Review

ANNALS OF MEDICINE & SURGERY

OPEN

Diverse clinical manifestations and management strategies in autoimmune polyglandular syndrome: a review of cases

Urooj Lalrehman, MBBS, MCPS(Med), FCPS(Med), FCPS (Endo)[a], Hafiz Muhammad Hamza, MBBS[b], Muiz M. Malik, MBBS[b], Mehdi Ali, MBBS[c], Uzair Nayab, MBBS[b], Somaiya Ahmed, MBBS[d,*], Ayaz Ahmed Awan, MBBS[b]

Abstract

Autoimmune polyglandular syndrome (APS) is a rare autoimmune disease that affects multiple endocrine glands. It can lead to various clinical manifestations. The primary objective of this review was to provide a comprehensive analysis of the clinical features and management strategies used in managing APS, based on a review of case reports. We emphasize disease pattern recognition and detection of atypical clinical signs, as well as the outcomes of various treatment modalities. Case reports from credible journals were searched in PubMed, resulting in a systematic literature review adopting the 2020 Preferred Reporting Items for Systematic Reviews and Meta-analysis guidelines. Of the 1173 records identified, 474 remained after duplicates were removed, and 49 full-text articles were reviewed. After further screening based on criteria such as associated disorders, patient age, follow-up, and treatment details, 12 articles were selected for the final analysis. The findings revealed that common endocrine dysfunctions in APS include Addison's disease and hypothyroidism, while non-endocrine manifestations, such as autoimmune encephalitis and pernicious anemia, can also occur. The most frequently adopted strategies were immunosuppressive and hormone therapies. The heterogeneity of APS indicates early diagnosis and individualized treatment strategies. Ultimately, this analysis identifies existing insufficiencies and provides recommendations for formulating standard operating procedures for the treatment of APS.

Keywords: Addison's disease, autoimmune polyglandular syndrome, autosomal recessive disease, endocrine disorder, hypothyroidism

Introduction

Individuals with at least two endocrine disorders in one cluster are said to have autoimmune polyglandular syndrome (APS). Autoimmune polyendocrine syndrome type 1 (APS-1), autoimmune polyendocrine syndrome type 2 (APS-2), and X-linked immune dysregulation polyendocrinopathy and enteropathy (IPEX) are common autoimmune polyglandular disorders[1]. Mutations in the autoimmune regulator gene (AIRE), found on chromosome 21q22.3, are the cause of a rare monogenic hereditary disease known as APS-1. The frequency of APS-1 is population-dependent and generally very low. However, it is more frequently seen among Iranian Jews (1:9000), Sardinians (1:14 400), and Finns (1: 25 000). Conversely, only a few occurrences of APS-1 have been reported in Eastern Asia[2]. It is associated with adrenal insufficiency, hypoparathyroidism, and persistent mucocutaneous candidiasis. Clinical diagnosis is based on the presence of two or more of these three signs[2]. APS-2 is related to chromosome 6 particularly because it is close to the markers for major histocompatibility complex genes responsible for the resulting organ failure. The class II human leukocyte antigen (HLA) alleles DQ2 and DQ8 and haplotypes HLADR3 and HLA-DR4 increase susceptibility to APS-2[3,4]. APS type 3 is defined by the co-occurrence of autoimmune diseases (excluding Addison's disease or hypoparathyroidism), autoimmune thyroid disease (AITD), and type 1 diabetes mellitus (T1DM), which are

HIGHLIGHTS

- APS is a rare autoimmune disease with diverse and atypical clinical manifestations.
- This review explores rare APS cases, including IgG4 disease and autoimmune encephalitis.
- Hormonal panels and autoantibody screening aid in managing complex APS cases.
- Immunosuppressive therapies and surgical approaches showed variable treatment outcomes.
- Calls for standardized APS treatment guidelines to improve patient care and outcomes.

[a]Medicine/Endocrinology, Jinnah postgraduate Medical center/ Jinnah Sindh Medical University, Karachi, Pakistan, [b]Foundation University School of Health Sciences, Islamabad, Pakistan, [c]Faisalabad Medical University, Faisalabad, Pakistan and [d]Sir Salimullah Medical College, Dhaka, Bangladesh

Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

*Corresponding author. Address: Sir Salimullah Medical College, Dhaka, Bangladesh. E-mail: somaiyaahmed1996@gmail.com (S. Ahmed).

Annals of Medicine & Surgery (2025) 87:2774–2783

Received 8 October 2024; Accepted 12 March 2025

Published online 28 March 2025

http://dx.doi.org/10.1097/MS9.0000000000003207

classified under this variant[5]. The pathology of APS-1 stems from mutations in the autoimmune regulator (AIRE) gene, resulting in the loss of immune tolerance and failure to eliminate autoreactive T cells in the thymus, leading to widespread autoimmunity across multiple organs, including the endocrine glands. In contrast, APS-2 develops through interaction between genetic predispositions (especially HLA haplotypes) and environmental triggers (such as infections)[6]. Autoantibodies commonly found in people at risk for APS-2, such as anti-21-hydroxylase, antithyroid peroxidase, and anti-glutamic acid decarboxylase, allow for the diagnosis of the disease in its early phases and before critical organ failure occurs[7]. Endocrine abnormalities in the same population are another approach that aims to prevent dangerous conditions, such as adrenal crisis or diabetic ketoacidosis, from occurring within individuals that are monitored[8]. In the case of APS-1, managing the condition entails hormone augmentation therapy in relation to its deficiencies, which includes administration of hydrocortisone for adrenal insufficiency, calcium and vitamin D for hypoparathyroidism, and antifungal therapy for chronic mucocutaneous candidiasis. Finally, except for the most severe or refractory cases of autoimmune manifestations, immunosuppressive therapies are not usually employed because of the negative impact of treatment, especially with regard to the risk of infection[9]. On the other hand, the aim of management in APS-2 is to treat autoimmune thyroiditis (AIT), type 1 diabetes mellitus (T1DM), and adrenal insufficiency with hormone substitution as a basis of treatment. It is also important to stress that long-term management is compulsory for APS-2 patients because there is a likelihood of the emergence of a new autoimmune disease which may warrant a change in therapy[10]. In addition to advances in screening genetic background and molecular diagnostics, the autoimmunities associated with APS are better identified, thereby improving the patient's quality of life. Early detection and risk assessment strategies for preventive therapy in high-risk groups can also lower the risk of acute endocrine crisis and lead to effective management of the disease[11]. Besides, novel curative approaches like targeted immunotherapies are being developed, but problems persist since there is a high risk for the development of infections and other autoimmunities owing to the existence of polymorphisms in cross-reacting antigens[12]. Although we have made progress in understanding different patterns of APS, challenges still exist regarding its diagnosis and treatment. Because of APS's complexity and diversity, management must adopt a multidisciplinary approach. This review elaborately analyzes 12 different case reports, focusing on the pattern of clinical manifestations and management strategies employed. Table 1 shows the comparative features and clinical characteristics of various types of APS. This comparison was based on data from numerous studies to elucidate the differences and overlaps of various APS types.

