

SCHMIDT'S SYNDROME: A CASE REPORT

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SYNOPSIS

The association between adrenal hypofunction and primary thyroid failure was first observed by Schmidt in 1926. Since his original description, many more cases have been documented, but there have been no cases described in Singapore to date. We describe one such case seen in a medical unit and review the work done in the field and the concept of the syndrome of polyglandular failure.

INTRODUCTION

In 1849, Addison (1) described a syndrome of apathy, weakness, anorexia, wasting, abdominal pain and skin discolouration which was only later ascribed to a combined deficiency of aldosterone and cortisol from disease of the adrenal glands.

Subsequently in 1926, Schmidt (2) documented the association between Addison's disease and hypothyroidism but was uncertain as to the link between the two entities. The association of Addison's disease of the adrenal glands and primary hypothyroidism is commonly referred to as Schmidt's syndrome.

It has only been in the last few decades that an autoimmune basis has been proposed as the unifying link between the two conditions and between other diseases found in association with this syndrome, namely diabetes mellitus, pernicious anaemia, primary hypogonadism, chronic active hepatitis, hypoparathyroidism, vitiligo and chronic mucocutaneous candidiasis.

Since Schmidt's description of his syndrome in 1926, many case reports have followed, but as far as we are aware, there have been no case reports from Singapore to date. In this paper, we describe such a case and review the concept of polyglandular failure.

CASE REPORT

CI a 40 year old Malay housewife was referred to us for complaints of anorexia of one year's duration accompanied by weight loss of about 20 kilogrammes. She also complained of lethargy and generalised hyperpigmentation of 7 month's duration. Apart from anorexia and weight loss, she denied other gastrointestinal symptoms.

She had a past history of hypertension of 4 years duration which was controlled on a potassium-thiazide combination. She had not been on antihypertensive treatment for 8 months when we first saw her. She denied a past history of tuberculosis and had received BCG inoculation during her childhood. The gynaecological history was unremarkable with no history of postpartum haemorrhage in her four pregnancies. The family history was not significant.

On clinical examination, she was found to be a slim lady of 50 kg who was generally hyperpigmented. There was patchy pigmentation of the buccal and palatal mucosa and scanty axillary and pubic hair was noted. There were no areas of vitiligo.

The cardiovascular examination was normal apart from a lowish blood pressure of 90/60 mm Hg. There was no postural drop. A goitre was not detected and clinically, the patient's thyroid status was equivocal.

Investigations revealed Hb 12.4 g/dl, Total White $8.8 \times 10^9/l$, Platelets $268 \times 10^9/l$, MCH 28.9 pg, MCV 84.3 fl, ESR 52 mm/hr. The iron/TIBC, B₁₂ and folate assays were normal. Urea 94 mg/dl, Sodium 124 mEq/l, Potassium 6.9 mEq/l, Chloride 100 mEq/l, Creatinine 3.4 mg/dl. The patient was not diabetic. Mantoux test was negative and the chest X ray did not reveal a tuberculous focus.

Endocrinological workup showed evidence of primary adrenal hypofunction. Plasma cortisol at 0800 hr was 3.6 ug/dl (normal range 8—23 ug/dl) and at 1600 hr was 3.9 ug/dl (normal range 8—23 ug/dl). There was no demonstrable rise in the plasma cortisol level during the short and long synecthen tests. Plasma ACTH was 840 pg/ml (normal range 20—80 pg/ml). CT scan of the abdomen showed atrophic adrenal glands with no demonstrable adrenal calcification.

Further tests revealed biochemical evidence of primary hypothyroidism: T₄ 3.8 ug/dl (normal range 4.6—12 ug/dl) T₃ uptake 79% (normal range 77—129), FTI 3.0 (normal 4.6—11.6) and TSH 14.7 mU/l (normal 1.3—4.7). Thyroid microsomal antibody was found to be present in the serum. Antithyroglobulin antibody was not detected. Ovarian function was normal.

Other autoimmune markers including ANF, rheumatoid factor, anti-parietal cell antibody and VDRL were not detected. Antiadrenal antibody assay was not done. The patient's HLA type was ascertained to be HLA A11, B7, using the NIH lymphocyte microcytotoxicity method (8).

A diagnosis of Schmidt's syndrome was made and the patient started on Tab. cortisone acetate 25 mg OM and 12.5 mg ON, followed three weeks later by Tab. 1-thyroxine 0.1 mg OM. On this regime of treat-

ment, the patient reported an initial regression of her symptoms. She experienced a general sense of well being and noticed some lightening of her skin pigmentation. Objectively, she had gained 8 kg in weight and her blood pressure had normalised. Biochemical studies confirmed the clinical assessment of adequate hormonal replacement.

