

An analysis of the relationship between serum cortisol and serum sodium in routine clinical patients



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ABSTRACT

Objectives: Adrenal insufficiency is an uncommon cause of hyponatraemia that should not be overlooked due to the severe consequences of an Addisonian crisis. Using the laboratory database of a large teaching hospital, we have explored the relationship between serum sodium and serum cortisol, and have estimated the frequency of hypoadrenalism in severely hyponatraemic patients.

Design and methods: Data were gathered over a 23 month period from the Laboratory Information Management System at the Leeds Teaching Hospitals NHS Trust for instances where serum sodium and cortisol had been measured on a single sample. Data were also gathered over the same time period for all patients with severe hyponatraemia (serum sodium ≤ 120 mmol/L) in order to determine the frequency of cortisol requesting and the incidence of adrenal insufficiency.

Results: Analysis of the data (n=3268 patients) revealed a trend showing higher cortisol concentrations in patients who were severely hypo- or hypernatraemic. The median cortisol concentration for patients with sodium ≤ 110 mmol/L was 856 nmol/L, and there was a gradual decrease in cortisol over the sodium range ≤ 110 –150 mmol/L ($R_s = -0.323$, $p < 0.0001$). Patients with sodium ≥ 151 mmol/L had a median cortisol of 725 nmol/L. 42% of the 978 patients with serum sodium ≤ 120 mmol/L had serum cortisol measured within two weeks, of whom 1.7% were diagnosed with adrenal insufficiency.

Conclusions: This dataset shows rising cortisol in response to hypo- or hypernatraemia, in keeping with the stress response to illness. The data show that adrenal insufficiency is a rare cause of hyponatraemia which may be overlooked.

1. Introduction

Hyponatraemia is the most common electrolyte disorder encountered by the clinical biochemist, and is associated with a significant mortality [1]. Hypernatraemia is also a risk factor for mortality in critically ill patients [2]. Since illness-related stress is a well-established cause of cortisol secretion, patients with a severe derangement of sodium homeostasis would be expected to exhibit a rise in cortisol. We have interrogated our laboratory information system (LIMS) to explore the relationship between serum sodium and cortisol in samples where both these analytes were measured.

Adrenal insufficiency is an uncommon cause of hyponatraemia, but one that should not be overlooked because an Addisonian crisis, once recognised, can be easily and safely treated with fluid replacement and corticosteroid [3,4]. Clinical practice guidelines on hyponatraemia advise that primary or secondary adrenal insufficiency should always be considered as a potential cause of

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hyponatraemia [5]. Despite this advice to measure serum cortisol in hyponatraemic patients, recent audits suggest that this is infrequently done [6,7]. We have analysed a large dataset to investigate the frequency of cortisol requesting in patients with severe hyponatraemia, and to determine the relative frequency of adrenal insufficiency in this cohort.

2. Methods

The reference range for serum sodium at the Leeds Teaching Hospitals NHS Trust is 133–146 mmol/L, in accordance with recommendations from UK Pathology Harmony [8]. Severe hyponatraemia was defined as a sodium concentration ≤ 120 mmol/L and severe hypernatraemia was defined as a sodium concentration ≥ 150 mmol/L [9]. The reference range for serum cortisol in a 9 am sample at the Leeds Teaching Hospitals NHS Trust is 150–600 nmol/L.

Data on samples where both serum sodium and cortisol had been requested were gathered from the laboratory information management system for 23 months (1st January 2013 until 30th November 2014). Using the NHS number as a unique identifier, only the first entry was included for each patient. Entries where clinical details indicated that the patient was on dexamethasone, prednisolone, hydrocortisone or undergoing a corticotropin stimulation test or other endocrine stimulation test were excluded from the dataset. Serum sodium and cortisol were measured on Advia 1800 or 2400 and Centaur XP analysers respectively (Siemens Healthcare, Camberley, UK). Serum sodium had typical analytical coefficients of variation (CV) of 0.6% at mean concentration 117 mmol/L and of 0.5% at 157 mmol/L. Serum cortisol had a typical analytical CV of 7.0% at mean concentration 133 nmol/L and of 6.7% at 1024 nmol/L.

