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ENDOCRINE PATHOLOGY IN SPINAL CORD INJURED PATIENTS ON MAINTENANCE DIALYSIS

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Summary. We studied the histopathological changes of the thyroid, adrenal and parathyroid glands, testes and pancreata in 15 patients with end-stage renal disease associated with long-standing spinal cord injury. All patients were males aged 42·7 ± 9·4 years and were treated with maintenance haemodialysis for 20·4 ± 17·7 months. Thyroid amyloidosis was present in eight of 12 glands and was extensive in four and moderate in four. Thyromegaly was noted in five of the glands with amyloid involvement. Of the 30 available adrenal glands, 26 showed amyloid involvement which was extensive in ten and moderate in 16. Of 18 testes examined all exhibited marked atrophy, decreased or absent spermatogenesis and marked peritubular and interstitial fibrosis. Amyloid involvement was also noted in two subjects. Pancreata were examined in 15 subjects with amyloidosis and pancreatitis noted in eight and four glands, respectively. Of the 22 parathyroid glands examined in nine subjects, hyperplasia was noted in 13 glands (four patients) and moderate amyloidosis was noted in six glands (two patients). Our results demonstrate a high prevalence of endocrine organ pathology in dialysis patients with longstanding spinal cord injury. Functional significance of these pathological findings is unclear and requires further investigation.

Key words: Spinal cord injury; Paraplegia; Endocrine pathology; Chronic renal failure; Dialysis; Amyloidosis.

Introduction

CHRONIC SPINAL CORD INJURY (SCI) of more than several years duration may be complicated by a variety of serious medical problems including acute and chronic infections, renal insufficiency and reactive amyloidosis, (Vaziri D. Cesario *et al.*, 1982; Tribe and Silver, 1969; Vaziri, *et al.*, 1982). In the past end-stage renal disease (ESRD) was the most commonly reported cause of death in these patients, (Vaziri, Cesario *et al.*, 1982), however, with the widespread availability of dialytic therapy death due to uremia is now uncommon. Modern supportive therapy, including dialysis has, therefore, led to the emergence of an enlarging population of chronic SCI patients with unique pathophysiological problems. There is very little information known regarding endocrine disease in this group of patients. Furthermore, clinical recognition of endocrine dysfunction, particularly thyroid and/or adrenal insufficiency may be difficult in the setting of SCI and ESRD. Here we report the histopathological changes involving the

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thyroid, adrenal and parathyroid glands, testes and pancreata in 15 chronic SCI patients with ESRD.

Patients and Methods

The available postmortem histopathologic data on the testes, pancreata, thyroid, parathyroid and adrenal glands were reviewed in 15 patients with chronic SCI and ESRD. The tissues had been examined grossly and microscopically by staff pathologists. In addition, the available clinical data were reviewed in each patient.

All patients were men aged 42 ± 9·4 years, range 29–54 years. The level of spinal cord injury varied from C4 to L2 and was cervical in four, thoracic in eight and lumbar in three cases. The duration of SCI was 20·7 ± 8·7 years, range 9–32 years. Each patient had an endogenous creatinine clearance of less than 5 ml/min. All patients had received maintenance haemodialysis for 20·4 ± 17·7 months, range 1–60 months utilizing hollow fibre or parallel flow dialysers and a conventional glucose-free dialysate. Patients were dialysed for periods of 4–6 hours two to three times per week. Other clinical data including etiology of renal failure, cause of death and associated diseases are summarized in Table 1.

Results

Gross and microscopic examinations had been performed postmortem on 15 subjects. Overall, 12 thyroids, 30 adrenals, 18 testes, 22 parathyroids and 15 pancreata were available for examination. The thyroid glands weighed 28·1 ± 9·4 grams and ranged from 18–50 grams (normal weight being 15–20 grams). Amyloid infiltration was reported in 8 of 12 glands and was extensive in four and moderate in four. Three of four glands with extensive amyloid infiltration were enlarged, while two of four glands with moderate involvement were enlarged. In the three glands without amyloid involvement, two had normal histology while moderate fibrosis was noted in one.