This initial response was not sustained however. The patient experienced an insidious return of her former symptoms of lethargy, anorexia and pigmentation and was seen by us six month's later. She was again found to be darkly pigmented with a lowish blood pressure of 90/60 mm Hg.

Her electrolyte status was deranged. The blood urea had climbed to 55 mg/dl and the creatinine to 1.3 mg/dl. The serum sodium was low at 128 mEq/l and the potassium was elevated 6.1 mEq/l. She was biochemically hypothyroid. T₄ was 6.4 ug/dl (normal range 4.6—12 ug/dl) and TSH was 14.6 mU/l (normal 1.3—4.7). Serum ACTH was markedly elevated at 1000 pg/ml (normal 20—80).

The patient denied non compliance with medication. She was reestablished with increased dosages of Tab 1-thyroxine 0.15 mg OM and Ta. cortisone acetate 25 mg BD. In addition, 9 α -fludrocortisone 0.1 mg OM was added. On this new regimen, there was regression of all her symptoms except her pigmentation, and normalisation of her blood pressure and electrolyte status.

DISCUSSION

Addison's disease is a potentially life threatening condition which must be recognised and quickly treated. The combined deficiency of aldosterone and cortisol gives rise to a characteristic picture which is quite unmistakable. However, the diagnosis may elude the clinician, since in its earlier stages of development, the symptoms and signs may be rather vague. This is most aptly illustrated in our patient in whom the diagnosis was not made till fully one year later when she presented to us. The characteristic pigmentation is one of the more specific signs which should alert the clinician to the diagnosis.

In order to establish an appropriate therapeutic regime in Addison's disease, it is important to ascertain the underlying adrenal pathology. Tuberculosis has been taught classically as being the cause of adrenal hypofunction in older textbooks of pathology. Certainly, in our local context and in areas where tuberculosis is still prevalent, TB must be excluded. The other causes of adrenal hypofunction are rare and include that of primary and secondary carcinomatous replacement of the adrenals, haemorrhage and fungal involvement such as histoplasmosis. With the decline of tuberculosis worldwide, the so called idiopathic variety has now come to form the major portion of the cases of primary adrenal failure.

Short of biopsy, establishing the etiology may at times prove difficult. However, there appear to be a few clinical clues which have been found to be useful; these being the duration of disease, the size of the adrenals on imaging, the presence of adrenal calcification and associated autoimmune endocrine disease.

In a series of 39 patients in whom the above parameters were analysed, Vita et al (3) found that adrenal calcification on imaging techniques was demonstrable in 54% of patients with autopsy proven tuberculous adrenal disease. In contrast, none of the patients with idiopathic adrenal atrophy had demonstrable calcification. Rare causes of adrenal calcification included carcinoma, histoplasmosis, blastomycosis and haemorrhage. Hence, while calcification is not specific for tuberculosis, its presence

effectively rules out idiopathic disease.

Vita (3) also found that small adrenals were the hallmark of the idiopathic variety. This contrasts with a more variable picture in tuberculous adrenals in which size appears to bear an inverse relationship to chronicity of the disease. Extra adrenal tuberculosis was detected in 77% of patients with TB adrenals and 54% of persons with the idiopathic variety making this parameter of no use as a discriminatory factor. We note that the clinical picture of our patient is in conformity with Vita's findings.

There is a highly significant association between idiopathic Addison's disease and other endocrine diseases. Vita et al (3) reported a 77% association whereas Solomon et al (4) found that 67% of such patients had other endocrine diseases. In contrast, only 14% of persons with TB adrenals had a second endocrine deficiency.

Turkington and Lebovitz (5) report that the commonest entities associated are that of hypothyroidism, diabetes mellitus and primary ovarian failure. They reported no significant difference between males and females and that the development of these conditions may predate or follow clinical adrenal insufficiency by up to 20 years. This fact behoves the clinician to follow up such patients at regular intervals over an extended period of time.

The detection of antiadrenal antibodies and our recent knowledge of the histocompatibility antigens have led us now to believe that so called "idiopathic Addison's disease" is an autoimmune condition which is part of an inheritable syndrome of "polyglandular failure".

In support of this contention, Eisenbarth et al (6) in an elegant study of 11 patients with polyglandular failure and 42 of their relatives found an increased gene frequency for HLA B8 in his study population, which is about 2.5 times the frequency in the white population (7). Furthermore, 45% of his study population carried the HLA A1, B8 haplotype which is 3 to 5 times the frequency of the white population. Of the relatives, 26% of the 42 had polyglandular failure illness. The frequencies of the A1 and B8 genes were increased in those affected.

