

# Clues for early detection of autoimmune Addison's disease – myths and realities

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**Abstract.** Bjorvatn Sævik A, Åkerman AK, Grønning K, Neramoen I, Valland SF, Finnes TE, Isaksson M, Dahlqvist P, Bergthorsdottir R, Ekwall O, Skov J, Nedrebø BG, Hulting AL, Wahlberg J, Svartberg J, Høybye C, Bleskestad IH, Jørgensen AP, Kämpe O, Øksnes M, Bensing S, Husebye ES (University of Bergen, Norway; Örebro University Hospital, Örebro; Karolinska Institutet, Stockholm, Sweden; Akershus University Hospital; Akershus University Hospital, University of Oslo, Lørenskog; Innlandet Hospital Trust, Hamar, Norway; Uppsala University, Uppsala; Umeå University, Umeå; Sahlgrenska University Hospital and Sahlgrenska Academy, University of Gothenburg; The Sahlgrenska Academy, University of Gothenburg; The Sahlgrenska Academy, University of Gothenburg, Gothenburg; Karlstad City Hospital, Sweden; Haugesund Hospital, Haugesund, Norway; Linköping University, Linköping, Sweden; University Hospital of North Norway; UiT The Arctic University of Norway, Tromsø, Norway; Karolinska University Hospital, Stockholm, Sweden; Stavanger University Hospital, Stavanger; Oslo University Hospital, Oslo, Norway; Karolinska Institutet, Stockholm, Sweden; Haukeland University Hospital, Bergen; University of Bergen, Norway). Clues for early detection of autoimmune Addison's disease – myths and realities. *J Intern Med* 2017; <https://doi.org/10.1111/joim.12699>

**Background.** Early detection of autoimmune Addison's disease (AAD) is important as delay in diagnosis may result in a life-threatening adrenal crisis and death. The classical clinical picture of untreated AAD is well-described, but methodical investigations are scarce.

**Objective.** Perform a retrospective audit of patient records with the aim of identifying biochemical markers for early diagnosis of AAD.

**Material and Methods.** A multicentre retrospective study including 272 patients diagnosed with AAD at hospitals in Norway and Sweden during 1978–2016. Scrutiny of medical records provided patient data and laboratory values.

**Results.** Low sodium occurred in 207 of 247 (84%), but only one-third had elevated potassium. Other common nonendocrine tests were largely normal. TSH was elevated in 79 of 153 patients, and hypoglycaemia was found in 10%. Thirty-three per cent were diagnosed subsequent to adrenal crisis, in whom electrolyte disturbances were significantly more pronounced ( $P < 0.001$ ). Serum cortisol was consistently decreased (median 62 nmol L<sup>-1</sup> [1–668]) and significantly lower in individuals with adrenal crisis (38 nmol L<sup>-1</sup> [2–442]) than in those without (81 nmol L<sup>-1</sup> [1–668],  $P < 0.001$ ).

**Conclusion.** The most consistent biochemical finding of untreated AAD was low sodium independent of

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the degree of glucocorticoid deficiency. Half of the patients had elevated TSH levels. Only a minority presented with marked hyperkalaemia or other nonhormonal abnormalities. Thus, unexplained low sodium and/or elevated TSH should prompt consideration of an undiagnosed AAD, and on clinical suspicion bring about assay of cortisol

and ACTH. Presence of 21-hydroxylase autoantibodies confirms autoimmune aetiology. Anticipating additional abnormalities in routine blood tests may delay diagnosis.

**Keywords:** Addison, adrenal insufficiency, autoimmune disease, cortisol, electrolytes, endocrinology.

## Introduction

Primary adrenal insufficiency, or Addison's disease (AD), is a rare endocrine disease occurring in 100–220 per million [1]. Autoimmune destruction of the adrenal cortex accounts for 80–90% of AD cases in developed countries [2], and risk genes pertaining to the adaptive immune system have been identified [3].

Detection at an early stage is important as delay in proper treatment may be fatal. Indeed, an undiagnosed and untreated AD is lethal [4, 5]. Alarmingly, up to half of the patients develop adrenal crisis before being diagnosed [6]. To avoid deadly outcome, it is crucial that physicians are able to recognize key symptoms and signs of adrenal crisis and know how to initiate treatment immediately upon clinical suspicion.

Autoimmune Addison's disease (AAD) typically presents gradually with unspecific symptoms as fatigue, weight loss, nausea and postural dizziness. These ambiguous features pose a major challenge to early detection. As a result, diagnosis is often missed and patients frequently receive other incorrect diagnoses and treatments [7, 8]. The fact that most patients have seen multiple doctors before the correct diagnosis is suspected suggests that appropriate hormone testing was not performed and emphasizes the need for new strategies for early identification [7].