Amyloid involvement was reported in 26 of 30 adrenal glands. Involvement was extensive in ten glands (five subjects) and moderate in 16 glands (eight subjects). In the remaining four glands (two subjects) the only abnormality noted was a small abscess. Of the 18 testes examined (nine subjects) all cases exhibited the following abnormalities: marked atrophy of the seminiferous tubules with predominence of sertoli cells, markedly decreased or absent histologic evidence for spermatogenesis and marked peritubular and interstitial fibrosis. Mild to moderate amyloid involvement of the small blood vessels was also noted in two subjects. Pancreata were examined in 15 subjects. The two most notable abnormalities were amyloidosis and pancreatitis present in eight and four patients, respectively. Amyloid involvement was graded as severe in one, moderate in six and mild in one subject. The pancreatitis was acute in two patients (haemorrhagic pancreatitis was reported in one of these patients) and chronic in two patients. Of the 22 parathyroid glands examined in nine subjects, the glands were enlarged with hyperplasia in four subjects (13 glands), moderate amyloid involvement was present in two (six glands), fatty infiltra-

TABLE I

Case No.	Sex	Age (years)	Level SCI	Duration SCI (years)	Associated diseases	Distribution of amyloidosis	Cause of ESRD	Cause of death
1	M	32	C6	9	Chronic pyelo, infected decubiti	*ABHKLPS	Chronic pyelo amyloidosis	Sepsis, gram negative
2	M	48	T10	30	Chronic pyelo, infected decubiti Osteomyelitis, acute pericarditis	AKLST	Chronic pyelo amyloidosis	Tamponade
3	M	54	T5	29	Chronic pyelo, left pyonephrosis	AKLPPtST	Chronic pyelo amyloidosis	Sepsis, gram negative
4	M	52	T4	32	Chronic pyelo, intra abdominal abscess	AK	Chronic pyelo amyloidosis	Sepsis, gram negative
5	M	52	C5	26	Chronic pyelo, bilateral pyonephrosis and perinephric abscesses, infected decubiti	AHKLST	Chronic pyelo amyloidosis	Sepsis, gram negative
6	M	47	T8	14	Chronic pyelo, infected decubiti, osteomyelitis	AKLPtST	Chronic pyelo amyloidosis	Sepsis, gram negative
7	M	50	L2	28	Chronic pyelo, infected decubiti	AKT	Chronic pyelo amyloidosis	Sepsis, gram negative
8	M	29	C5–6	18	Chronic pyelo, infected decubiti	AKLPPtST	Chronic pyelo amyloidosis	Sepsis, gram negative
9	M	47	T11–12	27	Chronic pyelo, infected decubiti	AKPST	Chronic pyelo amyloidosis	Pneumonia, gram negative
10	M	50	T10	30	Chronic pyelo, bilateral pyonephrosis, infected decubiti	AHKLPST	Chronic pyelo amyloidosis	Sepsis, gram negative
11	M	30	L1	8	Chronic pyelo, right pyonephrosis, infected decubiti	AHKLST	Chronic pyelo amyloidosis	Sepsis, gram negative
12	M	41	L2	20	Chronic pyelo, bilateral pyonephrosis	AKLPS	Chronic pyelo amyloidosis	Sepsis, gram negative
13	M	46	T8	19	Chronic pyelo, right perinephric abscess, infected decubiti	AHKPET	Chronic pyelo amyloidosis	Sepsis, gram negative
14	M	33	C4–5	11	Chronic pyelo, bilateral pyonephrosis and perinephric abscesses, infected decubiti	K	Chronic pyelo amyloidosis	Sepsis, gram negative
15	M	29	T8	10	Chronic pyelo, bilateral pyonephrosis	—	Chronic pyelo amyloidosis	Sepsis, gram negative

