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Review

Adrenal insufficiency in systematic lupus erythematosus (SLE) and antiphospholipid syndrome (APS): A systematic review

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ABSTRACT

Background: Adrenal insufficiency (AI) is associated with high morbidity and mortality. The aim of this systematic review was to enhance diagnostic approaches and summarize therapeutic strategies in the management of AI in patients with systematic lupus erythematosus (SLE) or antiphospholipid syndrome (APS).

Methods: A literature search of PubMed and Medline databases was performed and 91 publications containing 105 cases were included for the final analysis.

Results: The following frequency of clinical signs and symptoms was noted: abdominal pain (39.04%) was the leading symptom, followed by fever (33.33%), vomiting (23.81%), and nausea (19.05%). APS was present in 73%, SLE in 17% of the patients, while 2% had a diagnosis of both, SLE and APS. ACTH stimulation test (ACTHst) was performed in 18% of cases and 76.6% of them were unresponsive towards stimulation. Variable treatment approaches were used: hydrocortisone was most commonly used (38.09%), followed by fludrocortisone (26.67%), prednisolone (20.00%) and volume replacement treatment (11.43%), respectively.

Conclusions: This analysis highlights the importance of an early diagnosis and initiation of therapeutic management when AI is suspected. In line, signs and symptoms related to autoimmune diseases in patients with AI should be reviewed crtitically.

1. Introduction

Adrenal insufficiency (AI) is caused by adrenal gland dysfunction, leading to insufficient production of the steroid hormone [1,2]. It is categorized regarding its occurrence as primary Addison's disease in parenthesis, which results from an intrinsic factor of adrenal glands, or secondary AI, which is found more frequently and is caused by a lack of adrenocorticotropic hormone (ACTH) production of the anterior pituitary gland [1,2]. Regardless of etiology, it is essential to make an early diagnosis and initiate treatment in order to prevent life-threatening events such as adrenal crisis or shock [1].

Despite this importance of early detection and treatment of AI, only a paucity of published cases found AI as an initial presentation of autoimmune diseases [3,4]. Because AI is not included as a diagnostic criterion of various autoimmune diseases including systematic lupus erythematosus (SLE) or antiphospholipid syndrome (APS), detection rate of AI may remain low in theses autoimmune diseases. Conversely, it is often overlooked that AI patients may present with concomitant autoimmune diseases. Besides, the intersection of clinical manifestations between AI and autoimmune diseases or differential diagnosis of AI as initial presentation or consequence of autoimmune diseases has not been fully investigated [4].

Therefore, through comprehensive analysis of demographic patterns, etiology, clinical manifestations, diagnostic and therapeutic

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approaches reported so far, the aim of this systematic review was to enhance approaches and highlight the importance to make a diagnosis of AI in the context of previously diagnosed patients.

2. Methods

2.1. Search strategy of the literature and study selection

A systematic literature review according to the PRISMA guidelines (Preferred Reporting Items for Systematic Reviews and Meta-analyses) was performed. Three investigators (S.S.K., S.M.J. and I.S.H.) searched PubMed and MEDLINE databases for case reports of AI related to SLE or APS which were published until September 10th, 2017. The search terms were: "(adrenal insufficiency OR Addison OR adrenal failure OR adrenal hemorrhage OR lupus OR SLE OR APS OR anti-phospholipid syndrome.)". No language or date restrictions were applied. Three of the authors (S.S.K., S.M.J. and I.S.H.) screened the titles of the articles. When discrepancies occurred, they were resolved by discussions.

The articles were reviewed sequentially by title screening, abstract screening, and full text screening. After reviewing each manuscript, articles meeting one exclusion criterion were excluded. Exclusion criteria were: (1) articles not reporting on AI cases or not related to SLE or APS; (2) articles not containing cases; (3) letters or reviews; (4) articles which were not accessible in full-text.

To raise the reliability of the analysis, we also excluded case reports which did not contain (1) presenting symptoms of the patients, (2) treatment modalities, (3) outcome and survival.

In total, 592 articles were found by a PubMed and MEDLINE interface search. Firstly, those articles were reviewed by title screening. Two hundred ninety six articles were excluded; 296 were not reporting on AI related to SLE or APS. Secondly, 296 articles were reviewed by abstract screening. One hundred twelve articles were excluded. Among these, 68 did not report on cases with autoimmune diseases, 29 did not include case report, while 13 articles were not accessible in full text and 2 were reviews. Lastly, 184 articles were reviewed by full text screening. Ninety-three articles were excluded, including 50 not related to AI, 31 without reporting a case, 10 were reviews and two letters (comments). Finally, a total of 91 articles including 105 subjects were included. A detailed selection process of articles is presented in Fig. 1 and Supplementary Table 2.