Even if the classical picture of untreated AAD is well-described, it has rarely been subject to methodical review [9, 10]. Low sodium in combination with hyperkalaemia is considered strong indicators of AAD [6, 11, 12]. Other reported features include hypercalcaemia, mild normocytic anaemia, mild eosinophilia, lymphocytosis and increased creatinine [4, 11, 13]. Hypoglycaemia may be present, although said to be more frequent in children than in adults [14–16]. Once suspected, AAD is usually easy to diagnose by measuring a paired morning cortisol and adrenocorticotropic

hormone (ACTH), ideally supplemented with assay of 21-hydroxylase autoantibodies (21OH-Ab), an early and specific biomarker for AAD [17, 18].

Given the ambiguous presentation, and the fact that when eventually diagnosed, many are in adrenal crisis [19], we asked whether there are reliable clues in commonly taken blood tests that could facilitate early diagnosis of AAD.

## Material and Methods

### Subjects

We conducted a retrospective multicentre study to identify the laboratory findings in 137 Norwegian (diagnosed 1978–2016) and 135 Swedish (diagnosed 2000–2013) patients at diagnosis of AAD.

In Norway, informed consent was secured by only including patients registered in The National Addison Registry (ROAS), which covers >75 per cent of all Norwegian patients with AD. In Sweden, patients were included after signing an informed consent to the Swedish Addison Registry [20]. SAR contains clinical data and blood samples from approximately 50% of all Swedish patients with AAD [21]. We ensured population homogeneity by restricting inclusion to confirmed AAD, evidenced by the presence of 21OH-Ab. Adrenalectomy, secondary or transient insufficiency, incomplete medical records or diagnosis before 1978 (Norway) or 2000 (Sweden) led to exclusion.

### Information retrieval

Medical records provided patient data and laboratory values at diagnosis. We registered the following categorical variables: sex, acute hospital admission (if yes, administration of intravenous hydrocortisone and fluid), 21OH-Ab, autoimmune polyendocrine syndrome (APS), use of levothyroxine, and in Swedish patients, hyperpigmentation. Clinical and biochemical variables included age, height, weight, blood pressure, S-sodium, S-potassium, B-haemoglobin, S-alanine amino transferase

(ALAT), S-calcium, S-creatinine, S-glucose, random S-cortisol, stimulated S-cortisol, P-adrenocorticotropic hormone (ACTH), S-aldosterone, P-renin activity, P-renin concentration, S-dehydroepiandrosterone sulphate (DHEAS), S-thyroid stimulation hormone (TSH) and thyroid peroxidase autoantibodies (TPO-Ab). Laboratory values obtained after initialization of replacement treatment were excluded, except 21OH-Ab as assays in many cases were performed at a later time-point. Cortisol, ACTH, aldosterone, PRA and renin concentration values marked as 'less than' or 'more than' were entered as the stated number. To investigate the correlation between hypoglycaemia and age, glucose levels were divided into two groups of  $\geq$  or  $<3$  mmol L<sup>-1</sup>. To explore the inhibitory effect of cortisol on TSH levels, 29 of 145 patients were excluded due to ongoing treatment for hypothyroidism. TSH values were then dichotomized as elevated or not.

Laboratory methods have obviously been changed numerous times over the course of 38 years, and methods may have varied between hospitals. We chose to give measured values. When reference ranges clearly differed between hospitals, this is indicated in the text or converted to normal, elevated or low values.

#### Defining adrenal crisis

There is no universal consensus regarding definition of adrenal crisis, yet systolic blood pressure  $<100$  mmHg is a frequently suggested feature [22–24]. In this study, patients were categorized as having adrenal crisis when meeting the following three criteria: admitted acutely to hospital, found hypotensive (systolic BP  $<100$  mmHg) and on clinical judgement considered to be in an adrenal crisis.

#### Statistics

Results are expressed as median [range] or as mean ( $\pm$ standard deviation) when appropriate. The Mann–Whitney independent sample *U*-test was employed to compare differences between groups. Correlation between age and glucose, random cortisol and stimulated cortisol, random cortisol and ACTH, stimulated cortisol and ACTH, and random cortisol and TSH were determined using the Spearman's rank correlation analysis. *P*-values were two-tailed, and significance was considered established at 0.05 for group comparison analyses

and correlation of age and glucose, and 0.01 for the remaining correlations.

## Results

### Subjects

A total number of 272 individuals were included displaying a wide age range (5–79 years) and consisting of more women ( $n = 173$ ) than men ( $n = 99$ ). One-hundred and eighty-seven of 265 (69%) patients were diagnosed during an acute hospital admission, and 78 of 240 (33%) met the criteria of adrenal crisis. Adrenal crisis was associated with debut at slightly younger age (32.6 years ( $\pm 14.93$ ) vs. 38.4 years ( $\pm 14.48$ ),  $P = 0.04$ ). One-hundred and thirty-seven of 255 (54%) patients had a concomitant autoimmune disease at diagnosis or have been diagnosed with APS later on. Patient characteristics are summarized in Table 1.