*A = Adrenal, B = Bowel, H = Heart, K = Kidney, L = Liver, P = Pancreas, Pt = Parathyroid, S = Spleen, T = Thyroid

TABLE II

Case No.	Thyroid size (gms)	Thyroid histopathology	Adrenal histopathology	Testes histopathology	Pancreas histopathology	Parathyroid histopathology
1	—	—	Moderate amyloidosis	Marked atrophy seminiferous tubules. Absent spermatogenesis, marked interstitial fibrosis	Moderate amyloidosis	—
2	—	—	Moderate amyloidosis	Marked atrophy seminiferous tubules. Absent spermatogenesis. marked interstitial fibrosis moderate amyloidosis	Normal histology	—
3	18	Extensive amyloidosis	Moderate amyloidosis	Marked atrophy seminiferous tubules. Absent spermatogenesis, marked interstitial fibrosis	Moderate amyloidosis	Moderate, fatty infiltration
4	24	Normal histology	Extensive amyloidosis	—	Decreased islets	—
5	20	Moderate amyloidosis	Extensive amyloidosis	—	Acute haemorrhagic pancreatitis, pancreatic pseudocyst	—
6	35	Normal histology	Extensive amyloidosis	Marked atrophy seminiferous tubules. Absent spermatogenesis, marked interstitial fibrosis. Moderate amyloidosis	Acute pancreatitis extensive amyloidosis	Moderate amyloidosis
7	50	Extensive amyloidosis	Moderate amyloidosis	—	Mild fatty infiltration	Moderate hyperplasia
8	26	Moderate amyloidosis	Moderate amyloidosis	Marked atrophy seminiferous tubules. Absent spermatogenesis, marked interstitial fibrosis.	Moderate amyloidosis	Moderate amyloidosis moderate hyperplasia
9	30	Extensive amyloidosis focal thyroiditis	Moderate amyloidosis	—	Moderate amyloidosis	Moderate hyperplasia
10	35	Moderate amyloidosis	Moderate amyloidosis	Marked atrophy seminiferous tubules. Absent spermatogenesis, marked interstitial fibrosis	Moderate amyloidosis	Moderate hyperplasia

Case No.	Thyroid size (gms)	Thyroid histopathology	Adrenal histopathology	Testes histopathology	Pancreas histopathology	Parathyroid histopathology
11	20	Moderate amyloidosis	Moderate amyloidosis	—	Chronic pancreatitis	—
12	—	—	Extensive amyloidosis	Marked atrophy seminiferous tubules. Absent spermatogenesis, marked interstitial fibrosis	Moderate amyloidosis chronic pancreatitis	—
13	36	Extensive amyloidosis	Extensive amyloidosis	Marked atrophy seminiferous tubules. Absent spermatogenesis, marked interstitial fibrosis	Mild amyloidosis	Moderate hyperplasia
14	21	Normal histology	Small abscess	Marked atrophy seminiferous tubules. Absent spermatogenesis, marked interstitial fibrosis	Moderate fatty infiltration	Normal histology
15	22	Moderate fibrosis	Normal histology	—	Normal histology	Normal histology

tion was noted in one (two glands) and in two subjects (five glands) no abnormalities were noted.

As indicated in Table I, all patients with amyloid involvement of one or more endocrine glands also had involvement of other organ systems with renal amyloidosis being present in 100 per cent of these cases. The available medical records contained documentation of multiple acute and chronic infections in all patients. Chronic pyelonephritis had been present in all 15 cases (100 per cent). Pyonephrosis was present in seven cases (47 per cent), perinephric abscesses in five cases (33 per cent), infected decubitus ulcers had been present in 11 cases (73 per cent) and chronic osteomyelitis had been diagnosed in two cases (13 per cent). Gram negative sepsis was determined to be the major cause of death in 13 cases (87 per cent) while gram positive sepsis and cardiac tamponade were each the cause of death in one case. The data are summarised in Table I.

