Schmidt's syndrome in a Saudi family

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ABSTRACT

We present 3 patients from a Saudi family who are presented with polyglandular autoimmune syndrome type 2. They have Addison's disease with either autoimmune thyroid disease or insulin dependent diabetic mellitus. Although this syndrome is rare, the incidence among Saudi Arabia or the Arab population is not known.

Keywords: Polyglandular autoimmune, Schmidt's syndrome.

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Polyglandualer autoimmune syndrome type 2 is rare and occurs at all ages and in both sexes because it necessarily requires the presence of Addison's disease. It occurs in many generations of the same family. The syndrome is characterized by the presence of Addison's disease with either autoimmune thyroid disease or insulin dependent diabetic mellitus or both.

Case Report. ***Patient 1.*** A 58 year old Saudi female presented to Endocrinology clinic at King Abdul Aziz University hospital with a 5 month history of fatigue, dizziness and generalized skin hyper-pigmentation. She was diagnosed as Hashimoto's hypothyroidism and subsequently treated with thyroxin, however she was not compliant to her treatment. Also, there was no relevant history to favor chronic infections (such as tuberculosis) and no history of the use of medications such as anti coagulant and metastatic malignancies. She was diagnosed recently to be diabetic and her blood sugar was controlled with oral hypoglycemic drugs. She reached menopause at the age of 36 years.

On physical examination, the patient's blood pressure was 90/60 sitting and 70/50 standing. There was generalized hyper-pigmentation of the skin, which was most evident over the extensor surfaces, back, elbow, knees and creases of hands and face, the buccal mucosa, gingival mucosa and lower lips were hyper-pigmented. There was no evidence of vitiligo, alopecia or nail change. Laboratory results are shown in Table 1. A short corticotropin stimulation test showed a flat response graph.[1] A diagnosis of Polyglandular Autoimmune Syndrome Type 2 (Schmidt's Syndrome) was made on the basis of concomitant Hashimoto's hypothyroidism. Premature ovarian failure was presented with no other discernible causes ie. tuberculosis. The patient was started on oral hydrocortisone and fludrocortisone treatment, thyroxin and oral hypoglycemic drugs. Her symptoms of nausea, dizziness, fatigue and electrolyte abnormalities was resolved and thyroid function test became normal. The patient's skin hyper-pigmentation was lighter a few months later, but still persisted after subsequent follow up visits. However she had not developed any other autoimmune disease (eg. pernicious anemia, vitiligo, keratoconunctivitis, rheumatoid arthritis, myasthenia gravis, chronic active hepatitis or primary billary cirrhosis).

Patient 2. The patient's daughter is a 36 year old presented with similar history of fatigue, dizziness and skin hyper-pigmentation. Her menstrual cycle was regular and there was no evidence of primary ovarian failure.

On physical examination, the patient's blood pressure was 80/60 sitting and 60/40 standing. There

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Table 1 - Laboratory investiation in 3 cases.

Case	NA	K	FT4	TSH	Thyroid AB	Microsant AB	Chest x-ray	Microsant AB	Microsant AB
Grand Mother	127	6.7	15	36	1:80	1600	No calcification	No calcification	Normal abdominal U.I.
Daughter	132	3.9	8	12	1:320	1500	-ve	-ve	-ve
Grand Daughter	146	4.0	13.5	2.72	-ve	100	-ve	-ve	-ve

FT4 (NR10-25) pmol/L, TSH=NR (0.2-4) IU/L
Antithyrogulbin Ab=(NR>20), Antimicrosmol Ab (NR<100)

Table 2 - Clinical features of type 2 PGAS.

Female/Male Ratio - 1.8	
HLA associations - A1-BS	
Major components	**Minor components**
Addison's disease	Vitiligo
Thyroid autoimmune disease	Hypergonadotrophic hypogonadism
Insulin-dependent diabetes mellitus	Alopecia
	Atrophic gastritis
	Pernicious anemia

Table 3 - Classification of polyglandular autoimmune disease (PGADs).

Type 1 PGAD:	Chronic mucocutaneous candidiasis Idiopathic hypoparathyroidism Addison's disease (at least two need to be present)
Type 2 PGAD:	Addison's disease Thyroid autoimmune disease and Insulin-dependent diabetes mellitus
Type 3 PGAS:	Thyroid autoimmune disease and other autoimmune disease (excluding Addison's disease and hypoparathyroidism or both a) Insulin-dependent diabetes mellitus b) Chronic atrophic gastritis (with or without pernicious anemia) c) Vitiligo, Alopecia, Myasthenia gravis d.Hypergonadotrophic hypogonadism d) Non-organ specific autoimmune disease (eg. SLE, Sjogren syndrome, rheumatoid arthritis etc).
Type 4 PGAD:	Associations not falling into any of the previous categories (eg. Alopecia and vitiligo or both, IDDM, Myasthenia Gravis and Insulin-Dependent diabetes).

was marked skin hyper-pigmentation, however, there was no significant mucocutenous pigmentation. Her laboratory investigation is illustrated in Table 1 and Table 2.