### Clinical features at diagnosis

Medical records provided information on body mass index (BMI) in 91 adults. Twenty-two had BMI less than 18.5 kg m<sup>-2</sup>. There was no significant difference in BMI of patients with (20.1 [13.7–32.3]) compared to those without crisis (20.1 [15.8–34.4],  $P = 0.821$ ). Records of systolic and/or diastolic blood pressures were retrieved from 224 patients. Ninety-three patients (42%) presented with systolic blood pressure  $<100$  mmHg, and 59 (26%) patients had diastolic pressures  $<60$  mmHg. Hyperpigmentation was found in 87% of the Swedish patients at diagnosis.

Table 1 Patient characteristics

	Male	Female	Total
No. of patients (%)	99 (36)	173 (64)	272
Median age at diagnosis in years (range)	30 (6–79)	39 (5–77)	36 (5–79)
Diagnosis at acute hospital admission (%)	71 (74)	116 (69)	187 (71)
Adrenal crisis at diagnosis (%)	27 (32)	51 (33)	78 (33)
Patients with APS type I, II (%)	40 (46)	97 (58)	137 (54)

APS, autoimmune polyendocrine syndrome.

### Common laboratory findings

Sodium and potassium concentrations were available in 247 and 242 patients, respectively. Sodium below  $137 \text{ mmol L}^{-1}$  was present in 207 (84%). Potassium was  $>5.0 \text{ mmol L}^{-1}$  in 82 (34%). Eighty-one (34%) exhibited both low sodium and hyperkalaemia (Fig. 1). Only one patient had hyperkalaemia without low sodium. Electrolyte disturbances were significantly more pronounced in patients with an adrenal crisis with median sodium of  $127 \text{ mmol L}^{-1}$  [101–138] vs.  $132 \text{ mmol L}^{-1}$  [103–142] ( $P < 0.001$ ), and median potassium of  $5.0 \text{ mmol L}^{-1}$  [3.5–8.4] vs.  $4.5 \text{ mmol L}^{-1}$  [3.2–8.6] ( $P < 0.001$ ) compared to those without crisis (Table 2). Eight patients had severe hyperkalaemia ( $\geq 7 \text{ mmol L}^{-1}$ ) and accompanied by severe hyponatraemia ( $<125 \text{ mmol L}^{-1}$ ), very low cortisol ( $<80 \text{ nmol L}^{-1}$ ) and marked systolic hypotension ( $<80 \text{ mmHg}$ ) in all but one. The latter patient had sodium  $134 \text{ mmol L}^{-1}$ , cortisol  $114 \text{ nmol L}^{-1}$ , blood pressure 105/60 mmHg, but reached a stimulated cortisol of only  $131 \text{ nmol L}^{-1}$ .

Hypoglycaemia defined as S-glucose  $<3 \text{ mmol L}^{-1}$  was noted in 15 of 135 patients (type 1 diabetes mellitus (T1D) excluded) of whom two were  $<18$  years of age. In the remaining seven children tested, values ranged from 4.2 to  $6.0 \text{ mmol L}^{-1}$ . There was a small positive correlation between age

and glucose levels, regardless of whether patients with T1D were included ( $\rho = 0.169$ ,  $N = 153$ ,  $P = 0.037$ ) or excluded ( $\rho = 0.172$ ,  $N = 135$ ,  $P = 0.047$ ) (Fig. 2). Both the highest ( $22.2 \text{ mmol L}^{-1}$ ) and the lowest ( $1.1 \text{ mmol L}^{-1}$ ) values occurred in patients with T1D. The latter was found in a 57-year-old man with ongoing Graves' disease, T1D and asthma. The sudden drop in serum glucose for no apparent reason alerted the physician of possible increased insulin sensitivity due to an underlying AD, and necessary acute treatment and diagnostic workup were performed. Furthermore, a 5-year-old girl presented with serum glucose  $1.9 \text{ mmol L}^{-1}$ , sodium  $127 \text{ mmol L}^{-1}$ , potassium  $5.4 \text{ mmol L}^{-1}$  and calcium  $1.93 \text{ mmol L}^{-1}$ . She had recently been diagnosed with hypoparathyroidism, and suspicion of AAD was confirmed by cortisol  $218 \text{ nmol L}^{-1}$  paired with P-ACTH  $322 \text{ pmol L}^{-1}$ . After initiation of glucocorticoid replacement, calcium fell to  $1.48 \text{ mmol L}^{-1}$ , which could be due to fluid resuscitation and/or the inhibitory effect of cortisol on intestinal calcium absorption. Noteworthy, two of four siblings have later also been diagnosed with APS type 1.

Mean values of serum haemoglobin, alanine amino transferase (ALAT), calcium, creatinine and serum glucose levels were all well within their respective reference ranges, although aberrant values occurred at both extremes. Median creatinine levels were higher in patients with adrenal crisis compared with those without ( $91 \mu\text{mol L}^{-1}$  [46–656] vs.  $76 \mu\text{mol L}^{-1}$  [28–193],  $P = 0.003$ ) (Table 2).

