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AUTOIMMUNE POLYGLANDULAR SYNDROME TYPE II PRESENTING WITH SEVERE HYPONATRAEMIA AND AUTOIMMUNE BICYTOPAENIA

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ABSTRACT

Background: Autoimmune polyglandular syndrome type II (APS II) is a rare, multifactorial disorder characterised by a combination of primary adrenal insufficiency with other autoimmune endocrinopathies, most commonly thyroid disease and type 1 diabetes mellitus. The clinical presentation is variable, and non-specific symptoms often lead to delayed diagnosis.

Case description: We report the case of a 37-year-old female patient with a history of Graves-Basedow thyroid disease status post total thyroidectomy, admitted for dyspeptic symptoms, vomiting and severe hyponatraemia (112 mmol/l). Endocrinological evaluation revealed hypocortisolism with elevated adrenocorticotropic hormone (ACTH), reduced insulin, C-peptide and dehydroepiandrosterone sulfate (DHEAS) levels, and adrenal atrophy on MRI. Serological tests demonstrated IgA deficiency and positive anti-dsDNA antibodies of the IgM class. Additionally, the patient presented with bicytopaenia associated with autoimmune neutropaenia and detectable anti-granulocyte and anti-lymphocyte antibodies. The patient was diagnosed with APS II and started on hydrocortisone and fludrocortisone replacement therapy, resulting in subsequent clinical stabilisation.

Conclusion: In this case, Addison's disease represented the first clinical manifestation of APS II and presented with severe hyponatraemia. A rare aspect of this case was the presence of bicytopaenia with autoimmune neutropaenia, which is not a typical feature of APS II and thus expands its phenotypic spectrum. This case highlights the importance of early recognition of endocrine causes of severe hyponatraemia and demonstrates that APS II can also manifest with rare haematologic complications. Long-term follow-up is essential due to the risk of progression or the development of additional autoimmune disorders.

KEYWORDS

Autoimmune polyglandular syndrome type II, primary adrenal insufficiency, Addison's disease, hyponatraemia, autoimmune neutropaenia

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LEARNING POINTS

- Severe hypotonic hyponatraemia can be the dominant presenting feature of primary adrenal insufficiency; therefore, adrenal insufficiency should be actively considered in the differential diagnosis of profound hyponatraemia, especially when accompanied by gastrointestinal symptoms and volume depletion.
- Autoimmune polyglandular syndrome type II may rarely be associated with autoimmune cytopaenias (including neutropaenia); detection of anti-granulocyte/anti-lymphocyte antibodies and selective IgA deficiency should prompt haematologic and immunologic follow-up for evolving or additional autoimmune manifestations.

INTRODUCTION

Autoimmune polyglandular syndromes (APS) represent a heterogeneous group of disorders characterised by the combined involvement of multiple endocrine glands on an autoimmune basis, often accompanied by non-endocrine autoimmune manifestations[1]. They are traditionally divided into two main syndromes: APS type I and APS type II.

APS type II, also referred to as Schmidt's syndrome, is a polygenic, multifactorial disorder that predominantly manifests in adulthood, with an approximately fourfold higher prevalence in women with an estimated prevalence of 1:20,000[2]. APS II is characterised by a triad of primary adrenal insufficiency (Addison's disease), autoimmune thyroid disease and type 1 diabetes mellitus[1]. The diagnosis requires the presence of at least two components of the triad, one of which must be Addison's disease. Diagnosis of APS II relies on clinical suspicion, laboratory confirmation of the individual endocrinopathies and the presence of characteristic autoantibodies (e.g. anti-21-hydroxylase for Addison's disease, anti-thyroid peroxidase and anti-thyroglobulin for autoimmune thyroiditis, anti-glutamic acid decarboxylase (GAD) for type 1 diabetes) [3,4]. In clinical practice, it is important to consider APS II in patients who already have a diagnosed autoimmune endocrine disorder and develop symptoms suggestive of additional glandular involvement. Early recognition is crucial, as untreated hypocortisolism can lead to a life-threatening Addisonian crisis[5].

