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The syndrome of inappropriate secretion of antidiuretic hormone (SIADH) as a consequence of neck dissection

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Abstract

The syndrome of inappropriate secretion of antidiuretic hormone (SIADH) can have multiple causes. Surgical neck dissections may have an association with this syndrome and represent the basis for this study.

A retrospective review of 50 patients undergoing neck dissections was performed to evaluate for the development of hyponatraemia as a consequence of SIADH. Based on the results of this review, a prospective study of 20 consecutive patients undergoing 22 neck dissections was performed to determine the incidence of SIADH. A control group of 25 consecutive patients undergoing major non-neck dissection surgery was also studied.

SIADH developed in nine of 50 patients (18 per cent) of our retrospective group with a high incidence of development in those who had jugular vein ligation (JVL) (22 per cent), pre-operative radiation therapy (25 per cent) or squamous cell cancers (32 per cent). SIADH developed in six patients undergoing 22 neck dissections (27 per cent) in our prospective group. A high incidence was also noted for those with JVL (42 per cent), pre-operative radiation therapy (67 per cent) or squamous cell cancer (40 per cent). No patients developed symptomatic hyponatraemia. No patients in the prospective control group developed SIADH.

Neck dissection surgery is associated with a significant risk for the development of SIADH. Factors such as jugular vein ligation (JVL), pre-operative radiotherapy and squamous cell cancer appear to increase this risk.

Key words: Head and neck neoplasms; Hyponatraemia; Arginine vasopressin

Introduction

The syndrome of inappropriate secretion of antidiuretic hormone (SIADH) was first described in 1957 by Schwartz *et al.* The diagnostic criteria for this condition include a serum sodium of less than 135 mmol/l, decreased plasma osmolality to less than 275 mmol/kg serum water, no intravascular volume depletion, ascites or oedema and normal renal, adrenal and thyroid function (Parnes, 1993). Further laboratory confirmation of this condition is supported by an associated inappropriately elevated urinary osmolality (greater than serum) and urinary sodium concentration. Severe uncorrected hyponatraemia can lead to lethargy, seizures, coma, cardiac arrhythmias and death. The prompt diagnosis and treatment of SIADH is necessary to prevent this fatal outcome.

The role antidiuretic hormone (ADH), also known as arginine vasopressin (AVP), plays in the regulation of water in the body has been described elsewhere (Hays, 1976). The inappropriate secretion of AVP can occur as a consequence of multiple causes (Table I) including pain, fever, anaesthesia, (Deutsch *et al.*, 1966) surgery itself, (Arieff, 1986) or associated with malignancy (Williams *et al.*, 1960). Recent reports have supported the occurrence of SIADH associated with squamous cell cancers of the head and neck (Talmi *et al.*, 1992). Post-operative patients may have an increased level of AVP but the

TABLE I
CAUSES OF SIADH

Malignancy (i.e., small cell lung, carcinoma of pancreas)
Pulmonary disease (i.e., chronic obstructive pulmonary disease, tuberculosis)
Central nervous system disorders (i.e., subarachnoid haemorrhage, meningitis, increased intracranial pressure)
Medications
Anaesthesia
Endocrinopathies (thyroid and adrenal)
Pain
Fever
Surgery

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true incidence of SIADH appears to be rare. It has been suggested that an association between neck dissections and SIADH may exist and this was demonstrated clinically by Wenig (Wenig and Heller, 1987). It may be that an elevated cerebral venous pressure particularly associated with jugular vein ligation (JVL) is responsible for the development of SIADH in this setting. In our study we investigated the incidence of SIADH-related hyponatraemia in a retrospective series of patients who underwent neck dissections and then upon a consecutive prospective group to confirm our findings. A control group of consecutive non-neck dissection patients was prospectively evaluated as well to establish whether the development of SIADH is specific for patients who undergo neck dissections.