Discussion

Our results indicate that the vast majority of patients with chronic SCI and ESRD may have major histopathological abnormalities involving their endocrine organs. The predominant findings were moderate to extensive amyloid deposition present in 67 per cent of thyroids, 87 per cent of adrenals, 22 per cent of testes, 25 per cent of parathyroids and in 53 per cent of pancreatic sections examined. Marked testicular atrophy with arrest of spermatogenesis were noted in all nine cases, acute or chronic pancreatitis was present in 27 per cent and moderate parathyroid hyperplasia was present in 50 per cent of the cases examined.

Wide spread amyloidosis involving multiple organ systems was apparent in the majority of our patients with kidney involvement being the most extensive. It has been clearly established that the secondary amyloidosis associated with paraplegia is the result of longstanding suppuration of at least several years duration (Tribe and Silver, 1969). As is the case with many chronic SCI patients, all of our cases had a well documented history of chronic infections involving the urinary tract while chronically infected decubitus ulcers were present in 73 per cent and 13 per cent had chronic osteomyelitis. Of particular note, however, was the high frequency of pyonephrosis and/or perinephric abscess formation that were present in eight cases (53 per cent). Moreover, the leading cause of death was gram negative sepsis accounting for 87 per cent of mortality.

As moderate to extensive amyloid replacement of the thyroid and adrenals was present in most of our patients, some dysfunction of these glands might be expected even though the vast majority of glandular tissue must be ablated before clinical dysfunction becomes apparent. Little information is available concerning thyroid function with secondary amyloidosis of this gland, although there have been case reports of both hypo- and hyperthyroidism. (Jaimet 1951; Pasma and Hadders, 1952). In most of the cases reported, however, there has been no evidence for glandular dysfunction when sensitive biochemical studies were performed even when major structural changes of the gland were apparent. (Kennedy, Thomson *et al.*, 1974). Goitre has been described with thyroid amyloidosis with approximately 62 cases reported (Kennedy, Thomson *et al.*, 1974). In our patients we could not find information indicating that goitre had been

clinically recognized antemortum. On postmortem examination, however, five thyroids with amyloid involvement were noted to be enlarged. The presence of thyromegaly in the setting of chronic SCI should, therefore, suggest this diagnosis.

There is also a paucity of information in the literature regarding endocrine function in SCI. Clause-Walker *et al.* (1972) reported slightly reduced serum thyroxine (T4) levels in spinal cord injured patients paralyzed for less than 6 months as compared to chronic tetraplegics. Based on the results of a later study, however, these authors were able to show that the effects of spinal cord injury and paralysis *per se* do not lead to steady state alterations in thyroid, adrenal or pituitary function (Clause-Walker, Scurrig *et al.*, 1977). Recently, Prakash *et al.* (1980) evaluated thyroid function by laboratory testing in acute and chronic SCI patients and found only a 0·9 per cent incidence of hypothyroidism which was virtually identical to the incidence of this condition in the general population. In their study, patients were considered to have chronic SCI when duration of injury was greater than 3 months. It is not clear if any patients with long standing SCI of several years duration were included.

In their autopsy study on chronic paraplegics with renal failure published over 14 years ago, Tribe and Silver (1969) noted amyloid involvement in a high percentage of thyroids, adrenals, parathyroids and pancreatic secretions examined. Other similarities between our patients and theirs included the following:

1. A high frequency of chronic suppuration involving the urinary tract, skin, subcutaneous tissue and bone.
2. The presence of wide spread amyloidosis involving multiple organ systems with renal involvement being particularly frequent and severe.
3. Although moderate to severe amyloid involvement of the thyroid and adrenal glands were relatively common findings in both series, clinical evidence for overt hypothyroidism or Addison's disease was not apparent.

