Special Article

Schmidt's Syndrome (Thyroid and Adrenal Insufficiency) and Coexistent Diabetes Mellitus

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SUMMARY

The world literature covering the coincidence of Addison's disease and either diabetes mellitus and/or thyroid aberration has been reviewed.

In addition, ten new patients, eight with idiopathic and two with tuberculous Addison's disease, thyroid dysfunction and diabetes mellitus were studied.

Five of the eight patients with idiopathic Addison's disease showed significant titers of antiadrenal antibody and six of these eight showed significant titers of thyroid antibodies. However, neither of the two patients with tuberculous Addison's disease showed evidence of antiadrenal antibody, but one exhibited thyroid antibodies.

Patients with idiopathic rather than tuberculous Addison's disease showed a higher coincidence of diabetes mellitus and/or thyroid dysfunction. DIABETES *14*:300-04, May 1965.

The high incidence of coexistent diabetes mellitus and Schmidt's syndrome, thyroid and adrenal insufficiency, noted in our recent study of patients at The Johns Hopkins Hospital[1] has led to a further review of these multiple endocrinopathies. M. B. Schmidt[2] in 1926 under the title "A Biglandular Illness — Adrenal and Thyroid — in Addison's Disease" described two patients both of whom had nontuberculous Addison's disease and chronic lymphocytic thyroiditis although neither had clinical signs of hypothyroidism.

In addition to documenting the association of myxedema and nontuberculous Addison's disease, subsequent reports have also described other endocrine disorders, particularly diabetes mellitus in conjunction with Addison's disease[3-42] with a great enough frequency to suggest a more than chance relationship of these endocrinopathies.

The association of diabetes mellitus and Addison's disease was first described by Ogle[3] in 1886 and was extensively reviewed by Beaven et al.[11] in 1959. The latter investigators collected data on sixty-three cases with these two diseases, including eight of their own patients. In 33 per cent of these cases, the Addison's disease preceded the diabetes mellitus; in 59 per cent the diabetes preceded the Addison's disease, and in 8 per cent both disorders seemed to appear simultaneously.

When the Addison's disease developed first, it preceded the onset of the diabetes mellitus by an average of three years, but the interval was variable and might have been influenced by steroid therapy. However, available data from the literature indicate that no more than 2 per cent of the cases could have developed diabetes as a direct result of over zealous steroid replacement therapy. Of the thirty-seven patients who developed diabetes mellitus first, four also had thyrotoxicosis, and one had hypothyroidism.

Wehrmacher[33] in 1960 found seventy-three cases of concurrent Addison's disease and diabetes mellitus. He pointed out that the greater frequency of coincidence of the two diseases reported in recent years was most probably due to the improved recognition of both disorders and the increased survival time as a result of more effective therapy.

Table 1, which shows 113 cases of concurrent Addison's disease and diabetes mellitus based on both clinical and pathological findings, was tabulated from the literature[3-42] and includes fifteen of our own patients.[1] The diabetes preceded the Addison's disease in

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TABLE 1

Type of Addison's disease in association with other endocrinopathies[1,3-42]

Type of Addison's disease	Cases with coexistent diabetes mellitus		Cases with coexistent thyroid aberration		Cases with coexistent diabetes mellitus and thyroid aberration	
	Number	Per cent	Number	Per cent	Number	Per cent
Unspecified	21	19	15	11	4	14
Atrophy	76	67	92	66	22	79
Tuberculosis	16	14	32	23	2	7
Total cases	113	100	139	100	28	100

63 per cent; Addison's disease preceded diabetes in 23 per cent; the diseases apparently occurred simultaneously in 10 per cent, and the sequence was not specified in the remaining 4 per cent. The interval between the apparent onset of the two diseases was less than a year in 20 per cent of the cases. In those instances in which the period between the onset of the two diseases exceeded one year, the average interval was six years. The frequency of the coexistence of the two diseases was greater in males and corresponded with the greater incidence of uncomplicated Addison's disease in men.

