SHEEHAN'S SYNDROME: CLINICAL AND HORMONAL STUDIES IN 38 PATIENTS

by

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SUMMARY

Clinical and hormonal profile in 38 patients of Sheehan's syndrome were analysed. Their age ranged between 24-61 years and parity 1-9. Thirty-eight of them were amenorrhoic and 2 had oligomenorrhea. Hypothyroidism was the dominant clinical expression in all. In 9 of them this syndrome was suspected and later confirmed when the patients could not tolerate progressive thyroxine replacement. The mean basal PRL, TSH, LH and cortisol was significantly lowered in the patient group compared to age matched controls. Combined pituitary stimulation with 0.05 U kg/bw insulin, 100 ug TRH, 25 ug-GnRH in 10 randomly studied patients revealed variable reserve of mean, △ and AUC for all hormones. All patients responded well to thyroxine and corticosteroid replacement.

Introduction

Hypopituitarism due to pituitary necrosis following peripartum haemorrhage is a well defined clinical entity, described first by Sheehan (1937) and Sheehan and Murdoch (1938) between 1937-1938. This accounts for majority of cases of hypopituitarism (upto 80%) in the females in the developing countries (Ben Khalifa *et al*, 1975). In the classical (complete) form, the patients present with prolonged amenorrhea, features of hypothyroidism and hypocortisolism. It is not uncommon to find some of them presenting with profound hypoglycemia, hypotension or myxedema coma at the first hospital visit (Sankla, 1977). The partial (incomplete) form (Ben Khalifa *et al*, 1975) of this syndrome is recognized only through high degree of clinical suspicion and detailed endocrine investigations. The lack of a direct relationship between the severity of blood loss and the clinical manifestations of pituitary deficiency (Schneerberg *et al*, 1960; Murdoch, 1962), the chronicity of the illness (Sheehan,

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1961) and several atypical forms (Sheehan, 1961; Murdoch, 1962) constitute problems in diagnosis of this syndrome.

This study reports our observations on the clinical and the hormonal profile in 38 patients of Sheehan's syndrome diagnosed and followed up at the endocrine clinic of the Postgraduate Institute of medical education and Research, Chandigarh between 1972-1983.

Material and Methods

Thirty-eight patients, age 24-61 years, primi- to nineth para were included in this analysis. All patients had a detailed record of their history and physical examination. The routine haematological and biochemical workup included complete hemogram, estimations of serum sodium and potassium, cholesterol, protein bound iodine and blood glucose following a standard oral glucose tolerance test. The radiological investigations included X-rays of skull, antero-posterior, lateral and cones view of the pituitary fossa, chest and the dorsolumbar spine. The endocrine workup included estimations of growth hormone (hGH), prolactin (PRL), thyrotropin (TSH), thyroxine (T4), triiodo-thyroinine (T3), lutropin (LH), follitropin (FSH) and cortisol in the basal state using well standardised radioimmunologic procedures (Hartog *et al* 1964; Sialy *et al* 1977; Rastogi *et al* 1973; Sawhney and Rastogi 1974; Rastogi and Sawhney 1974; Rastogi *et al* 1973) with WHO quality control reagents and protocol. In 10 randomized patients combined pituitary stimulation tests with intravenous bolus of 0.05 unit of soluble crystalline insulin/kg body weight, 25 μg GnRH (Hoechst) and 100 /g TRH (Hoechst) were performed and the data were compared to identical hormone responses to appropriate stimuli in 10 age matched female control subjects in early follicular phase

Results

The frequency of various symptoms and signs encountered in the patients is depicted in Table 1. All but 3 had his-

TABLE I
Clinical Features of Sheehan's Syndrome
(Thirty Eight Cases)

Symptoms	No. of cases	Percentage	Signs	No. of cases	Percentage
Amenorrhea	36	94.7	Loss of pubic and axillary hair	38	100
Oligomenorrhea	2	5.3	Facial wrinkles	29	76.3
Failure of lactation	33	86.8	Dry skin	34	89.4
Inadequate lactation	5	13.2	Puffiness of face and/or oedema feet	15	39.5
Fatiguability	34	89.4			
Loss of appetite	28	73.6	Average weight	27	71.0
Aches and pains	21	55.2	+ 10 centile	9	23.7
Voice change	17	44.7	— 10 centile	2	5.3
Swelling of feet and body	13	34.2	Genital atrophy	20	52.6
Vomiting	2	5.3	Breast atrophy	13	34.2
Weight loss	2	5.3	Depigmentation of areola and nipple	26	68.4

tory of peripartum vaginal bleeding, 17 received blood/fluids infusion. Failure to spontaneously lactate was noted in 33, while in others, lactation was considered inadequate by the patient/her relatives. In 3 patients the features of Sheehan's syndrome appeared following normal pregnancy and uncomplicated child birth, but 2 of them had postpartum vaginal bleeding in their previous pregnancies. Twenty-nine patients presented with gross hypothyroidism. In others Sheehan's syndrome was suspected only when they failed to tolerate the increasing replacement doses of thyroxine. The interval between the peripartum haemorrhage and the diagnosis of the syndrome varied from 9 months to 12 years.

