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A CASE REPORT ON SCHMIDT'S SYNDROME

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Abstract:

A syndrome of apathy, weakness, anorexia, wasting, abdominal pain, and skin discoloration was initially reported by Addison in 1849. Later, the syndrome was imputed to a combined deficiency of aldosterone and cortisol from disease of the adrenal glands. After a while, in 1926, Schmidt recorded the association between Addison's disease and hypothyroidism. The relation between the two clinical scenarios still remained unveiled. (1)

The insight into endocrine autoimmunity was initially established by Witebsky et al. in 1957 as a result of sequential findings made during the nineteenth and twentieth centuries. He developed criteria to call an endocrine disease autoimmune. (2) Later on, in the 1980s, Neufeld and Blizzard introduced a classification of autoimmune polyendocrine syndrome (APS) based on clinical criteria and could identify four different classes of APS. (3) According to the medical professionals in Italy, Corrado Betterlea and Fabio Presotto, the usage of the term polyendocrine autoimmune syndrome is inappropriate, and the reason seems quite relevant. Since the APS represents not just multiple autoimmune endocrine diseases but also autoimmune endocrine diseases associated with non-endocrine autoimmune diseases; [for instance, type 1 DM and celiac disease and its association with non-endocrine autoimmune diseases (say, vitiligo and alopecia)], they coined a more suitable term called multiple autoimmune syndromes (MAS). (4)

In this patient, she was initially treated for hypothyroidism, which was later accompanied by Addison's disease and later diagnosed as Schmidt's disease. She is also a T2 diabetic patient. Her treatment included thyroxine, prednisolone, fludrocortisone, and other oral hypoglycemic agents, along with insulin. On her follow-up, her TSH was found to be normal, cushingoid features were reduced, and currently, she is closely monitored on her sugar levels.

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INTRODUCTION:

Schmidt's syndrome is a rare autosomal dominant disease and is classified as the second type of autoimmune polyglandular syndrome. It is characterized by Addison's disease (always present), thyroid autoimmune diseases, and/or type 1 diabetes mellitus. (4) Other concurrent non-endocrine autoimmune conditions include vitiligo, celiac disease, alopecia, pernicious anemia, myasthenia gravis, idiopathic thrombocytopenic purpura, Sjogren's syndrome, and rheumatoid arthritis. Schmidt's disease is often associated with genes that encode proteins that govern adaptive and innate immunity, predominantly HLA genes HLA-DR3, HLA-DR4, and non-HLA genes MICA5.1, CTLA-4, PTPN22, BACH, VTNR, and the CD25-IL-2 receptor. (5) Though Schmidt's disease can occur at any point in a person's life, it mostly affects middle-aged females. It has a prevalence rate of 1.4 to 2 per 100,000 people. (6) Also, it has a gender incidence of 1:3 in males vs. females. (7) As per the study done by Betterle et al., during the onset of the disease, 392 descriptive cases of APS patients led to the following conclusion: Autoimmune thyroid disease occurred in 69–88% of patients, and type 1 DM was seen in 23-52% of total patients. (8)

CASE REPORT:

A 50-year-old lady with a history of hypothyroidism came for a review regarding the latter in 2019. She was on Thyronorm 125 mcg once a day. Her ultrasonography showed atrophic thyroiditis and was anti-TPO positive. Her TSH then showed 0.07, so she reduced Thyronorm to 25 mcg once a day.

In 2020, she came with the chief complaints of Addison's disease, hypothyroidism, dyslipidemia, and type 2 diabetes mellitus. She described a history of chronic headache that lasted for more than 24 hours and was left hemi-cranial. The patient was also recorded as having eye, nose, and ear pain that was of the pulsatile type. On examination, she was found to have a cushingoid face and a left hearing impairment. Her blood pressure was 140/80mmHg, her pulse rate was 112/min, and her BMI was 24.2Kg/m2. Her nose examination was within normal limits, and her ear examination revealed tympanic membrane retraction on the left ear. She was advised to do a PTA impedance test. She also had sleep impairment, which aggravated during stressors. Her headache was also noted to be responsive to steroids. On the basis of her clinical examination and lab findings, she was confirmed with the diagnosis of polyendocrine syndrome type II (Schmidt's syndrome). Her sodium and potassium showed 139 and 3.4 mmol/L, TSH showed 1.32, and HbA1c was 8.1%. MRI brain routine: the pituitary was normal and successfully ruled out any secondary causes of headache. She was then prescribed Glyciphage SR 1g BD, Gliclazide 80mg BD, Fludrocortisone 100mcg OD, Prednisolone 5mg OD, Thyroxine 75mcg, and Atorvastatin 10mg OD. Her progress after a month showed reduced cushingoid features, but her post lunch sugars were not in decent control, so she was started on Inj. Human Mixtard (30/70) at 18 units OD.

