THE INCIDENCE OF CENTRAL ADRENAL INSUFFICIENCY IN EUVOLAEMIC HYPONATRAEMIA.

RESULTS OF A LARGE PROSPECTIVE STUDY

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INTRODUCTION

•The syndrome of inappropriate antidiuresis (SIAD) is the commonest cause of hyponatraemia. Data on SIAD is mainly derived from retrospective studies, often with poor ascertainment of the minimum criteria for the correct diagnosis.
• Reliable data on the incidence of adrenal failure in SIAD is unavailable.
• The aim of the study was to define the prevalence of undiagnosed adrenal insufficiency.

PATIENTS

This is a prospective, single centre, observational study of all consecutively hospitalized patients with SIAD, with hyponatraemia (≤ 130 mmol/L) in Beaumont Hospital, from January 1st to October 1st 2015.

INVESTIGATION OF ADRENAL FUNCTION

If the diagnostic parameters suggested SIAD, thyroid function tests and 0900h plasma cortisol measurements were requested.
A **0900h cortisol > 300 nmol/l (>10.9 mcg/dl)** was regarded as unlikely to reflect adrenal insufficiency of sufficient severity to cause hyponatraemia.
Where **0900h plasma cortisol was < 300 nmol/l (<10.9 mcg/dl), a short synacthen test was performed**. In addition, a short synacthen test was performed in patients with 0900h serum cortisol between 300 (10.9 mcg/dl) and 414 nmol/l (15 mcg/dl) if other parameters, such as hypotension or hypoglycaemia, were suggestive of adrenal insufficiency.
Normal response was defined as a cortisol peak above 500 nmol/l, 30 minutes post synacthen injection.
In patients with **chronic oral glucocorticoid**, SIAD patients were regarded as steroid deficient if they fulfilled the following criteria:

1) Prolonged adrenosuppressive doses of oral steroids (>4 mg prednisolone or equivalent).
2) There was failure to intervene with stress dose of steroids, as per good clinical practice.
3) There were additional clinical features, such as hypotension, hypoglycaemia or failure to respond to resuscitative measures, which suggested steroid insufficiency.
4) There was clear evidence of immediate improvement in all of the above with steroid therapy.

RESULTS

Data were obtained prospectively in 1323 patients who were admitted with hyponatraemia ≤130 mmol/L, or who developed hyponatraemia during hospital admission.
573 (43.3%) admission episodes in 516 patients were assigned an initial diagnosis of SIAD, based on classic diagnostic criteria.

	Diagnostic criteria obtained n (%)	Laboratory reference range	Patient results Median and (IQR)
Plasma Sodium (mmol/l)	573/573 (100%)	133-146	128 (126,130)
Urea (mmol/l)	573/573 (100%)	2.5-7.8	5.1 (3.9, 6.6)
UOsm (mOsm/kg)	498/573 (86%)	>100	437 (340, 545)
UNa (mmol/l)	491/573 (86%)	>30	50 (31,83)
TSH (mU/l)	524/573 (91%)	0.5-4.2	1.4 (0.89, 2.3)
09:00 h Plasma Cortisol (nmol/l)	413/492 (84%)	>300	453 (371,563)

Table 1. Description of number of patients (percentage) who had each laboratory result obtained during hospitalization. UOsm = urine osmolality, UNa = urine sodium.

EUVOLAEMIC HYPONATRAEMIA NOT DUE TO SIAD

40/476 (8.4%) patients had a 0900h plasma cortisol concentration <300 nmol/l, and underwent a short synacthen test. In addition, 8/476 (1.6%) patients with 0900h cortisol above 300 nmol/l had additional features (hypotension, nausea, unexplained weight loss) suggestive of adrenal failure and also had synacthen testing.

48 short synacthen tests were performed in total in the cohort of patients. 10/48 (21%) patients had a peak cortisol post synacthen < 500 nmol/L, all of whom had 0900h cortisol < 300 nmol/l.