Selection methodology

Eligibility criteria

This review focused on case reports of patients diagnosed with APS between 1 January 2014 and 1 September 2024. Both adult and pediatric patients were included to offer a comprehensive view of APS manifestations across age groups. Only case reports and case series published in English were considered to avoid translation issues. Studies were excluded if they involved animal models, non-clinical trials, systematic reviews, or grey literature.

Search procedure

The search was conducted using PubMed, which contains an extensive collection of medical literature. Data collection focused explicitly on APS case reports, ensuring detailed documentation of clinical manifestations, diagnostic pathways, and management strategies.

Search strategy

The Population, Concept, and Context (PCC) framework guided the search strategy, which was developed to answer the question.

- Population (P): "Autoimmune Polyglandular Syndrome," "Polyglandular Autoimmune Syndrome," "APS," "APECED," "Schmidt Syndrome".
- Concept (C): "Case Report," "Case Series," "Clinical Manifestations," "Symptoms," "Signs," "Diagnosis," "Treatment," Management.
- Context (C): "Endocrine Disorders," "Autoimmunity," Multisystem Disease.

Table 1

Comparison between the types of autoimmune polyglandular syndromes (APS)[13–17]

Feature	APS Type 1	APS Type 2	APS Type 3
Primary components	Chronic mucocutaneous candidiasis, hypoparathyroidism, adrenal insufficiency	Adrenal insufficiency, autoimmune thyroiditis, type 1 diabetes	Autoimmune thyroiditis with another autoimmune disease (excluding adrenal insufficiency)
Genetics	Autosomal recessive, AIRE gene mutation	Polygenic, HLA-DR3, HLA-DR4 associations	Polygenic, often linked with HLA-DR3 and HLA-DR4
Onset age	Childhood to early adulthood	Early to mid-adulthood	Adulthood
Gender predominance	Equal distribution between genders	Female predominance	Female predominance
Additional autoimmune diseases	Pernicious anemia, type 1 diabetes, autoimmune hepatitis	Pernicious anemia, vitiligo, myasthenia gravis	Celiac disease, type 1 diabetes, pernicious anemia
Frequency	Rare	Most common	Less common than APS type 2

APS, autoimmune polyglandular syndromes.

Table 2

Search strategy applied in PubMed (Medline)

Iteration	Keywords Used
S5	S1 AND S2 AND S3 AND S4
S4	"Polyglandular Autoimmune Syndrome" OR "Autoimmune Polyendocrinopathy-Candidiasis-Ectodermal Dystrophy" (APECED) OR "Schmidt Syndrome"
S3	"Case Report" OR "Case Series" OR "Clinical Manifestations" OR "Symptoms" OR "Diagnosis" OR "Treatment" OR "Management"
S2	"Autoimmune Polyglandular Syndrome" AND "Diagnosis"
S1	"Autoimmune Polyglandular Syndrome"

Limiters: Publication year from 2014 to present, using advanced search.

Table 2 outlines the strategy for searching and the key word iterations required to identify appropriate literature on autoimmune polyglandular syndrome.

Screening and selection

This systematic review was conducted following the 2020 update of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA-S) guidelines used for literature search reporting[18]. A total of 1173 records were identified through the primary database search, with no other supplementary sources. After eliminating 699 duplicates, a total of 474 records remained. From this pool, 425 were excluded based on criteria such as reviews, randomized controlled clinical trials (RCTs), and meta-analyses, leaving 49 records marked for full-text retrieval. An initial screening of 49 articles resulted in the selection of articles for further review. Of these 49 articles considered for a further review, 14 were eliminated as they only discussed simple streamlined APS cases without any pertinent associated disorder, included in their title or doi number. Six instances were excluded because they were not limited to autoimmune diseases but had other primary conditions. As far as five articles are concerned, they had similar co-occurring disorders, while three had less than six-year-old patients under discussion. Also, an additional five articles did not have proper follow-up, and four did not have adequate treatment, resulting in the definitive inclusion of 12 articles in the final review (Fig. 1).

Results

The clinical presentations, diagnoses, and outcomes of the 12 patients with APS and its associated diseases are summarized in Table 3. These individual cases illustrate the variation in the symptoms of APS and how different treatments have been used; they also provide information regarding the complexity and variability of this disease.

Discussion

Analysis of common themes

Several common medical traits and dilemmas emerged in 12 reviewed cases. The majority of individuals had several auto-immune conditions primarily affecting the endocrine system, with Hashimoto's thyroiditis, T1DM, and adrenal insufficiency[19,24] being more common than others. Other frequently coexisting disorders include autoimmune hepatitis (AIH), rheumatoid arthritis (RA), and autoimmune polyendocrinopathy[21,27]. For certain patients, especially those with overlapping or atypical symptoms, there exist a large number of significant diagnostic challenges, which makes diagnosis either difficult or delayed. For example, the syndrome of adrenal insufficiency could be concealed by other autoimmune symptoms at times, thus adding complexity to the clinical presentation. Hormonal replacement therapies (such as insulin for T1DM) are standard treatment methods, and hormone replacement therapies are not the only ones such as levothyroxine for thyroiditis and immunosuppressive treatments (e.g., corticosteroids); in some cases, doctors may also prescribe surgery. However, despite these interventions, it is difficult to achieve stability[27–30].