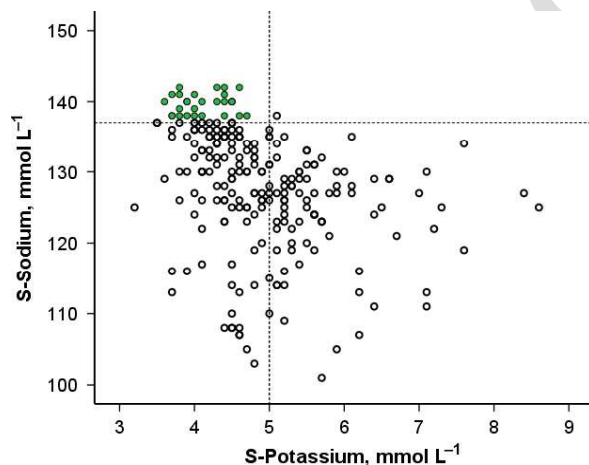
### Thyroid function

TSH was measured in 206 patients of which 53 (26%) had documented use of levothyroxine. In patients without known hypothyroidism, TSH was elevated in 79 of 153 (52%). TPO-Ab was only available in 22, but a positive test indicated untreated autoimmune hypothyroidism in eight cases. In the remaining 71, the elevated TSH might have been caused by lack of cortisol as there was a small, but significant negative correlation between TSH and random cortisol ( $\rho = -0.248$ ,  $N = 138$ ,  $P = 0.003$ ) (Fig. 3A).

### Assessment of adrenal function

A random serum cortisol value was recorded in 255 patients and was as expected found consistently low (median  $62 \text{ nmol L}^{-1}$  [1–668]) (Fig. 4A) and

LOW RESOLUTION COLOR FIG



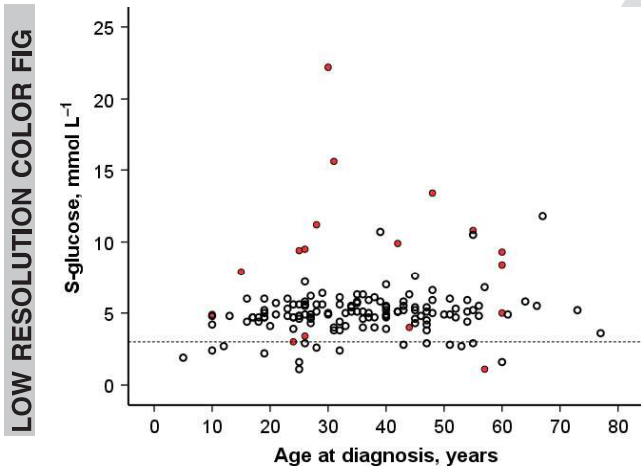
**Fig. 1** Relationship between S-sodium and S-potassium values. Horizontal dotted line depicts lower reference range for sodium, vertical dotted line upper reference range for potassium. Twenty-one patients with both  $s\text{-sodium} > 137 \text{ mmol L}^{-1}$  and  $s\text{-potassium} < 5.0 \text{ mmol L}^{-1}$  are marked in green (four patients with identical values).

Table 2 Laboratory values at time of AAD diagnosis

Laboratory parameter	N	Median (range)			P-value*
		Adrenal crisis at diagnosis	No adrenal crisis at diagnosis	All	
S-Sodium (mmol L <sup>-1</sup> )	247	127 (101–138)	132 (103–142)	130 (101–142)	<0.001
S-Potassium (mmol L <sup>-1</sup> )	242	5.0 (3.5–8.4)	4.5 (3.2–8.6)	4.6 (3.2–8.6)	<0.001
S-Creatinine (μmol L <sup>-1</sup> )	127	91 (46–656)	76 (28–193)	79 (28–656)	0.003
S-Hb (g dL <sup>-1</sup> )	219	13.8 (7.7–16.8)	13.4 (8.7–17.4)	13.5 (7.7–17.4)	0.770
S-ALAT (U L <sup>-1</sup> )	144	18 (0–144)	16 (0–191)	16 (0–191)	0.369
S-Calcium (mmol L <sup>-1</sup> )	146	2.38 (1.9–3.95)	2.33 (2.0–2.98)	2.33 (1.9–3.95)	0.231
B-Glucose (mmol L <sup>-1</sup> )	153	4.8 (1.1–10.7)	5.1 (1.6–22.2)	5 (1.1–22.2)	0.051
S-TSH (mIE L <sup>-1</sup> )	206	3.4 (0–117)	4.1 (0–180)	4.1 (0–180)	0.709
Random S-cortisol (nmol L <sup>-1</sup> )	255	38 (2–442)	81 (1–668)	62 (1–668)	<0.001
Stimulated S-cortisol (nmol L <sup>-1</sup> )	129	68 (2–437)	117 (11–703)	94 (2–703)	<0.001
P-ACTH (pmol L <sup>-1</sup> )	194	278 (1–1910)	274 (4–1319)	278 (1–1910)	0.054
S-Aldosterone (pmol L <sup>-1</sup> )	97	69 (42–256)	69 (27–230)	69 (27–256)	0.037
PRA (μg L <sup>-1</sup> h <sup>-1</sup> )	60	9 (3–158)	19 (2–240)	18 (2–240)	0.331
Plasma renin concentration (mIE L <sup>-1</sup> )	24	166 (79–2910)	176 (13–520)	170 (13–2910)	0.868
S-DHEAS (μmol L <sup>-1</sup> )	33	0.4 (0.12–0.9)	0.4 (0.04–2.8)	0.4 (0.04–2.8)	0.453