A second dataset was collected in order to determine the frequency of cortisol requesting in hyponatraemic patients. All sodium results ≤ 120 mmol/L from the same time-frame were gathered. Using the NHS number as a unique identifier, only the initial result was included for each patient. These were matched to a list of all cortisol results during a slightly extended time-frame (18th December 2012 to 14th December 2014). The proportion of patients with a sodium concentration of ≤ 120 mmol/L that also had a cortisol measurement within two weeks was calculated. The frequency of adrenal insufficiency (diagnosed by a short synacthen test) in patients with severe hyponatraemia was estimated by interrogation of electronic patient records for hyponatraemic patients with a cortisol measurement ≤ 440 nmol/L [7].

3. Results

The dataset from the first gather included sodium and cortisol results from 3268 patients, comprising 496 GP patients, 1635 inpatients, 1096 outpatients and 41 patients where no location was provided with the request. Fig. 1 shows the frequency distribution of (A) sodium and (B) cortisol concentration. Fig. 1(C) shows box and whisker plots for the median and interquartile range of cortisol for grouped sodium concentrations. These data revealed significantly higher cortisol measurements in patients who were severely hypo- or hypernatraemic ($p < 0.0001$, ANOVA with post-hoc Bonferroni's multiple comparison test, GraphPad Prism). The median cortisol value for patients with sodium ≤ 110 mmol/L was 856 nmol/L (standard deviation [SD] 234 nmol/L). There was a gradual decrease in cortisol concentration over the sodium range ≤ 110 –150 mmol/L (Spearman's correlation coefficient (R_s) -0.323 , $p < 0.0001$). The median cortisol value for patients with sodium concentration 141–150 mmol/L was 343 nmol/L (SD 418 nmol/L), representing a decrease of 513 nmol/L over this range. Hypernatraemic patients with sodium of ≥ 151 mmol/L had a median cortisol value of 725 nmol/L.

The second data gather yielded 978 patients who had severe hyponatraemia (sodium ≤ 120 mmol/L) in the 23 month time-frame, the majority of whom (92%) were in secondary care. 409 patients with severe hyponatraemia had a serum cortisol measurement within two weeks of the initial finding of hyponatraemia (42%). 7 of these patients had a diagnosis of adrenal insufficiency following a short synacthen test, representing 1.7% of the severely hyponatraemic patients who also had a cortisol measurement. The highest cortisol measurement in these patients was 306 nmol/L.

4. Discussion

Analysis of the data gathered from samples where both a serum sodium and cortisol had been requested from the same sample (excluding dynamic function tests) revealed a U-shaped distribution of cortisol in relation to sodium. The stress of both hypo- and hypernatraemia is sufficient to cause elevated cortisol. This finding should be expected as an appropriate stress response in view of the increased mortality seen in both these groups [2].

Hyponatraemia in hypoadrenalism is caused by hypovolaemia and renal sodium wasting, which in turn stimulates antidiuretic hormone (ADH). This secretion of ADH results in water retention and dilutional hyponatraemia. ADH secretion is further stimulated by hypothalamic corticotrophin releasing hormone (CRH) secreted in response to cortisol deficiency¹⁰.

Previous studies have found that adrenal insufficiency is not always considered as a cause of hyponatraemia [6,7]. Analysis of data from our second gather is in keeping with this statement; we found that for patients with severe hyponatraemia, only 42% had a serum cortisol measurement within two weeks of the initial finding of hyponatraemia. The percentage was similar for patients in primary care (46%) compared to patients in secondary care (42%).

Endocrine Society guidelines [3] state that a morning cortisol concentration < 140 nmol/L is highly suggestive of adrenal insufficiency. However, a serum cortisol value within the reference range does not exclude adrenal insufficiency in a critically ill patient. The guidelines recommend the use of the corticotropin stimulation test (short synacthen test) to establish the diagnosis. It is recognised that adrenal insufficiency may be misdiagnosed in severely ill patients with a low cortisol and blunted response to