Uncommon presentations

Furthermore, these instances epitomized numerous uncommon or uncharacteristic manifestations of APS, emphasizing its clinical diversity. One case involved the deficiency of isolated GnRH, an abnormal endocrine expression in APS that is rarely mentioned in the literature[27]. Another case presented with IgG4-related disease, a rare overlap that added complexity to the diagnosis and management[27]. Similarly, a case of SACD associated with vitamin B12 deficiency portrayed an uncommon neurological manifestation of APS-II[26]. Such bizarre presentations highlight the importance of increased clinical alertness as well as personalized diagnosis and treatment. One patient presented with a triad of Hashimoto thyroiditis, immunological crescentic glomerulonephritis mediated by ANCA, and secondary hyperparathyroidism that treated with 600 mg/d elemental calcium, 2.5 µg/d active vitamin D3, and immunosuppressive treatment. This comprehensive approach improves kidney function and controls thyroid and parathyroid disorders, indicating the need for timely diagnosis and individualized treatment[27]. Another patient had T1DM and immune thrombocytopenic purpura in addition to heparin-induced thrombocytopenia, where initiating insulin therapy and stopping heparin were essential for controlling hyperglycemia and purpura episodes[30].

Management outcomes

Hormone substitution therapies usually stabilize primary endocrine dysfunctions such as insulin treatment for T1DM and levothyroxine for thyroiditis[31–33]. Nevertheless, several patients have experienced numerous modifications in their therapeutic protocols because of persistent psychological disturbances or the emergence of fresh autoimmune disorders. For instance, some cases were complicated by conditions such as autoimmune hepatitis or IgG4-related disorder that required subsequent addition of immunosuppressive therapy like corticosteroids[28]. Surgical procedures such as thymectomy for patients suffering from

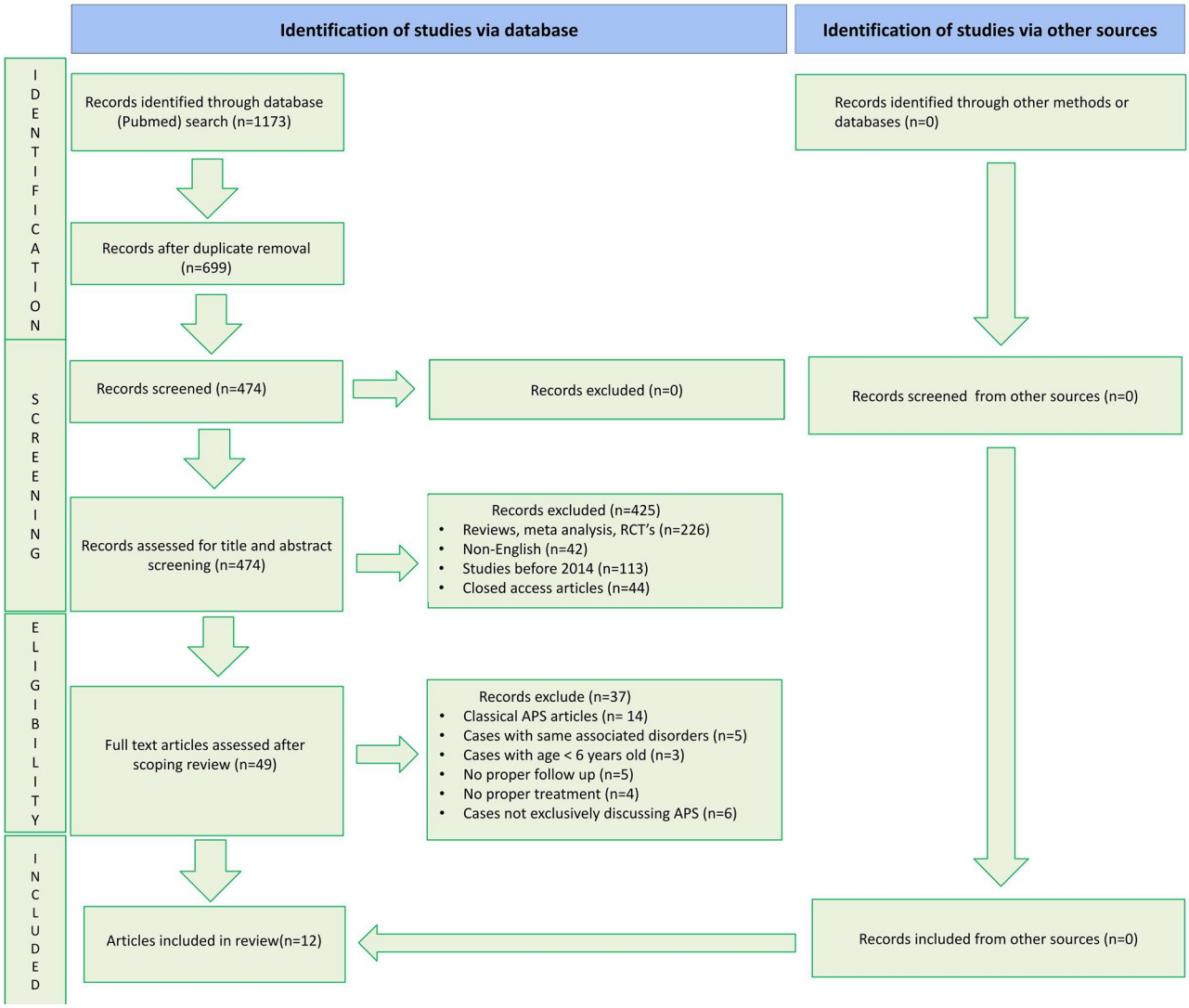

Figure 1. PRISMA flow diagram of the literature selection process. APS: autoimmune polyglandular syndrome; RCTs: randomized controlled clinical trials.

thymoma-related myasthenia gravis are effective in relieving specific symptoms; however, careful postoperative follow-up is needed[22]. When patients did not accept conventional therapies such as steroid-related treatments for IgG4[28], results were uncertain, indicating patients' compliance with the doctor's prescriptions has significant importance.