During her review after 2 months, her blood investigations showed the following values:

Table 1: Blood investigations of the patient on 8/29/20

Investigating parameters	Normal Range	Values
HbA1c	4 – 5.6 %	8.3 %
Mean blood glucose	< 99mg/dl	191.5 mg/dl
Sodium	135 – 145 mmol/L	141
Potassium	3.5 – 5.3 mmol/L	3.73
SGOT	10 – 40 IU/L	16 IU/L
SGPT	10 – 40 IU/L	17 IU/L
TSH	(0.3 – 4.5) 10^{-6}IU/L	2.56 10^{-6}IU/L
T. Serum Cholesterol	0 – 200 mg/dl	211 mg/dl
S. Triglycerides	0 – 150 mg/dL	182 mg/dl
HDL	40 – 59 mg/dl	62
LDL	0 – 100 mg/dl	132
Cholesterol/HDL ratio	0 – 4.5	3.4
VLDL	0 – 20 mg/dl	36.4

Based on the above blood reports, she was asked to continue the same medications except to add a top-up dose of Inj. Human Actrapid along with lunch instead of Gliclazide if the post-meal sugars were not under control. Later in November 2020, she was found to be mildly cushingoid, and her HbA1c was reduced to 7.9%. Her sodium and potassium were 142 mmol/l and 3.26 mmol/l, respectively. But she had c/o GI effects, for which it was recommended that she reduce the dose of Glyciphage to 500mg BD and increase insulin accordingly with Inj. Human Mixtard (30/70) 20 units AM and OD and Inj. Actrapid 10 units with lunch.
During her review in 2021, her HbA1c increased to 10.3%, and she had a TSH of 1.69. Her electrolytes were in the normal range. Then the treatment plan was initiated: increase the dose of Glyciphage from 500mg BD to 1000mg BD for the first 2 weeks, and if sugar levels are not yet controlled, increase Gliclazide to 80mg BD. Other prior medications were continued at the same rate. During her review after 3 months in November 2021, her HbA1c successfully dropped to 8.7%, and she was asked to continue with the earlier prescription. On her subsequent visit in November 2021, her HbA1c was 8.8% and her electrolytes were in the normal range. She was asked to continue the same medications and also to increase Inj. Human Actrapid to 16 units with lunch. In December 2021, due to the GI side effects, she was advised to reduce Glyciphage to 1g OD and start Teneligliptin 20mg OD instead. Further, she was asked to stop the injection of Actrapid, taken along with the lunch, and continue the injection of Human Mixtard to 22 units OD. To add on, she was stopped on Gliclazide and started on Amaryl 2mg OD, while other medications remained the same.

On her follow-up visit in May 2022, she was asked to continue the same medications, but her Inj. Human Actrapid at noon was stopped as she wanted an oral alternative. Thereby, she was stopped on Amaryl and started on Gliclazide 80 mg, 1-1-0. In her next follow-up in June, she complained of hypoglycemia at night (around 4:00 a.m.), and she was asked to maintain a serum monitoring blood glucose chart. Also, to have dinner by 7:00 p.m. and walk for 1 hour On her review in October, about taking intravitreal injections for retinopathy, her HbA1c was recorded to be 8.9% and her TSH was recorded to be (1.01) 10^{-6} IU/ml. She was then prescribed Fludrocortisone 100 mcg OD, Thyroxine 88 mcg, Atorvastatin 10 mcg OD, and Prednisolone 5 mcg OD (the dose needs to be doubled on the day and next day of the procedure). Her diabetes medications included Teneligliptin 20 mg OD, Inj. Human Mixtard 20U OD, Inj. Actrapid 10U with lunch, and Amaryl 2mg OD. During her latest follow-up in November, her BP was 140/70 mmHg and her BMI was 23.6 $kg/m^{2.}$ Her calcium, magnesium, albumin, sodium, potassium, and alkaline phosphatase were in the normal range, but her Vitamin D level was 9.2 ng/mL. So, she was asked to continue the same medications, along with cholecalciferol 60,000 UI once a week for 3 months, and requested to be reviewed after 6 months.