In addition to amyloid involvement, other significant pancreatic diseases were present in six patients (40 per cent) with acute or chronic pancreatitis being diagnosed in four of these cases. Of particular note was one patient with severe haemorrhagic pancreatitis and pancreatic pseudocyst formation. This patient also had underlying cholelithiasis which may have been a predisposing factor to pancreatitis. Chronic renal failure *per se*, however, may predispose to pancreatitis as has been suggested by the findings in a recent postmortem histopathological study. (Morrell, 1977). Other factors that might predispose SCI-ESRD patients to pancreatic disease include repeated episodes of volume contraction associated with dialysis, secondary hyperparathyroidism and the frequent occurrence of acute and chronic infections. (Morrell, 1977; Reiss, Canterbury *et al.*, 1969).

Regarding the parathyroid glands, significant abnormalities were noted in six cases (75 per cent). That moderate amyloidosis was present in two patients (25 per cent), further illustrates that even these glands can become involved with the reactive variety of this disease. The moderate hyperplasia present in four cases (50 per cent) was not unexpected considering that

secondary hyperparathyroidism is common in end-stage renal disease. (Reiss, Canterbury *et al.*, 1969; Griffiths, Zimmerman, 1977).

Of the endocrine organs examined, the testes showed the least evidence of amyloid involvement in that only two of nine patients had moderate disease. The predominant findings of marked tubular atrophy, markedly decreased or absent spermatogenesis and marked interstitial fibrosis present in all cases would suggest greatly compromised testicular function. Chronic SCI *per se* may predispose to testicular disease as seminiferous tubular lesions have been reported in approximately 50 per cent of paraplegic males. (Stemmerman, Weiss *et al.*, 1950). Also of interest, however, are the results of electroejaculation studies in chronic paraplegics, showing adequate spermograms in approximately 30 per cent (Francois, Maury, *et al.*, 1977). Furthermore, a number of procreation cases have been reported following natural methods or artificial insemination proving that selected chronic SCI patients are fertile. (Thomas, McLeish *et al.*, 1975; Francois, Maury *et al.*, 1978–79).

In chronic renal failure there is a high incidence of impotence and infertility suggesting testicular dysfunction. (Chen, Vidt *et al.*, 1970; Feldman and Singer, 1974). Biochemical studies, evaluating the hypothalamic-pituitary-testicular axis indicate Leydig cell dysfunction as testosterone levels are reduced and luteinizing-hormone and follicle-stimulating hormone are elevated (Holdsworth, Atkins *et al.*, 1977; Lim, and Fang, 1975). In addition, limited data have shown marked atrophy of the seminiferous tubules. It is possible, therefore, that the combined effects of chronic paraplegia and renal failure were responsible for most of the testicular abnormalities noted in our patients.

We unfortunately were able to find only limited data regarding the pituitary glands. In three patients, these glands were described as being grossly normal, histological examination; was however not performed. In view of the high incidence of serious bacterial infections and septic complications, one might anticipate finding lesions such as purulent hypophysitis, ischaemic injury and/or necrosis in some patients. Furthermore, an increased frequency of amyloid involvement might also be anticipated considering the high prevalence of secondary amyloidosis in SCI-ESRD. On the other hand, if the lesions noted to involve the other endocrine organs studied (e.g. thyroids, adrenals or testes) had functional significance, one might anticipate finding pituitary changes indicative of hormonal hypersecretion. Of course the best way to evaluate endocrine function objectively is by hormonal assay but unfortunately antemortum evaluation of the pituitary-adrenal, pituitary-thyroid or pituitary-gonadal axis had not been performed.

In summary, we have found a number of significant morphological and histopathological abnormalities involving the thyroids, adrenals, testes, parathyroids and pancreata in 15 patients with longstanding SCI and ESRD. The functional significance of these pathological findings is unclear and requires further investigation. Testicular dysfunction would certainly be anticipated in view of the histopathological findings noted and from the results of previous studies demonstrating gonadal dysfunction in association with SCI or ESRD. Regarding the thyroid and adrenal glands, although clinical dysfunction was not apparent, unrecognised dysfunction may have been present as typical signs and symptoms of insufficiency could have easily

been overlooked in the setting of SCI and ESRD. Moreover, subclinical disease with diminished functional reserve capacity may have been present. Based on our findings and on those of a previous autopsy study, a higher incidence of thyroid and adrenal dysfunction in patients with longstanding SCI and ESRD may be anticipated. A study designed to evaluate the pituitary-thyroid and pituitary-adrenal axis in these patients, therefore, would appear to be in order.

