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SHEEHAN'S SYNDROME

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INTRODUCTION

In his excellent publications dating from 1938 to 1968, Sheehan described the natural history, clinical signs and pathological findings of the syndrome which bears his name and results from postpartum necrosis of the anterior lobe of the pituitary gland[1–10]. The exact pathogenesis of the disease is not well understood, for many women who suffer severe hemorrhage at delivery apparently escape damage to the anterior pituitary.

Although infrequently reported in the US literature, this clinical entity was the most common cause of hypopituitarism among indigent women of Puerto Rico in the decade of the 1950s to the late 1960s. During that period, 100 cases were diagnosed in the hospital attached to the University of Puerto Rico School of Medicine. Of these, 72 were diagnosed from 1960 to 1970 and came under our medical supervision. The clinical and endocrinological evaluations of 50 of the 72 cases which were available to close follow-up have been published[11]. This review summarizes these findings and comments on the condition.

RESULTS

Clinical data

Of 28 patients diagnosed between 1951 and 1959, 16 died of cortisol insufficiency precipitated by concurrent illnesses. In contrast, only two patients died in the group diagnosed between 1960 and 1970. This marked decrease in mortality was secondary to a better and regular follow-up and an improvement in their education regarding the nature and life-endangering risks of the disease.

Fifty of the 72 patients diagnosed between 1960 and 1970 were thoroughly studied (Table 1). Forty-three (86%) had panhypopituitarism, whereas seven (14%) displayed selective pituitary deficiencies. Of the latter group, one had isolated thyroid stimulating hormone (TSH) deficiency, one had selective human growth hormone (HGH) and gonadotropin deficiency, two lacked HGH and ACTH and three had combined HGH, ACTH, and gonadotropin deficiency.

The age at onset of disease ranged from 20 to 52 years, with an average age of 33.7 years. The age at diagnosis varied from 27 to 65 years, with an average of 43.8 years. The duration of preceding illness at the time of diagnosis ranged from 5 months to 28 years, with an average of 10.5 years.

Table 1 A study in 50 subjects with Sheehan's syndrome

	Number	*Percentage*
Panhypopituitarism	43	86
Selective hypopituitarism		
TSH deficiency	7	14
HGH and gonadotropin deficiency	1	2
HGH and ACTH deficiency	2	4
HGH, ACTH and gonadotropin deficiency	3	6

Age at onset of diagnosis, 20–52 years (mean 33.7 years); age at diagnosis, 27–65 years (mean 43.8 years)
Duration of preceding illness (at time of diagnosis), 5 months–28 years (mean 10.5 years)

The obstetric history of the 50 subjects is summarized in Table 2. Twenty-nine patients (58%) delivered at home and 21 (42%) in the local government hospitals.

Mean parity was 7 ± 3 deliveries. Forty-three (86%) had experienced postpartum bleeding, most commonly caused by retained placental fragments. Of the five patients who had antepartum bleeding, one had an abortion at 7 months' gestation (whether spontaneous or induced not clear from the records), two had abruptio placenta at 9 months' gestation, one had a subarachnoid hemorrhage and Gram-negative bacteremic shock at 7 months' gestation, and the remaining patient had placenta previa and silent rupture of the uterus at 8 months' gestation. Almost half (48%) of the patients had postpartum bleeding that led to the clinical picture of Sheehan's syndrome. Eight patients (16%) had bleeding in earlier pregnancies but were able to conceive. Of these eight patients, two had selective ACTH deficiency, five had a picture of panhypopituitarism at the time of study, and one had selective gonadal insufficiency. A clinical history of shock at delivery was present in 34 cases (68%); seven did not develop shock and information was not available in nine cases.