In a nutshell, the diabetes treatment pattern of the patient can be seen in Table 2

Table 2: Diabetic treatment pattern of the patient

Year	Date	HbA1c	Blood Sugar	Treatment pattern
2020	20/05/2020	8.1%	-	Glyciphage SR 1g BD Gliclazide 80 mg 1-1-0 Took insulin but the dose is not recorded
	23/06/2020	-	Post lunch sugars were not in control	Glyciphage SR 1g BD Gliclazide 80 mg 1-1-0 Human Mixtard (30/70) 18 Units AM OD
	29/08/2020	8.3%	191.5mg/dl (Mean Blood glucose)	Glyciphage SR 1g BD Gliclazide 80 mg 1-1-0 Human Mixtard (30/70) 18 Units AM OD If post lunch sugars were not under control after 1 week, she was advised to take Inj. Actrapid with lunch instead of Gliclazide in the noon.

	10/11/2020	7.9%	FBS and PPBS are well controlled.	Glyciphage 500mg BD (dose reduced due to GI side effects) Human Mixtard (30/70) 20 Units AM OD Inj. Actrapid 10 Units with lunch.
2021	22/03/2021	10.3%	248.9 mg/dl (mean blood sugar) FBS: 100 - 102 mg/dl PPBS: 200 - 250mg/dl	Glyciphage 1g BD (dose increased due to uncontrolled sugar levels) Gliclazide 80 mg 1-1-0 (after 2weeks, if sugars are still not under control) Human Mixtard (30/70) 20 Units AM OD Inj. Actrapid 10 Units with lunch.
	17/06/2021	8.7%	203mg/dl (mean blood sugar)	Glyciphage 1g BD (dose increased due to uncontrolled sugar levels) Gliclazide 80 mg 1-1-0 Human Mixtard (30/70) 20 Units AM OD Inj. Actrapid 10 Units with lunch.
	14/09/2021	8.8 %	205.9 mg/dl (mean blood sugar)	Glyciphage 1g BD (dose increased due to uncontrolled sugar levels) Gliclazide 80 mg 1-0-0 Human Mixtard (30/70) 20 Units AM OD Inj. Actrapid 10 Units with lunch.
	06/12/2021	8.3%	191.5 mg/dl (mean blood sugar)	Glyciphage 1g PM OD (dose decreased due to GI side effects) Teneligliptin 20mg AM OD Amaryl 2mg AM OD instead of Gliclazide Human Mixtard (30/70) 22 Units AM OD Stopped Inj. Actrapid with lunch.
2022	26/05/2022	-	-	Teneligliptin 20mg AM OD Stopped Amaryl 2mg AM OD and started Gliclazide 80mg 1-1-0 Human Mixtard (30/70) 20 Units AM OD Stopped Inj. Actrapid with lunch.
	27/06/2022	-	Had h/o hypoglycemia at night	Teneligliptin 20mg AM OD Human Mixtard (30/70) 20 Units AM OD Inj. Actrapid 16 Units with lunch.
	13/10/2022	8.9%	208.7 mg/dl (mean blood glucose)	Teneligliptin 20mg AM OD Amaryl 2mg AM OD Human Mixtard (30/70) 20 Units AM OD Inj. Actrapid 10 Units with lunch.
	23/11/2022	-	-	Teneligliptin 20mg AM OD Amaryl 2mg AM OD Human Mixtard (30/70) 20 Units AM OD Inj. Actrapid 10 Units with lunch.

DISCUSSION:

Ogle, in 1886, described the association between diabetes mellitus and Addison's disease. (9). The relation between these endocrinological disorders was later investigated by many and is still not fully uncovered. Schmidt's disease is a polyendocrinological dysfunction due to an autoimmune disorder. It is often characterized by Addison's disease along with auto-immune thyroid disease and/or Type 1 diabetes mellitus. The predominant clinical combination is often Addison's disease and Hashimoto's thyroiditis, while the least seen clinical scenario is Addison's disease, Graves' disease, and type 1 diabetes mellitus. (6) Thus, the autoimmune thyroid pathology can be either hypothyroidism or hyperthyroidism. (10) Sometimes, other autoimmune diseases can come along with the major endocrinological pathologies in Schmidt's, and that includes Sjogren's syndrome, hypoparathyroidism, hypopituitarism, myasthenia gravis, rheumatoid arthritis, idiopathic thrombocytopenic purpura, alopecia, celiac disease, and pernicious anemia. (11)