Prognostic factors

Numerous factors have been reported to contribute to the long-term outcomes of patients with APS. Specific organ involvement also plays an important role, since adrenal failure and type 1 diabetes mellitus have been documented as having a highly significant morbidity risk if not treated properly. Additional autoimmune disorders such as RA or AIH also contribute significantly in this regard[21,22], and the future prognosis is made more complex by these factors because they require wider and longer treatment regimens. Lastly, patient treatment adherence to hormone replacement therapy, including immunosuppressive medications, has significant effects on the outcomes. Owing to side effects, non-adherence affects decisions or preferences, mainly causing disease instability and poor clinical outcomes[34]. These findings suggest the importance of a comprehensive, multidisciplinary strategy for managing APS, according to the patient's clinical presentation and needs.

Clinical implications

Diagnostic approach

A diagnostic methodology is necessary for the management of APS. For instance, patients with unusual autoimmune diseases should exhibit indications that they are highly suspected of having APS by their doctors if they have several endocrine disorders (as seen in the reviewed cases). The first screening should include broad hormonal panels to evaluate thyroid function (TSH, free T4, and T3)[32], adrenal function (cortisol, ACTH)[35], and glucose levels (fasting glucose, HbA1c). Given the prevalence of T1DM and autoimmune thyroiditis in APS, testing for autoantibodies such as anti-glutamic acid

Table 3

Summary of clinical presentations, diagnoses, and outcomes in patients with APS and associated disorders: a review of cases

Case	Age/ Gender	Symptoms	Diagnosis	Key Findings	Treatment	Outcome	Source
1	20-year-old male	Polyuria, polydipsia, history of chronic mucocutaneous candidiasis, adrenal insufficiency, autoimmune thyroiditis, alopecia	APS-1 with central diabetes insipidus	24 h urine output of 9.1 L, low urine osmolality (114 \milliosmoles per kilogram of water), normal adrenal and thyroid function, no significant MRI findings in pituitary/ hypothalamus	Desmopressin 0.1 mg every 8 h	Symptoms improved, urine output reduced to 3 L/day	Chen, 2021[19]
2	8-year-old male	Generalized convulsions, increased sleep, thirst, poor appetite, uncontrolled blood glucose	Anti-GAD antibody-positive, autoimmune encephalitis associated with APS-II	Abnormal EEG, MRI showing hippocampal changes, hypothyroidism, positive anti-GAD65 antibodies, elevated HbA1c	Insulin regimen, IVIG for 5 days, followed by oral prednisone and sodium valproate	Favorable outcome; discharged with oral medications	Sapana, 2023[20]
3	77-year-old female	Polyarthralgia, hyperglycemia, liver dysfunction	T1D and Graves' disease in RA and T2D	Poor glycemic control, positive GAD and TRAb antibodies, elevated free T3/T4, methotrexate liver toxicity	Insulin, methotrexate, adalimumab for RA, thiamazole for Graves' disease	Clinical course improved after therapy adjustments	Horino, 2020[21]
4	52-year-old female	Loss of appetite, fatigue, mucosal pigmentation, ptosis	APS-2, AIH, thymoma-associated MG	Adrenal cortex antibodies positive, decreased cortisol, thymoma detected, elevated anti-AChR-Ab	PSL, fludrocortisone, pyridostigmine (withdrawn), thymectomy, azathioprine for AIH	Symptom resolution post-thymectomy, decreased anti-AChR-Ab, no MG recurrence after 10 months	Inaba, 2020[22]
5	34-year-old female	Weakness, reduced vision, fatigue, weight loss, rash	APS type II, atypical scleromyxedema	Low free T4 and cortisol, positive anti-thyroid antibodies, adrenal cortex autoantibodies, lung fibrosis	Levothyroxine, methylprednisolone, glucocorticoids, plasmapheresis, interferon-alpha-2b (discontinued)	Symptom improvement, lifelong therapy	Prylutskyi, 2016[23]
6	42-year-old male	Extreme thirst, frequent urination, increased appetite, vertigo, weariness, dry mouth, breathlessness, unintentional weight loss, poor glycemic control	LADA with APS-3	BMI: 17.6 kg/m^2, BP: 90/50 mmHg, pulse: 120/min; poor glycemic control despite oral medications	Insulin therapy (10 units Lantus, 6 units rapid-acting); oral hypoglycemics stopped	HbA1c levels reduced; weight trending toward normalization; symptoms resolved	Rehman (2024)[24]
7	39-year-old male	Hyperglycemia, fever, headache, general fatigue, hallucinations, delusions, mood depression, convulsive seizures	APS-3 with acute-onset type 1 diabetes and anti-NMDA-R encephalitis	GAD-Ab: 300 U/mL, urinary ketone bodies: 3 +, anti-thyroglobulin and anti-thyroid peroxidase antibodies positive, mild anti-NMDA-R antibody positivity	Multiple insulin therapy, levetiracetam, steroid pulse therapy (methylprednisolone)	Hallucinations, delusions, and depression improved; Hasegawa-type dementia scale improved; returned to work; no recurrent symptoms after one year	Kurozumi et al. (2021)[25]
8	50-year-old male	Subacute onset weakness in limbs, tingling, numbness, urinary retention, constipation, alopecia, hyperpigmentation, vitiligo, confusion, disorientation	APS-II with subacute combined degeneration of the spinal cord (SACD)	Macrocytic anemia, pancytopenia, hyponatremia, positive anti-TPO antibody, positive intrinsic and parietal cell antibodies, low vitamin B12, cortisol, and ACTH levels, sensorimotor axonal polyneuropathy, MRI findings of SACD	Parenteral vitamin B12, folic acid, IV hydrocortisone, insulin, levothyroxine	Improvement in blood pressure, sensorium, and neurological symptoms; patient in follow-up	Bapat et al. (2022)[26]
9	43-year-old woman	Palpitations, emaciation, hyperhidrosis, hyperphagia, hunger, weight loss, menstrual cycle disorder, decreased libido	APS-3 with Graves' disease, LADA, and isolated GnRH deficiency	Low TSH, high FT3 and FT4, positive TRAb, GAD antibody >2000 IU/mL, C-peptide deficiency, normal pituitary MRI, abnormal GnRH stimulation test, HLA DQ2 and DR8 genotypes	Methimazole, intensive insulin therapy, estrogen replacement therapy (recommended but refused by patient)	Stabilization of thyroid function, improved glucose control, patient refused HRT for menopause management	Jiang et al. (2021)[27]

(*Continued*)

Table 3

(Continued).