Materials and methods

Retrospective analysis

The charts of 50 patients who underwent neck dissections at our institution from 1980 to 1994 were reviewed. The data collected included medical history, type of surgery, ligation or non-ligation of the jugular vein, unilateral or bilateral dissection, pre-operative and post-operative serum chemistry (including sodium, glucose, urea nitrogen and creatinine), type of malignancy, and pre-operative use of radiation therapy. There were 28 males and 22 females. Ages ranged from 16 to 90 years, with a mean of 63 years. There were 50 operations performed, of which 45 were unilateral and five were bilateral neck dissections. In patients who were hyponatraemic (serum sodium <135 mmol/l), serum osmolality was calculated if none had been measured. Calculation of serum osmolality was performed with the formula (2 × serum sodium + BUN/2.8 + Glucose/18) (Humphreys, 1991). In none of the retrospective patients was urinary osmolality or urine sodium concentration evaluable. SIADH was presumed possible for patients with hyponatraemia and decreased serum osmolality (<275 mmol/kg serum water).

Prospective analysis

On all patients in the prospective analysis, data evaluated included medical history, type of surgery, ligation or non-ligation of the jugular vein, unilateral or bilateral neck dissection, type of malignancy, and pre-operative use of radiation therapy. The serum chemistry was checked pre-operatively and on a daily basis post-operatively during the length of hospitalization. These included serum sodium level, glucose, urea nitrogen, and creatinine.

A total of 20 consecutive patients undergoing 22 operations for neck dissection was prospectively evaluated. Nineteen operations were for unilateral neck dissection and three were for bilateral neck dissection. Twelve of the operations included JVL. No bilateral JVLs were performed (Table II). Complete neck dissections were defined as those which included removal of all five nodal basins. There were 12 males and eight females. Ages ranged from 30 to 90 years, with a mean of 69 years.

TABLE II
NECK DISSECTIONS (22) – PROSPECTIVE STUDY

Complete neck dissections (18)	
11 Jugular vein ligations (JVL)	
7 Without JVL	
Supraomohyoid neck dissections (2)	
(Without JVL)	
Bilateral neck dissections (2)	
(Complete dissection ± JVL with contralateral supraomohyoid)	
1 JVL	
1 Without JVL	

Twenty-five consecutive patients were included in the control group, incuding patients undergoing any type of major surgery which did not involve neck dissection (Table III). In this group there were 15 females and 10 males. Ages ranged from 41 to 78 years, with a mean age of 67 years.

If patients in either the study or control group were found to be hyponatraemic (serum sodium less than 135 mmol/kg serum water) during the post-operative period, their serum osmolality as well as their urine osmolality and urine sodium concentration were measured. SIADH was diagnosed for patients with hyponatraemia who had concomitant serum hypo-osmolality (>275 mmol/kg serum water), with urine osmolality greater than serum and normal or elevated urinary sodium concentrations (greater than 30 mmol/l). Serum sodium concentration was to be corrected for the dilutional effects of hyperglycaemia by adding 1.5 mmol/l to the sodium concentration for each 100 mg/dl of glucose concentration above normal (100 mg/dl) beginning at a level of 200 mg/dl (Schwartz, 1979). No hyponatraemic patients, however, were hyperglycaemic requiring this correction to be performed.

All patients in this study were operated upon under general anaesthesia. Fluid given in the operating theatre was crystalloid, usually lactated Ringer's solution. Post-operative fluid administration was not standardized but was generally five per cent dextrose in 0.45 per cent NaCl solution. Intravenous fluid was discontinued once the patients could take adequate oral intake, which for the neck dissection patients was usually the first or second post-

TABLE III
CONTROL GROUP SURGERY

Laparotomy (benign disease)	6
Modified radical mastectomy	5
Thyroidectomy	5
Parotidectomy	2
Resection of mandible (benign disease)	1
Resection of nasopharyngeal mixed tumour	1
Laryngectomy	1
Resection tongue cancer	1
Axillary dissection	1
Resection of thigh sarcoma	1
Oophorectomy (benign disease)	1
	25