2.2. Extraction of the data

Three investigators (S.S.K., S.M.J. and I.S.H.) extracted the data independently. When discrepancies arose, three authors (S.S.K., S.M.J. and I.S.H.) discussed the value of the data. For each eligible case report, we extracted authors, journal name, publication year, age/sex, presenting symptoms of the patient, electrolytes Na/K (mEq/L), blood pressure (mmHg), remarkable past history, diagnosis of AI, diagnostic methods of AI, diagnosis, time gap between AI and diagnosis of SLE/APS, auto-antibodies, causes, treatments, outcome, and survival.

2.3. Analysis of case reports

From the extracted data, we rearranged the data by patients' age, sex, remarkable past history, etiologies of AI, interval between AI and previous disease, clinical presentation, diagnostic method leading to diagnosis, laboratory findings, cause, treatment, and medication to manage AI (including multiple modalities). We analyzed the data based on simple descriptive measures such as proportions of variables. To compare differences between AI in the context of SLE with that of APS was one of our end points in terms of analysis. Standardized units of cortisol levels (depicted as μg/dL) were used. As there are diverse criteria for the normal range of morning basal cortisol levels, random basal cortisol levels [5], and serum ACTH levels [6], we established a standard level by referring to the respective references. In addition, as criteria for ACTH stimulation tests, which are needed to confirm AI, were also variable, we also defined response criteria upon ACTH stimulation: serum cortisol < 20 μg/dL in a sample obtained 30–60 min after ACTH stimulation was defined as 'unresponsive', whereas ≥ 20 μg/dL after ACTH stimulation was defined as 'responsive' [7]. If the results of ACTH stimulation test were not specified in the respective reports, we defined these cases as 'unknown' with respective to the individual's response.

2.4. Statistical analysis

Statistical analyses were performed using SPSS for Windows version 18.0, SPSS Inc. Regarding continuous variables; Student's *t*-test was used for analysis. In categorical variables Chi-squared was used. Kaplan-Meier survival analysis was performed for analysis of survival. A *p*-value of < 0.05 was considered statistically significant.

3. Results

3.1. Demographic patterns and past histories of the patients

We analyzed 105 cases with AI and autoimmune diseases, including subjects with a diagnosis of either APS or SLE (Table 1). A list of the retrieved case reports is presented in Supplemental Table 2.

The peak of an AI diagnosis was between an age of 40-49 years (23.81%) with a similar distribution also reported for an age range of 30–39 years (20.95%). Only a minority (2.86%) was below 10 years at the time between diagnosis. A balanced occurrence related to gender was reported with a male preponderance (53.3% were male, respectively). During the time of last follow-up, a majority of patients were still alive (88.57%), while some died (3.81%) and the information was not given in the remaining reports (7.61%).

With regard to the past history of patients, it was further divided into cardiovascular, obstetric/gynecological, pulmonary, endocrinologic, renal, neurologic, rheumatologic and others according to the clinical manifestations of patients. A lack of past medical history was observed frequently (32.28%), followed by thromboembolic events including deep vein thrombosis (25.71%), pulmonary embolism (7.61%) and others (3.81%). In addition to thrombotic conditions, hypertension (5.71%) was the second most common diagnosis related to the cardiovascular category. Abortion or miscarriage (10.48%) was the most common obstetric and gynecological past history. Hashimoto thyroiditis (2.86%) was the most common endocrinologic past history. At the time of AI, a minority of patients were already diagnosed with diseases belonging to the spectrum of rheumatology, including APS (3.81%), SLE (2.86%), Sjögren syndrome (0.95%) or Raynaud's phenomenon (0.95%) and joint swelling (0.95%).

3.2. Time relationship between the diagnosis of AI and autoimmune disease

We divided patients into three categories according to the onset of AI in relation to a diagnosis of SLE or APS, namely prior to AI, concurrently diagnosed or a subject diagnosed with SLE or APS after a diagnosis of AI (Table 2).

A majority of patients was diagnosed with APS (73%), while 17% had a diagnosis of SLE and 2% were diagnosed with both, SLE and APS. In most cases, APS or SLE were diagnosed prior to or during the first admission related to AI. However, a proportion of patients were diagnosed with APS (17%) and SLE (11%) after a diagnosis of AI. While SLE and APS were the most frequent diagnoses, other autoimmune diseases such as Takayasu arteritis and systemic sclerosis were also found in AI patients [8].