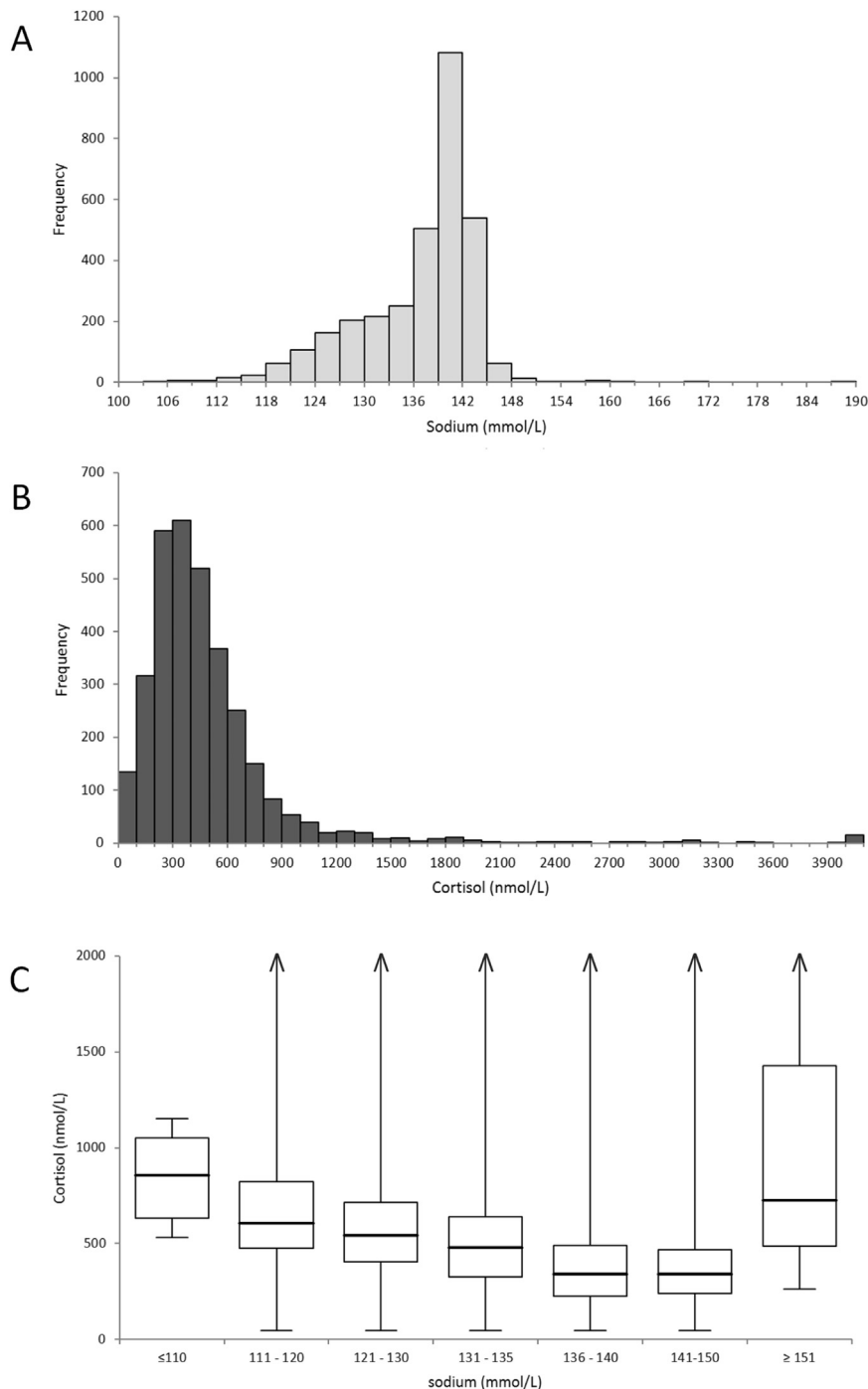


Fig. 1. Frequency distribution of (A) sodium and (B) cortisol results in patients with both measured together. (C) Box and whisker plots showing the range, first quartile, median and third quartile of cortisol values for each group of sodium results.

synacthen due to low cortisol binding globulin, a negative acute phase protein.

A clinical study of 28 patients with severe hyponatraemia due to adrenal insufficiency found a range of basal cortisol concentrations of 25–439 nmol/L in these patients [7]. We therefore used a cut-off of 440 nmol/L cortisol, and further interrogated the electronic record of severely hyponatraemic patients with a cortisol at or below this level in order to determine the proportion of hyponatraemic patients who had a diagnosis of adrenal insufficiency. In agreement with the findings of previous studies that endocrine disorders are an uncommon cause of hyponatraemia [7,10,11], we found that 1.7% of those patients with severe hyponatraemia and a cortisol measurement had a diagnosis of adrenal insufficiency.

Despite the relative rarity of endocrine causes of hyponatraemia, adrenal insufficiency should remain an important consideration in the clinical workup of the hyponatraemic patient due to the severe consequences of failure to treat with glucocorticoid replacement and volume repletion.

Competing interests

None.

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Ethical approval

Not required.

Contributorship

JHB conceived the project, JHB and EM analysed the data and wrote the paper and approved the final version.

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