The salient clinical features are summarized in Table 3. Gonadal insufficiency was present in 94% of the patients, cortisol insufficiency in 96% and thyroid insufficiency in 88%. The earliest sign of pituitary failure was the inability to lactate. Three patients had scanty menses for

Table 2 Obstetric history of 50 patients with Sheehan's syndrome. Mean parity 7 ± 3

	Number	*Percentage*
Delivery		
Home	29	58
Local hospital	21	42
Bleeding in pregnancy		
Postpartum	43	86
Antepartum	5	10
No history of bleeding	2	4
Pregnancies complicated by bleeding		
One (last)	24	48
More than one and no bleeding in last	8	16
More than one and bleeding in last	18	36
Source of bleeding		
Retained placenta	21	42
Placenta abruption	3	6
Placenta previa	2	4
Abortion	1	2
Vaginal laceration	1	2
Uterine atony	4	8
Subarachnoid hemorrhage and septic shock	1	2
Information not available	16	32
Shock		
Present	34	68
Absent	7	14
Unknown	9	10
Subsequent pregnancies after episode causing disease	8	16

Table 3 Clinical features in 50 patients with Sheehan's syndrome

Symptoms and signs	*Percentage*
Gonadal insufficiency	94
Failure to lactate	86
Loss of libido	84
Amenorrhea	88
Breast atrophy	74
Vaginal atrophy	88
Uterine atrophy	86
Cortisol insufficiency	96
Anorexia	72
Weight loss	80
Asthenia, weakness	98
Cachexia	6
Thyroid deficiency	
Cold intolerance	88
Dry skin	94
Hypoactive DTRs	94
Myxedematous facies	44
Secondary sexual characteristics	
Loss of body hair	100
Loss of pubic hair	98
Loss of axillary hair	98
Other	
Pallor	92
Polyuria and polydipsia	4
Pigmentation in the face	4

several months after the episode of postpartum bleeding, after which they became amenorrheic. Cachexia was an infrequent finding; however, when present it was usually due to an associated illness. Of three cachectic patients, two had pulmonary tuberculosis and one was severely malnourished. Signs and symptoms of severe hypothyroidism were present in 22 patients. Severe pallor secondary to ACTH deficiency was the rule in hypopituitarism, although chloasma, for example pigmentation of the face, was seen in two patients. This has been previously described by Sheehan in 1939[3]. Two patients complained of marked polydipsia and polyuria immediately following the episode of bleeding. However, symptomatology was interpreted as secondary to transient diabetes insipidus from which the patients recovered. The study of one of these patients was the subject of a previous report[12].

Endocrinological work-up

Human growth hormone reserve was studied in all the patients. In the basal state, HGH was undetectable. With estrogen-priming and challenging with either insulin-induced hypoglycemia or arginine infusion, only the patient with selective TSH deficiency had HGH reserve, as shown by an increase to 20 ng/ml upon arginine infusion.

Pituitary ACTH reserve was also studied in all patients using the metyrapone test. Only two patients, one with selective TSH and the other with selective HGH and gonadal insufficiency, had a normal response.

Cortisol reserve was studied in all patients before replacement therapy. The basal urinary hydroxycorticosteroids ranged from undetectable values to 1.0 mg/day in the patients who did not show pituitary reserve. The response to ACTH, 40 units twice a day for 4 days (ACTHAR gel) was arbitrarily classified as excellent, good, limited or none, according to the increase inurinary hydroxycorticosteroids after ACTH administration and the ability of these patients to tolerate stress. Seventeen patients had an excellent response (increase over 20 mg/day), nine showed a good response (rise < 20 but > than 12 mg/day), 13 had a limited reserve (increase < 12 but > 6 mg/day) and 11 had poor to no reserve (increase < 6 mg/day) and their responses were similar to those of Addisonians. Two patients who had limited cortisol reserve (increase in urinary hydroxycorticosteroids respectively to 8.8 mg/ day and 6.6 mg/day post-ACTH) died, one of cortisol insufficiency in another hospital in the community and the other in an accident. Both patients were receiving a daily maintenance dose of 25 mg of cortisone acetate. The combined weight of both adrenals in one patient was 5.4 g; histologically, the glands showed atrophy. The adrenals of the other patient were not weighed but were described as atrophied, measuring each $1.8 \times 1.0 \times 0.2$ cm. A correlation was made between the duration of illness and the adrenal reserve found in these patients. Of 14 patients whose disease had existed for 5 years or less, 12 showed an excellent or good adrenal reserve. Of 36 patients whose disease dated from 5 to 29 years, 24 showed a limited, poor or no reserve, and the remaining patients had a good or excellent response.