While the evidence for a link between polyglandular failure illness and the HLA A1, B8 haplotype is rather persuasive in Eisenbarth's (6) study, we feel that this particular association may not hold true in our local population. The A1, B8 haplotype is notably rare among the Chinese and Malays which comprise the local population. Chan et al (8) found the B8 gene to be non-existent in his study population of 106 local Malays. This finding is identical to an earlier study by Ting et al (9) in which the B8 gene was similarly found to be absent in 104 local Malays studied. Similarly, Chan (8) and Ting (9) found the A1 gene to be uncommon in Malays. In Chan's series, only 7.5% of Malays carry the A1 gene, a figure similar to Ting's finding of 9.6%.

Our patient was typed to be HLA A11, B7. It is difficult to draw any valid conclusions from a single anecdotal case report. Only as more cases are reported locally can we draw any conclusions about polyglandular failure illness and HLA association in Singapore.

Significant though the HLA associations may be, it is unlikely that the A1 and B8 genes themselves cause polyglandular failure. Most persons with this haplotype do not develop the illness and polyglandular failure occurs in persons without the A1, B8 haplotype as typified by our patient. Currently it is thought that another allele on chromosome 6 associated with this haplotype by linkage disequilibrium is involved in the pathogenesis. Undoubtedly our understanding of the

pathogenesis will be clearer as our knowledge of the HLA locus increases.

Apart from the HLA associations, current evidence for an autoimmune basis stem from the fact of there being antibodies directed at one or more endocrine glands in more than 80% of such patients (10). Also, abnormal suppressor T cell function has been detected in several cases and histological examination of affected glands usually reveals lymphocytic infiltration. Defective cell mediated immunity is characteristic of certain patients who develop candidiasis as part of the polyglandular failure syndrome.

Culminating from evidence accrued, it is now believed that polyglandular failure may be divided into two distinct groups (11). The first comprises the association of primary adrenal insufficiency to hypoparathyroidism and mucocutaneous candidiasis. Alopecia, pernicious anaemia, malabsorption and chronic active hepatitis can also occur. The mean age of onset of this disorder is 12 years and is currently termed Polyendocrine Deficiency Syndrome Type I. The mode of inheritance is unclear.

The second group comprises the association of primary adrenal failure to autoimmune thyroid disease and insulin dependent diabetes mellitus. This has been termed Type II and is also known eponymously as Schmidt's syndrome.

While the implications of such a classification have yet to be resolved fully, the immediate clinical significance of this is that otherwise numerous investigations may now be streamlined, saving time for the busy clinician and cost for the patient.

Schmidt's syndrome is an eminently treatable condition and the results of properly supervised treatment are mutually satisfying for both patient and physician. Improvement begins within days to weeks of treatment although the full effects can only be appreciated after a longer period of replacement therapy.

As opposed to secondary adrenal insufficiency from hypothalamic-pituitary disease where aldosterone production is unimpaired, therapy of autoimmune primary adrenal failure may require the use of mineralocorticoid supplementation in addition to glucocorticoid replacement. Traditionally, oral cortisone acetate in the dose 25 mg OM, 12.5 mg ON to mimic the normal diurnal rhythm has been advocated. This compound has to be metabolised to its active form cortisol by the liver and the total dose though varying from individual to individual should not exceed 50 mg/day. Patients requiring larger doses than this may have defects in absorption or metabolism of the compound and an alternative glucocorticoid should be used.

Cortisone has little mineralocorticoid activity and this may necessitate the use of fludrocortisone or desoxycorticosterone supplementation, as in this patient.

Criteria of adequate therapy include the return of blood pressure to normal, maintenance of normal fasting glucose levels, normalisation of electrolyte status, weight gain and improvement of appetite and strength. The relapse of this patient's symptoms after an initial period of improvement was thought to be due to a combination of on going disease process which was not accompanied by a commensurate increase in replacement therapy.

Continued close monitoring for adequacy of replacement and periodic screening for the development of the other accompaniments of polyglandular failure illness will feature prominently in the follow up of this patient.

CONCLUSION

Idiopathic (autoimmune) primary adrenal failure is

often associated with primary disease of other endocrine organs. Hence every patient with an idiopathic endocrine deficiency should be screened for insufficiencies in other endocrine organs. Their relatives should be similarly screened.

As the appearance of failure in other endocrine organs may not be manifest till many years later, periodic reevaluation over an extended period of time is to be advised.

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