CASE DESCRIPTION

The patient is a 37-year-old Caucasian woman with a known history of Graves-Basedow disease, status post total thyroidectomy, on long-term levothyroxine replacement therapy. She was admitted to the Department of Internal Medicine for dyspeptic symptoms of approximately two weeks' duration, vomiting and severe hyponatraemia, with an initial serum sodium concentration of 112 mmol/l. The initial diagnostic approach to severe hyponatraemia included evaluation of volume status, electrolyte abnormalities and potential alternative aetiologies. On admission, the patient was clinically hypovolemic, with persistent vomiting and dehydration. Despite the presence of normal serum potassium levels (4.2 mmol/l), which does not exclude primary adrenal insufficiency, the combination of profound hyponatraemia, hypovolaemia and systemic symptoms raised suspicion for an endocrine cause. The overall clinical presentation was not consistent with syndrome of inappropriate antidiuretic hormone (SIADH), which is typically characterised by euvolemia, and the subsequent confirmation of primary adrenal insufficiency supported this diagnostic conclusion. In the context of confirmed primary adrenal insufficiency, the hyponatraemia was interpreted as predominantly hypotonic and driven by cortisol deficiency–mediated impaired free-water excretion and mineralocorticoid deficiency–related renal sodium loss. Cortisol deficiency is known to promote inappropriate antidiuretic hormone (ADH) secretion, leading to impaired free-water excretion and dilutional hyponatraemia that may clinically mimic the SIADH secretion. However, unlike SIADH, primary adrenal insufficiency is typically associated with hypovolaemia due to mineralocorticoid deficiency and renal sodium loss, which was consistent with the patient's clinical presentation.

On admission, thyroid function tests confirmed adequate hormonal replacement. In the presence of clinical signs of dehydration, intravenous rehydration therapy was initiated, starting with hypertonic 3% NaCl solutions administered at an initial dose of 130 ml. The goal was to increase serum sodium by 5 mmol/l and relieve the patient's symptoms of severe hyponatraemia. Rehydration was subsequently continued using 0.9% isotonic NaCl at a dose of 500 ml per day. The therapeutic goal was to increase the serum sodium concentration by 6–8 mmol/l per day. Serum sodium was

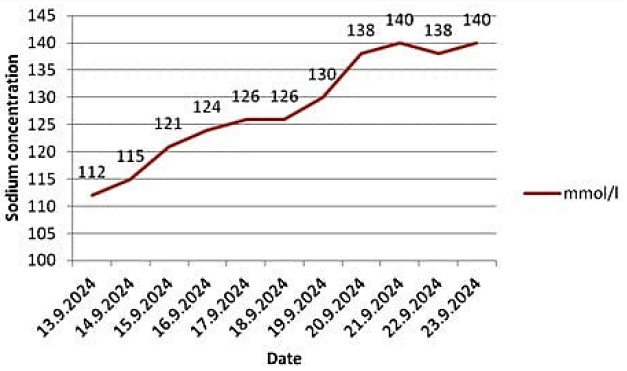


Figure 1. Time course of serum sodium levels during hospitalisation (initial sodium correction was achieved with hypertonic saline infusion, followed by stabilisation after initiation of glucocorticoid replacement therapy).

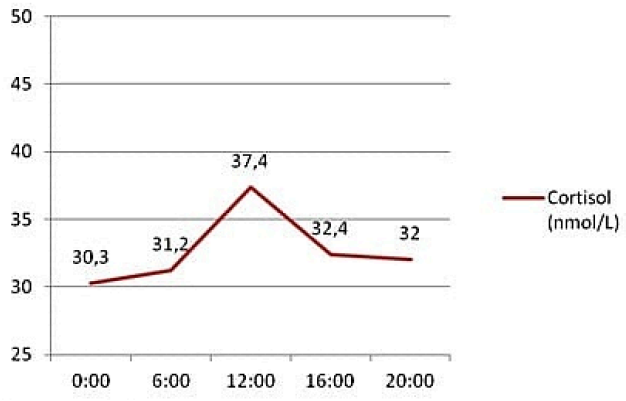


Figure 2. Diurnal cortisol rhythm. Serum cortisol levels measured prior to initiation of glucocorticoid replacement therapy (reference range: 140–690 nmol/l).