\*Between-group differences as calculated by Mann–Whitney *U*-test

Hb, haemoglobin; ALAT, alanine amino transferase; TSH, thyroid stimulation hormone; ACTH, adrenocorticotropic hormone; PRA, plasma renin activity; DHEAS, dehydroepiandrosterone sulphate.



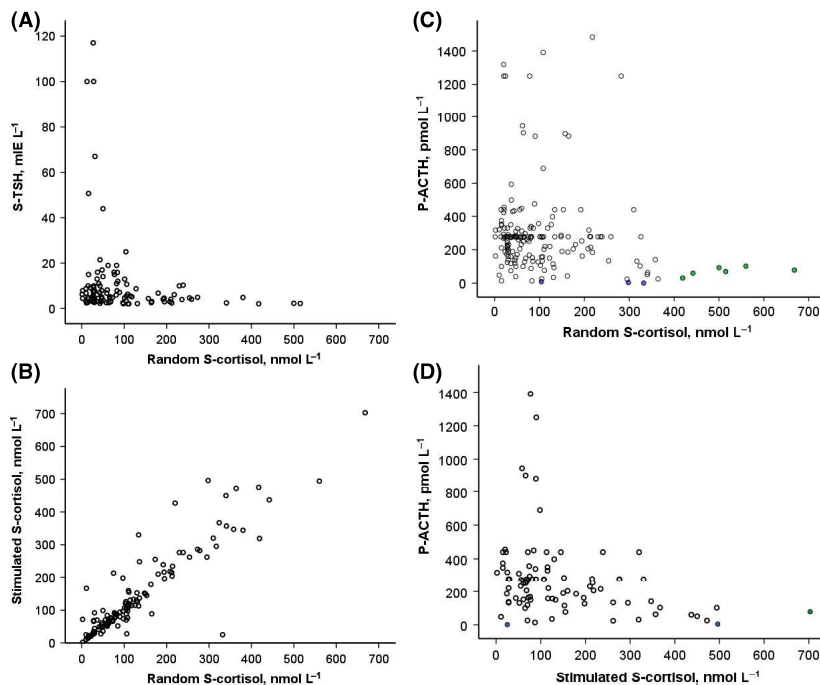
**10** Fig. 2 Relationship between S-glucose level and age at diagnosis. Dotted horizontal line marks cut-off value for hypoglycaemia, 3.0 mmol L<sup>-1</sup>. Eighteen patients with type 1 diabetes mellitus are marked in red.

below 140 nmol L<sup>-1</sup> in 202 (79%) patients. Conversely, values exceeded 500 nmol L<sup>-1</sup> in three patients prior to stimulation test. Two used oral contraception (OCP), which is known to increase

total cortisol due to higher cortisol-binding globulin (CBG) levels. The third patient suffered from both T1D and primary hypothyroidism and was diagnosed early. Screening revealed ACTH 102 pmol L<sup>-1</sup> and the presence of 21OH-Ab. Another three patients had values >400 nmol L<sup>-1</sup>, yet diagnosis was confirmed by minimal response to a cosyntropin stimulation test (cortisol increment ≤58 nmol L<sup>-1</sup>). All three had clearly elevated ACTH levels and were 21OH-Ab positive.

Cortisol was significantly lower in patients with adrenal crisis (38 nmol L<sup>-1</sup> [2–442]) compared to those without (81 nmol L<sup>-1</sup> [1–668], *P* < 0.001) (Table 2). Three of 73 patients in crisis had cortisol >300 nmol L<sup>-1</sup>, yet all three presented with severe hyponatraemia (110, 121 and 124 mmol L<sup>-1</sup>). Aldosterone was only measured in the latter two and found low in both (<69 pmol L<sup>-1</sup> and 75 pmol L<sup>-1</sup>, respectively).