3.3. Clinical presentations of patients with AI

Clinical presentations were sub-divided into the following

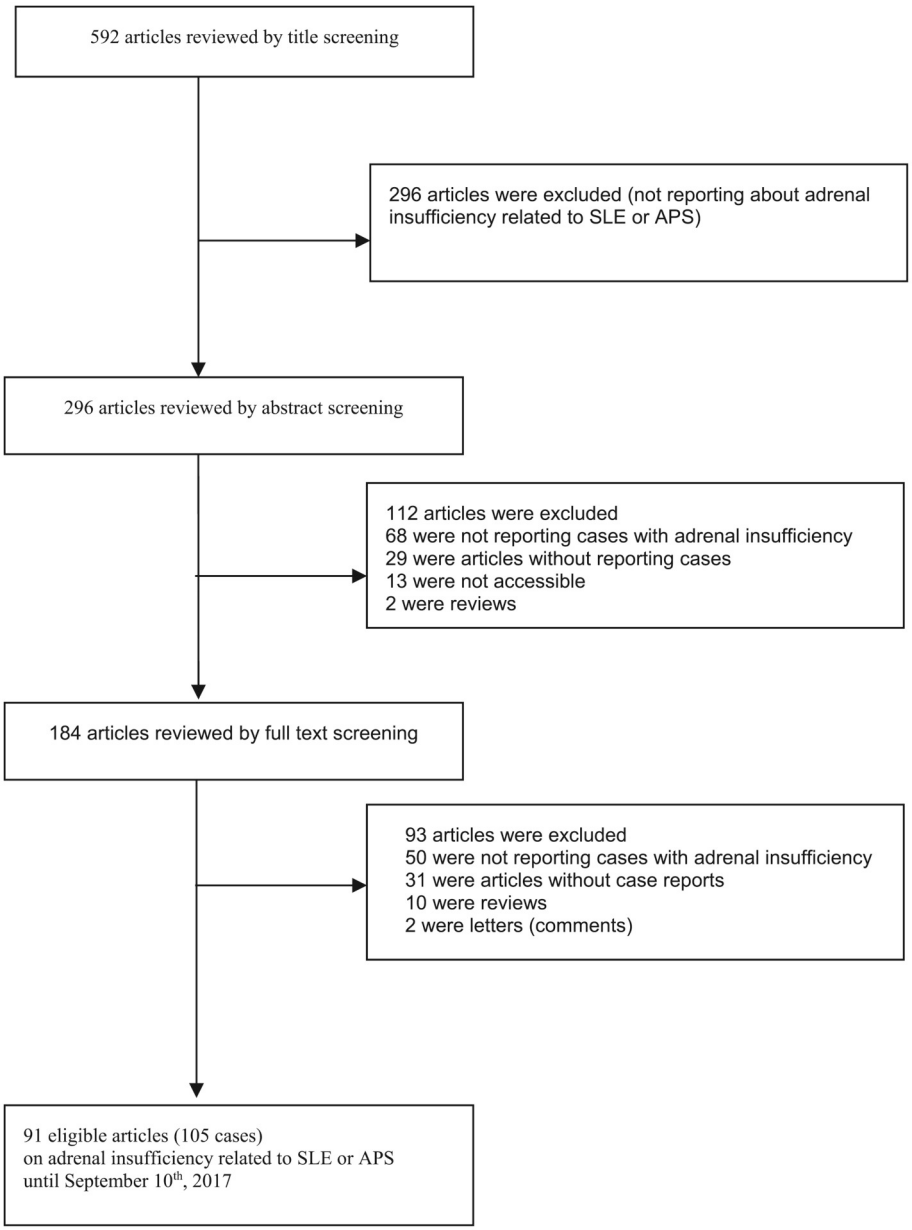

Fig. 1. Flow chart of the literature search. Abbreviations: APS (antiphospholipid syndrome), SLE (systemic lupus erythematosus).

categories: general condition, inflammation-related, pigmentation, pulmonary symptoms, cardiovascular symptoms, gastrointestinal symptoms, renal symptoms and neurologic symptoms (Table 3.).

At the time of AI diagnosis, a majority of patients presented with symptoms associated with the general condition and gastrointestinal system. Abdominal pain (39.04%) was the most common clinical presentation, followed by fever of unknown origin (33.33%), vomiting (23.81%), nausea (19.05%), weight loss (13.33%) and general weakness (9.52%). Pigmentation, a sign of excessive ACTH release, was identified in 7 cases (6.67%). Pulmonary symptoms such as cough (3.81%) or dyspnea (0.95%) as well as renal symptoms such as hematuria (0.95%) or proteinuria (0.95%) were relatively rare.