Case	Age/ Gender	Symptoms	Diagnosis	Key Findings	Treatment	Outcome	Source
10	52-year-old woman	Swelling of bilateral submandibular glands, low platelet count, type 1 diabetes mellitus (11 years)	APS-3 complicated with IgG4-related disease and Hashimoto's thyroiditis	Elevated IgG4 levels (405 mg/dL), positive anti-glutamic acid decarboxylase (GAD) antibody, positive anti-insulin antibodies, positive anti-thyroid peroxidase (TPO) antibody, storiform fibrosis, and plasma cell infiltration in glands, IgG4/IgG ratio > 40%	Multiple daily insulin therapy, bilateral submandibular gland resection, patient refused steroid therapy	Stable condition without steroid therapy for 2 years	Murata et al. (2024)[28]
11	51/Female	Enlarged thyroid, alopecia, renal insufficiency, fever, rash, arthralgia, mild anemia, exophthalmos, proteinuria, osteoporosis	Hashimoto thyroiditis, ANCA-mediated crescentic glomerulonephritis, thyrotoxicosis, Secondary hyperparathyroidism	Enlarged thyroid, elevated anti-TPO, anti-Tg, positive p-ANCA, MPO-ANCA, crescentic nephritis, elevated FT3/FT4, suppressed TSH, elevated PTH, osteoporosis (T score: −3.17 lumbar)	Levothyroxine sodium, methylprednisolone, calcium, vitamin D3	Improved renal function, transient thyrotoxicosis, managed osteoporosis	Tian S et al. (2020)[29]
12	77/Female	Thirst, fatigue, nausea, loss of appetite, high blood pressure, high heart rate, hyperglycemia, ketoacidosis, renal dysfunction, atrial fibrillation, purpura on legs	Basedow's disease, ITP, type 1B diabetes mellitus, HIT, APS type 3	Hyperglycemia (glucose: 737 mg/dL), ketonemia, suppressed insulin, anti-HIT antibody positive, thrombocytopenia ($40 \times 10^3/\mu L$), anti-GAD antibodies negative, APS type 3 diagnosis, history of stroke and atrial fibrillation, HLA-DRB1 and DQB1 alleles	Fluid replacement, insulin, heparin (discontinued due to HIT), prednisolone for ITP	Hyperglycemia and ketoacidosis improved with insulin, purpura disappeared after stopping heparin, ITP normalized after prednisolone therapy	Kinoshita T et al. (2018)[30]

APS: autoimmune polyglandular syndrome; GAD: glutamic acid decarboxylase; EEG: electroencephalogram; IVIG: intravenous immunoglobulin; T1D: type 1 diabetes; T2D: type 2 diabetes; RA: rheumatoid arthritis; anti-AChR-Ab: anti-acetylcholine receptor antibody; AIH: autoimmune hepatitis; MG: myasthenia gravis; LADA: latent autoimmune diabetes in adults; BP: blood pressure; BMI: body mass index; anti-NMDA-R: anti-n-methyl-d-aspartate receptor; HbA1c: hemoglobin a1c; TPO: thyroid peroxidase; ACTH: adrenocorticotropic hormone; MRI: magnetic resonance imaging; SACD: subacute combined degeneration of the spinal cord; TSH: thyroid-stimulating hormone; FT3: free triiodothyronine; FT4: free thyroxine; TRAb: thyrotropin receptor antibody; GnRH: gonadotropin-releasing hormone; HLA: human leukocyte antigen; IU/mL: international units per milliliter; mmHg: millimeters of mercury; kg/m^2: kilograms per square meter; mOsm/kg: milliosmoles per kilogram; HRT: hormone replacement therapy; anti-Tg: anti-thyroglobulin; p-ANCA: perinuclear antineutrophil cytoplasmic antibodies; MPO-ANCA: myeloperoxidase antineutrophil cytoplasmic antibodies; ITP: immune thrombocytopenia; HIT: heparin-induced thrombocytopenia; MRI: magnetic resonance imaging.

decarboxylase (GAD), anti-thyroid peroxidase (TPO), and anti-thyroglobulin antibodies is crucial[34,36]. When it comes to uncommon illnesses, such as those affecting the brain, more tests might be needed, including brain MRI, serum autoantibodies for diseases such as pernicious anemia or anti-NMDA receptor encephalitis[25], and EEG[20]. For those with potential dysfunction in organs outside the endocrine system, such as in IgG4-related disease[28], or issues involving the liver or glands depending on patient history, imaging techniques and biopsies can be performed to confirm the diagnosis and assess disease severity.

Treatment recommendations

The treatment of primary endocrine deficiencies largely relies on hormone replacement therapy. For example, insulin should be administered immediately in patients with T1DM, whereas those suffering from hypothyroidism require levothyroxine. Corticosteroid replacement with hydrocortisone or fludrocortisone is an absolute necessity in cases of adrenal insufficiency[31–33]. Immunosuppressive therapy should be considered when there are complicated conditions like autoimmune hepatitis, IgG4-related disease[28], and myasthenia gravis[22] in APS. Corticosteroids, employed alone or in combination with other immunosuppressants such as azathioprine or methotrexate, can control inflammation, thereby helping to prevent disease progression[21,27,37,38]. On rare occasions, when a thymoma is associated with myasthenia gravis, it may be necessary to perform thymectomy[22,39,40], after which close postoperative management is essential.

Hypoglycemic agents

In APS, especially types 1 and 2, patients frequently develop autoimmune T1DM, where the immune system attacks insulin-producing beta cells in the pancreas. The destruction of these cells leads to insulin deficiency, which necessitates insulin therapy. Insulin fits into the treatment framework for APS: T1DM is a typical manifestation of APS, requiring insulin therapy to maintain blood glucose control and avoid life-threatening complications such as diabetic ketoacidosis (DKA)[19,24,41]. Additionally, insulin therapy is a crucial part of a comprehensive treatment plan to manage multiple gland failures in patients with APS because it is frequently used in conjunction with hormone replacement therapies for other gland deficiencies, such as cortisol for adrenal insufficiency and thyroxine for hypothyroidism[41,42].