ACTH was 278 pmol L<sup>-1</sup> or higher in 99 of 194 patients (50%). Strangely, three patients had values <10 pmol L<sup>-1</sup> despite positive 21OH-Ab. In one of the patients, subsequent analyses revealed elevated ACTH. Another patient had a cortisol of



**Fig. 3** (A) Relationship between S-thyroid stimulated hormone (TSH) and random S-cortisol in patients without known concomitant hypothyroidism. (B) Relationship between stimulated S-cortisol and random S-cortisol. (C) Relationship between P-adrenocorticotropic hormone (ACTH) and random S-cortisol. Three patients with ACTH < 10 pmol L<sup>-1</sup> are marked blue, six patients with cortisol > 400 nmol L<sup>-1</sup> are marked green. (D) Relationship between P-adrenocorticotropic hormone (ACTH) and stimulated S-cortisol. Two patients with ACTH < 10 pmol L<sup>-1</sup> are marked blue, one patient with cortisol > 500 nmol L<sup>-1</sup> is marked green.

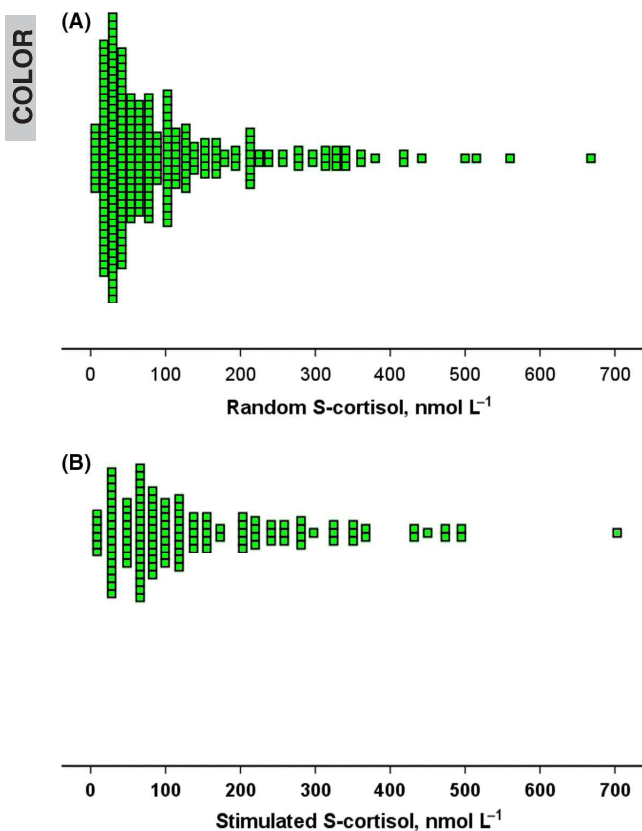
104 nmol L<sup>-1</sup>, and in yet another, AAD was detected at an early stage due to concomitant hypothyroidism, T1D, vitiligo and pernicious anaemia. There was a small, but significant inverse relationship between random cortisol and ACTH ( $\rho = -0.230$ ,  $N = 189$ ,  $P = 0.001$ ) (Fig. 3B). The correlation could be an underestimation because many values were not precisely measured but plotted as 278 pmol L<sup>-1</sup> when in reality >278 pmol L<sup>-1</sup>.

A cosyntropin stimulation test was performed in 129 patients (Fig. 4B). Using the cut-off 500 nmol L<sup>-1</sup>, all but one had a pathological test. The highest stimulated cortisol of 703 nmol L<sup>-1</sup> belonged to a 27-year-old woman. Of note, the increment in cortisol was minor (from 668) hinting to the presence of excessive CBG levels as noted above. All other clinical and biochemical investigations pointed towards AAD, including elevated ACTH and plasma renin activity, and the presence of 21OH-Ab. It later became apparent that she used OCP. In the remaining 128 patients, cortisol failed to rise above 500 nmol L<sup>-1</sup> (median peak of 94 nmol L<sup>-1</sup> [2–703]). In cases where the cosyntropin test was omitted, all patients had cortisol less than 110 nmol L<sup>-1</sup> and/or ACTH levels elevated above 20 pmol L<sup>-1</sup>. Overall, there was a strong, positive correlation between stimulated cortisol and random cortisol ( $\rho = 0.884$ ,  $N = 127$ ,  $P < 0.001$ ) (Fig. 3B).

A moderate, negative correlation was found between ACTH and random cortisol ( $\rho = -0.230$ ,  $N = 189$ ,  $P = 0.001$ ) (Fig. 3C) and ACTH and stimulated cortisol ( $\rho = -0.311$ ,  $N = 92$ ,  $P = 0.003$ ) (Fig. 3D). All correlations were significant, and the coefficient of determination ( $\rho^2$ ) was 78%, 5% and 10%, respectively.