3.4. Diagnostic work-up for suspected AI

In 105 case reported patients, there were 259 tests to diagnose AI (Table 4). Imaging studies were used 95 times (37%), 98% of them were CT/MRI and the residual 2% was ultrasonography. ACTH stimulation test (ACTHst) was performed in 18% of the cases. According to our categorization (reported above) [9], 76.6% of the included patients were unresponsive towards ACTH stimulation, while the result of the remainders is not known.

Morning basal cortisol levels were measured in 2% of the cases, showing a level $< 3\,\mu g/dL$ in all tests performed which is considered to be highly suggestive for a diagnosis of AI [10]. Random basal cortisol was measured in 24% of cases but considering its fluctuation, random basal cortisol was not regarded as a pathognomonic finding. 24 h urine-free cortisol was measured in 7 cases and majority of them (86%) were within a normal range ($< 50\mu g/day$).

Aldosterone levels were measured in 6 cases and half of them were undetectable and the rest were below 1.0 ng/dL which is still regarded as a lower than normal aldosterone level [11]. ACTH levels were measured in 38 cases and 84% of them were regarded as above the normal range.

3.5. Laboratory findings and blood pressure in patients with AI

We analyzed laboratory findings and vital signs of case-reported

Table 1
Age, sex and remarkable past history of case-reported patients with adrenal insufficiency.

Variables	Total number of patients (n = 105)
	Number of patients (%)
Age (years)	
< 10	3 (2.86%)
10–19	7 (6.67%)
20–29	14 (13.33%)
30–39	22 (20.95%)
40–49	25 (23.81%)
50–59	15 (14.29%)
60–69	12 (11.42%)
> 70	7 (6.67%)
Sex	
Male	56 (53.33%)
Female	49 (46.67%)
Survival	
Alive	93 (88.57%)
Dead	4 (3.81%)
Not informed	8 (7.61%)
Remarkable past history	
Cardiovascular	
Thromboembolic events	39 (37.14%)
Deep vein thrombosis	27 (25.71%)
Pulmonary embolism	8 (7.61%)
Other thromboembolic events	4 (3.81%)
Hypertension	6 (5.71%)
Myocardial infarction	2 (1.9%)
Mitral valve regurgitation	1 (0.95%)
Obstetric & Gynecological	
Abortion, miscarriage	11 (10.48%)
Cesarean section	2 (1.9%)
Hysterectomy	1 (0.95%)
Cystectomy	1 (0.95%)
Pulmonary	
Chronic obstructive pulmonary disease	1 (0.95%)
Lung cancer	1 (0.95%)
Endocrinologic	
Hashimoto thyroiditis	3 (2.86%)
Diabetes mellitus	2 (1.9%)
Diabetes insipidus	1 (0.95%)
Hypogonadism	1 (0.95%)
Renal	
Chronic kidney disease	1 (0.95%)
End stage renal disease	1 (0.95%)
Neurologic	
Epilepsy	1 (0.95%)
Hereditary spastic paraplegia	1 (0.95%)
Hemianopsia	1 (0.95%)
Rheumatologic	
Raynaud's phenomenon	1 (0.95%)
Joint swelling	1 (0.95%)
Others	
Appendectomy	1 (0.95%)
Hip replacement	1(0.95%)
Other surgery	2 (1.9%)
Depression	1 (0.95%)
Abscess	1 (0.95%)
Cellulitis	1 (0.95%)
HBV infection	1 (0.95%)
Drug (Heroin)	1 (0.95%)
Immune thrombocytopenic purpura	1 (0.95%)
Not informed	34 (32.38%)

patients with AI subdivided into 4 major categories; sodium, potassium, blood pressure and auto-antibodies. Among 105 patients, serum sodium levels were not reported in 37 patients (35.24%). Of the remaining patients, hyponatremia was observed in 53 cases (77.94%), while a normal sodium level was reported in 15 patients (22.06%). The potassium level was not reported in 59 (56.19%) patients. Among the remainders, 29 patients (49.15%) presented with hyperkalemia, 25 patients (42.37%) had normal potassium levels and 5 patients (8.47%)

Table 2
Etiologies of case-reported patients with adrenal insufficiency (AI) (Immediacy of diagnosis of AI and interval between AI and previous disease)

Previous disease and immediacy of diagnosis for AI	Total number of patients (n = 105)
	Number of patients (%)
APS	77 (73%)
Prior to AI	18 (23)%
Concurrent Dx	46 (60%)
Later Dx	13 (17%)
SLE	18 (17%)
Prior to AI	7 (39%)
Concurrent Dx	9 (50%)
Later Dx	2 (11%)
SLE/ APS	2 (2%)
Prior Dx of SLE, concurrent Dx of APS	1 (50%)
Concurrent Dx	1 (50%)
Takayasu arteritis	1 (1%)
Prior to AI	1 (100%)
Systemic Sclerosis	1 (1%)
Prior to AI	1 (100%)
Dx of AI without autoimmune diseases	6 (6%)

AI: Adrenal insufficiency; APS: Antiphospholipid syndrome; SLE: Systemic lupus erythematosus. Concurrent Dx; SLE/APS was diagnosed during the period of the first admission which is related to adrenal insufficiency; Prior Dx., SLE/APS was diagnosed before the first admission which is related to adrenal insufficiency; Later Dx., SLE/APS was diagnosed after the discharge from the first admission which is related to adrenal insufficiency.