Immunosuppressants

Hydrocortisone, a glucocorticoid, is essential for controlling adrenal insufficiency, which is frequently observed in APS (especially APS-1). Adrenal insufficiency in APS occurs due to autoimmune injury to the adrenal glands, which causes Addison's disease. Patients with autoimmune adrenal insufficiency (Addison's disease), a characteristic of APS-1 and possibly APS-2, require lifelong replacement medication with hydrocortisone to prevent adrenal crisis, which can be fatal if untreated; hydrocortisone is necessary during stress, sickness, or surgery, when the body's cortisol levels rise. In APS patients with adrenal insufficiency, the dose of hydrocortisone is increased during these intervals to avoid adrenal crisis, which can lead to shock, coma, or death if ignored[43]. The management of APS concomitant with rheumatoid arthritis (RA) requires anti-TNF agents[43]. Adalimumab hinders its activity by attaching to the TNF-α receptor, thus reducing joint inflammation. Hence, it helps curb or minimize further joint destruction due to RA while minimizing its symptoms. Ultimately, decreasing TNF-α drives the inflammatory cascade; therefore, adalimumab has helped to increase the quality of life and maintain joint functions[44,45].

Thyroid hormone replacement therapy

Levothyroxine is a synthetic version of thyroxine (T4), a hormone generated by the thyroid gland. In APS, autoimmune damage to the thyroid gland frequently results in hypothyroidism, which is defined as inadequate thyroid hormone production. Managing hypothyroidism in patients with APS is critical for maintaining metabolic balance and avoiding related problems[46]. Levothyroxine treats hypothyroidism symptoms such as tiredness, weight gain, cold sensitivity, depression, and cognitive impairment by restoring thyroid hormone levels. To minimize undesirable interactions, levothyroxine medication should be carefully coordinated with other therapies (such as hydrocortisone for adrenal insufficiency). For example, starting levothyroxine before proper treatment of adrenal insufficiency might result in an adrenal crisis due to increased metabolic demand[46,47].

Vitamin D

Many patients with APS, particularly those receiving long-term corticosteroid therapy (for adrenal insufficiency or other autoimmune disorders), are at a higher risk of osteoporosis and fracture[48]. Vitamin D, along with calcium, is essential for maintaining bone density and preventing corticosteroid-induced osteoporosis. Vitamin D affects the immune system by modifying T cell responses, thereby lowering the likelihood of excessive autoimmune reactions. Vitamin D promotes the transition from pro-inflammatory (Th1) to anti-inflammatory (Th2) immunological responses. In APS, when autoimmune damage affects many glands, vitamin D may potentially lower the intensity of autoimmune episodes[49].

Antidepressant therapy

Depression is widespread in individuals with chronic autoimmune disorders, including APS, due to the extended duration of the illness, hormonal abnormalities, and burden of managing many health concerns[50]. Antidepressants can help improve the quality of life of patients with APS who suffer from mental health disorders including sadness and anxiety. Selective serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs) are frequently recommended for treating sadness and anxiety in patients with APS. Depression in APS can be caused by both psychological stress and endocrine dysfunctions, such as hypothyroidism and adrenal insufficiency, which affect mood regulation[51]. Long-term autoimmune activity in APS can cause chronic inflammation, potentially affecting the brain and the central nervous system. Some antidepressants, such as tricyclic antidepressants (TCAs) and SNRIs, have been demonstrated to have anti-inflammatory and neuroprotective characteristics, which may be advantageous in lowering the

neuroinflammatory processes associated with autoimmune illnesses[50,51].

Estrogen replacement therapy

The variable effects of estrogen replacement therapy (ERT) on autoimmune diseases necessitate careful consideration of the condition and patient characteristics before. For instance, estrogen may have an influence on disease activity in systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA), among others[52]. This is because, immunologically, it is known that estrogens can affect immune responses either negatively or positively depending on the situation. In cases where, for instance, SLE flares up synchronously with hormonal changes, estrogen could be associated with an exacerbation of symptoms. In contrast, estrogen replacement can manage symptoms due to deficiency of this hormone particularly among postmenopausal females[53].

Follow-up and monitoring

Regular follow-up and continuous monitoring are crucial for APS management. This is due to the tendency of the syndrome to change over time, coupled with the emergence of new autoimmune disorders. The periodic assessment of endocrine function should be performed, which includes checking thyroid hormone levels, blood glucose levels, and adrenal function tests regularly. This is a significant step in identifying asymptomatic conditions before they develop into symptomatic ones[40].

Considering the possibility of long-standing complications such as those associated with chronic glucocorticoid consumption[54] or the evolution of autoimmune hepatitis, it is also advocated for liver function tests as well as bone density scans. Improving results and averting disease aggravation can be helped by educating patients about the need for adherence to medications, as well as making changes in their lifestyle together with regular clinical assessments. In addition, some sort of proactive comprehensive management strategies will enable clinicians to handle APS efficiently, enhance the quality of life of these individuals, and mitigate any chances of complications[40,55].

Future directions

In the future, larger multicenter studies should be conducted to validate the findings from this case series and gain an understanding of the entire spectrum of APS clinical manifestations and management outcomes. In addition, looking into new autoantibodies or immune dysregulation biomarkers as new diagnostic markers would enhance precise and timely diagnosis in atypical cases particularly in APS. Finally, research on long-term follow-up regarding different treatment modalities including hormone replacement therapy and immunosuppressive drugs would help to optimize management and improve patients' quality of life.

Conclusion

This review highlights the astonishing diversity of clinical presentations and management strategies among patients with autoimmune polyglandular syndrome. The reviewed cases demonstrate that APS can present with a wide spectrum of symptoms affecting different organ systems and requiring specific therapeutic approaches. Despite the heterogeneity observed, there were common themes, such as the importance of early diagnosis, hormone replacement therapy, and careful long-term follow-up as major determinative factors in managing APS effectively. For general physicians, internists, endocrinologists, and pediatricians, the key takeaway is that APS diagnosis is often missed in the early stages when patients are treated for other conditions. It is only after failure to respond to standard therapies that immune studies are performed, leading to a more accurate diagnosis. This highlights the importance of considering the potential relationship between APS and associated disorders. Treating these disorders separately can result in complications, so a more integrated approach is essential for timely diagnosis and effective management.

Ethical approval

Ethics approval was not required for this article as it is a review of previously published case reports. No new human or animal data were collected or used in the analysis, and the study involved reviewing data available in the public domain.

Consent

Informed consent was not applicable for this review, as the study is based on previously published case reports, which did not involve any new data collection from patients.