Aldosterone was measured in 97 patients, and 67 had levels <69 pmol L<sup>-1</sup>. The highest value noted was 256 pmol L<sup>-1</sup> and accompanied by cortisol 84 nmol L<sup>-1</sup>, ACTH 330 pmol L<sup>-1</sup> and plasma renin activity 65  $\mu\text{g L}^{-1} \text{h}^{-1}$ , confirming AD. Median aldosterone value was 69 pmol L<sup>-1</sup> in both groups. However, more than half (56%) of the measurements were entered as 69, meaning values were not detectable. Aldosterone was <69 in 21 of 26 patients (81%) with crisis, compared to 22 of 61 patients (64%) without. Comparison revealed slightly lower aldosterone in patients with versus without crisis ( $P = 0.037$ ) (Table 2).

Plasma renin activity (PRA) values were elevated in 57 of 60 Norwegian patients, only three exhibited values within the reference range (0.5–3.4  $\mu\text{g L}^{-1} \text{h}^{-1}$ ). In Sweden, plasma renin concentration was recorded for 24 patients and found elevated >40 mIE L<sup>-1</sup> in all but one. DHEAS was decreased <2  $\mu\text{mol L}^{-1}$  in 31 of 33 patients.



**Fig. 4** (A) Distribution of random S-cortisol values in 255 patients. (B) Distribution of cosyntropin-stimulated S-cortisol in 129 patients.

### Discussion

AD often has an insidious presentation with non-specific symptoms that delay diagnosis, often to the point that patients develop an adrenal crisis with risk of fatal outcome. An ongoing challenge is to recognize subtle symptoms and signs of AAD before a life-threatening crisis develop. We show that AAD is associated with low BMI, yet obesity does not rule out the diagnosis. In the Swedish cohort, the vast majority of patients presented with hyperpigmentation, making skin changes an important clinical clue of AD. However, the hyperpigmentation may be subtle, lacking or simply overlooked. This calls for the need for biochemical hints to raise suspicion of AD.

We here show that low sodium is the most consistent routine biochemical finding at diagnosis (Table 3). This adds to the challenge of prompt identification of AAD as sodium disturbances are

associated with a plethora of diseases and conditions with multiple aetiologies. Indeed, hyponatraemia is the most common electrolyte abnormality encountered in clinical practice [25]. Low sodium levels are, however, more common in older patients with high morbidity [26, 27]. Although AAD may start at any time of life, the majority of patients are diagnosed between 30 and 50 years of age [2]. We therefore recommend that an otherwise unexplained S-sodium  $<137$  mmol L<sup>-1</sup> should initiate evaluation for adrenal insufficiency, especially if accompanied by unspecific general symptoms in young- and middle-aged patients.

Of equal importance is the finding that hyperkalaemia only occurs in one-third of patients. Thus, the alleged hallmark of AAD, the combination of low sodium and hyperkalaemia, is only present in a minority. In contrast to common belief, we show that potassium levels hold limited value in AAD workup. Although the presence of hyperkalaemia may substantiate diagnosis, we show that normokalaemia is far more common, thus diminishing the frequently listed significance of potassium aberrations. In short, normokalaemia does not exclude the diagnosis, even in severely ill patients.

Hypoglycaemia occurred in both children and adults, yet the majority of patients were normoglycemic. We found a small, positive correlation between age and glucose levels. Thus, even a low normal glucose could add to suspicion of AAD, especially if seen together with low sodium in younger individuals. In patients with T1D, a sudden drop in insulin requirements or recurrent episodes of hypoglycaemia may be the first biochemical sign of AAD and should prompt further testing of adrenal function [28].

Of note, biochemical abnormalities in serum haemoglobin, ALAT and calcium were not consistent indicators of AD. One explanation could be that in general, patients are nowadays diagnosed at an earlier stage than 60 years ago [29], given better availability of hormone assays and the possibility of measuring 21OH-ab, an early biomarker of AAD. Also, interpretation of haemoglobin requires caution, as dehydration may camouflage a low value.

Elevated TSH was frequent, recorded in more than half of the patients who did not use levothyroxine. A high TSH value could indicate untreated hypothyroidism but might also be a sign of

**Table 3** Key biochemical features at diagnosis of autoimmune Addison's disease. The percentages are the fraction of patients fulfilling each criterion.

Common blood tests	
Low sodium (<137 mmol L <sup>-1</sup> , 84%)	
Elevated TSH (52%)	
High potassium (>5 mmol L <sup>-1</sup> , 34%)	
Targeted assessment of adrenal function (ref. 9)	
Pathological cosyntropin test (S-cortisol <500 nmol L <sup>-1</sup> , 99%)	
Elevated ACTH × 2 upper reference limit (97%)	
Elevated plasma renin activity	
Plasma renin concentration	
Low baseline cortisol (<140 nmol L <sup>-1</sup> , 79%)	
Low aldosterone (<67 pmol L <sup>-1</sup> , 69%)	
Other tests	
21-hydroxylase autoantibodies	

TSH, thyroid stimulation hormone; ACTH, adrenocorticotropic hormone.

unrecognized adrenal insufficiency due to decreased inhibitory effect of cortisol on pituitary TSH production [30]. It is crucial that physicians are aware of the inductive effect of levothyroxine on cortisol metabolism [31]. Indeed, we noticed several cases where initiation of thyroxine therapy led to worsening of the clinical condition [32], even precipitating an adrenal crisis. Irrespective of cause, elevated TSH accompanied by low sodium should trigger consideration of AD.