Table 3
Clinical presentation of case-reported patients with adrenal insufficiency.

Clinical presentation	Total number of patients (n = 105)
	Number of patients (%)
General condition	
Weight loss	14 (13.33%)
General weakness	10 (9.52%)
Fatigue	7 (6.67%)
Lethargy	7 (6.67%)
Confusion	7 (6.67%)
Malaise	5 (4.76%)
Headache	5 (4.76%)
Dizziness	4 (3.81%)
Skin rash	4 (3.81%)
Edema	2 (1.9%)
Myalgia	1 (0.95%)
Inflammation-related	
Fever	35 (33.33%)
Pigmentation	7 (6.67%)
Pulmonary	
Cough	4 (3.81%)
Dyspnea	1 (0.95%)
Pulmonary hypertension	1 (0.95%)
Cardiovascular	
Hypotension	8 (7.61%)
Chest pain	7 (6.67%)
Hypertension	1 (0.95%)
Tachycardia	1 (0.95%)
Gastrointestinal	
Abdominal pain	41 (39.04%)
Vomiting	25 (23.81%)
Nausea	20 (19.05%)
Diarrhea	4 (3.81%)
Constipation	1 (0.95%)
Hemoptysis	1 (0.95%)
Hepatosplenomegaly	1 (0.95%)
Renal	
Hematuria	1 (0.95%)
Proteinuria	1 (0.95%)
Polyuria	1 (0.95%)
Neurologic	
Back discomfort, Flank Pain	7 (6.67%)

Table 4
Methods of diagnosis of case-reported patients with adrenal insufficiency.

Methods	Total number of methods (n = 259)
	Number of methods (%)
Imaging study	95 (37%)
CT/MRI	93 (98%)
Ultrasonography	2 (2%)
Random basal cortisol*	62 (24%)
< 3 μg/dL	42 (68%)
> 3 μg/dL and < 10 μg/dL	16 (26%)
> 10 μg/dL	1 (2%)
Not recorded in the article	3 (5%)
Morning basal cortisol*	4 (2%)
< 3 μg/dL (Highly suspected AI)	4 (100%)
> 3 μg/dL	0 (0%)
Cortisol after ACTH stimulation test*	46 (18%)
Unresponsive (< 20 μg/dL)	44 (96%)
Responsive (> 20 μg/dL)	0 (0%)
Unknown	2 (4%)
Aldosterone*	6 (2%)
Undetectable	3 (50%)
< 1.0 ng/dL	3 (50%)
ACTH*	38 (15%)
High	32 (84%)
Normal (7.2–63 pg/mL)	6 (16%)
24 h urine-free cortisol	7 (3%)
High	1 (14%)
Normal(< 50 ug/day)	6 (86%)

AI: adrenal insufficiency; CT: computed tomography; MRI: magnetic resonance imaging; ACTH: adrenocorticotropic hormone.
All the measured cortisol values were converted to μg/dL, (i.e. from nmol/L, ng/mL to μg/dL).

* Classification for random basal cortisol level is for convenience; Random basal cortisol level alone cannot confirm AI and considering its fluctuation in serum, its normal reference range is controversial. Reference for morning basal cortisol level: (HÄGGE et al. 1987 [5]). An early morning low serum cortisol concentration (< 3 μg/dL [80 nmol/L]) is strongly suggestive of AI. Reference for cortisol level after ACTH stimulation test (Kasper et al. 2015 [9]). Normal random serum aldosterone range: 3–16 ng/dL (Levy et al. 1990 [11]). Normal serum ACTH level range: 7.2–63 pg/mL (Siu SC et al. 1990 [6]).

presented with hypokalemia. Blood pressure levels were available for 64 (60.9%) patients. 44 patients (68.75%) presented with hypotension, while hypertension and normal blood pressure were reported 10 (15.63%) and 19 (29.69%) cases. Regarding auto-antibodies, 94 (89.52%) patients' data were available. Anti-cardiolipin antibody was most frequently detected (56 patients, 59.57%), followed by lupus anticoagulant (51.06%) and anti-nuclear antibody (31.91%). Other information about laboratory findings is presented in Table 5.