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TABLE IV
DEVELOPMENT OF SIADH

Retrospective group:	Incidence (%)	Statistical significance
Neck dissections	9/50 (18%)	–
Potential risk factors		
JVL	8/36 (22%)	NS ($p = 0.41$)
Pre-op RT	3/12 (25%)	NS ($p = 0.668$)
Squamous cell carcinoma	8/25 (32%)	S ($p = 0.023$)

Prospective group:	Incidence (%)	Statistical significance
Neck dissections	6/22 (27%)	S ($p = 0.0069$)
Control group	0/25 (0%)	
Potential risk factors		
JVL	5/12 (42%)	NS ($p = 0.162$)
Pre-op RT	4/6 (67%)	S ($p = 0.025$)
Squamous cell carcinoma	6/13 (46%)	S ($p = 0.046$)

operative day. Hyponatraemia which developed was treated with the cessation of intravenous fluid administration.

Statistical analysis of the results of this study were carried out with the Fisher exact two-tailed test (Selvin, 1995). The risk factors of JVL, pre-operative treatment with radiation therapy and neck dissection for squamous cell cancer were evaluated for statistical significance.

Results

Retrospective analysis (Table IV)

Out of 50 patients, SIADH was presumed in nine patients (18 per cent) whose serum sodium dropped below 135 mmol/kg serum water, with a serum osmolality either measured or calculated to be equal to, or lower than, 275 mmol/l. A total of 25 patients was identified as having squamous cell cancer. Of these, eight patients met the criteria for SIADH (32 per cent) ($p = 0.023$). Many other diagnoses were associated with neck dissection in this retrospective group (See Table V). There were 36 patients who underwent JVL, of whom eight patients developed SIADH (22 per cent). Only one patient out of 14 without JVL developed SIADH (seven per cent). This difference, however, did not reach statistical significance ($p = 0.41$). Twelve patients had radiation therapy as an adjuvant prior to surgery and three developed SIADH (25 per cent). Thirty-eight patients did not have radiation therapy pre-operatively and six (16 per cent) developed SIADH. This difference was not statistically significantly different ($p = 0.668$). SIADH developed within the first few days post-operatively but as these patients were not being prospectively followed specifically for this, we can not determine the onset of SIADH accurately. Nadir serum sodiums were in the range of 123–134 mmol/l, with a mean value of 130 mmol/l.

TABLE V
RETROSPECTIVE NECK DISSECTIONS – PATHOLOGICAL DIAGNOSES

Squamous cell cancer	25
Papillary thyroid cancer	13
Follicular thyroid cancer	2
Hurthle cell cancer	2
Malignant melanoma	3
Adenocarcinoma of salivary gland	1
Basal cell cancer	1
Malignant mixed tumour	1
Malignant histiocytoma	1
Anaplastic carcinoma	1
	50

Prospective analysis (Table IV)

In our prospective study, out of 20 patients, six developed laboratory confirmed SIADH, associated with 22 neck dissections (27 per cent). Squamous cell cancer of the head and neck region was the most common reason for neck dissection, along with several other diagnoses (Table VI). The range of nadir serum sodium levels for the SIADH patients was 127–134 mmol/l with a mean level of 130 mmol/l. Serum osmolality ranged from 264–275 mmol/kg serum water and urine osmolality was in the range of 498–528 mmol/kg water. Urinary sodiums were inappropriately elevated for hyponatraemic patients, with a range of 37 to 237 mmol/l with a mean urinary sodium concentration of 129 mmol/l (normal = 30–90). Five of the six patients who developed SIADH had JVL as part of their neck dissections. Of the 12 patients who underwent JVL, five developed SIADH (42 per cent). Only one patient of 10 who did not have JVL developed SIADH (10 per cent) ($p = 0.162$). This patient, however, previously had (six years before) a contralateral neck dissection that included JVL. If this patient is excluded from the analysis, the incidence of developing SIADH as it relates to JVL would be statistically significant at $p = 0.045$. All six patients who developed SIADH had a diagnosis of squamous cell cancer. None of the nine patients with diagnoses other than squamous cell cancer developed SIADH. This difference is significant ($p = 0.046$). The performance of JVL, however, may have affected these results in that it was predominantly the patients with squamous cell cancer that had JVL (10 of 13 *versus* two of nine). Six patients had planned pre-operative radiotherapy and four developed SIADH (67 per cent). This was a significantly different result than for the non-pre-operatively irradiated patients (13 per cent) ($p = 0.025$). Three other patients in this prospective study group developed transient hyponatraemia but did not qualify diagnostically for SIADH (absence of decreased serum osmolality).