We show that aberrancy in cortisol, ACTH, aldosterone, plasma renin activity and concentration, and DHEAS values are reliable markers of AD. Once suspected, diagnosis of AAD is often easily confirmed by targeted investigations. Notably, we show that a low random cortisol value is strongly and significantly associated with a low stimulated cortisol value. However, normal cortisol does not rule out AD. Also, we here demonstrate the potential deceptive effect of OCP in elevating CBG-bound cortisol. The lack of increment in cortisol by cosyntropin can give a hint of an underlying undiagnosed AD and underlines the importance of obtaining a careful medication history. Equally important, practically all patients presented with elevated ACTH. The vast majority also exhibited aberrant values of aldosterone and renin. We therefore recommend a low threshold for measurement of ACTH, aldosterone and renin in addition to cortisol upon suspicion of AAD.

There is no universal consensus regarding definition of adrenal crisis, although a number of proposals have been put forward. The most recent definition [24] requires 'an acute deterioration in health' and hypotension relieved following parenteral glucocorticoid administration. Here, we defined adrenal crisis as patients admitted acutely to hospital, found hypotensive (systolic BP <100 mmHg), and on clinical judgement considered to be in an adrenal crisis. In our cohort, more than 70% were diagnosed in relation to acute hospital admission. Less than half of these presented with hypotension. Thus, our finding of 33% in crisis at debut may be an underestimate. Importantly, one patient presented with cortisol <1 nmol L<sup>-1</sup> and sodium 103 mmol L<sup>-1</sup>, and another patient had a cortisol of 50 nmol L<sup>-1</sup> and potassium of 8.6 mmol L<sup>-1</sup> at diagnosis. Both patients were acutely admitted to hospital but failed to be defined as in an adrenal crisis as the blood pressure was >100 mmHg. We therefore recommend that systolic blood pressure <100 mmHg be considered indicative of but not mandatory for adrenal crisis.

Additional data from the registries revealed that more than half of patients had at least one other autoimmune endocrine disorder, either present at debut of AAD or acquired later in life. Thus, physicians should be aware of the increased risk of AAD in conjunction with other organ-specific autoimmune disorders, and we advocate a low threshold for testing adrenal function in these patients.

Assay of 21OH-Ab is probably the earliest indication of a developing AAD. In patients with autoimmune disease and unexplained vague symptoms such as fatigue or abdominal symptoms, screening for 21OH-Ab is warranted and may secure an early diagnosis of AAD. Moreover, early detection of 21OH-Ab is useful to identify possible candidates for immunosuppressive therapy aimed at reversing and even curing AAD [33].

Diagnostic accuracy of AAD was ensured by scrutiny of patient records and solely including patients who had received follow-up treatment and care of his or her AAD over time. Unfortunately, the true prevalence of AAD is not known for all of the participating centres, and we were therefore unable to estimate the proportion of patients included. Still, the ROAS registry covers the vast majority of Norwegian patients with AAD (>75%), and in



Sweden, virtually all invited patients agreed to participate. Also, the relatively high number of included subjects, recruitment from multiple hospitals and different decades, all contribute to reduce selection bias to a minimum and increase the generalizability of our findings.

However, the retrospective, multi-centred design is susceptible to various biases. First, it offers limited control with reported data. In most cases, medical records did not provide information on the time of blood sampling, thus possibly confounding the interpretation. This was especially true for cortisol and ACTH measurements. Although cortisol and ACTH reveal clear circadian variation, it can be assumed that this is largely lost in AAD when the adrenal cortex is continuously stressed by high ACTH. Secondly, the laboratory methods and assays have changed in the course of 38 years and there are variations between the laboratories. Thirdly, not all parameters of interest were recorded for every patient. However, even with these weaknesses, our results from a large collection of patients reflect real-world data, and the information clinicians will encounter when evaluating their patients.

In conclusion, low sodium was the only consistent finding amongst routine blood tests, independent of degree of adrenal insufficiency. Elevated TSH was present in more than half of the patients. High potassium, however, only occurred in one-third. We urge that low sodium and or elevated TSH without obvious explanation should trigger consideration of AAD, and on clinical suspicion bring about assay of a paired cortisol and ACTH. Importantly, initiation of levothyroxine can precipitate deterioration in the clinical condition and even induce an adrenal crisis. Early detection of AAD is vital, as delay in diagnosis put patients at risk of lethal adrenal crisis.

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#### Conflict of interest statement

The author reports no conflicts of interest in this work.

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