The aldosterone reserve and ability to conserve sodium upon sodium deprivation was studied in 13 patients, seven of whom were chosen because they had initially shown hyponatremia when first admitted in cortisol insufficiency. All had dilutional hyponatremia which was corrected by fluid restriction and treatment with intravenous hydrocortisone and intramuscular cortisone acetate. None of the patients received desoxycorticosterone (DOCA). Of the seven who had hyponatremia, one had excellent cortisol reserve, two had good reserve, three had limited reserve and one had no reserve. The remaining six patients were selected because they had either a limited or very little cortisol reserve. Additional important clinical data included the presence of old pulmonary tuberculous lesions in three of the patients, two of whom showed no cortisol reserve and the other very limited cortisol reserve. These patients were kept on a 110 mEq sodium diet for 10 days and on the subsequent 7–10 days they were placed on a 8–14 mEq sodium diet. All the patients were kept on their maintenance dose of sodium levothyroxine and, in place of their maintenance dose of cortisone acetate, they were administered an equivalent dose of dexamethasone. Upon sodium restriction, 12

patients attained sodium balance in 2–7 days. One patient was unable to tolerate the low sodium diet and the study had to be stopped on the 4th day, at which time she had not attained sodium balance. No appreciable change in the serum sodium level was observed in all patients during sodium restriction. In nine patients, the aldosterone secretory rate (ASR) was measured on the 7th day of dietary sodium restriction. The ASR ranged from 169 to 535 μg/day. Values for ASR in healthy subjects on a sodium intake of 10–50 mEq of sodium diet are from 100 to 300 μg/day. In one patient, the ASR was measured on the 4th day of sodium restriction and was 283 μg/day. In the remaining patient, it was measured while on the 110 mEq sodium diet and was 160 μg/day. In two patients on a low sodium diet in whom ASR testing was not performed, urinary aldosterone was measured and was considered normal. The urinary aldosterone was low in one but did not correlate with the ASR, which was normal. An adequate response of aldosterone excretion or secretory rate therefore was seen in all patients, including the three in whom the possibility of tuberculosis of the adrenals was considered. The normal response to sodium restriction and the adequate aldosterone excretion or ASR ruled out the possibility of coexistent primary adrenal insufficiency secondary to tuberculous involvement of the adrenals.

Thyroid reserve

The thyroid reserve was determined by measuring the 24-h radioactive iodine (RAI) uptake before and after TSH stimulation in 32 subjects (29 hypothyroid and three euthyroid) and measuring the protein-bound iodine (PBI) before and after stimulation with 10 units of TSH daily for 2 days in 24 patients. The hypothyroid group were classified as responders or non-responders to TSH. In 21 patients with hypothyroidism, the difference in the 24-h RAI from the basal value ranged from 14 to 60%, with a mean difference of 26%. The remaining eight patients had a response similar to that seen in primary hypothyroidism, the difference in the post-TSH 24-h RAI ranging from 2 to 9%. Forty-eight percent of the responders had severe hypothyroidism, whereas 75% of the non-responders had a severe form of the disease. The inadequate response to TSH tended to correlate better with the severity of the disease than with the duration of the illness. The euthyroid group had a normal response to TSH. The PBI pre- and post-TSH was measured in 24 patients (15 already treated with sodium levothyroxine in whom it was discontinued 3 weeks before testing and six, all hypothyroid, but not treated; three were euthyroid). In the three euthyroid patients, the increase in PBI ranged from 1.4 to 2.6 μg/dl. The six hypothyroid patients had never been treated and the severity of their disease ranged from mild to severe. The change in PBI from the basal value was either decreased or had an insignificant rise in the three patients with myxedema. In the three patients with mild to moderate hypothyroidism, as well as in four of the patients receiving treatment, the increase in PBI corresponded to that seen in euthyroid patients; the remaining 11 had an insignificant or negligible change in PBI post-TSH.