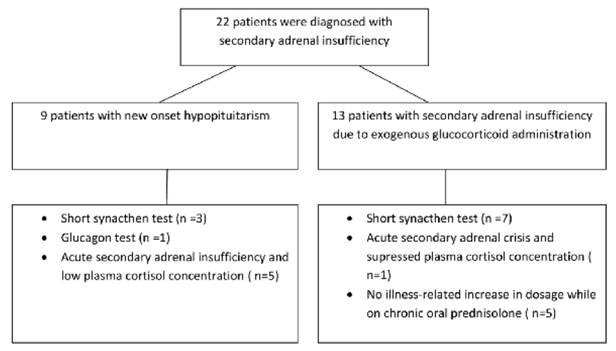

Figure 1. Depiction of the utilized diagnostic procedures in the group of patients with secondary adrenal insufficiency and euvolaemic hyponatraemia.

EUVOLAEMIC HYPONATRAEMIA DUE TO NEW ONSET HYPOPITUITARISM

	AGE	SEX	ADMISSION DIAGNOSIS	pNA (MMOL/L)	0900H CORTISOL (NMOL/L)	SST PEAK (NMOL/L)	OUTCOME
P1	61	M	Previous GIST tumor. New pituitary metastasis from unknown primary tumor	126	110	260	Sodium normalized after 48 hours of HDC. ACTH deficiency. Hypopituitarism due to metastatic disease.
P2	37	F	Metastatic melanoma on Ipilimumab. Presented with extreme fatigue, nausea	130	25	53	Remained hyponatraemic (132 mmol/L) despite steroids. ACTH deficiency due to hypophysitis. Underlying SIADH secondary to malignancy
P3	79	M	Multiple falls, fractures and repeated TBIs	124	152	370	Resolved with HDC therapy. Probably partial ACTH deficiency due to multiple TBIs.
P4	73	M	Pituitary apoplexy, headaches, vomiting, 3rd nerve palsy, hypotension.	116	49		Hyponatraemia resolved at day 3 on intravenous HDC. Adrenal crisis due to acute ACTH deficiency.
P5	68	F	Extreme fatigue, nausea. New diagnosis of empty sella and panhypopituitarism.	121	56	90 (GST)	Normalized after 2 days of oral HDC. ACTH deficiency due to empty sella.
P6	37	M	Viral meningitis.	128	158		Hyponatraemia resolved in 2 days with HDC treatment. Probably transient secondary AI due to viral meningitis.
P7	67	M	Extensive SAH, suprasellar cistern, sylvian cistern, intraventricular haemorraghe with obstructive hydrocephalus	130	275		Resolved after 48 hours with intravenous HDC. Partial ACTH deficiency due to extensive SAH
P8	57	F	SAH, Right MCA aneurysm with craniotomy and evacuation of SDH and clipping of aneurysm.	127	236		Resolved after 4 days with intravenous HDC. Partial ACTH deficiency due to SAH with SDH extension
P9	83	M	Extensive SAH complicated with LRTI, hyponatraemia worsened while on enteral nutrition.	127	262		Remained hyponatraemic after hospital discharge despite intravenous HDC. Probably underlying SIADH due to Venlafaxine 75 mg PO.

Table 3. Description of 9 patients who presented with evolaemic hyponatraemia and secondary adrenal insufficiency due to new onset hypopituitarism.
pNa = plasma sodium, SST = short synacthen test, HDC = hydrocortisone, TBI = traumatic brain injury, RTA = road traffic accident, SAH = subarachnoid haemorrhage, MCA = middle cerebral artery, SDH = subdural haematoma, LRTI = low respiratory tract infection, GST = glucagon stimulation test.