Sources of funding

No source of funding.

Author's contribution

U.L. supervised, conceived, designed, and did statistical analysis and editing of the manuscript and is responsible for the integrity of the article. H.M.H. conceived, designed, and did statistical analysis and editing of the manuscript and is responsible for the integrity of the article. M.M.M., M.A., U.N., S.A., and A.A. A. conceived, designed, and reviewed manuscript writing and approved the final version of the article. U.L. and H.M.H. did review and final approval of the manuscript.

Conflicts of interest disclosure

No conflict of interest.

Guarantor

Urooj Lalrehman and Hafiz Muhammad Hamza will accept full responsibility for the work.

Research registration unique identifying number (UIN)

Not applicable.

Provenance and peer review statement

It was not invited.

Data availability statement

Data are publicly available.

Acknowledgments

None.

Presentations

None.

References

[1] Husebye ES, Anderson MS, Kämpe O. Autoimmune polyendocrine syndromes. N Engl J Med 2018;378:1132–41.
[2] Perniola R, Fierabracci A, Falorni A. Autoimmune Addison's disease as part of the autoimmune polyglandular syndrome type 1: historical overview and current evidence. Front Immunol 2021;12:606860.
[3] Kraus AU, Penna-Martinez M, Shoghi F, *et al*. Monocytic cytokines in autoimmune polyglandular syndrome type 2 are modulated by vitamin D and HLA-DQ. Front Immunol 2020;11:583709.
[4] Pham-Dobor G, Hanák L, Hegyi P, *et al*. Prevalence of other autoimmune diseases in polyglandular autoimmune syndromes type II and III. J Endocrinol Invest 2020;43:1–9.
[5] Betterle C, Furmaniak J, Sabbadin C. Type 3 autoimmune polyglandular syndrome (APS-3) or type 3 multiple autoimmune syndrome (MAS-3): an expanding galaxy. J Endocrinol Invest 2023;46:643–65.
[6] Anderson MS, Su MA. AIRE expands: new roles in immune tolerance and beyond. Nat Rev Immunol 2016;16:247–58.
[7] Schatz DA, Winter WE. Autoimmune polyglandular syndrome. II: clinical syndrome and treatment. Endocrinol Metab Clin North Am 2002;31:339–52.
[8] Sperling MA, Angelousi A, Yau M. Autoimmune polyglandular syndromes. In: Feingold KR, Anawalt B, Blackman MR *et al*, eds. Endotext. South Dartmouth, MA; 2024. Available from https://www.ncbi.nlm.nih.gov/books/NBK279152/.
[9] Bornstein SR, Allolio B, Arlt W, *et al*. Diagnosis and treatment of primary adrenal insufficiency: an endocrine society clinical practice guideline. J Clin Endocrinol Metab 2016;101:364–89.
[10] Kahaly GJ, Frommer L. Polyglandular autoimmune syndromes. J Endocrinol Invest 2018;41:91–98.
[11] Vitozzi S, Correa SG, Lozano A, *et al*. A novel missense mutation in the AIRE gene underlying autoimmune polyglandular syndrome type 1. Immunogenetics 2024;76:69–74.
[12] Jung SM, Kim WU. Targeted immunotherapy for autoimmune disease. Immune Netw 2022;22:e9.
[13] Paparella R, Menghi M, Micangeli G, *et al*. Autoimmune polyendocrine syndromes in the pediatric age. Children (Basel) 2023;10:588.
[14] Guo CJ, Leung PSC, Zhang W, *et al*. The immunobiology and clinical features of type 1 autoimmune polyglandular syndrome (APS-1). Autoimmun Rev 2018;17:78–85.
[15] Micangeli G, Menghi M, Profeta G, *et al*. The impact of oxidative stress on pediatric syndromes. Antioxidants (Basel) 2022;11:1983.
[16] Michels A, Gottlieb P. Autoimmune polyglandular syndromes. Nat Rev Endocrinol 2010;6:270–77.
[17] Dittmar M, Kahaly GJ. Genetics of the autoimmune polyglandular syndrome type 3 variant. Thyroid 2010;20:737–43.
[18] Page MJ, McKenzie JE, Bossuyt PM, *et al*. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71.
[19] Chen J, Lu T, Liu C, *et al*. Autoimmune polyglandular syndrome type 1 with diabetes insipidus: a case report. BMC Endocr Disord 2021;21:154.
[20] Sapana T, Li W, Tian F, *et al*. A case report of anti-GAD65 antibody-positive autoimmune encephalitis in children associated with autoimmune polyendocrine syndrome type II and literature review. Front Immunol 2023;14:1274672.
[21] Horino T, Ogasawara M, Ichii O, *et al*. Autoimmune polyglandular syndrome type 3 variant in rheumatoid arthritis. Rom J Intern Med 2020;58:40–43.
[22] Inaba H, Ariyasu H, Iwakura H, *et al*. Autoimmune polyglandular syndrome type 2 and autoimmune hepatitis with thymoma-associated myasthenia gravis: case report. BMC Endocr Disord 2020;20:47.
[23] Prylutska O, Degonskyi A, Tkachenko K. A case of autoimmune polyglandular syndrome type 2 associated with atypical form of scleromyxedema. Ethiop J Health Sci 2016;26:503–07.
[24] Rehman UL, Hamza HM, Malik MM, *et al*. Association of latent autoimmune diabetes of adults with type 3 polyglandular autoimmune syndrome: a diagnostic challenge. J Pak Med Assoc 2024;74:990–92.
[25] Kurozumi A, Okada Y, Nishio K, *et al*. Case of autoimmune polyendocrine syndrome type 3 complicated with anti-N-methyl-D-aspartic acid-receptor encephalitis. J Diabetes Investig 2021;12:290–92.
[26] Bapat P, Kushwaha S, Gupta C, *et al*. Autoimmune polyglandular syndrome type II presenting as subacute combined degeneration of spinal cord: a neuroendocrinology crossroad. Rom J Intern Med 2022;60:123–26.
[27] Jiang Q, Wu T, Zhang Y, *et al*. Case Report: a rare case of coexistence of autoimmune polyglandular syndrome type 3 and isolated gonadotropin-releasing hormone deficiency. Front Immunol 2021;12:734685.
[28] Murata Y, Haneda M, Miyakawa N, *et al*. Autoimmune polyglandular syndrome type 3 complicated with IgG4-related disease. Intern Med 2024;63:425–31.
[29] Tian S, Xu B, Liu Z, *et al*. Autoimmune polyglandular syndrome type III associated with antineutrophil cytoplasmic autoantibody-mediated crescentic glomerulonephritis: a case report and literature review. Medicine (Baltimore) 2020;99:e19179.
[30] Kinoshita T, Kamei S, Nakamura Y, *et al*. Onset of type 1 diabetes mellitus and heparin-induced thrombocytopenia in a patient with Basedow's disease and idiopathic thrombocytopenic purpura: novel combination as autoimmune polyglandular syndrome. J Diabetes Investig 2018;9:1381–82.
[31] Alrufaidi AM, Alnashery MM, Alghanimi AA, *et al*. An uncommon presentation of autoimmune polyglandular syndrome type 1 (APS-1): a case report. Clin Case Rep 2024;12:e9015.
[32] Schulz L, Hammer E. Autoimmune polyglandular syndrome type II with co-manifestation of Addison's and Graves' disease in a 15-year-old boy: case report and literature review. J Pediatr Endocrinol Metab 2020;33:575–78.
[33] Sun Y, Kan X, Zheng R, *et al*. Hashimoto's thyroiditis, vitiligo, anemia, pituitary hyperplasia, and lupus nephritis—a case report of autoimmune polyglandular syndrome type III C + D and literature review. Front Pediatr 2023;11:1062505.
[34] Ralli M, Angeletti D, Fiore M, *et al*. Hashimoto's thyroiditis: an update on pathogenic mechanisms, diagnostic protocols, therapeutic strategies, and potential malignant transformation. Autoimmun Rev 2020;19:102649.
[35] Martin-Grace J, Dineen R, Sherlock M, *et al*. Adrenal insufficiency: physiology, clinical presentation, and diagnostic challenges. Clin Chim Acta 2020;505:78–91.
[36] Tsiortou P, Alexopoulos H, Dalakas MC. GAD antibody-spectrum disorders: progress in clinical phenotypes, immunopathogenesis, and therapeutic interventions. Ther Adv Neurol Disord 2021;14:175628642 11003486.
[37] Van Mierlo T, Fournier R, Ingham M. Targeting medication non-adherence behavior in selected autoimmune diseases: a systematic approach to digital health program development. PLoS One 2015;10:e0129364.
[38] AlAbbasi O, Magliyah MS, Ahad M. Long-term keratitis treatment with topical cyclosporin A in autoimmune polyglandular syndrome type 1. Am J Ophthalmol Case Rep 2021;21:101009.
[39] Conigliaro P, D'Antonio A, Pinto S, *et al*. Autoimmune thyroid disorders and rheumatoid arthritis: a bidirectional interplay. Autoimmun Rev 2020;19:102529.
[40] Förster G, Krummenauer F, Kühn I, *et al*. Das polyglanduläre autoimmunsyndrom type II: epidemiologie und manifestationsformen [polyglandular autoimmune syndrome type II: epidemiology and forms of manifestation]. Dtsch Med Wochenschr 1999;124:1476–81.
[41] Hansen MP, Matheis N, Kahaly GJ. Type 1 diabetes and polyglandular autoimmune syndrome: a review. World J Diabetes 2015;6:67–79.