3.6. Main causes of AI in case-reported patients

Ten symptoms were reported in AI patients and were present in 94 out of 105 patients (89.52%). Hemorrhage was the leading cause, which was observed in 36 patients (37.89%). Other common findings were infarction and adrenal hematoma, which was found in 19 (20%) and 7 (7.37%) patients, respectively. A detailed list is highlighted in Table 6.

3.7. Treatment of AI

Treatment details were obtained from a total of 100 patients (95.24%). In general, treatment strategies varied considerable, but steroids, volume replacement and anti-coagulants were most commonly used. Regarding steroid treatment, hydrocortisone was most commonly used (40%), followed by fludrocortisone (28%) and prednisolone (21%). Other steroids, such as mineralocorticoids, cortisone and glucocorticoids were used in < 10%. Volume replacement was initiated in 12 patients (12%), with a predominant prescription due to fluid resuscitation (9%). Regarding anti-coagulation, warfarin was prescribed in 23 patients (23%), while 14 patients (14%) received heparin. Other therapeutic measures were also used, and among them, antibiotics were applied in 13 patients (13%). The respective treatment forms are summarized in Table 7.

3.8. Combined treatment strategies of AI

Single therapy was initiated in 44 patients (44%) and steroids were the leading agent (37 patients). Multiple treatment approaches were used in the remaining 56%, whereas a majority of patients received two therapies (43%). Among them, most received a combination of steroids and anti-coagulation (25%). A full list of combination treatment is highlighted in Table 8.

Table 5
Laboratory findings of case-reported patients with adrenal insufficiency.

Laboratory findings	Total number of patients (n = 105)
	Number of patients (%)
Sodium	
Normal	15 (14.29%)
Hyponatremia	53 (50.48%)
No information	37 (35.24%)
Potassium	
Hyperkalemia	29 (27.62%)
Normal	25 (23.81%)
Hypokalemia	5 (4.77%)
No information	46 (43.81%)
Blood Pressure	
Hypertensive	10 (9.52%)
Normal	19 (18.1%)
Hypotensive	44 (41.9%)
No information	41 (39.1%)
Auto-antibodies	
Anti-cardiolipin antibody	56 (53.3%)
Lupus anticoagulant	48 (45.71%)
Anti-nuclear antibody	30 (28.57%)
Anti-dsDNA antibody	13 (12.38%)
Anti-ß2 glycoprotein I	12 (11.43%)
Anti-phospholipid antibody	6 (5.71%)
Anti-SS-A antibody	4 (3.81%)
Anti-smith antibody	4 (3.81%)
Anti-adrenal antibody	3 (2.86%)
Anti-ssDNA antibody	2 (1.9%)
Anti-RNP	2 (1.9%)
Rheumatoid factor	1 (0.95%)
Not informed or undetectable	11 (10.48%)

Sodium normal range: 135–145 mEq/L, Potassium normal range: 3.5–5.0 mEq/L. Blood pressure normal range (SBP/DBP): 90/60–140/90 mm Hg.

Table 6
Cause of case-reported patients with adrenal insufficiency.

Cause of AI	Total number of patients (n = 105)
	Number of patients (%)
Hemorrhage	36 (34%)
Infarction	19 (18%)
Normal imaging	11 (10%)
Adrenal hematoma	7 (7%)
Adrenal enlargement	6 (6%)
Adrenal mass	6 (6%)
Thrombotic tendency	4 (4%)
Adrenal atrophy	2 (2%)
Empty sella syndrome	2 (2%)
Hyporenemic hypoaldosteronism	1 (1%)
Not informed	11 (10%)

Table 7
Treatment of case-reported patients with adrenal insufficiency.

Treatment	Total number of patients (n = 105)
	Number of patients (%)
Steroids	
Hydrocortisone	40 (38.09%)
Fludocortisone	28 (26.67%)
Prednisolone	21 (20%)
Mineralocorticoid	6 (5.71%)
Glucocorticoid	6 (5.71%)
Cortisone + azathioprine	6 (5.71%)
Cortisone	3 (2.86%)
Corticosteroid	3 (2.86%)
Methylprednisolone	2 (1.9%)
Fludrohydrocortisone	2 (1.9%)
Other steroids	11 (10.48%)
Volume replacement	
Fluid resuscitation	9 (8.57%)
Crystalloid/Colloid	1 (0.95%)
Transfusion	1 (0.95%)
Plasmapheresis	1 (0.95%)
Anti-coagulants	
Warfarin	23 (21.9%)
Heparin	14 (13.33%)
Aspirin	6 (5.71%)
Other anticoagulants	9 (8.57%)
Intravenous immunoglobulins	2 (1.9%)
Other agents	
Antibiotics	13 (12.38%)
Cyclophosphamide	3 (2.86%)
Immunosuppressive agents	2 (1.9%)
Vasodilator	2 (1.9%)
Phenytoin	1 (0.95%)
Levothyroxine	1 (0.95%)
Anticonvulsant	1 (0.95%)
Gabexate mesilate	1 (0.95%)
Haloperidol	1 (0.95%)
Procedure	
Adrenalectomy	1 (0.95%)
Not Informed	5 (4.76%)