Osteoporosis

When these patients were first studied, the technology for bone densitometry was not available. When it became available, Aguiló[13] proceeded to study a group of these patients still under our care using single photon absorptiometry. Bone mineral density, measured at the distal third of the non-dominant arm using a Norland SPA densitometer, showed in 40 of these patients that their bone mineral content and bone mineral density were significantly lower than that of age- and sex-matched controls in Puerto Rico. These patients received thyroid and adrenal physiologic replacement therapy but no estrogen replacement therapy. Twenty-three of these patients were enrolled in a longitudinal bone study with the aim of studying changes in bone mineral content (BMC) with passing time. At a mean of 5.5 years, ten (43.5%) had increased their BMC (Group 1), nine had decreased BMC (Group 2), and four remained unchanged. Group 1 had initial BMC measurements that were significantly lower (0.578 ± 0.04 g/cm) than those in Group 2 (0.764 ± 0.03 g/cm). The age of Group 1 was 65.5 ± 2.6 years and that of Group 2 was

65.2 ± 3.3 years. Group 1 was younger at the onset of the disease (29.2 ± 2.1 years vs. 35.9 ± 2.5 years), and the duration of the disease was 7 years longer (36.3 ± 2.6 years vs. 30.4 ± 3.1 years). There was no difference regarding race, body mass index, physical activity and sun exposure. Pertinent biochemical and hormonal parameters showed no differences except for serum alkaline phosphatase, which was higher than normal upper limit (115 IU/l) in both: 131 ± 17 in Group 1 vs. 121 ± 16 in Group 2; $p < 0.05$.

Upon loss of estrogen support, a rapid phase of bone loss ensues (Riggs type 1) followed by a more gradual age-related loss (Riggs type 2). Aguiló concluded that Group 1 resembled that reported by Kruse and Kuhlencordt[14] who found a positive bone balance in 25% of 108 postmenopausal females, based on histomorphometric data, and proposed a triphasic course of osteoporosis.

COMMENT

Panhypopituitarism is usually characterized by the sequential loss of somatotropic, gonadotropic, adrenocorticotropic and thyrotropic functions[15,16]. The same order holds true in most of the cases of Sheehan's syndrome. Whereas hypopituitarism associated with pituitary tumors often presents in an incomplete form, in Sheehan's syndrome the opposite is true. Indeed, 43 (86%) of our 50 studied cases exhibited a total deficiency of the hormones produced by the anterior pituitary gland.

Studies characterizing human growth reserve in adult hypopituitarism have dealt mainly with pituitary neoplasms. Only eight among a total of 79 cases included in the largest series[17–20] have been cases of Sheehan's syndrome. Of these 79, only four had significant levels of HGH, none of whom had Sheehan's syndrome. In this series of 50 patients, only one had HGH reserve and this patient also had isolated TSH deficiency. Of all pituitary functions evaluated, that of growth hormone secretion was the most consistently abnormal. Thus, a deficient output of growth hormone represents a sensitive and early index of pituitary failure.

With the use of metyrapone, the pituitary ACTH reserve in man can be studied in a quantitative manner. Our clinical experience in the use of this test is similar to that of other investigators. Liddle and associates[21], using the urinary 17-ketosteroids and 17-hydroxycorticosteroids as parameters to measure the response to metyrapone, encountered absent pituitary ACTH reserve in the two patients with Sheehan's syndrome that they studied. Kaplan[22] studied four patients with Sheehan's syndrome, none of whom showed pituitary ACTH reserve as measured by an increase in the urinary Porter Silber chromogens and 11-desoxycorticosteroid after metyrapone administration. Only two of our 50 patients showed pituitary ACTH reserve, both of whom had selective tropic deficiencies.