monitored closely during therapy, and the rate of correction remained within recommended safety limits; no neurologic complications suggestive of osmotic demyelination occurred. On the seventh day of hospitalisation, following correction of dehydration intravenous therapy was discontinued, and oral NaCl supplementation was initiated in the form of three capsules daily, each containing 1 g of NaCl. The increase in serum sodium concentration is shown in *Figure 1*. Under this treatment, gradual normalisation of sodium levels to physiological values was achieved and dyspeptic symptoms partially resolved.

During the subsequent course, additional endocrine examinations on the third day of hospitalisation revealed hypocortisolaemia with a morning serum cortisol of 31.2 nmol/l (reference range: 140–690 nmol/l). Subsequently, samples were collected to assess the diurnal rhythm of cortisol, which also demonstrated significantly reduced cortisol concentrations throughout the day and night. The results are presented graphically in *Figure 2*. Further endocrine evaluation revealed markedly elevated ACTH levels of 523.6 ng/l (reference range: 7.2–63.3 ng/l), decreased concentrations of C-peptide 0.53 µg/l (reference range: 0.78–1.89 µg/l), insulin 0.9 mU/l (reference range: 3–25 mU/l) and DHEAS <0.08 µmol/l (reference range for adult females: 0.8–8 µmol/l). Due to the patient's deteriorating condition, hydrocortisone replacement therapy was initiated. An ACTH stimulation test was not performed because the patient was already receiving steroid substitution; glycated haemoglobin (HbA1c) was 3% (reference range: 4–5.6%). The very low HbA1c was interpreted with caution, given the presence of anaemia, which may affect HbA1c reliability. During hospitalisation, repeated capillary and plasma glucose measurements did not demonstrate hypo- or hyperglycaemia, and type 1 diabetes mellitus was not confirmed; outpatient follow-up of glycaemic status was recommended. Serological testing and an autoantibody panel – anti-GAD, anti-insulin, anti-IA2 (insulinoma-associated protein-2) were negative. Further hormonal studies showed aldosterone 92.4 pmol/l (reference range: 70–300 pmol/l), renin 0.44 ng/l (reference range for plasma renin concentration: 0.2–2.4 ng/l), metanephrine 0.12 nmol/l (reference range: <0.5 nmol/l) and normetanephrine 0.4 nmol/l (reference range: <0.9 nmol/l). In the subsequent work-up, testing for anti-21-hydroxylase antibodies was performed, which yielded positive results.

Due to persistent dyspeptic symptoms, an esophagogastroduodenoscopy was performed and yielded negative findings, with incidental cardia incompetence. Given the presence of bicytopaenia (leukopenia with neutropaenia and normocytic, normochromic anaemia), additional serological tests were performed, which were negative for HIV, Epstein-Barr virus, cytomegalovirus, parvovirus B19 and hepatitis B and C. Serum levels of