Table 8
Combination of treatment for case reported patients with adrenal insufficiency.

Treatment	Total number of patients (n = 105)
	Number of patients (%)
Single kind of therapy	44 (41.9%)
Steroids only	35 (33.33%)
Anticoagulant only	8 (7.61%)
Diuretics only	1 (0.95%)
Two kinds of therapy	43 (40.95%)
Steroids + anticoagulants	27 (25.71%)
Steroids + volume replacement	4 (3.81%)
Steroids + antibiotics	3 (2.86%)
Steroids + gabexate mesilate	1 (0.95%)
Steroids + haloperidol	1 (0.95%)
Steroids + hydroxychloroquine	1 (0.95%)
Steroids + levothyroxine	1 (0.95%)
Anticoagulants + volume replacement	4 (3.81%)
Immunoglobulin + cyclophosphamide	1 (0.95%)
Three kinds of therapy	10 (9.52%)
Steroids + anticoagulants + antibiotics	3 (2.86%)
Steroids + antibiotics + volume replacement	3 (2.86%)
Steroids + anticoagulants + procedure	1 (0.95%)
Steroids + anticoagulants + anticonvulsant	1 (0.95%)
Steroids + anticoagulants + immunoglobulin	1 (0.95%)
Steroids + volume replacement + cyclophosphamide	1 (0.95%)
Four kinds of therapy	4 (3.81%)
Steroids + anticoagulants + antibiotics + immunosuppressive agents	1 (0.95%)
Steroids + anticoagulants + immunosuppressive agents	1 (0.95%)
Steroids + anticoagulants + diuretics + vasodilators	1 (0.95%)
Steroids + antibiotics + mannitol + anticonvulsant	1 (0.95%)
Not Informed	5 (4.76%)

4. Discussion

AI occurs in 93–110 in a million people [12,13] and the most common cause is autoimmune destruction [14]. There are two types of AI, primary AI and secondary AI [15]. (1) Primary AI, also known as Addison's disease, results from autoimmune adrenalitis in about 80–90% [16]. The other causes of primary AI are related to drugs, genetic disorders such as congenital adrenal hyperplasia, adrenal infection, adrenal hemorrhage, adrenal metastases and adrenal infiltration [1]. In addition, it is known to be related to many autoimmune diseases such as thyroid disease, diabetes, vitiligo, premature ovarian failure, and pernicious anemia [17]. (2) Secondary AI is usually related to dysfunction of hypothalamus or pituitary gland, caused by brain tumor growth, surgery, irradiation, or exogenous steroid use suppressing hypothalamic-pituitary-adrenal (HPA) axis [15]. Both primary AI and secondary AI present clinical features of glucocorticoid deficiency such as fatigue, weight loss, nausea and vomiting. Therefore, replacement of glucocorticoid is the most important management to avoid acute adrenal crisis [1,18]. In addition, mineralocorticoid replacement is essential in primary AI, which has the symptoms or signs of mineralocorticoid deficiency such as dizziness, salt craving, and hyponatremia [1].

It is important for clinicians to be aware of acute AI when a patient with clinical signs of shock is not improving despite initiation of appropriate treatment, i.e. intravenous fluids or inotropics. In addition, nonspecific symptoms such as abdominal pain, nausea, vomiting, or fever can be crucial features of AI [19]. Despite general measures to improve symptoms, immediate initiation of intravenous glucocorticoid replacement is mandatory to treat acute AI [20].