The response to intravenous and intramuscular ACTH has been described as an accurate means of quantitating adrenocortical reserve in several disease states[23,24]. The administration of ACTH, either intravenously or intramuscularly, to hypopituitary subjects must be repeated on several consecutive days in order to reactivate a dormant adrenal cortex resulting from prolonged absence of endogenous ACTH secretion. In Addison's disease, no steroid response to ACTH is seen, whereas in hypopituitarism a gradual increase in urinary steroid excretion has been described. Adrenal unresponsiveness to ACTH stimulation in hypopituitarism has also been documented[20,25,26]. Chakmakjian[20] reported no increase of urinary steroid excretion after the daily intravenous administration of ACTH for 5 days in five patients with Sheehan's syndrome.

Our data support the findings of others in demonstrating that a lack of adrenal steroid response to ACTH can be seen in hypopituitarism and that it does not necessarily means the presence of Addison's disease.

In our attempt to correlate the adrenal reserve with the duration of illness, we observed that 90% of the patients who had the disease for less than 5 years had a good or excellent adrenal reserve, in contrast to 38% of the patients who had the disease for longer than 5 years. Thus, a positive correlation exists between adrenal unresponsiveness and the duration of illness in approximately two-thirds of the patients, clearly showing that with time the adrenal cortex

becomes progressively atrophied due to severe lack of ACTH.

Aldosterone secretion is largely independent of ACTH regulation, and patients with hypopituitarism should be able to maintain sodium balance upon sodium restriction.

The hyponatremia seen in hypopituitarism is associated with water retention and mimics the syndrome of inappropriate secretion of antidiuretic hormone (ADH)[27]. Ahmed and colleagues demonstrated increased levels of arginine vasopressin in the plasma of patients with either hypopituitarism or Addison's disease[28]. A decrease in the plasma ADH activity and simultaneous improvement of water excretion were observed in these patients during therapy with glucocorticoids. Turin and colleagues[29] demonstrated a reduction in aldosterone secretion in patients with inappropriate secretion of ADH. In a study with an untreated patient with hypopituitarism who showed water retention, hyponatremia, urinary sodium loss and a low aldosterone secretory rate upon dietary sodium restriction, the same authors[30] suggested that the decreased secretion of aldosterone and wasting of sodium in chronic hypopituitarism are related to the persistence of excess ADH. This concept gains strength from the studies of Bartter and associates[31] who showed that volume expansion produced by the administration of vasopressin and water may increase the urinary excretion of sodium and decrease the excretion of aldosterone.

Our studies favor the latter concept and, in order to avoid the effect of antidiuresis in sodium excretion and aldosterone secretion, the studies of our patients were conducted during glucocorticoid and thyroid replacement. This past observation is of clinical and therapeutic importance in the management of hyponatremia in hypopituitarism. In these patients with Sheehan's syndrome, hyponatremia has always been associated with water retention, and prompt diuresis and correction of hyponatremia upon cortisol administration are well known. In contradistinction to Addisonians, never in our experience have hypopituitary patients needed mineralocorticoids for the maintenance of sodium balance. In this group of patients, the ASR upon ACTH stimulation has not been studied as Williams and co-workers[32] did in a group of patients with hypopituitarism and steroid suppression. These authors showed a higher urinary sodium excretion and a significant delay in increasing the ASR, although eventually a normal secretion was achieved. The mean ASR in the hypopituitary group was significantly less than in the normal or the steroid-suppressed subjects. Whether the abnormalities in aldosterone secretion on sodium restriction and ACTH stimulation play a role in the hyponatremia of hypopituitarism is questionable. If this were so, hyponatremia would not be corrected with fluid restriction and cortisol administration alone. The concept of inappropriate secretion of ADH is favored to explain the hyponatremia of hypopituitarism. At the time of our study, the response of the serum PBI and the RAI to TSH stimulation was the conventional test to differentiate primary from secondary hypopituitarism[33,38]. Taunton and colleagues[37] showed that the response in hypopituitary subjects was less the longer they had the disease. Sheehan[3] was the first to postulate that a dormant thyroid gland unstimulated by TSH might in time become fibrotic and therefore unresponsive to TSH. Fletcher and Berford[39] showed that the unresponsiveness to TSH correlated better with the severity of the disease than with the duration of the disease, as was the case in these patients with Sheehan's syndrome.