RÉSUMÉ

Nous avons étudié les changements histopathologiques du thyroïde des glandes parathyroïdes, des testicules et du pancréas en 15 patients avec une maladie rénale associée avec une blessure au cordon méduallire. Tous les patients étaient mâles, agés de 42·7 ± 9·4 ans. On les a traités avec l'hémodialyse pendant 20·4 ± 17·7 mois. On a trouvé de la thyroïde amyloidosis en 8 des 12 glandes, 4 étaient extensives et les autres quatre moderés. On a vu la thyromégalie en 5 des glandes avec l'amyloide. Des 30 glandes surrénales à notre disposition, 26 ont montré l'amyloide qui était extensive en 10 glandes et moderée en 16 glandes. Il y avait également 18 testicules examinées qui ont montré l'atrophie distincte, un abaissement ou une absence de la spermatogenèse et une pertitublaire marquée et une fibrose intestiel. Egalement, l'amyloide était trouvé en 2 patients. On a examiné les panacreta en 15 patients avec l'amyloidose et la pancréatite, on y a trouvé 8 et 4 respectivement. Il y avait 22 glandes parathyroïdes examinées en 9 patients. On a trouvé de l'hyperplasie en 13 glandes (4 patients) et l'amyloïdose en 6 glandes (2 patients).

Nos résultats montrent une haute prédominance de la pathologie de l'organe endocrine dans les patients amyloises avec une blessure du cordon médullaire. La signification functionelle de ces découvertes pathologique n'est pas claire et elle demande des recherches plus profondes.

ZUSAMMENFASSUNG

Wir haben die gewebepathologischen Veränderungen in den Schilddrüsen, Nebennieren- und Nebenschilddrüsen, in den Hoden und Bauchspeicheldrüsen von 15 Patienten, die an akuter Nierenerkrankung in Verbindung mit seit langer Zeit bestehender Wirbelsäulenverletzung litten, untersucht. Alle Patienten waren männlichen Geschlechts im Alter von 42,7 ± 9,4 Jahren and waren für 20,4 ± 17,7 Monate mit aufrechterhaltender Hämodialyse behandelt worden. Schilddrüsenamyloidose war in 8 von 12 Drüsen vorhanden, ausgedehnt in 4 und mäβig in den anderen 4. Thyromegalie wurde in 5 Drüsen, die von Amyloidose betroffen waren, festgestellt. Von den 30 zur Verfügung stehenden Nebennierendrüsen waren 26 von Amyloidose betroffen, ausgedehnt in 10 und mäβig in 16. Von den 18 Hoden, die untersucht wurden, zeigten alle Verkümmerung, verminderte oder fehlende Samenbildung und zwischenräumliche und peritubulare Fibrosis. 2 der Patienten waren auch von Amyloidose betroffen. An 15 Patienten wurden die Bauchspeicheldrüsen untersucht und in 8, bzw. 4 Drüsen wurde Amyloidose und Entzündung der Bauchspeichedrüse festgestellt. Von den 22 Nebenschilddrüsen, die an 9 Patienten untersucht wurden, wurde Hyperplasie in 14 Drüsen (an 4 Patienten) und mäβige Amyloidose in 6 Drüsen (2 Patienten) festgestellt. Unsere Befunde zeigen eine hohe Tendenz zur inkretorischen Organpathologie in Dialysepatienten mit seit langer Zeit bestehender Wirbelsäulenverletzung auf. Die maβgebliche Bedeutung dieser pathologischen Befunde ist unklar und erfordert weitere Untersuchungen.

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