Patient 3. The grand daughter is 14 years old and presented with similar symptoms. On physical examination, there was marked muco cutaneous hyper pigmentation in buccal mucosa and lower lips. Laboratory investigation and short corticotripin test is illustrated in Table 1.

A diagnosis of PGAS type 2 was made. The daughter was started on oral hydrocortisone, fludrocortisone and thyroxin. The grand daughter was only treated with oral hydrocortisone.

Since this syndrome might be autosomal dominant with variable penetrane, we did a screening test for the remainder of the family members with organ specific antibodies in the United Kingdom. Unfortunately, the samples were lost and the family refused to repeat the test.

Discussion. The association between Addison's disease and other endocrinopathies was probably first described 1886. In 1926 Schmidt's presented 2 cases of Addison's disease with cortical atrophy and lymphocytic infiltration of the adrenal, as well as lymphoid infiltration in the thyroid.[1] Polyglandualer autoimmune syndrome (PGAD) type 2 is rare, because it necessarily requires the presence of Addison's disease.[2] Considering that the prevalence of idiopathic Addison's disease has been suspected to be 30-60 cases/million inhabitants[3] and that about 50-75% of Addisonian patients may be affected by thyroid autoimmune disease and insulin dependent diabetes or both, it may be estimated that type 2 PGAD occurs in 15-45 cases per million inhabitants in the general population.[4] The syndrome may occur at all ages and in both sexes but is most commonly found in middle aged females. Type 2 PGAD most often occurs in many generations of the same family as in the cases described.[6] Inheritance is consistent with autosomal dominance with incomplete penetrance. These patients have an increased frequency of the HLA A1, B8 AND DR3 haplotypes.[5]

The clinical presentation of Addison's disease is a result of the biochemical shutdown of glucocorticoids, mineralocorticoids and androgens. Our patients demonstrated significant postural hypotension, dizziness and fatigue. These observations were due to the lack of glucocorticoids. The laboratory abnormalities in our patients included hyponatremia, and hyperkalemia, which are secondary to glucocorticoids and mineralocorticoids deficiency. The treatment is to replace the deficient glucocorticoids and mineralocorticoids with oral

hydro cortsione and flurocortisone. In primary adrenal insufficiency (Addison's disease) hyperpigmentation (as in our cases) is due to direct stimulation of melanin synthesis induced by circulating peptides from the pituitary proopiomelanocortin precursor molecule from which ACTH is derived.[7] Since Addison's disease is always competent of PGAS type 2, the skin manifestations reviewed will be found in both disease states. These include accumulation of pigment in sun exposed areas, site of trauma or pressure, darkening of the axilla, groin, nail, mucous membranes, previously existing nevi and almost disease specific finding of darkened Palmer areas. Addison's disease and PGAS type 2 cutenous hypo-pigmentation in the form of vitiligo, is seen in 4-5% of the patients. This is due to underlying autoimmune disorder and melanocytes being destroyed by auto antibodies.[8] The 3 most common causes of primary adrenal insufficiency (intrinsic disease of adrenal glands) are autoimmune adenalitis (Addison's disease) in 65-85%, tuberculosis 30% and metastatic disease (rare). Infection in our patient was ruled out by negative tubercaline test and negative chest x-ray and plain abdominal x-ray for calcification of tuberculosis which is common in Saudi Arabia as compared to HIV infection. An additional endocrine abnormality that might be found in PGAS type 2 but in a much lower frequency is hypogonadism as shown with the grand mother who presented with primary premature ovarian failure. Hypoparathyroidism and chronic mucocutaneous candidiasis are not component of PGAS type 2 (Table 2 and 3).[9] Non endocrine abnormalities may include pernicious anemia, vitiligo, myasthenia gravis, autoimmune thrombocytopenic, purpura, Sjogren's syndrome and rheumatoid arthritis.[10,11] It has been demonstrated that patients with PGAS type 2 produce auto-antibodies to cytochrome p450c21 hydroxylase.[12] Thyroid diseases associated with Schmidt's syndrome are thyrotoxicosis, primary myxedema, Hashimoto's thyroiditis, atrophic asymptomatic thyroiditis, Grave's disease and isolated endocrine opthalmopathy.[13]

An overall diagnosis of PGAS type 2 was confirmed in this Saudi family. One of the basic caveats in endocrinology is that glandular abnormalities tend to occur together. Continuous suspicion of other glandular hypo-function should be maintained in follow up of these patients, since the risk of multiple glandular involvement is significant. (Addison's disease and Hashimoto's hypothyroidism).[14]

Family members should be alerted to the high prevalence of endocrinopathies especially among the first degree relatives of patients with poly-glandular autoimmune type 2. Parameters such as anti organ antibodies, although occasionally helpful, have not been shown to be consistently useful in predicting the future development of clinical organ specific autoimmune disease.[15] HLA typing is useful as does evaluation of humoral and cell mediated immunity which helps to identify patients at risk of this syndrome.[16]

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