SIADH developed on the first post-operative day in four of the six patients who developed this

TABLE VI
PROSPECTIVE NECK DISSECTIONS–PATHOLOGICAL DIAGNOSES

Squamous cell cancer	13
Papillary thyroid cancer	3
Medullary thyroid cancer	2
Metastatic melanoma	3
Mandibular ameloblastoma	1
	22

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condition. The other two patients developed hyponatraemia on the second and fifth post-operative days, respectively. No patients developed symptomatic hyponatraemia, and simple cessation of intravenous fluids corrected this problem in all patients.

Hyponatraemia less than 135 mmol/l lasted from two to 17 days (mean of 5.5 days). One patient, however, inadvertently did not have serum sodiums checked beyond two post-operative days. She was discharged from the hospital on the second post-operative day while still hyponatraemic (serum sodium 128). She was included in the data as having SIADH for two days duration; however, this may have been longer.

Of the 25 patients who were prospectively evaluated as a non-neck dissection control group, nine patients developed asymptomatic hyponatraemia less than 135 mmol/l (range 132–134). No patients, however, fulfilled the criteria for SIADH. All had normal serum osmolalities. The absence of SIADH in this control group of major, non-neck dissection patients compared to the 27 per cent of neck dissections that developed SIADH is a statistically significant difference ($p = 0.0069$).

Discussion

SIADH is a syndrome associated with hyponatraemia and serum hypo-osmolality as a consequence of inappropriate secretion of the neurohypophyseal hormone, AVP. This syndrome has been associated with multiple disease states and conditions (Table I). Post-operative patients have been noted to have elevated AVP levels, possibly as a consequence of multiple factors, including anaesthetic medications, pain, fever and hypovolaemia. Up to 4.4 per cent of surgical patients have hyponatraemia; (Chung *et al.,* 1986) however, SIADH itself is rarely seen. It has been suggested that patients undergoing neck dissection surgery are at an increased risk of developing this syndrome (McQuarrie *et al.,* 1977). Our results lend strong support to this proposition. We believe the criteria used in our study for the diagnosis of SIADH allowed for an accurate diagnosis of this syndrome. No patients had oedema associated with their hyponatraemia, or physiological or biochemical signs suggestive of dehydration with hypotonic fluid resuscitation (decreased urine output, increased urea nitrogen, creatinine, and uric acid levels). No patients had clinical evidence of pre-operative hypothyroidism or signs suggestive of hypoadrenalism (hyperpigmentation or elevated potassium levels) that would confound our diagnosis. All patients had normal serum pre-operative chemistry values and normal chest X-rays to rule out pulmonary disease.

The increased incidence of SIADH after neck dissections may be related to an increase in intracranial venous pressure. This has been demonstrated to occur as a consequence of JVL in dogs (McQuarrie *et al.,* 1977) and in humans (Royster, 1953). In our study, 42 per cent of the prospective study group of patients undergoing JVL developed SIADH. The statistically significant association of pre-operative radiation therapy with the development of SIADH in this group as well, lends support to the possibility of increased intracranial venous pressure relating to the development of SIADH. Radiation therapy may compromise cervical venous drainage as a consequence of fibrosis, leading to increased intracerebral venous pressure.

