypothyroidism, type 1 diabetes, pernicious anemia, Addison disease, among others. Literature explains that the thyroid gland and stomach, share a common embryologic origin. The thyroid gland develops from the primitive gut and shares the same endodermal origin with parietal cells of stomach [12]. A fact is that megaloblastic anemia associated with autoimmune thyroiditis, can happen because of malabsorption of folate or vitamin B12. There might be a temporal relationship between the two for instance as many as 10% of the patients with hypothyroidism, caused by autoimmune thyroiditis, have pernicious anemia [13]. I believe one of the noteworthy features in this case report was that this patient had characteristics of Hashimoto's thyroiditis because of thyroid peroxidase antibodies found. Adding to this, the fact of having the patient testing positive to anti-parietal cell antibody which can be hard to find in common day sufferers of hypothyroidism, led to the diagnosis of pernicious anemia.

Finally, literature also mentions the fact that the regimen of treatment in pernicious anemia with subclinical hypothyroidism should be daily injections of

1000 μg of vitamin B-12 for the first week, then weekly injections for the first month followed by monthly injections for the rest of the patient's life is used because of the negligible toxicities associated with therapy [14]. Our patient followed a regimen of weekly cyanocobalamin injections which proved to solve the patient's epigastric pain and energy levels.

4. Conclusion

In this report, we highlight the symptoms of subclinical hypothyroidism, its associations with complex metabolic and unique immunological syndromes, and specific lab findings in the thyroid panel. It is a norm to follow TSH and T4 levels with levothyroxine being the standard of treatment in clinical practice. In addition, the recommended approach to use levothyroxine and escitalopram oxalate improves hypothyroidism symptoms including cognitive functions, and depression. While extensive literature indicates a standard approach to treatment, much research is still warranted to compare effectiveness between levothyroxine and escitalopram oxalate and understand the physiological links between subclinical hypothyroidism and other immunological disorders.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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