The life span of those patients with both diseases was shorter than that of patients with either disease alone. Where sufficient information was available, it indicated that 58 per cent of the patients died within a year of the time of the dual diagnosis. In 74 per cent of the cases studied at autopsy the adrenals showed idiopathic atrophy, 22 per cent showed tuberculosis, and 2 per cent showed neoplasm. Of the remaining three cases, one case of amyloidosis, one of hemochromatosis and one of histoplasmosis were found.

The much higher coincidence of diabetes mellitus and idiopathic rather than tuberculous Addison's disease is interesting since the incidence of diabetes mellitus is higher in patients with tuberculosis, and the incidence of tuberculosis is higher in patients with diabetes mellitus.[43] The incidence of tuberculous and nontuberculous Addison's disease is about equal.[44-46] However, there is not sufficient data available to determine if the diabetes associated with idiopathic Addison's disease has unique characteristics.

Thyroid changes, like diabetes mellitus, occur much more frequently in conjunction with idiopathic adrenal atrophy than with adrenal tuberculosis. This information is verified by the summary of cases from published reports which appears in table 1. All 139 patients had Addison's disease which is classified according to type (unspecified, atrophic, or tuberculous) associated with lymphocytic thyroiditis and/or thyroid dysfunction.

The coexistence of the three endocrinopathies, diabetes mellitus, adrenal insufficiency, and thyroid dysfunction, is presented in table 2. Part A depicts eighteen cases described in the literature[6,11,12,14,15,17,21,22,24,26,30,32] and part B summarizes ten additional patients studied at The Johns Hopkins Hospital.[1] All ten patients were in a stable state of health when studied, and were maintained on 25 mg. of cortisone or its equivalent, in divided daily doses.

Glucose determinations were done on venous serum using the glucose oxidase method,[47] and the glucose value in relation to the age of the patient was carefully considered before a diagnosis of diabetes mellitus was rendered.[48] Rather than manifesting the anticipated flat oral glucose tolerance test, these ten of the total fifteen patients studied showed biochemical aberrations of diabetes mellitus (part B of table 2 and reference 1). The data summarized in table 1 point to the preponderance of nontuberculous Addison's disease in conjunction with the diabetes mellitus and thyroid dsyfunction. The results of the antibody studies which were conducted on all fifteen patients with Schmidt's syndrome (part B of table 2) seen at The Johns Hopkins Hospital suggest a possible correlation of antibodies with thyroid and adrenal dysfunction. However, a cause and effect relationship has not been established. At present insulin antibody determinations of these patients are being carried out. Diabetes mellitus in conjunction with Schmidt's syndrome may well represent a part of a spectrum of multiple endocrinopathies.

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TABLE 2: PART A

Schmidt's syndrome in association with diabetes mellitus: clinical and pathological reports from the literature