SLE is a systemic autoimmune disease characterized by presence of tissue-binding autoantibodies and immune complexes resulting in multi-organ damage [21,22]. According to the Systemic Lupus International Collaborating Clinics (SLICC) classification criteria in 2012, SLE can be diagnosed when the patient satisfies 4 or more criteria, requiring at least one clinical criterion such as malar rash, oral ulcer, synovitis, alopecia, serositis, renal involvement, neurological involvement, hemolytic anemia, leukopenia, or thrombocytopenia as well as one immunologic criterion such as antinuclear antibodies, anti-dsDNA antibodies, anti-Sm, antiphospholipid antibodies, low complement, or direct Coombs' test [23]. Clinical features of SLE are heterogeneous and include endocrine manifestations such as autoimmune thyroid disease (3–24% of patients with SLE), diabetes mellitus, increased fracture risk, and vitamin D deficiency, even though these features are not included in the diagnostic criteria of SLE [24]. The association between AI and SLE, however, has not been analyzed so far, mainly because coexistence of SLE and AI is rare and only a few cases have been reported until now [25]. The mechanism of this association is unknown but it is proposed that common autoimmune mechanisms or vasculitis may provoke AI in SLE patients [26]. Overall, the 10-year survival rate of patients with SLE is reported to be approximately 90% [27], but no information exists regarding survival rate of SLE with concomitant AI.

APS is an autoimmune disease characterized by antiphospholipid antibodies which affect coagulation system and presence of recurrent thrombosis or fetal losses [28]. Though endocrine abnormalities involving adrenal, thyroid, pituitary, parathyroid, ovaries, testes, and diabetes mellitus are not a common manifestation or complication of APS, AI has been reported as the most common endocrine manifestation of APS [29]. In general, AI is rarely observed in APS patients, but is more common than in SLE patients. Adrenal crisis as complication of AI can occur in patients diagnosed with SLE or APS [30]. Previous studies

highlighted that 0.4% of patients with APS had primary AI and AI can be the first manifestation of APS [29,31]. Espinosa et al. [32] firstly described the relationship between AI and APS. The etiology of AI associated with APS has not been fully understood; however, it might be explained by vascular thrombosis followed by hemorrhagic infarction of the adrenal gland, being particularly vulnerable to thrombotic events because of a single venous drainage [29,33].

In our analysis, we analyzed 105 cases with AI associated with autoimmune diseases including SLE or APS. The mortality rate of the patients with AI was 3.81%. Given the young age of patients at diagnosis, the mortality rate is rather high and this further highlights the importance of an increased awareness to diagnose AI.

The past medical history of a significant number of patients was positive for cardiovascular diseases, especially deep vein thrombosis. The unique vascular structure of rich arterial supply and limited venous drainage the adrenal gland may prone towards thrombotic events, especially in the context of APS [34]. Furthermore, adrenal hemorrhage was a frequent finding and it is supposed that thrombosis in adrenal veins occurs as a primary event, eventually leading to hemorrhage or infarction of the adrenal gland [33].

Moreover, analyzing the time gap between a diagnosis of AI and the respective autoimmune disease, we found that most cases with AI already had an established diagnosis of the underlying autoimmune disease. However, we found that AI was not diagnosed immediately in many cases, and it might be suspected that neglecting the possibility of AI in the context of autoimmunity may account for the delay of diagnosis, probably leading to inappropriate treatment.

We found that the clinical presentation of patients with AI was as expected, showing gastrointestinal symptoms such as abdominal pain, nausea and vomiting in most cases. Even in the absence of specific features of AI, we propose that AI should be considered as potential differential diagnosis.

In terms of diagnostic work-up for AI, ACTH stimulation test was performed in 18% of the patients, which is considered to be the best tool to confirm AI. Among them, 76.6% were unresponsive, suggesting that most AI patients with autoimmune disease had primary AI. However, since ACTH stimulation test is complicated, our data suggest that appropriate treatment should be given immediately if AI is suspected.

Treatment of patients with AI was initiated according to generally accepted guidelines, among which hydrocortisone and fludrocortisone were used most frequently. Since the patients have been diagnosed with a variety of underlying diseases, most patients received a “multi-target” treatment strategy. Most importantly, every patient received steroid treatment and we can conclude that early steroid initiation is crucial to maintain the high survival rate of patients and reduce overall mortality.

There are some limitations of our work. First, we could not analyze the relationship between the diverse treatment modalities and outcome of patients analyzed in our study. Second, we were not able to obtain data from all cases published so far. Third, a publication bias might be applicable, since we have included mainly single cases in our analysis.

In conclusion, given the paucity related to AI and autoimmune disorders, we believe that this systematic review will increase general awareness about this relationship and may further improve patient management in future. Thus, it seems crucial to extend the diagnostic work-up to investigate potential signs and symptoms related to autoimmune diseases. We feel that further research is necessary to decipher the relationship of autoimmunity and endocrine diseases.

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Conflicts of interest

The authors disclose no conflicts of interest.

Author contributions

J.I.S. designed study, coordinated data acquisition, analyzed and interpreted the data, drafted the manuscript. All authors also participated in the parts of these and read and approved the final manuscript.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.autrev.2018.06.014.

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