Mild anaemia (Hb<10.0 g/dl) was noted in 6, serum sodium below normal (< 130 meq/L) in 7, but none had hyperkalemia. Serum cholesterol ranged from 105 to 390 mg/dl and the protein bound iodine (PBI) 1.1 to 5.6 μg/dl (normal 4-8 μg/dl). None had fasting hypoglycemia and the blood sugar values were in the range of 60-90 mg/dl in most of them. The rise in blood sugar following oral glucose showed a flat response (all values < 110 mg/dl) in 18 out of 23 cases studied. One patient had associated diabetes mellitus and was controlled with diet and chlorpropamide.

The circulating levels of various hormones in the basal and stimulated state in the patient group and controls are given in Tables II and III. The hormone

TABLE II

Mean Basal Hormone Levels in Patients and Controls

Hormone	Patient Group (N=38. mean ± SE)	Controls (n, 50; mean ± SE)	'p' Value
GH ng/ml	0.84 ± 0.11	1.37 ± 0.4	>0.2
PRL mU/L	58.56 ± 7.78	272.5 ± 96.26	<0.02
TSH uU/ml	0.69 ± 0.32	2.15 ± 0.33	<0.01
LH U/L	1.6 ± 0.62	8.4 ± 2.7	<0.02
FSH U/L	2.79 ± 1.04	6.1 ± 1.6	<0.05
Cortisol nmol/L	6.25 ± 1.55	17.1 ± 1.7	<0.001

TABLE III

Circulating Hormones After Appropriate Provocative Stimuli in 10 Patients with Sheehan's Syndrome and Normal Cycling Healthy Women Volunteers

	Controls		Patients	
	Δ Mean ± Sem	AUC Mean ± Sem	Δ Mean ± Sem	AUC Mean ± Sem
GH ng/ml	14.9 ± 3.5	578.2 ± 55.4	1.0 ± 0.3**	34.1 ± 5.9**
PRL mU/L	2174.5 ± 376.3	2462.4 ± 467.3	62.07 ± 18.5**	47.5 ± 22.5*
TSH uU/ml	21.0 ± 3.7	687.8 ± 115.5	2.3 ± 0.6**	117.3 ± 38.9**
LH U/L	61.2 ± 8.1	1778.5 ± 81.6	2.3 ± 0.7**	157.9 ± 42.5**
FSH U/L	24.7 ± 4.3	822.4 ± 142.7	2.15 ± 0.7**	128.3 ± 50.6**
Cortisol	59.3 ± 8.2	1400.4 ± 259.9	33.6 ± 6.2*	447.0 ± 63.1*

** $p<0.001$ * $p<0.02$

responses to appropriate stmiuli in the patient and control groups are displayed in Fig. 1.

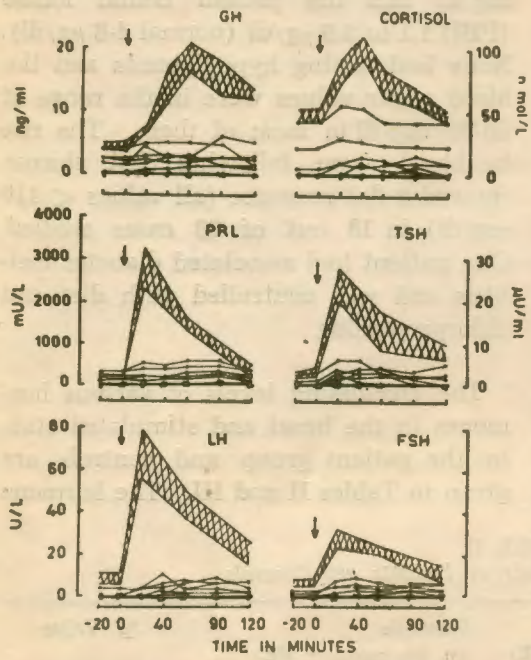

Fig. 1

GH, Cortisol, PRL, TSH, LH and FSH responses to insulin-hypoglycemia-TRH-GnRH in patients with Sheehan's syndrome. The shaded area represent the hormonal responses in control subjects in mid follicular phase. Note: subnormal responses in patients with Sheehan's syndrome.