EUVOLAEMIC HYPONATRAEMIA ON A BACKGROUND OF CHRONIC EXOGENOUS GLUCOCORTICOID ADMINISTRATION

	AGE	SEX	ADMISSION DIAGNOSIS	pNA (MMOL/L)	0900H CORTISOL (NMOL/L)	SST PEAK (NMOL/L)	OUTCOME
P1	84	F	Exacerbation of COPD on frequent oral prednisolone.	125	132	218	Hyponatraemic (127 mmol/L) at discharge. Underlying SIADH due to COPD.
P2	89	M	COPD on inhaled budesonide.	118	68	363	Sodium normalized on oral steroids. Secondary AI due to exogenous glucocorticoid administration.
P3	62	F	End-stage COPD. Prednisolone recently stopped. Infective exacerbation.	124	175	393	Sodium normalized on IV steroids. Secondary AI due to exogenous glucocorticoid administration.
P4	48	F	Bronchiectasis, on fluticasone Admitted with pneumonia	125	122	257	Plasma sodium normalized in 4 days with oral HDC. Secondary AI due to exogenous glucocorticoid administration.
P5	80	M	COPD and pneumonia. Inhaled budesonide.	121	71	300	Sodium normalized on Hydrocortisone 10 mg BD. Secondary AI due to exogenous glucocorticoid administration.
P6	69	F	Inhaled budesonide for Asthma. Post op hyponatraemia	122	145	479	Sodium normalized after 12 days with fluid restriction. Underlying SIADH due to Venlafaxine 150 mg PO.
P7	77	F	Bronchiectasis, on inhaled Fluticasone. Urosepsis.	119	272	487	No treatment with hydrocortisone during admission. Discharged with hyponatraemia (131 mmol/L). Probably underlying SIADH due to bronchiectasis
P8	70	M	Sjogren. Prednisolone 40 mg stopped abruptly.	121	62		Hyponatraemia rresolved on steroids. Adrenal crisis due to steroid withdrawal.
P9	91	M	Syncopal episode Chronic SIAD due to pulmonary fibrosis	125	Prednisolone 5 mg not increased		Hyponatraemia resolved after 5 days with stress steroids
P10	80	M	Humerous fracture. On prednisolone for RA	127	Prednisolone 5 mg not increased		Hyponatraemia resolved after 3 days with stress steroids
P11	77	F	Nausea, vomiting, fits Prednisolone for temporal arteritis.	119	Prednisolone 5 mg not increased		Acute adrenal crisis. Overcorrection of plasma sodium (18 mmol/l in first 48 hours) after steroid dose increase
P12	78	F	Symptomatic hyponatraemia, Chronic SIAD.	125	Prednisolone 5 mg for COPD GOLD III not increased		Hyponatraemia resolved in 48 hours with FR and steroid.
P13	75	F	Acute pancreatitis and ischaemic colitis.	130	Prednisolone 5 mg for SLE not increased		Hyponatraemia resolved in 48 hours with stress steroids

Table 4. Description of 13 patients who presented with euvolemic hyponatraemia on a background of chronic exogenous glucocorticoid administration. P9-P13 represent 5 patients in whom oral prednisolone was not increased despite intercurrent diseases. pNa = plasma sodium, RA = rheumatoid arthritis, COPD = chronic obstructive pulmonary disease, FR = Fluid restriction, SLE = Systemic Lupus Erythematosus.

CONCLUSIONS

•SIAD is a diagnosis of exclusion. All patients must be investigated to rule out secondary adrenal insufficiency.
•In a large, prospective and well-defined cohort of euvolaemic hyponatraemia, undiagnosed secondary adrenal insufficiency co-occurred in **3.8%** of cases initially diagnosed as SIAD.
•**Undiagnosed pituitary disease** was responsible for **1.5%** of cases presenting as euvolaemic hyponatraemia.
•The relationship between hypopituitarism and premature death is well established, and adrenal crisis in response to acute illness is a major cause of excess mortality in patients with hypopituitarism and adrenal insufficiency.
•Screening for adrenal insufficiency in hyponatraemia not only focuses treatment of the acute episode, but also enables us to identify strategies to improve long term welfare.

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