Clinically, SIADH was seen in 10 of 17 neck dissection patients by Wenig (Wenig and Heller, 1987). In his study, very low serum sodiums were seen, with nadirs ranging from 118 to 132 mmol/l. The patients were generally symptomatic, while in our study no patients were symptomatic and the lowest nadir of sodium was 127 mmol/l. Possibly this was a consequence of different fluid resuscitative efforts, both intra-operatively and post-operatively.

An association was noted in our study between the development of SIADH and neck dissection for a diagnosis of squamous cell cancer (SCC). This positive association reached statistical significance both retrospectively ($p = 0.023$) and prospectively ($p = 0.046$). In our prospective study, six patients out of 13 operations (46 per cent) performed for SCC developed SIADH, while no patients out of nine operations for another diagnosis developed SIADH. This positive association, however, may be confounded by the fact that most of the squamous cell cancer patients had JVL performed. Of 13 neck dissections for SCC, 10 had JVL, while only two of nine neck dissections for another diagnosis had JVL. It is possible, however, that SIADH can occur as a consequence of ectopic production of AVP associated with squamous cell cancer of the head and neck. This association has been made recently by Talmi *et al.,* who noted a three per cent incidence of SIADH in 1 436 patients treated at the University of Iowa (Talmi *et al.,* 1992) and subsequently was able to demonstrate elevation of AVP levels in 38 per cent of pre-operative squamous cell cancer patients (Talmi *et al.,* 1996). None of our SCC patients had evidence of SIADH pre-operatively, which suggests that it may be the surgery itself (neck dissection) that causes SIADH. We cannot rule out, however, the possibility of SIADH developing as a consequence of intra-operative fluid administration in predisposed patients with baseline elevated AVP levels. We tend to believe, however, that it is the surgery itself which is responsible for SIADH in the post-operative period, for several reasons. Malignancy-associated SIADH is a rare event, and none of our patients were noted to be hyponatraemic preoperatively. SIADH as well did not develop until the second post-operative day in two out of our six SIADH patients, and lasted for an average of 5.5 days. We would expect SIADH to be short-lived after removal of the ectopic source of AVP, especially considering the short half-life of AVP in the serum (two minutes) (Talmi *et al.,* 1996).

It is not possible, however, for us to determine in this study the independent contribution of each of the possible risk factors for the development of SIADH that we have elucidated. The factors of JVL, pre-operative radiation therapy, and SCC often overlap in the same patients and confound statistical tests of significance for a study group of this limited size. Clearly further studies are required.

It is clear, however, that neck dissection surgery, performed in a group of patients largely for malignancy of the head and neck, is associated with the development of SIADH, as compared to other major non-neck dissection surgeries. In our prospective groups of 22 neck dissections performed, six (27 per cent) developed SIADH, as compared to none out of 25 control operations. This difference was statistically significant at a p value of 0.023. Major surgery can be associated with mild hyponatraemia but this, in general, is a consequence of hypotonic fluid resuscitation and possible sodium loss and not related to SIADH. Our control group allowed the inclusion of neck surgeries without neck dissection, since our premise was that it is specifically neck dissection surgery that predisposes to SIADH, which proves to be the case.

All patients developing SIADH in our study were asymptomatic and easily treated with discontinuation of intravenous fluids upon recognition of this condition.

For patients who develop symptomatic or more profound hyponatraemia, more aggressive treatment measures would be required. Fluid restriction to less than 500 ml per day and the use of normal saline administration, along with Lasix diuresis, should correct most patients with this condition. For more serious cases, hypertonic saline or medications such as demeclocycline or lithium carbonate would need to be used.

Conclusion

In conclusion, this study confirms an association between neck dissections and the development of SIADH. We suggest that patients undergoing this type of surgery should be monitored closely in the post-operative period for hyponatraemia, and corrective measures should be undertaken without delay to prevent complications of this condition. Intra-operative and post-operative over-resuscitation with hyponatraemic solutions should be avoided.

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