Discussion

Pituitary necrosis following peripartum haemorrhage and hypotension is generally avascular in nature resulting from a fall in hypothalamo-pituitary portal perfusion pressure (Sheehan and Stanfield 1961). The gestational lactotroph hyperplasia and the consequent increase in pituitary size (Goluboff and Erzin 1969) perhaps make the gland more volunerable to necrosis in the circumstance. Additionally, autoimmune damage of the pituitary either through circulating autoantibodies (Engelberth and Jezkova 1965) or a sequalae to lymphocytic hypophysitis (Asa *et al* 1981) may contribute to postpartum hypopituitarism. The extent of pituitary necrosis varies widely from case to case, when it is extensive surviving cells are seen mostly in the lateral lobes and scarcely in the pars tuberalsis while in those with submaximal necrosis, larger areas are spared from infarction (Sheehan and Stanfield 1961).

Sheehan's syndrome can often be diagnosed from a good clinical history (Murdoch 1962; Sheehan 1961; Murdoch 1962; Krishan *et al* 1974). Absence of postpartum, breast enlargement and adequate lactation, gradual loss of sexual hair over the pubis and axillae infrequent menses leading to/or an abrupt amenorrhea, asthenia and lethargy in most patient suggest this diagnosis (Daughaday 1981).

Hypothyroidism dominates the clinical expression but development of frank myxoedema may be delayed for years or even decades (Daughaday 1981). The interval between recognition of Sheehan's syndrome and the episode of peripartum haemorrhage is variable, ranging between a few months to several years (Daughaday 1981). In several cases spontaneous menses and normal pregnancies have been recorded following a peripartum Haemorrhage and development of the syndrome. The pituitary functions then deteriorate in such patients following term delivery to the complete form of this disorder (Jaskson *et al* 1969).

All patients included in this report had classical history and physical findings of Sheehan's syndrome and in all except 3 patients, the symptoms of hypopituitarism following peripartum haemorrhage.

At presentation all had features of hypothyroidism and evidences of multiple trophic hormone deficiency. The circulating basal levels of LH, FSH, TSH, PRL, cortisol, T3 and T4 were significantly lower in the patients group ($p < 0.05$ to < 0.001) compared to age matched normal controls. The patients described here thus represent those with severe form of the syndrome.

Low basal circulating pituitary hormones and their dependent target gland secretions perhaps result from a decrease in functioning pituitary cell mass as well as inability of the hypothalamic releasing hormones to reach the effector cells in the pituitary (Sheehan and Stanfield 1961). Observations that in some of such partients, increment in circulating LH and FSH occur following infusion of GnRH but not a prior treatment with clomiphene (Ayala *et al*) (which acts by increasing endogenous GnRH) (Franchimont *et al* 1975) supports this view. However in some patients spontaneous ovulation and pregnancy has been recorded suggesting sufficient endogenous secretory activity of the gonadotrops as well as GnRH cells in the medio-basal hypothalamus.

Data on circulating pituitary hormone responses to appropriate provocation in Sheehan's syndrome are meagre (Table IV) Coscia *et al* 1974; Schwinn *et al* 1975; Batrinos *et al* 1978; Shahmanesh *et al* 1980). Further with variability in the extent of pituitary damage comparison of pituitary function tests in different studies becomes difficult. A decrease in TSH and PRL responses to TRH or PRL responses to sulpiride have been seen in the majority of patients (Coscia *et al*

TABLE IV

Showing Pituitary Function Tests in Sheehan's Syndrome

Author	Nature of Pituitary stimulation	No. of Patients studied	Hormone response
Coscia et al	GnRH	9	Subnormal LH response in 5, 2 fold rise in LH in others
Schwinn et al	GnRH, TRH and insulin hypoglycemia, arginine infusion	3	Lowered response to GnRH in all 3, lowered TSH, hGH and adrenal status
Batrinos et al	Sulpiride	2	No rise in PRL
Shahmanesh et al	GnRH, TRH and insulin hypoglycemia	14	Three fold rise in LH in 10 out of 12, more than 1½ times, rise in FSH in 8 out of 14, and TSH in 5 out of 7.
Present study	Insulin hypoglycemia, GnRH-TRH	10	Little or no change in PRL in all the 11 cases and hGH in all the 5 cases studied significantly low GH, PRL, LH, FSH, TSH and cortisol responses (Δ and AUC) in the patients group.

1974; Schwinn *et al* 1975). Similarly, failure of insulin hypoglycemia to provoke a GH response is another consistent observation (Shahmanesh *et al* 1980). On the other hand, significant increments in LH but not in FSH have been seen in over 50% of patients studied (Batrinos *et al* 1978). Possibly, the location of GH and PRL secreting cells in the lower and lateral regions of the pituitary gland are more volunerable to necrotic damage compared to those of centrally located gonadotrophs. (Purves 1966). We, however, recorded significantly lower responses to appropriate provocative stimuli in respect of all pituitary hormones in our study. This consistency in observation in our study is very likely due to severity of hypopituitarism in our patients.

We thus favour the recommendation of doing TRH-insulin-hypoglycemia test to assess pituitary reserve of GH, TSH, PRL in patients with Sheehan's syndrome particularly in those with lesser clinical evidence.

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