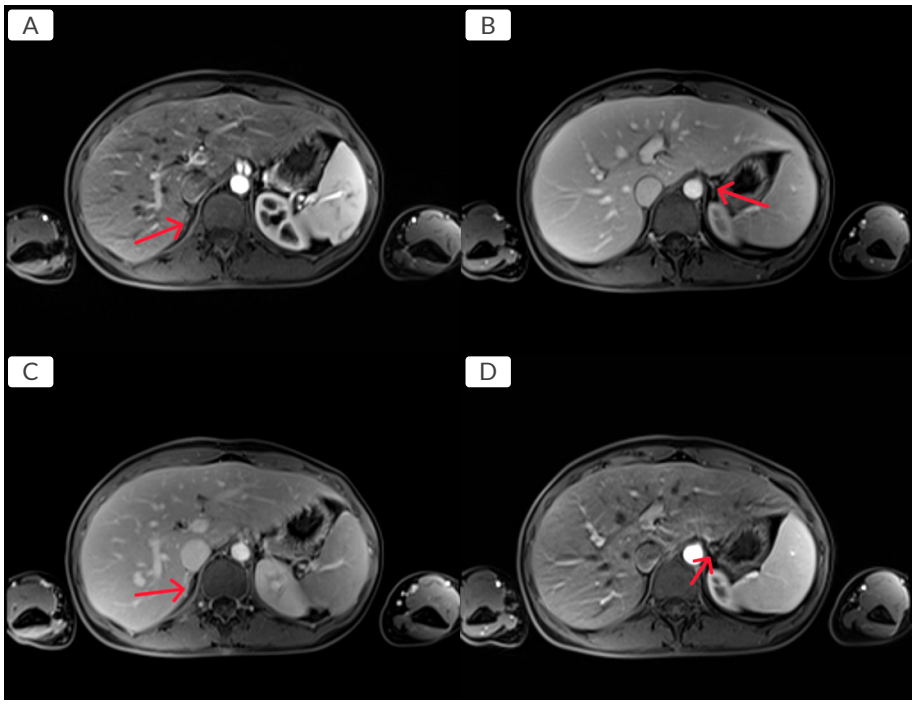


Figure 3. Axial contrast-enhanced MRI images demonstrating marked bilateral adrenal gland atrophy, consistent with chronic primary adrenal insufficiency.

Parameter	Admission	Discharge	Follow-up in 3 months
WBC (×10^9/l)	3	2.9	3.1
RBC (×10^{12}/l)	4.01	3.14	3.56
Haemoglobin (g/l)	124	96	112
MCV (fl)	85.9	88.9	88
Platelets (×10^9/l)	300	203	212
Sodium (mmol/l)	112	140	141
Potassium (mmol/l)	4.2	3.9	4.1
Chlorines (mmol/l)	85	108	102

Table 1. Laboratory results at the time of admission, discharge and at three-month follow-up.

vitamin B12 and folate were within the physiological range. The patient was not taking any medications that could potentially suppress bone marrow activity. Laboratory tests excluded iron deficiency, and there were no signs of haemolysis. The patient also had no evidence of hypersplenism and showed no signs of malnutrition. Further evaluations did not reveal evidence of systemic lupus erythematosus, rheumatoid arthritis, tuberculosis or other diseases that could explain the bicytopaenia. Haematologic assessment suggested anaemia of chronic disease. Anti-granulocyte and anti-lymphocyte antibodies were detected, supporting an autoimmune aetiology of the bicytopaenia. Immunologic testing revealed neutropaenia of likely autoimmune or secondary origin and an IgA antibody deficiency. Rheumatologic evaluation demonstrated the presence of anti-dsDNA antibodies of the IgM class.

A magnetic resonance imaging (MRI) of the brain revealed a pituitary microadenoma measuring up to 2 mm, assessed as an incidental finding. After consultation with an endocrinologist, the patient was initiated on hydrocortisone replacement therapy (10–7.5–5 mg orally) for probable primary adrenal insufficiency (Addison's disease, peripheral form). Follow-up testing of the diurnal cortisol rhythm on this replacement regimen confirmed adequate hormonal compensation.

A subsequent MRI of the adrenal glands demonstrated marked adrenal atrophy *(Fig. 3)*. Based on the comprehensive clinical and laboratory findings, a diagnosis of autoimmune polyglandular syndrome type II was presumed and fludrocortisone was added to the hydrocortisone replacement therapy. Although renin and aldosterone were within the reference range, sampling was performed after intensive fluid and sodium replacement, which may blunt renin–aldosterone activation. Fludrocortisone was therefore initiated based on the overall clinical context of primary adrenal insufficiency and the need to support volume and electrolyte stability.

The patient was discharged in a stable condition with recommendations for regular endocrinology and haematology follow-up. The patient is currently being followed at the endocrinology and haematology outpatient clinics. She attends regular follow-up visits, and her condition remains stable *(Table 1)*.