The findings in this series of Sheehan's syndrome suggest that, due to ACTH and TSH deprivation, the adrenals and the thyroid can become atrophied and unresponsive to stimulation to the tropic hormones; however, in the majority of the instances, the target glands are dormant rather than atrophied and are responsive to the tropic hormones.

Recently, Haddock and associates have shown an overall morphometric vertebral fracture weighted prevalence of 11.2% in a population-based study in a female population 50 years and older in the city of San Juan[40,41]. Of the 48 females out of 398 who had fractures, 19 had an early menopause at mean age 39 ± 4.7 years. Although the asssociation did not reach statistical significance, an early menopause at age less than 45 years is an important risk factor for fractures and osteoporosis, more so if patients do not receive estrogen replacement. Cooper and

associates[42] found that women with vertebral fractures had an earlier menopause, fewer births and higher prevalence of clinically diagnosed hyperthyroidism. Thus, women with Sheehan's syndrome who develop the disease in their reproductive years are more prone to develop osteoporosis and fractures, for they are diagnosed late in the course of the disease and have not received hormonal replacement therapy.

These patients received replacement therapy with cortisone acetate 25 mg daily divided in two doses, sodium levothyroxine in the amount that normalized the PBI, supportive treatment for underlying diseases and education about the disease and its life-threatening risks. A letter was given to every patient and her immediate family, stating the nature of the disease and what to do in case of illness or if taken unconscious to emergency rooms of government hospitals.

CONCLUDING REMARKS

In the last four decades, we have seldom seen new cases of Sheehan's syndrome in the University Hospital. The main reasons are improvements in the prenatal and delivery care of the indigent population. Whereas, in the past, 58% of the patients with Sheehan's syndrome were delivered at home, from the 1970s onwards all indigent patients delivered in hospitals. Since 1993, a Health Reform was implemented in Puerto Rico based on managed care. All but one of the secondary hospitals was sold to private enterprise and the main care of patients is now in the hands of primary physicians who seldom refer patients to the specialists as it affects their income, which is capitated. Fewer and fewer physicians are practicing Obstetrics because of the high insurance and fewer physicians are selecting Obstetrics and Gynecology for training. Responding to the urgent need of preparing a skilled health professional for the delivery of maternal and infant care services in Puerto Rico, the Graduate School of Public Health of the University of Puerto Rico Medical Sciences Campus has initiated a Nurse Midwifery Education Program, which offers a Graduate Certificate option and a Master of Public Health/Nurse Midwifery[43]. This program is supported by the US Department of Health and Human Service, Health Resources and Service Administration, the Government of Puerto Rico, and the Department of Health of Puerto Rico, and is accredited by the American College of Nurse-Midwives. The nurse-midwife is a registered nurse educated in two disciplines, nursing and midwifery. The nurse-midwife cares for essentially healthy women before, during and after childbirth.

The nurse-midwife works as an interdependent health-team member in a setting that provides physician consultation and referrals for complications[44]. Thus, the time will eventually come when deliveries in the indigent population may again be performed by midwives, as was the case in the first half of the 20th century, but this time by a skilled health professional who is part of the health team. The Department of Health of the Commonwealth of Puerto Rico must follow closely all the statistics regarding prenatal and delivery care so as to identify all cases with postpartum hemorrhage or the deliveries complicated with bleeding in order to identify the potential cases that may develop Sheehan's syndrome. Good prenatal and delivery care is a must to be able to prevent Sheehan's syndrome.

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