Though the exact cause of the syndrome is unknown, genetic predisposition and autoimmunity play an important role in its pathogenesis. (12) Since polyglandular discrepancies are involved in this syndrome, the symptoms differ in the affected individuals depending on the type of glands affected. Addison's disease occurs when the adrenal cortex becomes dysfunctional and produces insufficient glucocorticoid hormones. The glucocorticoid deficiency results in increased excretion of sodium and decreased potassium release. This can further trigger hypotension and dehydration. Thus, in this patient, she was treated with prednisolone 5 mg OD to suppress the immune system and fludrocortisone 100 mcg to treat electrolyte imbalances.

In hypothyroid patients, symptoms often seen include an enlarged thyroid gland in the neck, dull facial expression, poor memory, puffiness, swelling around the eyes, droopy eyelids, and dry, thinning hair. In this patient, she had been on a different thyroxine dosing schedule based on her TSH levels. Meanwhile, if Schmidt's is associated with Grave's disease, it causes enlargement of the thyroid gland and protrusion of the eyeballs as a result of hyperthyroidism. In associated diabetes mellitus patients, the pancreas fails to produce adequate or any insulin. As a result, patients develop frequent urination, thirst, hunger, weight loss, skin itchiness, vision changes, and an increased healing span for cuts and bruises.

In a hypo parathyroid-associated situation, calcium levels decrease due to decreased parathyroid hormone production, and the symptoms manifested are weakness, muscle cramps, burning and numbness in the hands, nervousness, memory loss, headaches, wrists and feet cramping, and facial muscle spasms. Secondary sexual characteristics are absent in patients with gonadal failure. Patients with pernicious anemia lack the intrinsic factor responsible for vitamin B12 absorption. Symptoms of this disease would manifest only after years of no absorption of vitamin B12, as the liver stores vitamin B12 in large quantities. The clinical features of this disease include shortness of breath, fatigue, weakness, rapid heartbeat, angina, anorexia, abdominal pain, indigestion, intermittent constipation, and diarrhea.

In Schmidt's patients with vitiligo, they develop white spots on almost all parts of the skin. This happens due to the absence of melanocytes, which causes reduced pigmentation on the skin. In Celiac sprue patients, intolerance to gluten happens as a result of the chronic hereditary intestinal malabsorption disorder, and the symptoms exhibited are weight loss, chronic diarrhea, abdominal cramping and bloating, intestinal gas, abdominal distention, and wasting of the muscles. In the case of patients with myasthenia gravis, there would be a chronic neuromuscular disease that is characterized by weakness and rapid fatigue of the voluntary muscles. (13)

There is no particular test to identify Schmidt's syndrome. But the risk can be calculated using an antibody screening test. Addison's disease can be diagnosed using serum cortisol levels, and the differential diagnosis of adrenal insufficiency can be made by checking the serum ACTH level and screening for antibodies to 21-hydroxylase. For identifying thyroid disorders, TSH, FT4, and/or total T3 levels are checked. Screening for antithyroid antibodies, anti-thyroglobulin antibodies, and thyroid stimulating immunoglobulins can help in understanding the autoimmune etiology. Other associated disorders are diagnosed using an individual disease diagnosis protocol.

Treatment of Schmidt's disease also involves treatment of the individual disorders. Treatment of hypothyroidism involves treatment with levothyroxine, initially adjusted every 4–6 weeks to maintain TSH and thyroxine levels in the midrange. In the case of Addison's disease, glucocorticoid and mineralocorticoid treatment regimens are initiated. The glucocorticoid dose is often adjusted as per the degree of stress in surgery or acute illness. The usual

mineralocorticoid treatment regimen starts with fludrocortisone 0.1 mg/day and is adjusted with blood pressure, volume status, weight, plasma renin activity, sodium, and potassium. It also has to be noted that, if hypothyroidism and Addison's disease occur together, the patient has to be initially treated for Addison's disease as the vice-versa can trigger adrenal insufficiency and crisis. Other associated disorders are treated individually according to the protocol. (14)

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