DISCUSSION

The most common initial clinical manifestation of APS II is Addison's disease, which often presents with non-specific symptoms such as fatigue, gastrointestinal complaints and weight loss[5]. Hyponatraemia may represent the dominant – and occasionally the sole – initial finding in APS II, as was the case in our patient. Early recognition of the endocrine cause of hyponatraemia is crucial, as delayed diagnosis of Addison's disease is associated with increased morbidity and mortality[6]. Although hyperkalaemia is a classic feature of primary adrenal insufficiency, normal potassium levels may be observed, particularly in early disease stages or in the presence of gastrointestinal losses and should not preclude the diagnosis.

Our patient met the diagnostic criteria for APS II by the coexistence of Addison's disease and prior Graves-Basedow thyropathy. The autoimmune aetiology of primary adrenal insufficiency was further supported by the presence of anti-21-hydroxylase antibodies, which are highly specific for autoimmune Addison's disease. Despite reduced C-peptide and insulin concentrations, type 1 diabetes mellitus was not present at the time of evaluation; however, continued clinical and metabolic surveillance was recommended. The patient did not exhibit hyperglycaemia during hospitalisation, diabetes-associated autoantibodies (anti-GAD, anti-IA2, anti-insulin) were negative and the exceptionally low HbA1c was interpreted cautiously in the context of anaemia. Reduced insulin and C-peptide levels in this context likely reflected metabolic suppression related to hypocortisolism rather than established autoimmune diabetes, particularly in the absence of hyperglycaemia and diabetes-associated autoantibodies. A particularly novel and noteworthy aspect of this case was the presence of autoimmune bicytopaenia, characterised by neutropaenia and serological positivity for anti-granulocyte and anti-lymphocyte antibodies. Haematologic manifestations

are not typical features of APS II and have been reported only sporadically in the literature, most commonly as pernicious anaemia or autoimmune haemolytic anaemia[7]. The simultaneous occurrence of Addison's disease and autoimmune cytopaenia is therefore rare and represents a potential expansion of the immunologic phenotype of APS II. The underlying pathogenesis remains incompletely understood, but it is hypothesised to involve cross-reactivity between adrenal and haematopoietic antigens, defects in regulatory T-cell function and shared susceptibility linked to human leukocyte antigen (HLA) class II alleles[8]. Given the presence of autoimmune neutropaenia, increased vigilance for infectious complications is warranted, particularly in the setting of adrenal insufficiency. The anaemia observed at discharge was transient and consistent with anaemia of chronic disease.

Another noteworthy finding was IgA antibody deficiency and the presence of anti-dsDNA antibodies of the IgM class. Isolated positivity of anti-dsDNA antibodies of the IgM class has uncertain clinical significance and is not specific for systemic lupus erythematosus. In our patient, clinical evaluation and additional immunological testing did not support a diagnosis of systemic lupus erythematosus or other systemic autoimmune disease. The finding was therefore interpreted as a marker of broader autoimmune predisposition rather than a disease-defining feature[9].

Bone marrow biopsy was not performed because the clinical, laboratory and immunologic findings did not suggest primary bone marrow pathology. The bicytopaenia was mild to moderate, stable, and lacked features of haematologic malignancy or marrow failure, while alternative causes were excluded. The presence of anti-granulocyte and anti-lymphocyte antibodies and partial haematologic improvement after glucocorticoid replacement supported an immune-mediated and potentially reversible mechanism, making bone marrow biopsy unlikely to add diagnostic value.

Management of APS II is based on lifelong hormone replacement therapy for the affected glands, with adequate glucocorticoid and mineralocorticoid substitution forming the cornerstone of treatment[10]. In our case, initiation of hydrocortisone and fludrocortisone therapy led to stabilisation of the patient's clinical condition and normalisation of electrolyte balance.

This case highlights the need to consider endocrine causes in severe hyponatraemia and emphasises the importance of multidisciplinary management and long-term follow-up in patients with APS II due to the risk of additional autoimmune complications.

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