[42] Guarnotta V, Pillitteri G, Gambino G, *et al*. Levothyroxine and insulin requirement in autoimmune polyglandular type 3 syndrome: a real-life study. J Endocrinol Invest 2021;44:1387–94.
[43] Obermayer-Straub P, Manns MP. Autoimmune polyglandular syndromes. Baillieres Clin Gastroenterol 1998;12:293–315.
[44] Nassar-Sheikh Rashid A, Schonenberg-Meinema D, Bergkamp SC, *et al*. Therapeutic drug monitoring of anti-TNF drugs: an overview of applicability in daily clinical practice in the era of treatment with biologics in juvenile idiopathic arthritis (JIA). Pediatr Rheumatol Online J 2021;19:59.
[45] Jankowska K, Dudek P, Stasiek M. Autoimmune polyendocrine syndromes associated with autoimmune rheumatic diseases. Reumatologia 2023;61:225–38.
[46] Lakhani OJ, Tripathi S, Indu KC, *et al*. Levothyroxine replacement before glucocorticoid replacement leading to adrenal crisis in a case of autoimmune polyendocrine syndrome type II (Schmidt syndrome). Thyroid Res Pract 2015;12:116–18.
[47] Kang MS, Sandhu CS, Singh N, *et al*. Initiation of levothyroxine in a patient with hypothyroidism inducing adrenal crisis requiring VA ECMO: a tale of preventable disaster. BMJ Case Rep 2019;12:e230601.
[48] Dineen R, Behan LA, Kelleher G, *et al*. The contribution of serum cortisone and glucocorticoid metabolites to detrimental bone health in patients receiving hydrocortisone therapy. BMC Endocr Disord 2020;20:154.
[49] Akkurt Kocaeli A, Erturk E. Bone mineral density and vitamin D status in patients with autoimmune polyglandular syndromes: a single tertiary care center experience. Horm Metab Res 2024;56:128–33.
[50] Pryce CR, Fontana A. Depression in autoimmune diseases. Curr Top Behav Neurosci 2017;31:139–54.
[51] Elsayed M, Negm E, Gahr M, *et al*. Autoimmune polyglandular syndrome type 2 and recurrent depression. Ann Med Surg (Lond) 2023;85:494–96.
[52] Lateef A, Petri M. Hormone replacement and contraceptive therapy in autoimmune diseases. J Autoimmun 2012;38:J170–6.
[53] Moulton VR. Sex hormones in acquired immunity and autoimmune disease. Front Immunol 2018;9:2279.
[54] Krez A, Liu Y, Kanbour S, *et al*. The skeletal consequences of epidural steroid injections: a literature review. Osteoporos Int 2021;32:2155–62.
[55] Czubek E, Alcer K, Varjacic M, *et al*. The importance and effectiveness of nutritional counselling in patients with autoimmune thyroid diseases in Poland. Cost Eff Resour Alloc 2022;20:63.