Author	Age	Race and sex	Type of Addison's disease	Duration of Addison's disease (yrs.)	Thyroid disease type	Thyroid disease duration (yrs.)	Other
Gastineau et al.[21]	52	F	Unspec.	13	Myxedema	12	
Gastineau et al.[21]	27	M	Unspec.	21	Myxedema	9	
Gastineau et al.[21]	58	F	Unspec.	5	Myxedema	5	
Christy et al.[15,43]	40	WF	Unspec.	9	Hypothyroidism	Concurrent c̄ Addison's	Hypogonadism 2 years prior to Addison's and hypothyroidism. Increased gonadotropin. Diabetes mellitus seven years p̄ Addison's and thyroid. No antibodies to thyroid, adrenal, ovary, pancreas (1960). Serum retested; positive for adrenal and thyroid antibodies.
Beaven et al.[11]	60	F	Non-TBC	15	Goiter c̄ mild thyrotoxicosis	2 years p̄ Addison's 15 years p̄ Addison's	Two sisters had thyroidectomies for thyrotoxicosis. Diabetes mellitus 13 years p̄ onset of Addison's disease. Patient's daughter diabetic at age 19.
Breslaw[14]	52	WF	Non-TBC	>6 mo.	Hyperthyroidism	4	Diabetes mellitus Dx concurrently c̄ hyperthyroidism, 4 years before Dx Addison's disease.
Crispell et al.[17]	19	WF	Atrophic	1	LT, Hypothyroidism	Dx on admission	Amenorrhea for 1 year — nl. levels of urine gonadotropin. (All gonadal deficiencies confirmed as primary by laboratory studies.)
Knowlton et al.[26]			Atrophic		LT		
Bernstein[12]	44	WM	Atrophic	8	LT, Hypothyroidism	5	Diabetic 1 year before clinical onset of Addison's disease, 4 years before myxedema. Increased sensitivity to insulin.
Thorn et al.[32]	21	M	Non-TBC	4	Hypothyroidism		
Thorn et al.[32]	31	F	Non-TBC	5	Hypothyroidism		
Thorn et al.[32]	27	M	Non-TBC	8	Hypothyroidism		
Thorn et al.[32]	27	F	Non-TBC	2	Hypothyroidism		
Thorn et al.[32]	32	M	Non-TBC	4	Hypothyroidism		
Heim[22]	F		Atrophic		LT		
Johnson[24]	39	M	Atrophic		LT, Hypothyroidism		
Goven[6]	54	WF	Atrophic		LT		
Rowntree et al.[30] LT*	20	M	Atrophic		Hyperthyroidism	Concurrent c̄ Addison's	Diabetes mellitus detected 1 year prior to Addison's disease and hyperthyroidism.

*LT = lymphocytic thyroiditis.

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TABLE 2: PART B

Clinical reports from The Johns Hopkins Hospital

Patient	Sex and race	Type of Addison's disease	Age at onset of symptoms	Order of onset*	Age at time of GTT	Criteria for diabetes mellitus. Glucose concentration on oral GTT (mg. per 100 ml. blood). Time in min. p̄ oral administration of 1.75 gm. glucose/kg. 0 60 90 120 180	Immune studies Adrenal antibodies	Thyroid antibodies	Other
W.B.	MW	Idiopathic	11	TAD	43	Diabetic acidosis	Pos.	Neg.	Strong FH for goiter, diabetes. Five members of immediate family have thyroid antibodies. Patient on 35 units NPH daily.
V.W.	FC	Idiopathic	39	DTA	41	2 hr. p.c. 160, 175 mg. glucose/100 ml.	Pos.	Pos.	Allergy to phenobarbital.
E.R.	MW	Idiopathic	14	ADT	16	92 162 179 161 117	Neg.	Neg.	Anaphylactoid reaction to ACTH. Brother with diabetes.
I.A.	FW	Idiopathic	35	ADT	52	103 163 182 154 126	Neg.	Pos.	
H.S.	FW	Idiopathic	9	ATD	10	89 168 142 127 120	Pos.	Pos.	
M.D.	MW	Idiopathic	26	ATD	50	Prediabetic GTT as defined by Conn and Fajans[44]	Pos.	Pos.	BFP STS; FH hyperthyroidism. Raynaud's phenomenon.
R.M.	FW	Idiopathic	35	ATD	57	91 167 182 153 134	Neg.	Pos.	Recurrent urticaria.
M.S.	FW	Idiopathic	28	ATD	36	106 173 151 129 124	Pos.	Pos.	Allergic to sulfa, PCN,† Demerol, Phenobarbital, LE Prep positive.
D.F.	FC	TBC	28	ATD	37	113 217 236 221 205	Neg.	Neg.	PH positive for TBC, phylectenular keratitis and syphilis. FH positive for TBC and arthritis.
F.M.	MW	TBC	30	(A/T)D	56	105 220 243 237 214	Neg.	Pos.	Positive Rose test.

*Order of onset: T = Thyroid abnormality; A = Addison's disease; D = Diabetes mellitus.
†PCN = Penicillin.

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